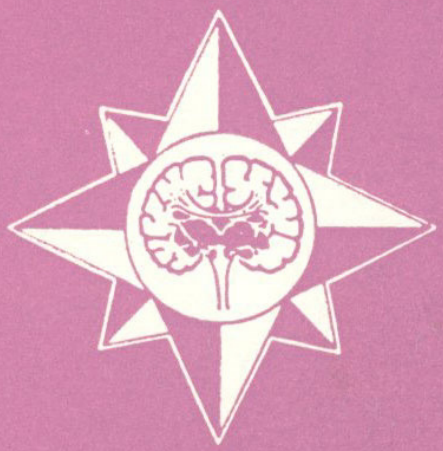
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Man and Drugs

VICTOR SORIANO
Montevideo - URUGUAY

Eons of years ago the elements with ciclopean fury were wrestling trying to find their place in the process of creation while shaping the earth.

But there was something in prospect more important than the imposing mountains that arose amidst shakings and thunders, more important than the molten rocks boiling in a sea of fire. And that was the tiny seed of life which had to travel through the many species and flourish in consciousness.

That seed took to mature millions of years to be carried like a torch by its most noble bearer, Man.

Ignorant of where it came from, Man was thrusted with it like a dart aiming at the infinite...

In its endless voyage through the times the world has changed for the Homo Sapiens many times in its looks and meanings as consciousness was getting clearer and closer to the ultimate reality.

To this have contributed many wise men who have poured into the rich reservoir of the colective culture the fruit of their dedicated lives.

Many times endangered by abortive souls who seek power that they afterwards misuse. Humanity has nevertheless been ascending reckless towards its destiny, through patient work and clear intelligence.

Man has the most precious instrument to perform his task, his own brain, the plasticity of which is always ready to acquire new concepts, to invent new devices, to be trained for more audacious feats and adventures never before experienced.

His intelligence weaves in the magic loom of the brain as Sherrington called it, miriades of electric pulses which come from Huxleys Doors of Perception travels through the intricate nerve net rending the most precious gift given to the living matter: Awareness.

Out of it Man discovers laws that govern the physical world, preserves his own life and the ones of his kind avoid errors in thought and action, create new things out of the old stuff already at hand.

If intelligence and imagitation are to be successfully used, awareness ought to be always vigilant. Linked as they are, the highest functions of the intelect, one reinforces the other. Speaking about man of meditation and intuitive thinking, Emerson said "These kind of men are for us of such utility because they have the perception of identity and reality." Let us say that they know the nature of the rules with which they are measuring and interpreting the World, and the need to control and check both of them.

The nervous system being so precious in its function in getting and applying knowledge, and at the same time so puzzling and marvelous in its dazzling performance of numerous events as is elusive in hiding its mysteries as how matter thinks, I believe that this Symposium on Neurotropic Drugs and Behaviour explained by a group of highly qualified scientists from different countries will shed light upon one of the most far reaching prospects in the future of mankind.

It deals with the very essence of pharmacology in relation with the nervous system. Just how the chemical substances influence the functioning of the different neurological mechanisms, altering its ways and doings in normal or pathological state, and the proper way of handling them, justifies

the enthusiasm aroused by this newcomer in Medicine: Neurochemistry.

It is a challenge to disclose in this field of investigation an enigma which for long has entangled philosophers, physicians, psychiatrists, psychologists, etc.

How out of neurochemical interchange generating or being generated by electrical pulses, we are endowed with consciousness.

For the time being we must be content with having at our command the tools to regulate in a highly satisfactory fashion the nervous machinery slowing down tense feelings, enhancing the depressive one, stimulating and soothing at the same time the different integrating forces seeking like an orchestra conductor to elicit the exact tune of every one of them till the symphony of life is rendered in full harmony.

Many are the neurological conquests in modern medicine due to neurochemical findings, dramatic illnesses like Parkinsonism, Epilepsy, disturbance in the functions of learning memory.

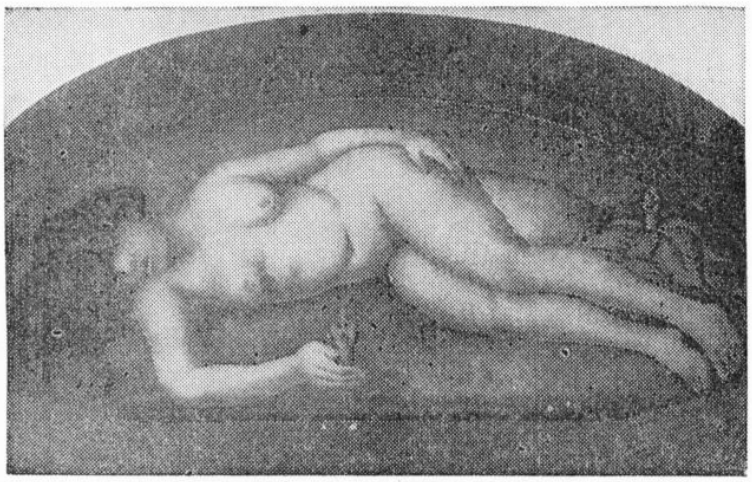
Proud as we must be of all these conquests of the last decades of Medicine, we ought to shed a retrospective look to our humble ancestor who, dwelling in a cave thousands of years ago, was trying to save his endangered life from an illness he didn't understand with a remedy he didn't know.

Being a child of the earth, he recurred to her to cure his ailments, and by trial and error he was setting the basis of modern Pharmacology. Soon this ancestral investigator discovered that there were herbs for curing, some for killing and others for strange dreams which endowed his narrow life with a breath of mystery and transcendence.

Through the centuries these herbs of mother earth became so precious for his imagination that soon he erected them as divine and were the source of sacred rites.

Compassionate earth has given its children nourishment and herbs that placate their pains. Here we see (Fig. 1) through

FIGURE 1



the magnificent art of Diego Rivera the Mexican painter, a colossal fresco that represents Mother Earth sleeping while holding in its hands a growing plant.

What kind of dreams did she have? Some of them must have been real nightmares that instilled in the growing seed its delirious nature — plants thet Lewin, the great German toxicologist, baptized as "phantasticas".

Thus the Peyotl, a Mexican cactus that will not attract the attention for its aspect in a country where beautiful plants and dazzling flowers shed light and colour everywhere. The Peyotl, so sacred to the Aztecas, is a small cactus Laphora Williamsil that holds on its body the "biggest show on earth". The peyotl shared its sacred dignity with two other plants, the Ololinqn and the Teonacatl. That is the most important triad of vision induced plants in that country.

On the plains of Tamaulipas and Jalisco in an almost desertic region amid rocks and sand, there grows the Peyotl, a cactus covered with white silky hair and emerging

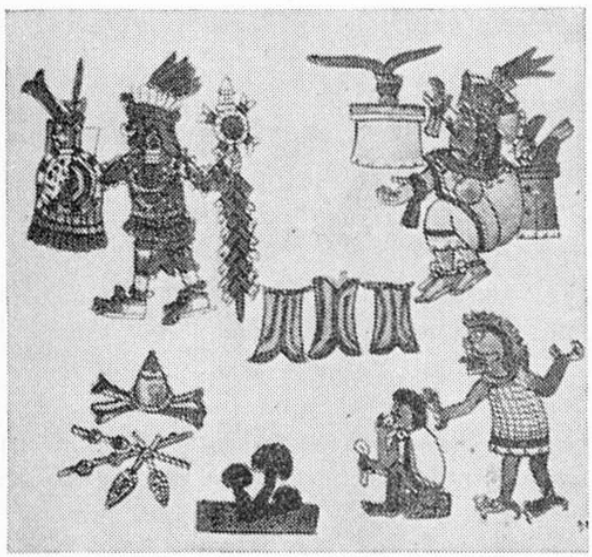
from a carrot like a root its small body of a dark green colour.

Every year before the dry season begins, a religious peregrination is performed to get what they considered to be the meat of the gods, the Peyotl.

Cleansing rituals, prayers, abstinence from any kind of sin, are the due preparation for such a reverential procession. When the group arrives at the site where the plant is, they throw arrows in every direction to reject evil spirits. Then very carefully without damaging the plant they dig a circle around it and remove it from the earth. The joyous group return singing and elevating altars all the way back. Everyone of the participants receives pieces of Peyotl that they keep for the festivities. The fleshy body of the Peyotl is cut in round pieces surrounded with white hair and known as mescal buttons, exposed to the sun to dry until they get a brownish hue.

Fig. 2) This figure taken from the Codex Magliabecchi, shows that the ancient inhabitants of Mexico knew the nature of the different plants .

FIGURE 2



At the bottom on the right we can observe an Indian eating a magic mushroom while it is observed by Mictlantecuhtly, the god of Death.

On the upper part we can see the god of the Seeds. This figure of Xiutechtli informs us that the knowledge of the drug in ancient Mexico is used to alleviate the suffering of the men sacrificed to the god of the Fire.

Fig. 3) Quetzalcoatl (spirit) danees before Tezcatlipoca (matter). The worlds of matter and spirit are coexistent.

The mescal buttons chewed in sacred rites gave the participants the sensation that the doors of the heavens were opened to them and that they could approach the deities personally and implore their protection.

FIGURE 3

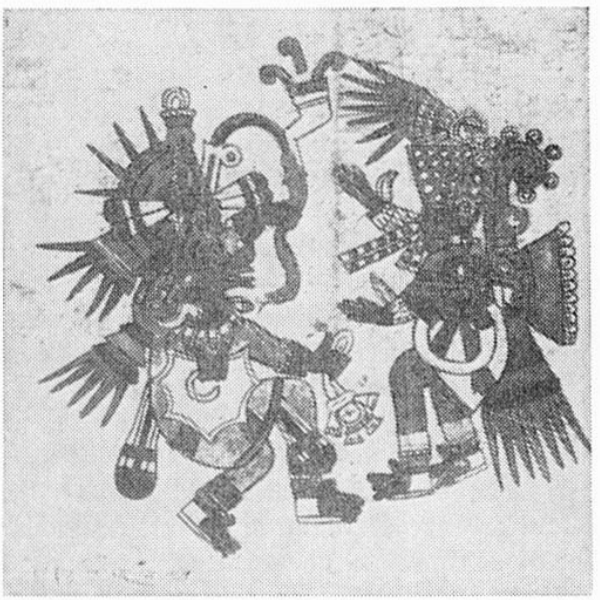
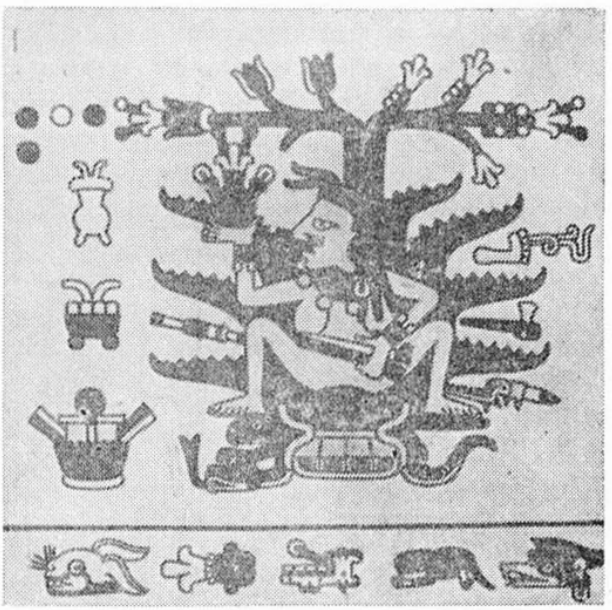


Fig. 3 bis) The goddess Mayahuel discovered that the juice of the plant, when fermented made a beverage inducing content-pulque.

FIGURE 3 bis



As time elapsed, the Peyotl crossed the frontiers of the United States and it was cultivated and adopted by the Indian Apaches and Comanches. But the Peyotl aimed higher and conquered the attention and curiosity of the distinguished people so a visa was given for the drug "trip" to very qualified passengers such as Dr. Weir Mitchell, Aldous Huxley, Haverlock Ellis, William James and Timothy Leary.

Aldous Huxley, a man of books, had a significant hallucination. He saw books red like rubies, emerald books, books bound with white jade, agata books, lapizlazulis and aquamarina, yellow like topace, so intrinsically significant that it "seemed they would leave the shelves at any moment and approach me demanding my attention with insistency".

Even under the effect of the drug, Huxley maintained control over his judgements, which reveals an orderly spirit and checked by such intellectual discipline that it overcame the hallucination of the drug.

Before Huxley, the first one to taste the drug was Weir Mitchell; he had pleasant visions but he arrived at the conclusion that the effect of the drug upon the organism is not such as to be enthusiastic about it, and expressed: "These functions are very expensive. Nevertheless, the experience is worthwhile the strong headache and indigestion, but not a second one."

Others, under the effects of mescaline, had incoherent visions such as waves of coloured flowers that transform themseleves into butterflies, precious glittering stones.

Spider waves of indescribable colours, or monstruous animals. Some have the terrific experience that Baudelaire qualified as the sense of the infinite. Like disintegrated bodies floating in the air a true array of colours that affects principally the brain visual areas and makes them feel transported to a charmed region. But not always senses are delighted with the show; there are Peyotl eaters who experience suffering and terrors.

Dr. Weir Mitchell who was not willing to take a second trip passed the drug to be experimented by the only psychologist of his time who showed some interest in investigating the effects of the drug. A celebrity of this field — William James. Even though he was by nature a researcher of the mystics and that his characteristic could facilitate the sacred fantasies of the Peyotl, he only got from this experience a strong stomach ache. When he wrote to his brother about it, he said,: "I ate only one bud three days ago and I was violently sick for twenty four hours and had no other symptoms whatever, except that one and the Kaztzenjemmer (hangover in German) the following day. I will take the vision on trust." And that was that.

Unhappily not everybody could get away from peyotl so easily. There were people that in spite of the rosary of disagreable symptoms like vomiting, paleness, loss of apetite, insomnia, uneasiness that accompanies the drug ingestion, they stick to it because they experiment afterwards a divine ebriety. Sometimes this has a dangerous turn and they have a diabolical experience, they perceive monstruosities which fill them with vague terrors, sensation of imminent disaster, etc.

Aldous Huxley's opinion is that our brain acts as a regulator that protects the individual mind from the enormous pressure of the Cosmic one.

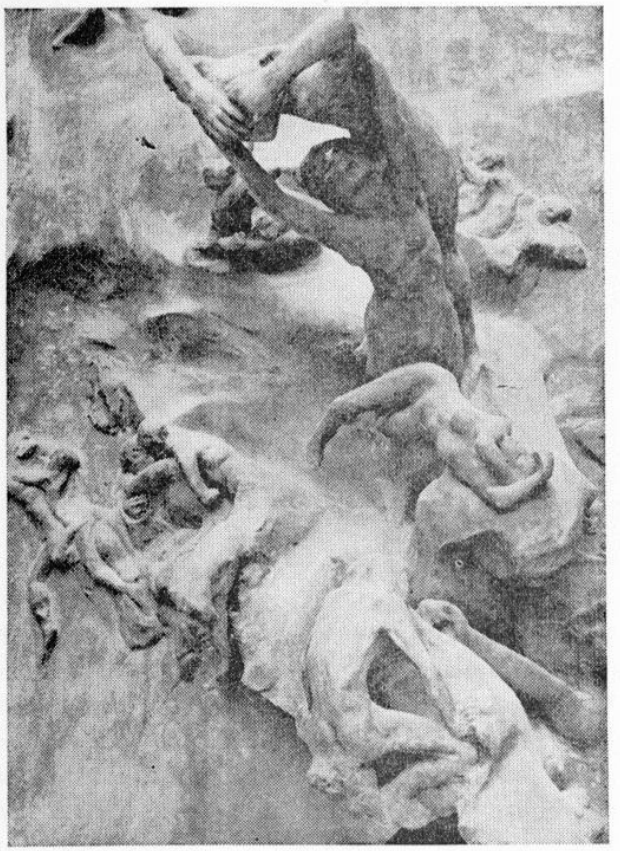
From the physiological point of view this drug seems to interfere with the process of oxidation of the brain cells. This has been evident by studying pieces of brain cells in vitro and studying the effects of the drug on them.

But famous men in the field of Chemistry, bring to attention the fact that pieces of brain studied in vitro and to which they have given barbiturates and that act in identical fashion that in interfering in the processes of oxidation of the brain cells don't arouse ecstasy vision, but the taker goes peacefully to sleep. It has been studied that the mescaline does not go pure up to the brain, because taking it with radioactive material, it disappears at the liver level and it is believed that another product generated there on an unknown chemical nature, is stimulated and it is the one fully responsible of the hallucinatory effects of the Peyotl eating.

MARIHUANA

Fig. 4) We have chosen the beautiful sculpture of Rodin "The Doors of Hell" to illustrate how the addicts are falling, pushed by the vice, into the bitter waters of desperation.

FIGURE 4



Under different names in different countries, the marihuana has been known in Arabia and India since a very long time ago.

Marco Polo and other travellers always told marvels of this drug which presumably inspired the Arabian Nights.

A wise man from China and a lover of philosophy like the famous Chinese Emperor Sheng Neng, referred to this drug in his book of pharmacology published 2737 years before our era; he suspected of a herb that gave happiness very easily and called it the "Sin Liberator".

Afterwards in new generations that were not so strict it was regarded as "that which gives pleasure".

Mixed sometimes with the dark waters of witchcraft others regarded it as celestial blessing. The hashich arrives to our days with its strange promise of happiness.

It is known that from Canabis Sativa male and female plants; the flowering leaves of both secrete resin which is pure hashich.

It is also known as Canabis Indica and was thus known in the antiquity. In India, Bombay, there are special fields where it is cultivated as a celestial guide; the strongest of the varieties came from Yarkan in Central Asia with the name of charas and enters India via Tibet. Of all the different ways to take the hashich the most horrible one is that used in a rite in Tibet where it is mixed with human fat, and served in skulls in profane ceremonies of the Dugpas. In Egypt and Orient it is smoked in special pipes, similar to those used in opium.

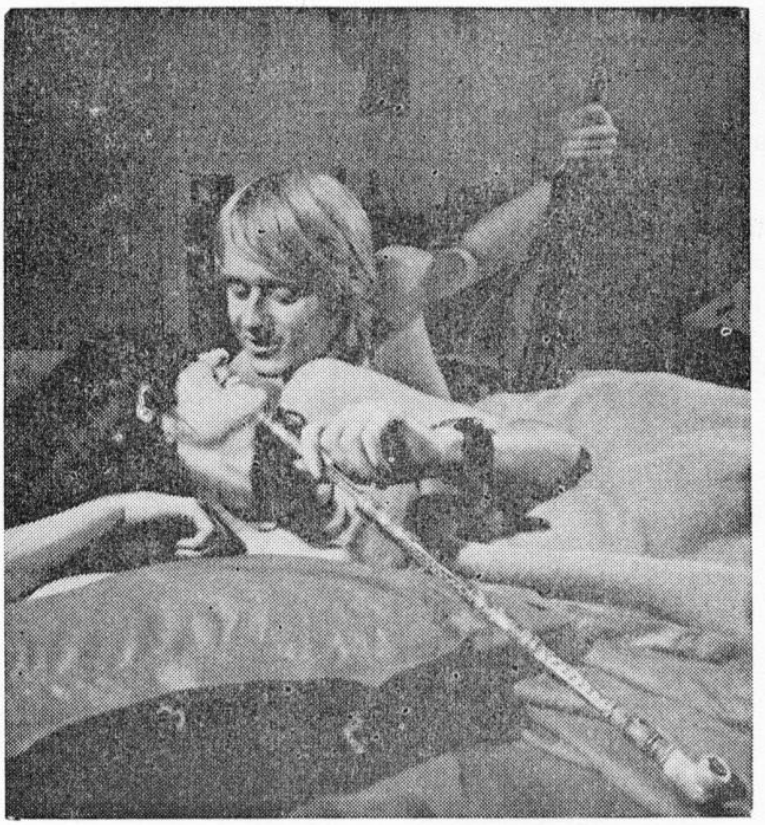
Fig. 5) Here you may see how distinguished ladies on Fifth Avenue enjoyed the Canabis Sativa in oriental disguise in 1876.

Fig. 6) The same pipe could be observed in this scene of a modern movie picture. In France the élite of the men of Letters



FIGURE 5

FIGURE 6



founded a club which was called: "Club des Hashishim". Expecting to heighten their inspiration, Gautier and Baudelaire formed part of it.

Under the title "The Theater of the Seraphines" Baudelaire made a dramatic description of his experiences where the artist and scientist met in exactness. Man is a limited being; his physical entity is contained in a vessel of earth, but it is limited not only physically, but mentally as well. When the mold of the reality that contains him falls in excesses he can be as ridiculous as the description made by Baudelaire in one of his commentaries entitled "The Man-God". He expresses therein that under the effects of the drug certain people begin to feel like God. Another description of his says: "What euforic feelings! What a glorious exaltation! All the contradictions disappear. All the philosophical problems become cristal clear. A voice inside is saying: Now you have the right to feel superior to all the other men. Nobody knows what you know neither can they understand all you think. They cannot even understand all your good will toward them. You are an unknown King to the multitudes and the only one that has this knowledge. Baudelaire continues in this monomania of the man who enjoys feeling inside of him the divine omnipotence, to conclude later that the man who lives in an artificial paradise is also an artificial god.

A very sane reflexion.

OPIUM

Lost in the midst of the remotest past, a potent destroyer of pain and grief has come down through the ages bringing its tragic ambivalence that makes of just one substance the messenger of heaven and hell: opium.

The vast plains covered with Papaver Somniferum with their graceful flowers of soft wrinkled white and purplish petals thin as silk paper hides its treasure in a kind of round little vessel container where a gelatin-like substance surrounds the seeds.

People mostly women can be seen bussy scarifying the poppy's capsules. From these scratches a whitish matter will flow, a kind of latex that afterwards, when

it is dried, will be scraped, and collected in lumps from a half to two pounds.

It is estimated that every foot of plantation would render 5 grams of opium and that 15 to 60 kilograms would be obtained from each hectare.

Time does not allow us to go into details concerning the process of opium which contains 30 important alcaloids, among them morphine, codeine, tebaine, papaverine, and narcotine.

Nothing is evil in Nature, except for the use that man makes of it.

There is a hidden law that the use of everything is trusted to the will of man, the transgression of which is sinful.

Thus opium rightly used is a bliss for mankind; wrongly used, it brings death, shame and despair.

It was known by the Egyptians and there are references to it in the papirus of Ebers. Mnemosine, the Greek goddess of the Memory and mother of the Muses is known as the goddess of the Poppies, and is much venerated in Crete.

Demeter, daughter of Chronus and Rea, goddess of the Harvest has corn and poppies among her symbols. It was known in Sumer in the city of Gilgamesh and its name is written on the tablets of that time. In Greece Teofrastro includes it in his book of the History of the Plants.

After the battle in which prince Eugene defeated the Turkish army of Mustafa II near Louvens and when the victorious soldiers were rapaciously spoiling the dead that covered the battlefield, they saw that they had priapism post mortem. Sahs attributes the phenomenon to the opium that the turkish soldiers used to take to give them courage during the battle. Opium was eaten long before many other means were taken until now when many people are used to chewing it in Egypt and Asia Minor.

The shortage of opium during the Second World War made many addicts turn to laudano, which they injected into themselves without taking good care of sterilizing the syringe, causing many deaths by tetanus. Among them was the great poet Roger-Lacompte.

Opium was also taken in pills mixed with sediments which greatly increased its content of morphine.

Many addicts preferred to smoke it mixed with tobacco or natural in a special pipe of 40 cms. in length and 3 of diameter of bamboo or horn and with a receptacle of earthenware where the opium is placed to be smoked, with its characteristic position near the lamp that maintains the drug burning. Many were the celebrities who succumbed to opium for different reasons. Let us name some of them.

Cardinal Richelieu used to take it to alleviate his painful ulcers. Lord Erskine Member of Parliament, Baudelaire, Jean Cocteau was one of its devotees, and so was Savonarola in spite of all his puritan fury; and also Samuel Taylor Coleridge.

These were some of the writers who took opium, along with De Quincey, whose "Confessions of an English Opium Eater" is considered a priceless document regarding the experiences of opium. Let us just transcribe a short sentence written by de Quincey taking opium to alleviate an excruciating rheumatic pain:

"I was necessarily ignorant of the whole art and mystery of opium taking; and I took it to every disadvantage. But I took it during one hour. What a resurrection! What an apocalypse of the world within me; that my pains had vanished was now a trifle in my eyes. This negative effect was swallowed up in the immensity of those positive effects which had opened before me, in the abyss of divine enjoyment thus suddenly revealed. Here was panacea, a Pharmakin nepenthes for all human woes; here was the secret of happiness, about which the philosophers have disputed for a penny, and carried it in the waistcoat pocket. Portable ecstasies might be corked up in a pint bottle, and peace of mind could be sent down by mail." These were De Quincey's words.

This wonderful passage by one whom we could appoint as the advocate of the Devil, says here what the moralist fears of the drug, that takes the place of conscious living and moral responsibility, and the burdens of the soul that ought to be solved perfecting the personality is transferred to

a pill, leaving humanity entangled with unsolved conflicts.

Even though Nature prevents the approach to the drug with a disagreable sensation, man insists in being immoral, his earthly paradise is soon lost and he is a defenceless creature in the hands of vice like a pawnbroker who takes far more than he gives. Soon the opium taker has a dependence on his substance. He begins to suffer from his stomach and intestinal tract; he develops a hepatic insufficiency, palpitations, syncope, propensity to get emphisema, pulmonar congestion, atrophy of the sebaceous gland, and of the skin and wrinkles.

Morphine, one of the derivates more powerful than opium, owes its name to its narcotic quality and honors the god of the sleep Morpheus.

This drug was used during the war to lessen the dramatic pains of amputations. At first morphine was given even for a headache, until the doctors noticed its devastating effects. Like all vices, it soon finds a circle in which it is fashionable to degrade the body in an exotic way.

Ladies of the high society met to have injections of morphine. Jewellers offered them syringes made of gold and boxes with precious stones in which to carry it. The devil must have been very busy in those days. Even a doctor in Paris used morphine as a means to kill the Ballet brothers in order to obtain their fortune. He was discovered and guillotined. The artists also used the drug to excel on the stage.

Morphine, like all other durgs, heavily taxes the organism. There are disturbances of the internal glands. The tyroid and the pancreas are the ones most affected by the morphine. The metabolism of sugar is very deficient, all the nervous system is unbalanced and experiences a great excitability.

It can produce sterility, but when a woman addict is pregnant, the child shares with her the burden of her sin. There is no safe place against the drug, no barriers that defend an inocent life before its birth. The child becomes an addict. It suffers along with its mother the withdrawal of the drug. Its movements are agitated showing evidences of carency. At first when these children were born in apparent good health they died in a few days amid dreadful convulsions. Then they realized that if they gave some opiates to these children, they had immediate relief.

In 1960 and 1961 the doctors at Bellevue Hospital of New York reported that out of 100 cases of morphine children, 60 were fatal.

Another potent alcaloid extracted from morphine was discovered by Dr. Dresser in Berlin. He called it Heroish and he thought that he had discovered a mighty substance to cure tuberculosis. And he endowed his brain child with all the blessedness of the world. Nothing to fear about it. No addiction, no complication. And besides, he expected that it would liberate of addiction the people taking morphine.

It turned out to be just the opposite to his expectation.

More powerful than morphine, it soon conquered new adepts also those on older drugs tried the thrill of heroine.

Recent reports from the Bureau of Children Welfare in New York inform that the number of expecting mothers addicts to heroine are alarmingly increasing. From 200 in 1966, to 489 in 1970 and more than 550 in 1971.

The child born under this condition is almost always a premature one. Scarcely nine hours after its birth it will experience the sufferings of hell.

A coarse tremor will vibrate in its defenceless little body. Convulsive jerkings will agitate its knees and accompany the twitching of its arms. In physiological despair it will scratch its face until it bleeds. The sheets of its bed will be moist with perspiration hardly ever seen in a normal child. It will have difficult breathing. If medical care can't come to its aid immediately it will turn into that dreadful state of people deprived from herooine called "cold turkey". It may have terrible convulsions, dehidratation and death.

Almost all these mothers come from slums where vices propagate like fire. The future of the babies and their life expectancy depends on how long the mother has been taking drugs and also how much she takes of it. Also if she has had any shots imme-

diately before the birth, as many women addicts have done to have the baby under the heroine effects. If so, the child will feel earlier the effects of the withdrawal and the symptoms would be more dramatic.

These heroine mothers are a great problem to the doctors who never know if the babies are at full term, because the drug upsets the menstrual cycle, and the women don't know when they began their pregnancy.

The baby in need of help will get a dosis of clorphromazine (1 mg per pound of baby weight) divided in four dosis given by mouth or injected. Law protecting infancy extends its care to the unborn child and considers this case as a child abuse. It is also concerned about its future. It cannot be considered an addict as it has not the psychological make-up that conforms an addict. So they are seeking that the child may grow in a healthier environment.

There are special institutions for these neglected children, and in a world of misery it is heart-warming to learn that there are some families that voluntarily give shelter to the children of addict mothers.

It is distressing enough to learn that there have been 4.000 cases of neglected and child abuse in 1971 begging for food, alone in the middle of the night. The heroin substance is not for these poor children.

The well organized fight against drugs is trying to raise this case affecting the biological welfare of all mankind.

While this is attained Methadone is the only helping hand for the clouded life of the heroine mothers.

C O C A

On the warm slopes of the eastern Andes is cultivated a thick bush with glossy leaves known since immemorial times as a "divine plant": COCA.

Garcilaso de la Vega, an Inca himself by his mother's ancestors wrote about it: "Coca is a shrub the height and thickness of the vine; it has a few branches and on them many delicate leaves the width of the thumb and about half the length of the thumb and of an agreable odor but not very sweet... so pleasant is coca that the Indians prefer it to gold and silver and precious stones... They chew it but do not swallow it; they merely savour the fragrance and swallow the juice. Coca," Garcilaso continues, "preserves the body from many infirmities and our doctors (that is, doctors in Spain) use it in powder form to stop and placate the swelling of wounds... Coca meant almost everything even in the pre-Inca periods; archeological findings corroborate that Coca was the companion of the dead.

The bulk that denounces a coca chewer is so characteristic that even in a fine Chimu black ceramic vase shaped as human head with geometrical decoration it is shown. There is a distinct bulge in the right cheek caused by a quid (jacchu) formed by coca leaves. It is usually chewed in conjuction with a paste of quinoa stalks, which heighten its effects.

At first only, used according to the Inca regulations by the nobility, the soothsayers known as amantuas the chasqui-coures who had to travel at high speed in cold and high regions and to those advanced in years. After the conquest this control was overthrown and coca was within the reach of everybody. And it was so alarming to see the widespread of the drug among the white that a council was organized in Lima that threatened to excomulgate those who indulged in the use of coca, as a devil's idolatry.

It was an item of commerce and many people got rich with it. It was regarded as "the green gold of the Yungas".

In an altiplano street market in Peru we saw a bale of coca and an indian with a bulk in his cheek chewing it. Because of its euforic effects it is widely used. The hard condition in which they live and work can only be borne with the aid coca.

Also the miners who, after having the bulk of coca in their mouth, they don't experiment hunger or tiredness all along their rough work.

In 1950 there were four million people chewing coca in Peru, and there is no sign that the situation has changed in spite of all the efforts made trying to liberate these people of this vice, as in all the others, draws in health and gives instead a sensation of happiness.

FIGURE 7



Fig. 7) This fine ceramic shows a little purse for carrying coca. The coca user soon shows the disastrous effects of the drug on his organism. He acquires a brutish air, his walk is vacilant, he has skin flacidity, his muscles are feeble and his complection of a grey-yellow colour. The eyes are socketed and dull, with a deep blue ring underneath and green teeth. They have not the strength corresponding to their age, and they look very old before their time.

For a long time coca was unknown in medical circles and it is interesting to recall the way its anesthetic effects became known.

In 1860 Albert Nieman in Germany got an alcaloid from the coca leaves which he called cocaine. He tried this substance on his tongue and was surprised to discover that the same had lost all sensitivity, and he could not distinguish between hot and cold. Nieman, a chemist, did not realize the medical importance of his discovery.

Later three men were attracted by the idea of trying this substance. They were a rising celebrity, Sigmund Freud, a young colleague of twenty, Karl Koller and a friend of his, Leonhard Konigstein. Koller, an oculist, was looking for a substance that would facilitate the operation on the eye with the patient awake. He tried this substance casually on his tongue and discovered that even if he pressed it with his teeth, he felt nothing. Hurriedly he tried it on a frog eye and the frog did not move even when he pressed it. So he tried it on his own eye. And so, assured of his success, he performed an operation on the eye with this new anesthetic in front of the astonished doctors. Nowadays, other alcaloids allow us to perform this feat but it was the coca that opened the doors to this kind of achievement. Freud was lured by the drug and its effects and used it on himself and was very enthusiastic. Thus many dentists, otorhinolaryngologists, etc., unaware of the danger hidden in the drug, used it. The enthusiasm began to cool down when a Russian surgeon, Dr. Kolamine, performing an ablation of a tumor of the intestine, miscalculated the dosis and the patient died.

Desperate, Kolamine feeling guilty, put an end to his life with a bullet in his head.

Soon cases of addiction were discovered, and Erlenmayer denounced this abuse of cocaine therapy as a "shame for our profession". It also became fashionable in artistic circles, always prone to try new sensations, and among the gangs of snobs of every country.

The person trying cocaine will experience a sensation of cold in his face. A kind of ebriety and well-being similar to that of alcohol. Full of energy and willing to talk and move, to this period of exaltation follows one of depression. It has midriasis, he will feel terror, anguish and with lack of breath. These disagreable symptoms will continue until another dosis of cocaine is taken.

But as a Greek philosopher said: "The measure is the best of everything".

To find the right one means wisdom. So cocaine and its derivates rightly used are a tool to restore health, not to destroy it.

L S D

LSD came to the general knowledge nimbed with a scientific aureola as a marvellous

drug. At first it was thought that it would enable the psychiatrist to learn the symptoms of his patients, but afterwards it conquered the soul of those who took it and they became its worshipers.

It has been widely known how it was discovered by Albert Hoffman, how he felt its hallucinatory effects and its psychotropic properties.

Delirium accompanied by caleidoscopic visions, dizziness, and the most important of all the qualities, the deformation of the vision, confusion, depersonalization, etc. There have been many reports from people who have taken the drug: some experienced geometrical figures of changing colours, others had the annoying sensation that all his members had life, or they disappear, or their proportions change grotesquely.

FIGURE 8

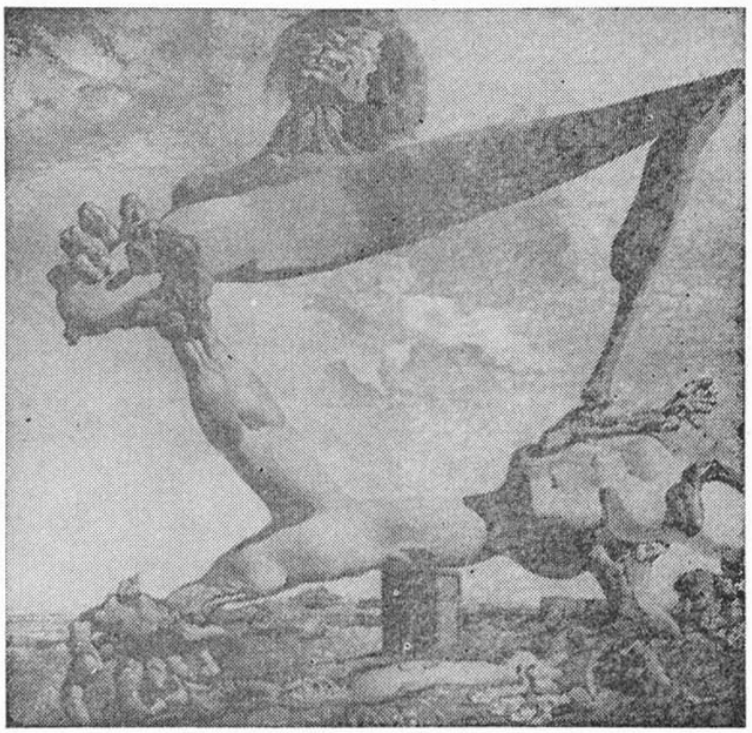


Fig. 8) It have found that this beautiful painting of Dali "Premonition of Civil War" in which the artist symbolically shows a body tearing itself apart can be transferred to the drama of the Lysergic Acid addict whose sensations are at war with the reality.

We have always learned during history about drug addicts in every country and civilization and regarded this as a lack of education of cultural maturity. But now a new phenomena seems to invade the ranks of our youth and more and more the children are becoming drug addicts and a kind of short-cut to happiness and wisdom who find it very easy to build their own standards of what the world of tomorrow must be.

Are they to be condemned?

Many of the drugs like the LSD were in the past object of research, and many are now undergoing similar tests: Thanks to this, we, the medical men, have an army of therapeutic weapons at our command to fight illnesses and some of the most dramatic are those concerning the illnesses of the mind.

They have really liberated the mental patient of the horrors of the past houses of reclusion where they were treated worse than the beast and that is so clearly shown in a known picture, in which compassionate Dr. Pinel is liberating the inmates from the chains.

Mental chains of painful emotions are now also being severed by way of chemical compounds.

But the devil has a queer way of doing things. While many are trying to preserve the soul from suffering by means of drugs,

he has utilized drugs in the same proportion to poison the healthy ones.

And that is the case with LSD. A substance of study and research — The curiosity of man goes beyond his own safety. That is his gift and his curse.

Since Adam man has been recklessly doing what he should not. He has everything to be happy, but the Lord placed a restriction. "Of every tree of the garden you may freely eat. But of the tree of Knowledge you shall not eat of it, for in the day that you eat thereof, you shall surely die".

And as the Lord left them alone and they were tempted they took a hearty bite of the forbidden fruit.

FIGURE 9



Fig. 9) As it is shown in this wonderful painting "The Fall of Man" by Tiziano.

It is with a kind of sadness that this question is poised:

Why did such a brilliant mind like that of Aldous Huxley, so rich in internal life, need to ingest psychodelic substances? Why did he believe as he stated that: "Along with many scientists I considered the discovery of psychodelic drugs one of the three major scientific conquests of the twentieth century, the other two being the splitting of the atom and the manipulation of the genetic structures".

His decision to go into psychodelic experiences was backed and done under the guidance of Dr. Humphrey Osmond.

His impressions are collected in his well known "The Doors of Perception". Many people have experienced first with one drug and afterwards turned to another more powerful and destructive one.

Among the people whose experiences have been more widespread and which have exert-

ed a decisive influence on the fascination of youth in trying the drugs, are those personalities who by their well earned fame like Aldous Huxley or in a high position as a University teacher like Leary in Harvard and more recently Reich in Yale, people who are endowed with an aureola for the youngsters who sanctify the drug.

It has been with a sense of objectivity that I would like to talk about these personalities, since I don't really know what their experiences are, or if in some tortuous way the drugs have warped the sense of perspective and responsibility, of otherwise clear, selective, and enchantingly discriminative minds.

Aldous Huxley's approach to the drug has always been with an inquisitive mind and trying through his studies to add light to this kind of experience.

Sometimes he showed an excessive enthusiasm carried away by his visions, sometimes he doubts, defending himself from the tricky effects of the drug.

Not all the people have excercised the mind the way he did for many decades of life; not everybody can discriminate even in a normal state the erroneous from the real. This is what makes it more dramatic for that child that has not yet lived, and wants to learn "how to expand his mind".

Anybody who takes the drug and lacks the conditions or affectionate nature and concern for the others could never stretch his mind like Huxley's with or without the drug. This is what makes it more painful to observe the titanic and uneven wrestling of a rational man with the irrational forces declenched by the drugs.

It became a custom for Huxley to analize his natural dreams with his second wife, and in a way they reveal to us many traces left by the drug. This one is the last dialogue held on his deathbed and I only choose the part which is of more significance for this audience.

These are the words of a man who, though lured by beauty has never deceived his calling for truth.

Aldous Huxley says: "It suddenly dawned upon me that that's what I have been thinking. It shows the almost boundless nature of the Ego ambition. I dreamed it must have been two nights ago... that in some way I was in a position to make an absolute... *Cosmic gift* to the world. I don't exactly know how, but anyhow, in doing this I had been sort of flying around immense spaces, and I have been looking into windows and helping people. I should have the sort of star role. And then people were saying, well, this must be a dress rehearsal really, and we'll get down to the real thing. At least I think it was. It is very difficult for me to keep the current of these things I kept saying "When do we start" and people just laughed... When are we going to start this enormous cosmic work...

His wife asked: "To whom did you say this?"

Aldous answered: "I don't know to whom it was. But it was a sort of general question, the answer of which was always a shrugging of shoulders and a laugh. And... this whole thing has been very strong because in a way it was absolutely terrifying, showing that when one thinks one's got beyond oneself, one hasn't.

And I was always sort of bumping my head against walls in an attempt to get out and to do things.

I began with this marvellous sense of cosmic gift, and then ended with a rueful sense that one must go on. But it was very important to find the truth of the matter.

Laura, his wife, asked: "It sounds as though it was similar to an LSD insight."

Aldous said: "It was an insight, but at the same time the most dangerous of errors, inasmuch as one was worshipping oneself. It is very interesting to see how easily it would be to succumb to a completely false revelation.

We recall here a saying of Confucius which was dear to Huxley and also applies to him. "It is man who makes truth great, not truth which makes man great".

I think that these words during his last days on earth are the best message he could leave to those that blindly seek in the shadows of the drug that it come to man through evolution, good will and hard study and light of knowledge.

During the last moments of his life and dying from cancer, Huxley would ask in writing (he could hardly speak), to be gi-

ven 100 mg. His wife administrated this to him even when his doctor didn't approve it. The psychiatrist who was a leader on LSD when consulted said that in his conditions it wouldn't make any difference. Afterwards another shot was given to him. And thus aldous Huxley left the earth on a trip of LSD.

To whom much is given, much is demanded. It seems an ethical law that the person endowed with high talents be responsible for leading from the eminence of their superior minds the thoughts of their generation.

Thus Huxley was freely disposing of a treasure confided to him: his brilliant mind. How could this affect the young generation? Is not a man free to do whatever he thinks with his own body?

Nobody knows, not even Huxley, in which subtle way his mind has been changed. In a book about his life, his wife commenting about the excesses that are critizised in young people going into drugs, says in Islan, the last book of Huxley that such abuses were avoided because young people were given the moshka medicine (the drug) as part of their education once a year, under supervision, beginning at adolescence. Now finally, many doctors and educators, she comments, admit that the education of young people in the use of the psychodelics, rather than being prohibited, is called for." As early as 1953 the year he underwent his first psychodelic experience, Huxley wrote:

"It is too much to hope that a system of edcuation may some day be devised which shall give results in terms of human developments commensurate with time, money, energy and devotion expended? If such a system of education may play a part by making it possible for young people to taste and see". "...what they have learned by second hand, or directly at a lower level of intensity, in the writings of the religious, or the works of poets, painters and musicians."

The very word psychodelic was coined in 1957 by Aldous Huxley and Dr. Osmond It means mind-revealing or mind-opening. Representing the characteristics of mescaline, LSD and psilobin, extracted from a Mexican mushroom.

Timothy Leary, known as the prophet of the LSD, is another of the worshippers of this substance that stretches the mind beyond our understanding. I sincerely believe that they are convinced of the predicament they impart to the youth and that is what makes them more dangerous.

Timothy Leary, like Adam and Huxley, took what was forbidden, the mescaline.

But instead of losing a paradise, they thought that they had found one and that it was an act of love to offer it to others. Again we may ask in what degree the personality changes. Before going to Mexico, Leary was one of the most brilliant professors at Harvard University in charge of the Psychiatric Chair. Here is the account of his first encounter with the psychodelic drugs: In 1960 at the beautiful place of Cuernavaca in Mexico, Leary ate 7 vision inducing mushrooms. Many years after he wrote about it: "I learnt that I was dead; that I, Timoty Leary, was dead. The Timothy Leary of small lies, was gone. I could see behind and see my body resting on the bed. I recalled my life and many events already forgotten. The discovery that the human brain possesses infinite possiblities in latency and that I could move at my wish in the dimension of space.

Terrified and completely convinced I woke up from a long ontological dream. After that illumination I have spent most of my energy in trying to understand the possibilities revealed to my nervous system and in making them valuable for the others."

Back at Harvard he got a young and promising psychologist Dr. Richard Alpert on his side to experiment with hallucenogenic drugs. Aldous Huxley, who was giving a conference in United States, encouraged them to continue this kind of experiences.

Soon the taking of the drug became for Leary a true religion. His first experience that we had transcribed is referred by him as "Without a doubt the most profound religious experience in my life"... Afterwards he would admit: "I have repeated this biochemical ritual for me sacramental

and almost always I have been in respect and owe before the religious revelations so dazzling like one of my first experiences..."

I need not say it here because it is known by everybody, how the students took the new revelation with such enthusiasm that many of them were seen talking alone on the streets. There were accidents, and all this brought the Leary career at Harvard to a halt. There were bitter fights, periods in prison, etc.

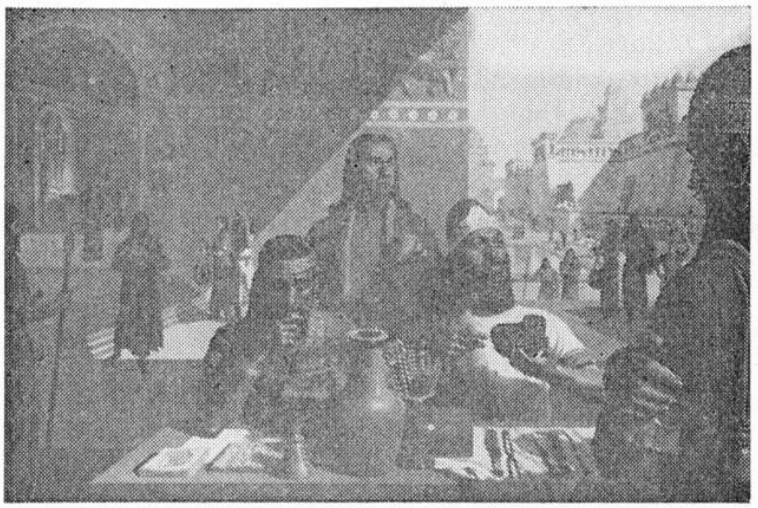
He and his followers changed locations many times. They rented houses or lived in the mansions of millionaires who sympathized with the drugs in order to continue with their rites.

But all this, plus many other fervent adepts had made an impact on our epoch that we cannot ignore.

Art is always avid of new perspectives and I don't think that the drug can create an artistic feeling where there is none, but on the other hand, art may in a very clear and beautiful way show us about some of the elements that the drug has placed in the consciousness of our time.

Fig. 10) The liver is of fundamental importance in transforming chemically the drug that produce hallucinatory effect. The Babylonians have known for a longtime the importance of the liver trying to guess from its study the future of man.

FIGURE 10



THE EYE

The miracle of the human vision is betrayed by its owner who is induced by the chemical elements within the drug to create visions or exalt in an unusual way the one perceived. It is common in LSD addicts to refer to an eye that stares at them or sockets void of eyes.

The art, influenced by psychodelic experiences has tried to induce the brain to psychodelic trips bonbarding the sense till that which is observed is caught in a psychodelic mood.

Since every feeling creates a neurochemical reaction in an evironment provoking what the drug induced to see it may be understandable what a person on a trip feels.

There is a plastic eye whose changes of light and the movements of some jelly substance inside of it hipnotizes the observer and makes him to lose the sense of time.

There is also a kind of cave completely hand painted, including the ceiling, walls and floor. The sound, smells, add dramatism to the environment there are images of a great coloring and significance.

It has been filmed a strange picture entitled "All of us are one". It is a superposition of images, sound, the beating of a heart, strobotics lights, etc., a true audiovisual bombarding.

All the people engaged in this kind of art or show has tried the drug and repro-

duced some of the feelings experienced with it.

In a scientist, Dr. Gerald Oster, professor of chemistry in Brooklyn. His trip with the LSD caused his "a fabulous impression". The wonderful magnificence of the phosphens was enough for him to embrace a painters career and to dedicate himself to make known to others what he had perceived under the effects of the drugs. He uses his images with fosforescent colours and the form changes also with the chargement of light. Here we see Dr. Oster pressing his eyes in the middle of one of his visions.

When we are looking a group playing beat music aided by psychodelic lights. The audience, especially young people, enjoy this fantastic atmosphere. This is an innovation also borrowed from the drug.

Ballet has been for a long time one of the most grateful of the arts, and the human body acquires the beauty that sheds nobility on all its aspects.

Modern ballet by Alwin Nikolai has a dramatic turn in this kind of art. Human individuality is lost in an array of colored lights. They sometimes seem to be converted into caterpillars — their bodies are distorted. It is a beautiful but dehumanized art, where colour movement are not messengers of feeling. A mixture of psychodelic ballet with abstract art.

Fig. 11) This ballet is called IMAGO; it has a contorted movement that places emphasis on the lines of the dresses.

Fig. 12) In this picture we can observe a curious combination of dresses and heads.

Fig. 13) This one is another of the figures in which plasticity of the movement, light and music disolve the human body in a creation of the mind.

Fig. 14) This picture of ballet called "Tensile Movement" the dancers move between geometric patterns. Light is constantly playing against these strange figures altering their relationship in space and time.

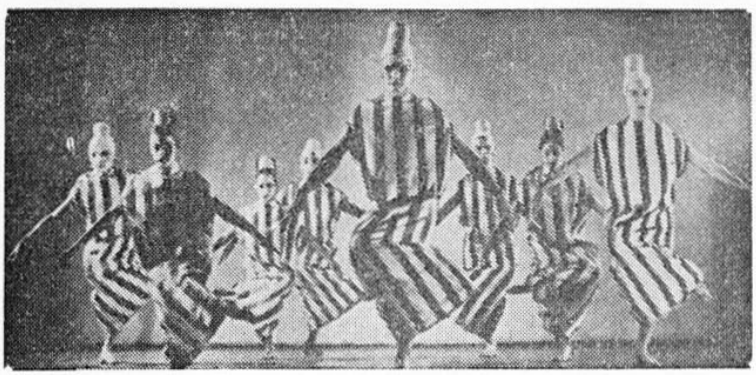


FIGURE 11

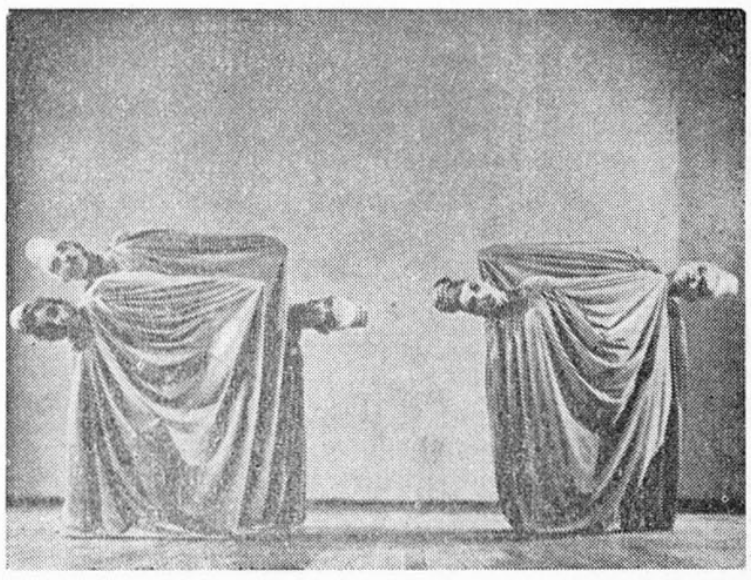


FIGURE 12



FIGURE 13

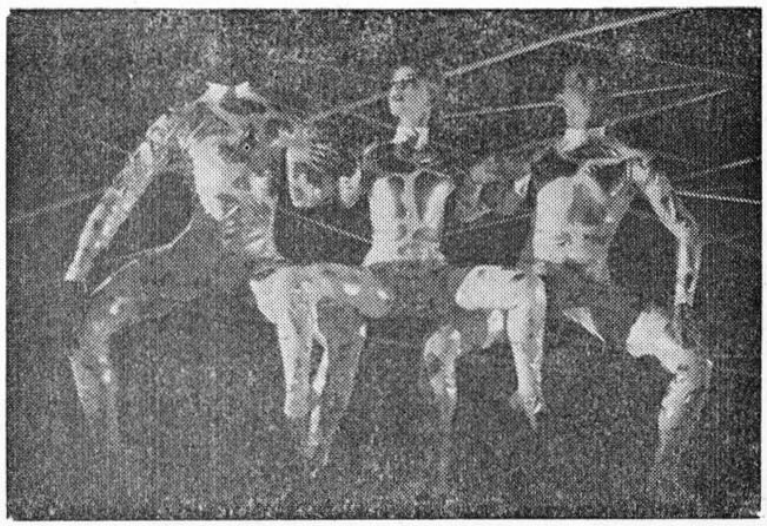


FIGURE 14

Art is always beautiful and self revealing, whatever the form it takes, and has for its own sake a meaning for life, and even if distorted has the function of being a testimony of our times.

Not all adolescents who take drugs receive that advice from their elders and teachers. But it is very upsetting to think that young people who frequent the university to mature in health and useful citizens, get lost for themselves and also for the society to which they pertain.

These are the words of Charles Reich, a Yale professor, the famous author of the Greening of America" a bestseller on his own right. Reich has a brilliant mind, a captivating prose, and clever angles of vision on the problems posed in his book. But I left open to everyone the consideration of the following paragraph of his bestseller:

"The present generation insists upon being open to all experiences. It will experiment with anything. Even the new "trip" does not fit in any preconcibed of the individual's personality. If a conscious person old or young, is asked whether he wants to see a far-out film,-try a new drug or spend a week in a nature food commune, he feels uncomfortable and refuses; the experiment is of our keeping with this already established character. The new to his character. At the same time the new generation constantly tries to break away from the older established form which must be questioned. Accepted patterns of thought must be broken; what is considered "rational" thought must be opposed by "non-rational" thought, drug thoughts, mysticism impulses, etc.

Of course, the latter kind of thought are not really not rational at all, they merely introduce new elements into the sterile rigid outworn "rationality" that prevails today".

Thus spoke Reich.

Let us see the effects of the expanded mind, new religion and consciousness and freedom from the archaic scheme of life.

Fig. 15) In this picture we see an adolescent girl smoking marihuana. Modern research has demonstrated that many adults were introduced to the use of their drug by their own children. A young girl of founten presented to her father four marihuana cigarettes on the Father's day.

Fig. 16) This is Manson, the leader of a group that lived in a communal life, free from conventionalism, in a "do as you please" Law.

A group of girls are the women of the family. All of them worship LSD when they can get it.

They were accused of the most horrible murder of five people among which was included Sharon Tate, a beautiful and talented movie actress in her eighth month of pregnancy. Miss Atkins, one of the Manson girls told the police that Manson ordered his followers to commit murder, to instill fear in man himself, man, the establishment.

The aggressive feelings, the total indifference as to the consequences, made us reflect on the fact that the liberation of the drug ought to be carefully studied.

Maybe the drug would act as in the story of Dr. Jekyll and Mr. Hyde, where a respectable and handsome doctor took a drug which made all his base instincts rule his uncontrolled personality.

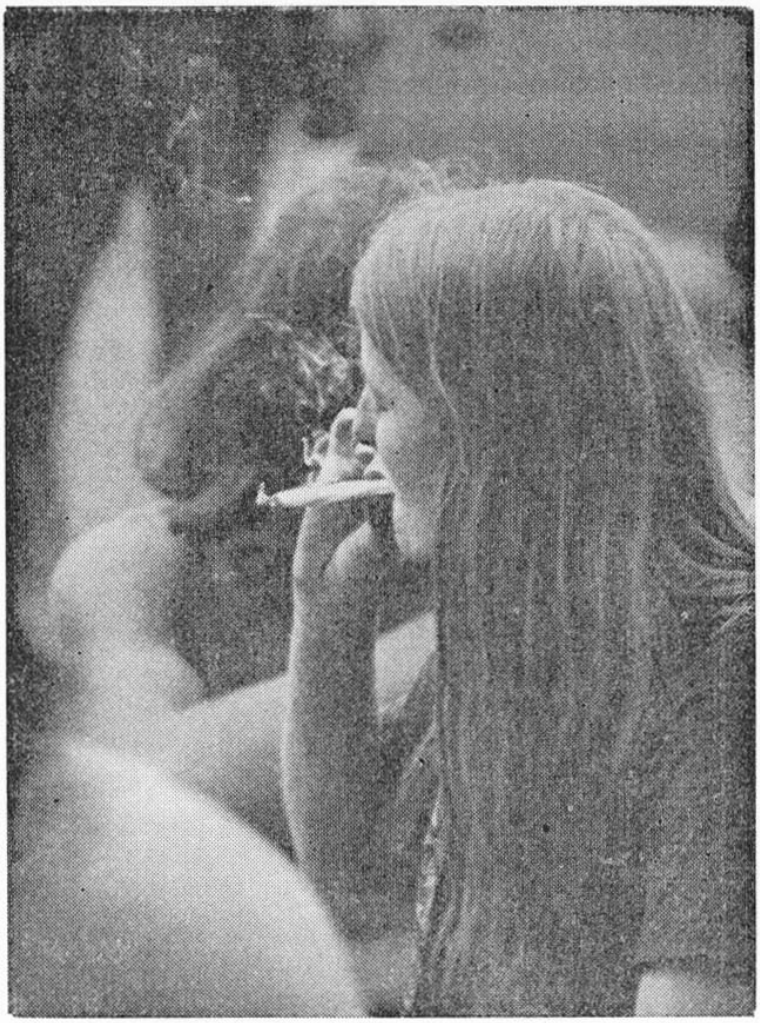
In the dramatic transformation of Dr. Jekill and Mr. Hyde and they have disguised all the moral transformation occurring in his split personality.

Fig. 17) Let us see in a member of the Manson familly a curious resemblance.

This was Charles Watson as he appeared in his highschool yearbook, and after his mind was expanded with LSD, arrested along with Manson on the charge of murder.

This is the story of James "Groovy" Hutchinson. Even with some psychiatric help he never learned to read. Yet in spite of his shortcomings he was a very pleasant companion, always ready to make a clown of himself to get a laugh. From quite different backgrounds, Groovy and Linda Fitzpatricks met. She was a cultivated rich girl who wanted to become a painter. She was

FIGURE 15



frequently at Greenwich Village and began her career as drug culture. This is something they take seriously, and she graduated from acid to speed.

Part of the last days of Groovy were spent lying with Linda on a sleeping bag on the street. The two of them were found dead that night in the boiler room of a deserted tenement. Their head bashed in by bricks. This double murder occurred in October 1967.

Fig. 18) These two young people were more fortunate; they found shelter in a free clinic where doctors took care of them.

This make us to think after looking at all these grim pictures that those who genuinely advise the young people to try drugs, are like the picture of Bruegel, of the Parable of the Blind trying to lead the blind.

Thus they are providing and sending lives to the fires of hell, burning in anguish like the dramatic and beautiful painting of the famous Mexican painter Orozco: "Man of Flames".

These broken lives are something to think about. With all the freedom in his soul man cannot escape the influence of other men. Let us hope that this may be always a beneficial one.

As the little motherless duck follows the steps of the man that took care of it in its early life, and it is imprinted to do so, the young people are also imprinted by the words of those who guide their minds.

It has been very costly for man to escape irrationality, to have a healthy inhibition to profit from the experience of the past, to appreciate his luminous future. To risk all these gains for a false paradise, to waste the best of his years trying to enlarge his mind in an already shrunken head, is really painful.

Life can't be cheated; there is a lot of work to do, and myriads of things to be

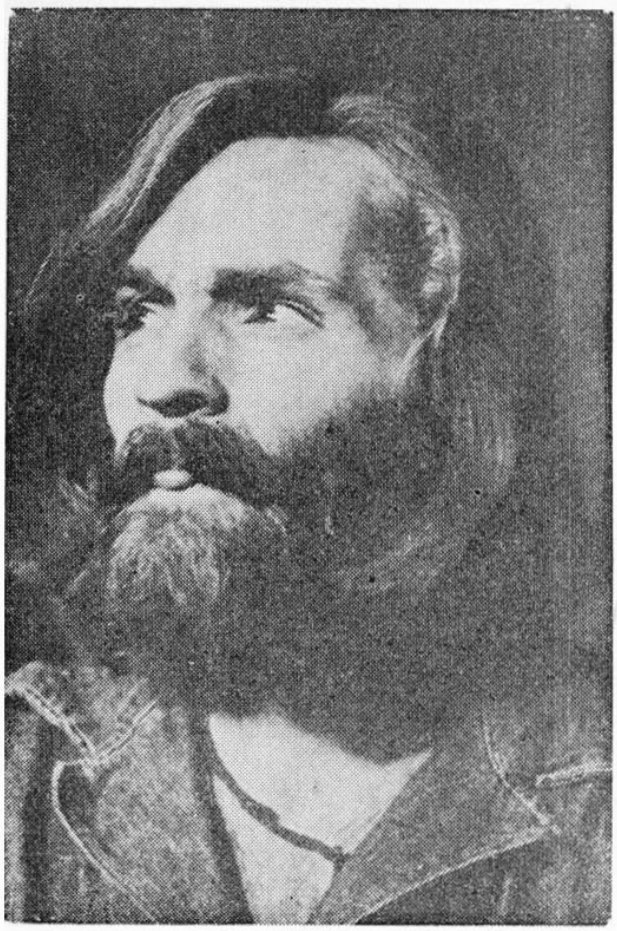


FIGURE 16

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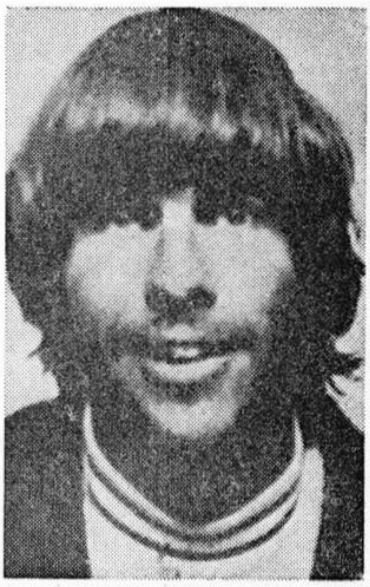


FIGURE 17

enjoyed in this magnificent world of ours. As Marie Curie said: "We must think that we have been created for something and that this must be attained whatever it cost".

Look at Nature is so beautiful that no pills could match its serene beauty.

For ages the best tranquilizer given to man that tunes its placid atmosphere, has also dramatic instantes like in the sunset in which the sky is bleeding while the day is dying in front of trees like centinels erect.

And there is grandeur when we observe two galaxies that meet in the interstellar space, and in spite of their destiny the stars don't collide because there are billions of kilometers between them. This magnificent view puts an end to the need of taking drugs to open the mind to the glory of the heavens.

FIGURE 18



In the article "Man and Drugs" we have written part of the Lecture delivered as an opening to the Sixth Symposium of the "Fulton Society on Neurotropic Drugs and Behavior" held in Barcelona along with the Xth "International Congress of Neurology".

We want to express our most hearty thanks to the President of the International Congress of Neurology Dr. Antonio Subirana and the Secretary Dr. J. M. Espadaler and all the Members of the Executive Council, for the kind cooperation and the wonderful hospitality toward the Fulton Society.

The Palace of Congresses in beautiful Barcelona, was a marvellous setting for this new hommage to John Fulton's memory.

A brilliant group of outstanding scientists from different parts of the world shed light in the puzzling mysteries of how drug's chemical compounds acts and modify the Behaviour of the Nervous System and the Mind.

We thanks all of them for their wonderful contribution to Medical Sciences and we hope that our readers will profit and enjoy their enlightened words.

VICTOR SORIANO

Computer Analysed EEG and Behavioral Changes After Psychoactive Drugs

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Introduction

In addition to long-term EEG studies during chronic treatment with psycho-active compounds, much valuable information about the effects of drugs on the EEG may be rapidly obtained from short-term studies in normal volunteers. We have measured changes in the EEG over a 24 hour period after the administration of drugs and have analysed then by means of both power spectral analysis and iterative interval analysis. Concomitant behavioural changes were also assessed.

This kind of research requires, of necessity, the availability of a digital computer both for the EEG analysis and its statistical evaluation, but has proved itself effective in detecting the central actions of new drugs, in predicting their clinical usefulness and estimating the effective dose range after a single oral application Fink [2, 3], Itil [4]. When combined with psychological and physiological testing, short term computer assisted analysis of the EEG can be seen to provide a valuable tool for the development of new psycho-active drugs.

Methods

For the calculation of the *power spectrum* Bente [1], the Idiiom-Univac U-1108 system was used.

1. Long-time spectra (here T = 3 minutes) were used to study the qualities of the EEG.
2. Short-time spectra (here T = 13.6 seconds) were calculated sequentially in order to determine the internal dynamics of the process.

In addition, a new kind of interval analysis called *iterative interval analysis* - an improvement over previous interval analyses in that it does not depend on an estimated baseline - was employed, Matejcek [5].

Using these methods we have investigated the following compounds during the last year: chlorpromazine (as reference drug), clozapine (Leponex^R), thioridazine (Melleril^R), d-amphetamine, a new anorexic agent AN-448 (Sanorex^R), YG 19-256, an indenopyridine with anti-aggressive activity, and placebo.

Results

In this report we shall discuss the results obtained with chlorpromazine and clozapine and compare them with those obtained with thioridazine and YG 19-256.

In the spectral analysis clozapine appeared qualitatively similar to chlorpromazine. With both drugs there was an increase in the relative power of waves in the slow frequency band (1 - 7 cps) as well as a progressive slowing of the dominant alpha activity together with a decrease in the percent power in the alpha and beta range.

Apart from these similarities important differences were nonetheless apparent. The grade and variation of the EEG parameters were distinctly different and the time course

of action was variable. The variation was more pronounced with chlorpromazine and larger deviations from the initial values, with a maximum occurring after 6 hours, were evident. With clozapine, on the other hand, the progressive development of changes in the spectrum was more steady, with maximum changes occurring 4 1/2 hours after application of the drug.

These findings may be related to our knowledge from clinical experience that clozapine in contrast to chlorpromazine, produces no Parkinsonic phenomena during chronic therapy of schizophrenia. These differences may be explicable in terms of different effects of the two drugs on adrenergic and cholinergic receptors. In addition there is evidence which suggests that they have different effects on the dopamine content in the Corpus Striatum.

From the *clinical* point of view both substances act similarly as neuroleptics and both produced slight somnolence in the experimental subject at a dose of 25 mg p. o. However, clozapine in contrast to chlorpromazine in the same subject, produced somnolence after a short period of stimulation and depersonalisation. These clinical observations support our view that different mechanisms of action are involved.

By comparing the results of the *iterative interval analysis* performed with four of the psycho-active compounds we studied (chlorpromazine, clozapine, thioridazine and YG 19-256 indenopyridine) with their respective control levels and the results obtained with placebo, interesting differences were apparent in the abundance of waves in the various frequency bands.

With clozapine, there was a slight increase of 1 - 3 cps waves in the slow *delta* band between 2 - 4 hours after drug administration which was followed by a decrease between 6 and 24 hours. In contrast there was a slight but general increase in delta activity with thioridazine and a general decrease with YG 19-256.

In the *theta* band there was an increase in the number of waves with all substances, with chlorpromazine and thioridazine being very similar, while more variability was seen with YG 19-256.

In the *alpha* band, only YG 19-256 showed an initial increase (between 1 1/2 and 2 1/2 hours) whereas with all the other substances there was a clear decrease in the abundance of alpha.

The drugs could be differentiated most clearly in their effects on activity in the *beta* band (13 - 33 cps). With clozapine there was a pronounced and steady increase in this fast activity from 1 1/2 - 24 hours. The results with chlorpromazine were very variable with marked deviations from control values in both positive and negative directions. With thioridazine and YG 19-256 the abundance of fast activity varied little from the control baseline. It would seem therefore that quantification of activity in the beta band by means of the Iterative Interval Analysis could provide a potent discriminator between various psychoactive substances.

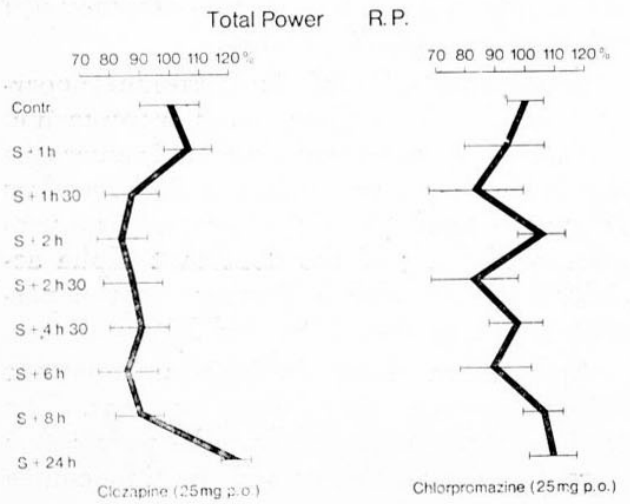


Fig. 1. — *Comparison of changes of total electric power (spectral analysis of the EEG) after 25 mg chlorpromazine and 25 mg clozapine in the same normal volunteer over 24 hours.*

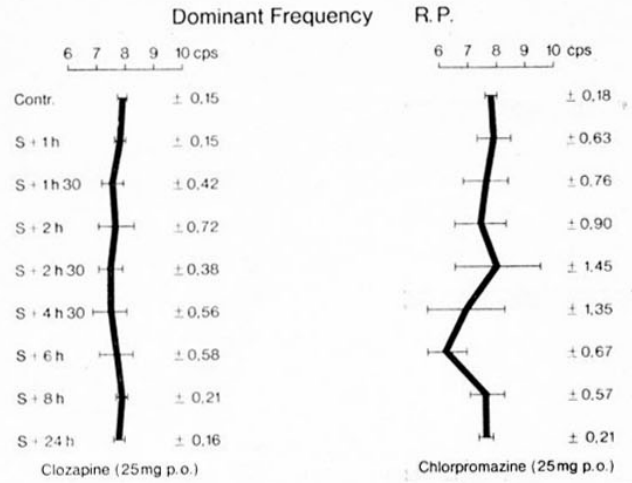


Fig. 2. — ***Comparison of changes in dominant frequency with chlorpromazine and clozapine in the same person over 24 hours.***

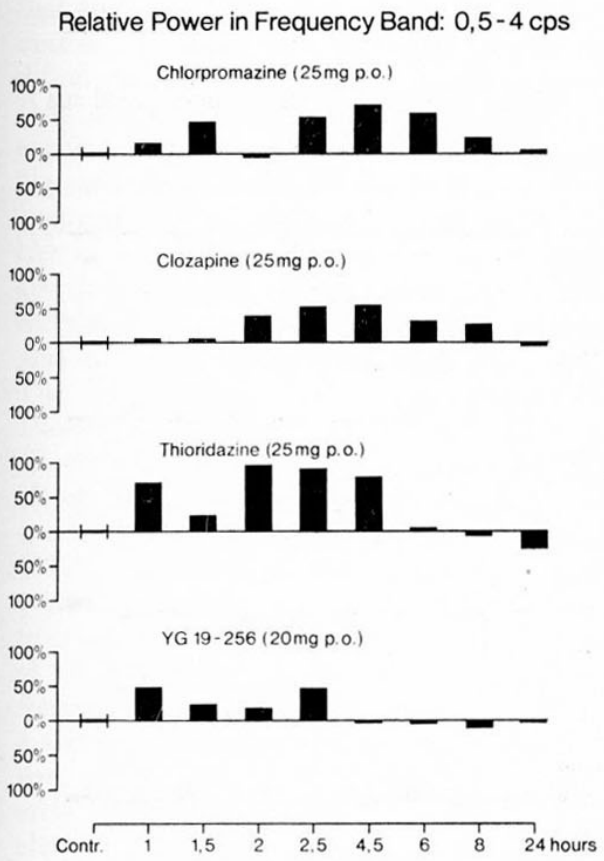


Fig. 3. — ***Comparison of changes of relative power in the delta band of the EEG for the 4 compounds studied.***

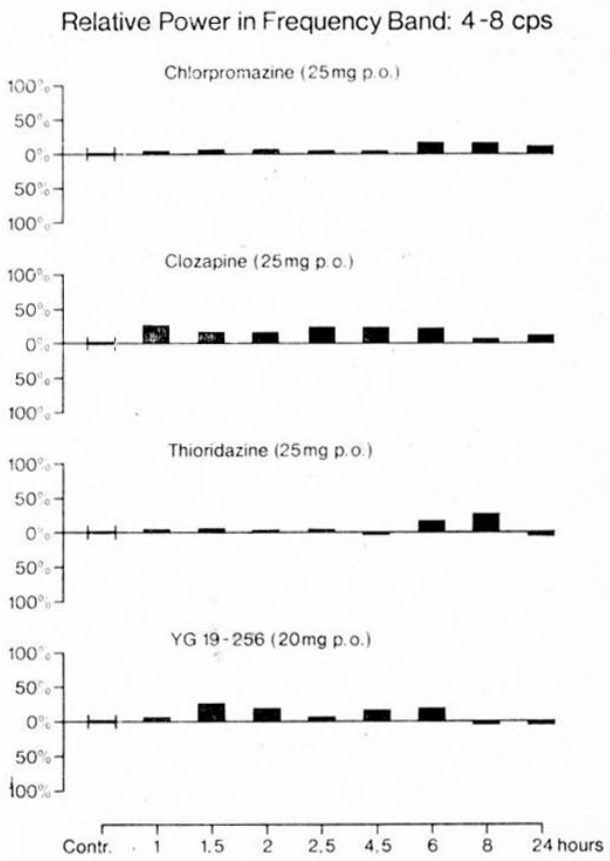


Fig. 4. — ***Comparison of changes of relative power in the theta band of the EEG for the 4 compounds studied.***

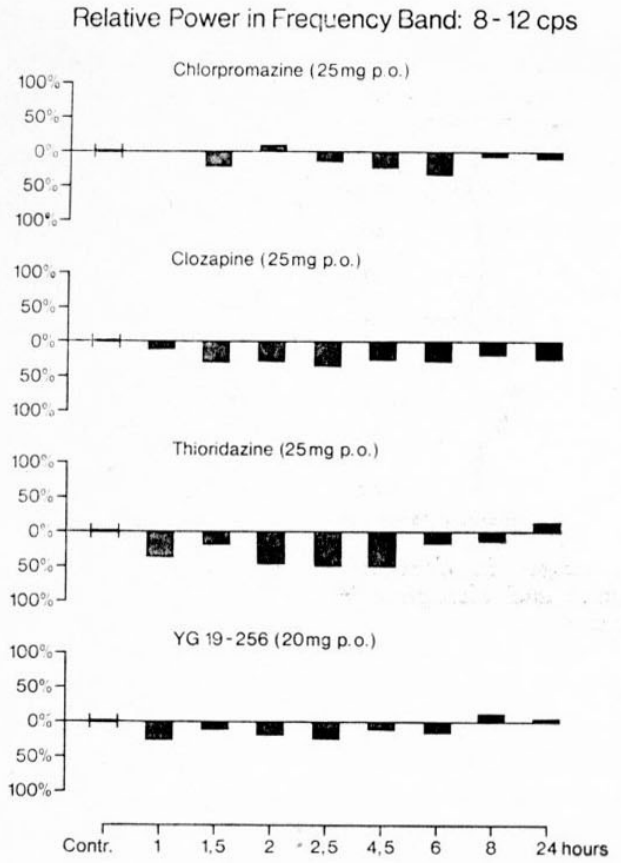


Fig. 5. — ***Comparison of changes of relative power in the alpha band of the EEG for the 4 compounds studied.***

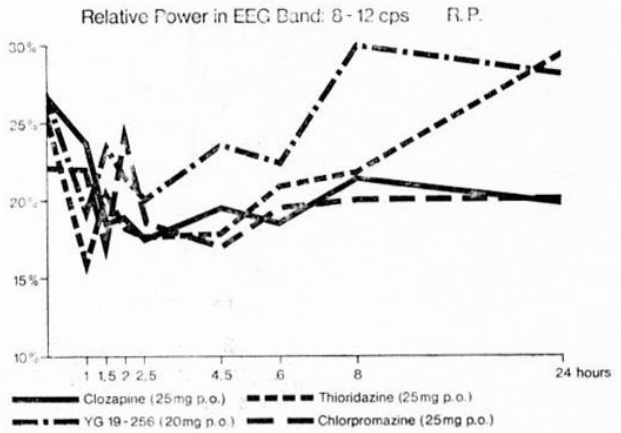


Fig. 6. — ***The graphic description of changes in the alpha band of the EEG over time.***

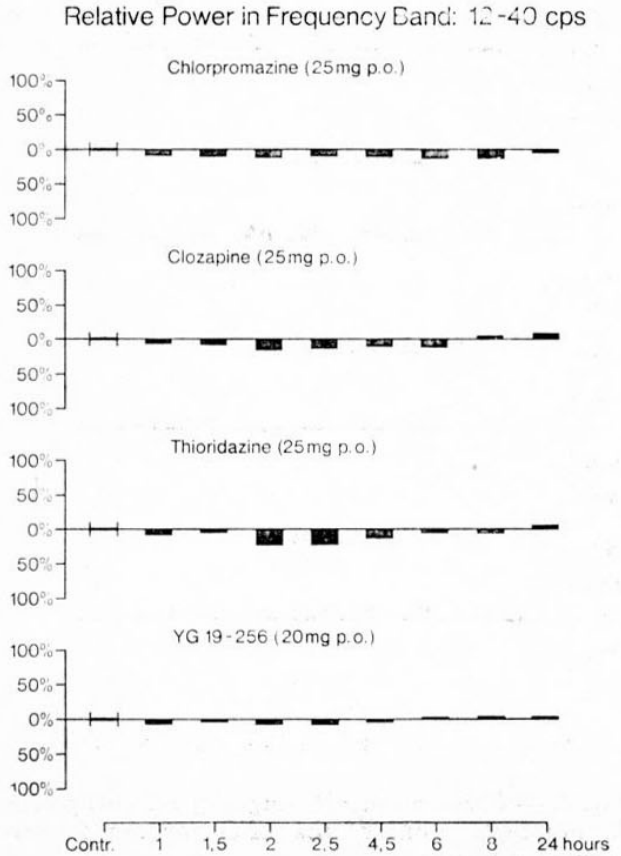


Fig. 7. — ***Comparison of changes of relative power in the total beta band (12 - 40 cps) of the EEG for the 4 drugs studied.***

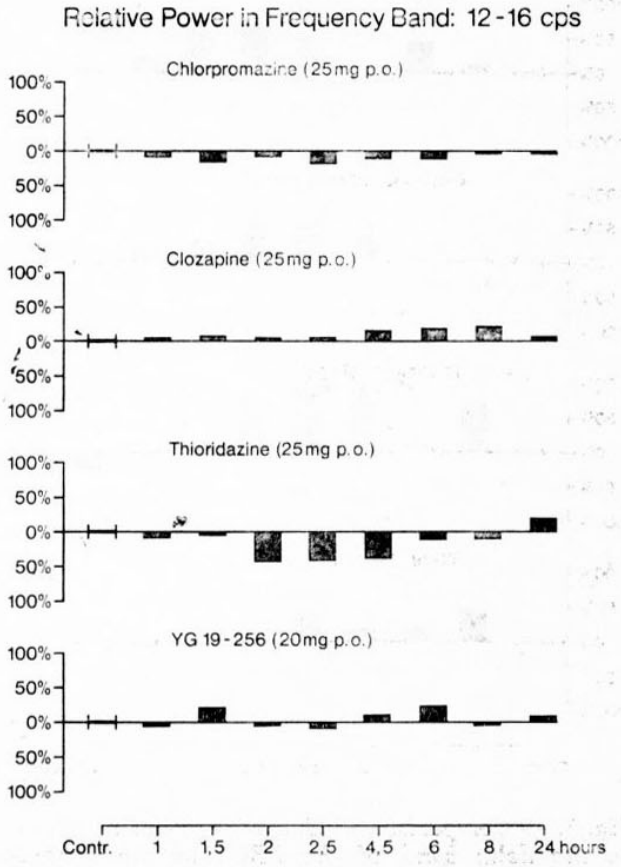


Fig. 8. — ***Comparison of changes of relative power in the lower beta band (12 - 16 cps) of the EEG for the 4 drugs studied. Notice the difference between clozapine and the other compounds.***

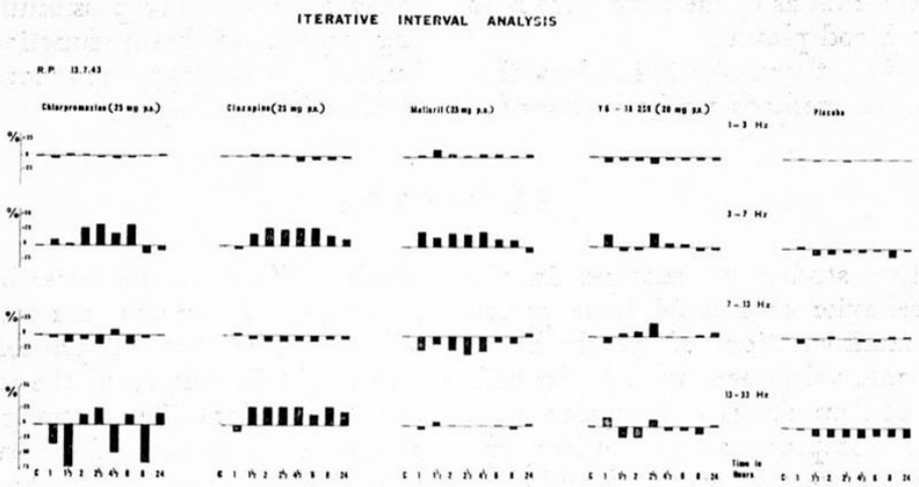


Fig. 9. — *Comparison of changes in the various frequency bands for the 4 compounds studied and for placebo (iterative interpal analysis). Notice again the differences between clozapine and the other compounds in beta activity (here 12 - 33 cps).*

Discussion

From the results obtained it can be seen that the three neuroleptics tested, chlorpromazine, clozapine and thioridazine, in addition to having similar clinical effects - they improve unusual thought content and excitement and reduce mannerisms, posturing and hallucinations in psychosis, and suppress activity in autonomous brain centres especially in the sympathetic system - also have similar effects on the EEG: they increase the abundance of slow frequencies and decrease the mean alpha frequency. The fourth drug, the indenopyridine YG 19-256 which has strongly anti-aggressive effects in animals, has completely different effects on the electrical activity in the brain and also had different subjective effects.

Returning to the three neuroleptics, it is evident that by means of quantitative electroencephalography a finer differentiation of their effects is possible. Clozapine, in contrast to the other two drugs studied, had a specific influence on activity in the lower part of the beta band: it increased the relative power of 12 - 16 cps waves. This electrophysiological specificity of clozapine very probably corresponds with its unique clinical effects, namely a powerful antipsychotic and tranquilising action without producing the extra-pyramidal motor complications during chronic treatment which are commonly observed with other neuroleptics.

In general, quantitative analysis using a computer allows a more careful and rigorous study of the EEG particularly of the abundance, relative power and distribution of waves of high frequencies and very low amplitudes, which was previously virtually impossible from a visual analysis of the tracings. These faster parts of the EEG spectrum, which were relatively neglected during the early development of electroencephalography, have definite significance for human mental processes, Volavka [8], and for emotional reactivity, Roubicek [6]. Further, in recent studies of electrical brain activity during maturation and senescence, we have been able to show that beta waves between 13 - 20 cps are of different clinical and psychological significance from those above 20 cps, Roubicek [7].

In addition to increasing the diagnostic potential of the EEG, quantitative analysis of the kind described here can also provide valuable information about the pharmakokinetics of a drug. For example, other studies with clozapine have indicated that the times when maximal changes are observed in the EEG (i. e. 2 hours after administration) correspond closely to those where

highest concentrations of the drug have been measured in blood plasma.

In conclusion, therefore, it is clear that the quantitative methods we have described today offer exciting possibilities for analysing aspects of brain function relevant to human psychology, psychopathology and psychopharmacology.

SUMMARY

Comparative studies of changes in the EEG and behavior over a 24 hour period after the administration of psycho-active drugs to normal volunteers were performed. The effects of four drugs - chlorpromazine, thioridazine, clozapine and the indenopyridine YG 19-256 were investigated and compared with their pre-drug control levels and with placebo. Two quantitative computer assisted techniques were employed: power spectral analysis and iterative interval analysis.

Results indicated that the three neuroleptics had qualitatively similar effects on the EEG. Nonetheless important differences were also apparent; clozapine in contrast to chlorpromazine and thioridazine, had specific effects on the lower beta band (12-16 cps) - an increase in relative power. It was suggested that this phisiological specificity might be related to the unique clinical effects of clozapine - strong anti-psycotic action in the absence of the extra-pyramidal side effects which are typical of other neuroleptic drugs. The indenopyridine YG 19-256, was different from the three neuroleptics tested both in its behavioural effects and in its effects on the EEG.

From these results it was apparent that the methods employed were capable both of detecting the central actions of these drugs and of discriminating between those with different clinical effects.

SUMARIO

Se realizaron estudios comparativos de cambios en el EEG y conducta durante un período de 24 horas después de suministrar drogas psicoactivas a voluntarios normales. Los efectos de cuatro drogas: clorpromazina, tioridazina, clozapina, el indenopiridina YG 19-256 fueron investigados y comparados con sus niveles de control previos a las drogas y con placebo. Se emplearon dos técnicas asistidas por computadora cuantitativa: análisis de poder espectral y análisis iteractivo de intervalo.

Los resultados indicaron que los tres neurolépticos tenían efectos similares cualitativamente sobre el EEG. No obstante también eran evidentes importantes diferencias; la clozapina en contraste a la clorpromazina y la tioridazina, tuvo efectos específicos sobre la banda inferior beta (12-16 cps) —un aumento en poder relativo.

Fue sugerido que esta especificidad fisiológica podría tener relación con los efectos clínicos únicos de clozapina — acción fuerte antisicótica con ausencia de los efectos colaterales extrapiramidales, que son típicos de otras drogas neurolépticos. La indenopiridina YG 19-256, fue distinta de los tres neurolépticos ensayados tanto en sus efectos de conducta como en los relativos al EEG.

De estos resultados, era evidente que los métodos empleados fueron adecuados tanto para descubrir las acciones centrales de estas drogas y de discriminar entre aquellas con diferentes efectos clínicos.

RÉSUMÉ

Il a été réalisé des études comparatives des changements dans le EEG et comportement durant une periode de 24 heures après l'administration des drogues psychoactives à des volontaires normaux. Les effets de quatre drogues: chlorpromazine, tio-

ridazine, clozapine, l'indenopiridine YG 19-256 ont été investigués et comparés avec ses niveaux de contrôl précèdent aux drogues et ce placebo, ils ont été employees deux techniques étudiees par computation quantitative: analyses de pouvoir spectral et analyses itéractive d'intervale.

Les résultats démontrèrent que les trois neuroleptiques avaient des effets semblables qualitativement sur le EEG. Toutefois il y avait d'evidentes différences importantes: la clozapine en contraste a la chlorpromazine et la tioridazine, a eu des effets specifiques sur la bande inférieure beta (12-16 cps) - une augmentation en pouvoir relatif.

Il a été suggéré que cette spécificité physiologique pourrait avoir une relation avec les effets cliniques uniques de clozapine - action forte antipsychotique avec absence des effets colaterales extrapiramidales, qui sont typiques d'autres drogues neuroleptiques. La indenopirine YG 19-256 fut distincte des trois neuroleptiques essayés, tant dans ses effets de conduite comme en ceux relatifs au EEG.

De ces résultats, il était évident que les methodes employées furent adéquates tant pour découvrir les actions centrales de ces drogues et discréminer entre celles-ci avec différents effets cliniques.

ZUSAMMENFASSUNG

Es wurden vergleichende Untersuchungen über die Veränderungen im Elektroenzephalogramm und im Verhalten über einen Zeitraum von 24 Stunden nach der Einnahme psycoaktiver Drogen durch normale Freiwillige durchgeführt. Die Wirkung von vier Drogen: Chlorpromazin, Thioridazin, Clozapin und dem Indenopyridin YG 19-256, wurden untersucht und mit den Kontrollniveaus vor Einnahme der Drogen und nach Placebo verglichen. Zwei Techniken wurden verwendet gestützt auf quantitative Komputermessung: Analyse der Spektralfähigkeit und Analyse iteractivo des Intervall.

Die Ergebnisse zeigten, dass die drei Neuroleptica ähnliche Wirkungen in qualitativer Beziehung auf das Elektroenzephalogramm hatten. Trotzdem vurden auch bedeutende Unterschiede deutlich; Das Clozapin im Gegesatz zu Chlorpromazin und Thioridazin hatte spizifische Wirkungen auf das untere Band Beta (12-16 cps) - eine Steigerung im relativer Wirkung.

Eswurde angeregt, dass diese physiologische Spezifizierung in Verbindung stehen könnte mit den klinischen Wirkungen allein des Clozapin - starke antipsychotische Wirkung ohne kollaterale extrapyramidale Effekte, wie sie für andere neuroleptische Mittel typisch sind. Das Indenopyridin YG 19-256 war verschieden von den drei untersuchten Neuroleptica, sowohl in seiner Wirkung auf das Verhalten wie bezüglich des EEG.

Aus diesen Resultaden ergibt sich deutlich, dass die angewandten Methoden entsprechend waren sowohl um die zentralen Wirkungen dieser Heilmittel darzustellen als auch um unter ihnen die verschiedenen klinischen Wirkungen zu unterscheiden.

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Three long-acting neuroleptic drugs. Comparative study

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Of the series of diphenyl - butyl - piperidinic drugs synthesized in Janssen's laboratory, three are of the greatest interest for clinic psychopharmacology. We have been able to try them in the Department of Psychiatry of the National Institute of Neurology: at first, fluspirilene; later, pimozide and recently penfluridol.

Once we have summarized our findings in the 3 groups of patients, we shall attempt to confirm the characteristics, advantages and, specially, the accurate therapeutic profile of each of the drugs mentioned.

I.— Fluspirilene

We carried out our clinical trial with fluspirilene in 29 hospitalized patients in the Psychiatric Department of the National Institute of Neurology; 18 were females and 11 males. Ages ranged from 15 to 56 and diagnoses included 18 cases of squizophrenia (hebephrenic, paranoid and paranoic), 4 cases of psychotic bout in mentally retarded, 1 non-specific psychotic bout, one atypical psychosis, one epileptic equizophreniform psychosis, 2 puerperal psychoses (one of which in epileptic) and one post-surgical bout.

Since the drug is administered parentarally and lasts through approximately one week, it is necessary to assess the optimum therapeutic dosis, that is, the dosis with which maximum curative action is attained without, or with few, side effects. This dosis has always been aimed at by giving 1/2 or 1 c.c. every week and gradually increasing it. If we bear in mind that the average optimum dosage ranges usually around 5 c.c. per week, this dosis adjustment should take at least four weeks. Since our ward is for acutely ill patients and the average stay period is of 6 weeks, we had to devise another system. We believe this to have been an original contribution to methodology. We chose to start with 1/ c.c. and add another 1/2 every day until we induced a parkinsonian syndrome with neuroleptic impregnation. It is true that the system is controvertible, that the dosage is not accurate, but starting from that first impregnation we would lower or increase the amount in the next week and after two weeks we had adjusted a dosage; procedure which, following the orthodox method, would have taken from 4 to 6 weeks.

We had, in general, good results: 2 cases got worse, 6 were not modified, 3 showed a slight improvement, 4 remarkable improvement and 15 excellent results. Bearing in mind that our human material encompassed a great variety of diagnoses and that many of them had a bad prognosis, the assay acquires a fair importance [1].

We concluded then, and still believe, that fluspirilene is a neuroleptic drug of moderate sharpness, more remarkably successful in cases of wide symptomatology. So far as side effects and complications, we found only a tendency to produce a slightly more marked hypotension than expected with chlorpromazine, for instance.

Fluspirilene, together with phluphenacine enanthate has opened an important chapter in contemporary psychopharmacology. Many efforts are being made in order to find long acting products which may help keep chronic patients under control with a minimum of side effects and without the problems of multiple administrations during the day.

II.— Pimozide

The first report from Janssen's laboratory about the product labeled R-6238, that is, pimozide, dates from 1966. In Mexico, in April 1971, a symposium was organized on therapeutic findings of local researchers. We had the opportunity of carrying out a clinical trial in 50 patients from the Department of Psychiatry of the National Neurological Institute, on which no screening was made for age or sex.

Pimozide was administered orally, once a day, since its effects last approximately 24 hs., that is 5 to 6 hours longer than halloperidol. To find the maximum dosage for each patient, we used the same method used with fluspirilene. We would give half a tablet the first day and increase the dosage every subsequent day until reaching a slight degree of neuroleptic impregnation. That was considered the basic dosage around which slight refining adjustments are made, generally to decrease it.

Diagnoses were as follows: 1 case of schizophreniform psychosis in epileptic; 6 of incipient schizophrenia; 2 of paranoia: 1 of involutive melancholia; 1 of senile psychosis; 1 of senile dementia; 2 of obsessive —compulsive psychoneurosis; 1 of hypochondriac neurosis ;5 of psychopathic personality; 1 Laurence-Moon-Biedl Syndrome; 1 psychotic bout in mentally retarded and 1 Morgagni-Morell Syndrome. Ages ranged from 16 to 85 and the disease's time of evolution was of 1 to 20 years.

The doses used varied from 0.5 to 14 mgs. and the optimum average dosis per day was of 4 mg/day. There was a follow-up of at least two months.

In no case did the disease get worse, five cases interrupted treatment during the first week; in six cases there was no response to treatment with Pimozide; in 21 patients good results were attained and in 18 the results were excellent. This rate of success renders the antipsychotic efficiency of this neuroleptic drug unquestionable. The authors sharpened their observations in order to find the drug's target symptomatology. We believe it to be an excellent drug for support treatment of psychotic patients, mainly because of its low ability to produce undesirable side effects and due to the fact that it has a remarkably stimulating action on the affectivity of patients treated. It is not the drug to choose in cases of psychomotor excitation or acute hallucinatory symptomatology.

The anatomopathological findings in one case do not show any lesions that might be considered as resulting from Pimozide. It is at present the most adequate long acting oral neuroleptic for long term support treatment of psychotic patients for whom adequate social rehabilitation is aimed at. [2].

III.— Penfluridol

This research with the so-called longoperidol (penfluridol) is still under course. We are able, however, to report the preliminary results obtained in 25 patients from the Department of Psychiatry of the National Neurological Institute and some treated in the out patient Service of the same hospital.

Diagnoses were as follows: on unspecific psychotic bout in temporal disrythmia, 2 latent schizophrenias, 2 residual schizophrenias, 1 paranoid psychotic bout in deeply mentally retarded, 2 unspecific psychotic bouts and 2 psychopathic personalities.

Ages ranged from 16 to 40 and the disease's evolution period was from 6 months to 26 years.

The dosage used ranged from 5 to 80 mg., and the maximum support dosis was of 20.4 mg per week.

Only in one case did the disease get worse, 1 case dropped the treatment after the first interview, in 2 cases there were no results, in 4 they were dubious, in 5 good and in 11 excellent. The rate of success is a clear sign of the antipsychotic efficiency and long action, for 7 days or longer, that this neuroleptic drug has.

It is not the drug to choose in cases of psychomotor restlessness, but it may be used in cases of many hallucinations. Because of its clear antipsychotic action after only one weekly administration, its low ability to produce undesirable side effects, its evident action on affective flattening and its relatively simple handling, we believe it to be, at present, one of the drugs to be chosen for support treatment and resocialization of chronic psychotic patients. [3].

Comments

It seems strange that after 20 years that the scientific age of pharmacology began, so few references have been made to it in scientific journals and centers. Perhaps the editorial in the recent issue of the brilliant British journal, Psychological Medicine, of May 1972 is one of the few exceptions which may be quoted [4]. There, in only two and a half pages, Marley makes a lucid analysis of the fruitful link which is what precisely for the past 20 years has related pharmacology and psychiatry. And I refer to these questions because I sincerely believe that long-acting neuroleptic drugs in the one hand, and the so-called polivalent psychotropic drugs, on the other, are the two most important recent contributions that this psychopharmacology which is not even 25 years old has made to psychiatry.

The number of circumstances which have allowed our team to carry out the trial of the three neuroleptic drugs synthesized by Janssen, has been truly fortunate. We feel that they will be the tool of what has been the social psychiatry, which at present is vigourosly developing in Europe and the United States, and begins to do so in Mexico. The easiness with which one may administer this type of drugs permits the controlled psychopathic patient to be reinserted into his usual environment and, in a considerable number of cases, to his past activities. We dealt in more detail with these aspects in the paper we have recently read in Río de Janeiro [2].

In Table I we have summarized the therapeutic results obtained in 30 cases treated with fluspirilene, 50 handled with pimozide and 24 who received penfluridol. It may be easily appreciated that the amount of good results and remarkable improvements do confirm the promising findings of European researchers in the first phases of their study.

Table II shows the average dosis for each of the studied neuroleptics as well as the minimum and maximum doses used. It also points out different ways of administration. It is clear that one only weekly dosis administered orally, seems the best one in most cases.

Advantages and major inconveniences appear in Table III. Here again, like in previous ocassions, we would like to emphasize that the study must not be made as far as the number of cases treated or new ones derived from the chosen chemical family, but as far as the attempt to give a detailed account for each drug's indication. Thus, there would be some cases where the weekly injection of fluspirilene would solve some of the problems of a mental health centre located in a rural or suburban area. In contrast, pimozide may, together with an intelligent psychotherapy, control an incipient schizophrenia, as we have shown in our research. Finally, we had mentioned the obvious advantage that penfluridol shows, because of its easy administration.

It seems to us that in this way we have put forth and described our general impressions as to the use of fluspirilene, pimozide and penfluridol. However, we would not like to leave the impression that this chapter is more or less closed. Together with the specificity that each drug will gradually be found to have, new techniques will have to be devised and made perfect in order to extend the effects of the drug's active beginning and thus guarantee an adequate control of the patient's psychopathy, for him to suffer from less and less side effects and complications.

TABLE I. — Therapeutic Results

	FLUSPIRILENE	PIMOZIDE	PENFLURIDOL
Worsening or dropping	2	5	2
No modification	6	6	2
Good Results	7	21	9 (?)
Remarkable improvement	15	18	11
TOTAL OF CASES	30	50	24

TABLE II. — Average Dosis, vias and way of administration

FLUSPIRILENE	PIMOZIDE	PENFLURIDOL
5 c.c. / week (10 mgrs. / week) (from 1 c.c. to 19 c.c.)	4 mgr. / day (from 0.5 to 14 mgs.)	20.4 mgs. / week (from 5 to 80 mgs.)
Weekly I. M. injection	Daily, single oral dosis	Weekly, single oral dosis

TABLE III. — Advantages and Inconveniences

	FLUSPIRILENE	PIMOZIDE	PENFLURIDOL
Advantages	Rapid action Better control	Affective stimulant Few side effects	Easy to administer Few side effects
Inconveniences	Hypotension, Narrow margin; Prompt neuroleptic impregnation	Daily administration	Slower action

SUMMARY

Clinical findings obtained with research with fluspirilene in 30 cases, pimozide in 50, and penfluridol in 24 are presented (the latter is only reported preliminarily). Their differences are further analysed and their advantages and inconveniences are evaluated.

Long-acting neuroleptic drugs are one of the main advancements of contemporary psychopharmacology and their research must be encouraged.

RESUMEN

Son expuestos los hallazgos clínicos logrados con la investigación con fluspirilena en 30 casos, pimocida en 50, y penfluridol en 24 (el último es informado solamente en forma preliminar). Se han analizado además sus diferencias, y han sido evaluadas sus ventajas e inconvenientes.

Las drogas neurolépticas de acción prolongada son uno de los adelantos principales de la psicofarmacología contemporánea y debe ser estimulado su estudio.

RÉSUMÉ

Les résultats cliniques obtenus a partir de la recherche du fluspirilene dans 30 cas, du pimozide dans 50 et du penfluridol dans 24 sont ici présentés; en ce qui concerne le penfluridol, il ne s'agit que d'un rapport préliminaire. Ensuite les différences sont analysés et les avantages et inconvénients sont soumis a l'analyse.

Les médicaments neuroleptiques d'action prolongée constituent l'un des acquis fondamentaux de la psychopharmacologie contemporaine et il convient de poursuivre la récherche dans ce sens.

ZUSAMMENFASSUNG

In der vorliegenden Arbeit wird ueber Forschungsergebnisse berichtet, die bei der Untersuchung von Fluspirilen anhand von 30 Faellen, von Pimozid in 50 Faellen, und von Penfluridol anhand von 24 Faellen erzielt wurden (bezueglich des Penfluridols wird hier nur ein vorlaeufiger Bericht vorgelegt). Anschliessend werden die hierbei zutagegetretenen Unterschiede naeher untersucht und die jeweilligen Vor- und Nachteile der Substanzen gegeneinander abgewogen.

Neuroleptika mit protrahierter Wirkung stellen eine der grossen Errungenschaften der modernen Psychopharmakologie dar, deren weitere Erforschung mit aller Intensitaet betrieben werden sollte.

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Mechanism of Action of Tricyclic Antidepressants, Pharmacological and Biochemical Basis.

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Tricyclic antidepressants or imipraminics as some authors refer to them, are the drugs currently most widely used for the treatment of depression. This group of substances have a pharmacological and biochemical profile well established. However, little is known about their mechanism of action. In spite of the great number of papers appeared during these last years in relation to this aspect, we find ourselves with these drugs in a practically similar situation to the one that Brodie et al. [7], pointed out in an interesting review about psychotropic drugs. "... A major goal of psychopharmacology is to explain how drugs alter mental states by modifying neurophysiological and biochemical processes in the central nervous system. This goal is still far distant, for we cannot yet describe how drugs affect gross neural pathways, much less their subtle effects on discrete neurons..." Many hypothesis have been, nevertheless proposed, based upon the pharmacological and biochemical knowledge of these substances and these hypothesis also have constituted the starting point of a series of theories intended to give a biochemical basis to the depressive syndrome.

Discarding the inhibition of the monoamine-oxidase, Pletscher & Gey [41], Pulver et al. [40], Kivalo et al. [31], among the most suggestive hypothesis, deserve some consideration the following: *noradrenergic*, *cholinergic*, *dopaminergic*, and *serotoninergic*. Our fundamental purpose is to analize the pharmacological and biochemical aspects of imipraminics which constitute the basis for these different ways of thinking.

Noradrenergic hypothesis

This hypothesis considers that antidepressant drugs of the imipramine type owe their effects to an increase in activity of central adrenergic receptors. This hypothesis is sustained by some experimental data:

I. Marked potentiation by imipraminics of the peripheral responses obtained by sympathetic stimulation or by exogenous administration of norepinephrine or epinephrine.

II. To maintain the levels of brain norepinephrine within its normal values, so that the imipraminics can antagonize, in the animals, the sedation elicited by reserpine or by the benzoquinolizines, Suser et al. [50].

III. Enhancement of the central effects of amphetamine and amphetamine like drugs, Carlton [12].

In relation to the first aspect Sigg [48] first demonstrated that imipramine potentiated the effects of norepinephrine on the cat's nictitating membrane. These results were subsequently confirmed by other authors, including us, using different biological preparations, as well as different derivatives of imipramine, Schaeppi [43], Sigg et al. [49], Thoenen et al. [52], Kauman et al. [30], Cuen-

ca and Valdecasas [17], Ursillo and Jacobson [55].

Generally, it is considered that the mechanism responsible for this sensibilization is the blockade by these substances of the norepinephrine membrane pump of the synaptic terminals preventing the reuptake of the neurotransmitter into the adrenergic nerve endings. Actually most compounds of this group show in more or less proportion at central and peripherally sites, a blocking effect of the norepinephrine uptake, Axelrod et al. [5], Glowinski and Axelrod [25], Iversen [29], Titus and Spiegel [53].

Since this process is considered the main mechanism of inactivation of the released norepinephrine, Whitby et al. [56], its inhibition will determine that the neurotransmitter remains for a longer time in contact with the postsynaptic membrane, leading to a more intense stimulation. This stimulant activity upon the noradrenergic section of the brain is considered to be the basis of the antidepressant efficacy of these compounds, Kopin [32], Neff y Costa [38].

The second experimental fact pointed out, constitutes also a demonstration of the participation of the adrenergic system, at least, in one of the pharmacological responses that imipraminics produce. These experiments become of special importance if we consider that the lack of effect of imipraminics to antagonize the reserpine sedation, when the store of brain norepinephrine has been depleted, is restored, when these stores have been refilled.

The third aspect, has a limited value because it is based at the same time on a hypothesis. Actually, even it has been preconized that amphetamine and amphetamine like drugs owe their central effects to the releasing of norepinephrine. At the moment there does not exist a definitive demonstration that this may be the fundamental mechanism.

The pharmacological and biochemical effects until now discussed and certain clinical observations:

—Increase in urinary elimination of normethanephrine in depressive states in remission phases.

—Decrease of vanillylmandelic acid under imipraminic treatment, Schildkraut et al. [45, 46].

—Decrease in the urinary elimination of ciclic AMP in deeply depressed patients. Paul et al. [39].

—Prevention of the depression which determines alpha - methyl - dopa by inhibition dopamine β-oxidase, Dominic and Moore [23].

add some support to the noradrenergic hypothesis. On these basis, Schildkraut et al. [46], proposed that mood is related to catecholamine levels or activity in the brain. Some depressive states will be consequent to a relative decrease of brain norepinephrine, meanwhile, in the manic states, exist an excess of this amine. Following this way of thinking, antidepressant drugs will increase norepinephrine at the level of its especific receptors in the brain whereas lithium salts, which are effective in the treatment of manic and hypomanic states, may decrease central noradrenergic mechanisms. In relation to the last statement, Forn and Valdecasas [24] have shown that lithium reduces the cyclic AMP formation elicited by norepinephrine brain slices incubated with ^{14}C-adenine. Nevertheless, the advancing course of investigations has offered us new experimental facts that makes wise reconsidering the validity of this conclusions. So, for example, the observation that some substances as, iprindol and opipramol, chemically related to imipraminics and endowed clinically with antidepressive activity do not inhibit the uptake of norepinephrine, but enhance its effects, Lathi & Maickel [33], puts in doubt that this biochemical effect may be the only mechanism responsible for the increase of the central adrenergic tone. The always possible, but difficult to demonstrate sensibilization of the receptors can most likely be responsible of such increase. In fact, in experiments carried out by us, Cuenca et al. [15, 16], Rivera [42], we observed that desipramine potent inhibitor of the uptake of norepinephrine, potentiated the maximal response of the amine in the isolated rat vas deferens. This potentiation can only be explained by a sensibilization of the adrenergic receptors, Rivera [42]. Indepen-

dently of the mechanism in both cases an increase in central adrenergic tone follows.

Another aspect which deserves consideration, is the "locus" in which the blocking of norepinephrine uptake is acomplished. Most authors, Carlsson [11], Boullin & O'brien [6], consider that tricyclic antidepressants act at the level of the neuronal membrane inhibiting the mechanism of transport of norepinephrine, the so called "membrane pump", Carlsson [10]. Through this mechanism, the biogenic amines liberated from their nervous endings are taken again into the neuronal space. However, the demonstration that desipramine, for example, inhibits the indirect sympathomimetic effects of tranylcypromine, Cuenca et al. [19], Cuenca et al. [20], Cuenca et al. [21] and other indirect acting sympathomimetic drugs, Cuenca et al. [15, 16], but does not modify their entrance to the intraneuronal space, Brodie et al. [8], speak in favor of an action at the level of the storage granules. The possible role of this intraneuronal action in the mechanism of imipramine like drugs should be investigated.

Finally and maintaining ourselves inside the frame of the adrenergic system, we can not forget one aspect to which it has not been paid too much attention. We refer to adrenergic blockade produced by imipramine, desipramine and related substances when they are used at high doses or in denervated organs, Cuenca et al. [18], Hrdina & Garattini [27], Turker & Khairallah [54], Scriabine [47], Hrdina & Ling [28]. This effect demonstrated in a whole series of peripheral biological preparations has been considered as the responsible of the hypotension observed in clinics, McCulloch & Story [37]. But the possible significance of this action at central level is at the moment unknown.

Cholinergic hypothesis

The possibility that tricyclic antidepressants exert their action through a central anticholinergic effect has been underlined by some investigators, Cairncross et al. [9], Mandell et al. [34].

This assumption is based on the potent anticholinergic activity of all the substances which form part of this group. Actually, all imipramine like drugs exhibit in more or less proportion (GP 45437 > * amitriptyline > protriptyline > desipramine > opipramol) ** a central and peripheral anticholinergic action, Sigg [48], Domenjoz and Theobald [22], Sulser et al. [50], Theobald et al. [51], Aichinger et al. [1], Atkinson and Ladinsky [4]. This peripheral cholinolitic activity is responsible for most of the unwanted effects that appear when used in clinics.

Nevertheless, if the anticholinergic activity of imipraminics were responsible of their clinical efficacy, other central acetylcholine antagonists should also result themselves effective in such depressive states.

Dopaminergic hypothesis

In contraposition to the possible role of cerebral norepinephrine in the mechanism of action of tricyclic antidepressants, some authors consider dopamine as the neurohormone responsible of the activity of these substances. This affirmation is favoured by the experiments carried out by Havlicek and Sklenovsky [26] and by Creveling et al. [14]. The first authors demonstrated that the administration to animals of 3,4-dihidroxifenilserine, an aminoacid which by descarboxilation transforms itself in norepinephrine without the previous formation of dopamine, determines a depressive behaviour. On the other hand, Creveling et al. [14], pointed out that the experimental reserpinic depression was antagonized by the administration of DOPA, but not by the administration of 3,4-dihydroxifenilserine in spite of this substance restores the central levels of norepinephrine.

It is unknown the possible mechanism of sensibilization of dopamine at central level, therefore, although at the beginning it was thought in a blocking of uptake, Carlsson [10], in an ingenious form, demonstrated that tricyclic antidepressants did not block the pump of the dopaminergic neu-

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* Methylated dibenzocycloheptene with a lateral chain similar to amitriptyline.

** Antagonism of carbamylcholine action on the isolated fundus of the rat stomach, Atkinson and Ladinsky [4].

affirm that the possible participation of dopamine in the problem which occupies us, still has to be solved.
rones membrane. In conclussion we can

Serotoninergic hypothesis

The possibility that tricyclic antidepressants owe its action to a sensibilization of the effects of serotonine at central level has been also suggested basing upon a series of experimental and clinical facts. Actually before it was discovered, that imipramine inhibited the uptake of norepinephrine, Marshall et al. [35], demonstrated that this substance inhibited the uptake of serotonine by the platelets.

More recently, Carlsson [10], using an analogue of monoamines, the compound H 75/12 has demonstrated that imipraminics, particularlly the tertiary amines (imipramine, clorimipramine, and amitriptyline) prevent the uptake of this substance by the serotoninergic neurones and consequently the displacement of serotonine of its specific stores and its subsequent metabolism.

On the other hand, several authors have described the clinical efficacy of tryptophane in certain depressive states, alone or associated to MAO inhibitors or to peripheral inhibitors of the descarboxilases, Matussek [36].

The whole of these observations and the decrease in the excretion of tryptamine, Coppen et al. [13] and 5-hydroxyndoles in the cerebrospinal fluid observed in the depressive states, Ashcroft and Sharman [3], justify that the investigations intended to clarify the mechanism of action of tricyclic antidepressants continue in this sense.

SUMMARY

We consider four hypothesis to explain the mechanism of action of tricyclic antidepressants: Noradrenergic, cholinergic, dopaminergic and serotoninergic.

Noradrenergic hypothesis considers that antidepressant effect is related to an increase in activity of central adrenergic receptors.

We observe, favouring this hypothesis, that desipramine, that inhibits the uptake of norepinephrine, potentiates the maximal response of the amine in the isolated rat.

Cholinergic hypothesis considers that action of tricyclic antidepressants is arised by a central anticholinergic effect. This is disputable because other central acetycoline antagonists do not improve depressive states.

Dopaminergic hypothesis is supported by authors that consider dopamine as responsible of the activity of these substances. Which has not been demonstrated.

Serotoninergic hypothesis affirms that tricyclic antidepressants operate by sensibilization of the effects of serotonine at central level.

Finally we can say that we have not yet evidence to decide which is the way of acting of tricyclic antidepressants.

RESUMEN

Consideramos cuatro hipótesis para explicar el mecanismo de acción de los antidepresores tricíclicos: Noradrenérgica, colinérgica, dopaminérgica y serotoninérgica.

La hipótesis noradrenérgica establece que el efecto antidepresivo se debe al aumento de actividad de los receptores adrenérgicos centrales.

Nosotros observamos en favor de esta hipótesis que la desipramina que inhibe el consumo de norepinefrina, potencializa la mayor respuesta de la amina en la rata aislada.

La hipótesis colinérgica considera que la acción de los antidepresivos tricíclicos está determinada por un efecto anticolinérgico central . Lo cual es discutible porque otros anticolinérgicos no mejoran los estados depresivos.

La hipótesis dopaminérgica, es sostenida

por autores que consideran a la dopamina como responsable de la actividad de las sustancias que estudiamos. Lo cual no está demostrado.

La hipótesis serotoninérgica establece que los antidepresivos operan por sensibilización de los efectos de la serotonina a nivel central. En resumen puede decirse que aún faltan pruebas para decidir cual es el modo de acción de los antidepresivos tricíclicos.

RÉSUMÉ

Nous considérons hypotheses pour expliquer le mécanisme d'action des antidépressifs tricicliques noradrénergiques polynergiques, dopaminergiques et serotominergiques. L'hypothèse noradrenergique établie que l'effet antidépressif se doit à l'augmentation d'activité des recepteurs adrenergiques centrales. Nous observons en faveur de cette hypothese, que la disipramine qui inhibe le consume de norepinephrine, potentialize la meilleure réponse de l'anime au rat isolé.

L'hypothese colinergique considère que l'action des antidepressifs tricicliques est déterminée par un effet anticolinergique central lequel, est discutable, parce que les autres anticolinergiques n'ont pas améliorés les états dépressifs.

L'hypothese dopaminergique, est defendue par les auteurs qui considèrent la dopamine comme responsable de l'activité de la substance que nous étudions, ce qui n'est pas démontré.

L'hypothèse serotoninergique démontre que les antidépressifs opèrent par sensibilisation des effets de la seretonine au niveau central.

En résumé on peut dire qu'il manque preuves suffissantes et concluantes pour affirmer quel est le mode d'action des antidepressifs tricicliques.

ZUSAMMENFASSUNG

Wir betrachten vier Hypothesen, um den Wirkungsmechanismus der trizyklischen Antidepressoren zu erklären: die noradrenergische, kolinergische, dopaminergische und serotoninergische.

Die noradrenergische Hypothese meint, dass der antidepressive Effekt verursacht ist durch die Erhöhung der Aktivität der zentralen adrenergischen Rezeptoren. Wir beobachten zur Unterstützung dieser Hypothese, dab das Desipranin, dab den Verbrauch des Norepinephrin hindert, die stärkere Antwort auf Amin in der isolierten Ratte potentialisiert.

Die kolinergische Hypothese meint, dab die Wirkung der antidepressiven Trizyklischen bestimmt wird durch einen zentralen antikolinergischen Effekt. Dies ist umstritten, weil andere anticholinergische Mittel depressive Zustände nicht bessern.

Die dopaminergische Hypothese wird von Autoren verteidigt, welche das Dopamin für verantwortlich für die Aktivität der Substanzen, welche wir untersuchen, halten. Was nicht bewiesen ist.

Die serotoninergische Hypothese meint, daB die antidepressiven Mittel durch Sensibilisierung der Wirkungen des Serotonin in der zentralen Zone wirken. Zussamenfassend kann gesagt werden, dab noch die Beweise fehlen, um zu entscheiden welches das Wirkungsmodus der trizyklischen Antidepressiva ist.

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Discussion over the communication of Profesor Cuenca

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The problem which states the work of Dr. Cuenca is of great interest.

During many years we have been occupying ourselves with this theme, when we used to form part with Dr. Cuenca, of the team of Professor Valdecasas. During a long time the hypothesis of a mechanism of action of tricyclic antidepressants through an increase in the availability of noradrenaline at the level of the central synapsis has been the most generally accepted. The arguments in favor of this type of mechanism of action are numerous, but is more discussible the place over which would be exerted the effect. Probably the action over the adrenergic mechanism is multiple, but it cannot be limited to an inhibition of the uptake of noradrenaline, because there are antidepressants in this group, that do not inhibit this process. An intervention in the adrenergic mechanisms looks of all sort without doubt although not exclusive.

Maybe it hasn't been considered well enough the possibility that tricyclic antidepressants are adrenolitics at elevated dosis, may these substances act as parcial agonists in front of the central receptors.

The cholinolitic hypothesis also, does not lack of a solid base. The hallucinogenic effect of the atropinic drugs has been known for a long time and the cholynolitic actions of the tricyclics are very obvious.

We had the occasion to observe various cases of urinary Paressia in latent prosthatic patients, submitted to a therapy of imipramine or amitryptiline.

This action, possibly may be therapeutically of minor importance, because other central anticholinergics —antiparkinsonians— are not at the utilized dosis antidepressives.

The dopaminergic hypothesis has less experimental basis. We must point out, nevertheless, that the administration of L-Dopa produces in many patients an obvious pschycothonic effect, observing in depressed patients an authentic state of excitation. In all case, the effect will not be produced at the uptake level of dopamine, but could exist other mechanisms which are to be demonstrated.

The inhibition of serotonine uptake "in vitro" was demonstrated before than the inhibiting effect of adrenaline uptake. Imipramine has more effect over serotonine uptake, meanwhile desimipramine has more effect on the noradrenaline uptake. The antidepresive effect of Thryptophane in some depressive states, specially associated with M. A. O. inhibitors, or peripheric inhibitors of decarboxilation, speaks in favour of the antidepressive effect of the increase of central levels of serotonine.

It is very probable, therefore that the effect of tricyclic antidepressants will be multidirectional, with variations in the participation of the responsible mechanisms, depending on the drug used. We don't know the part which may have the antidepressive action, the antihistaminic effect of some antidepressive as amitriptiline, though some antihistaminics are capable of inhibiting the uptake of norepinefrine (cocain-like effect) and in certain persons there are antihistaminics as the phenindamine, capable of producing excitation.

It is a chapter, in every way exciting, because the better knowledge of the mechanism of action more decisive in the antidepressive effect, can conduct to obtain molecules more specific therapeutically and free of unwanted effects.

Differential Effects of Agents Which Alter CNS Monoamine Levels Upon Acoustic Responses in the Basal Ganglia of Freely Moving Rats

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Introduction

In 1912 Kinnier Wilson [41] first demonstrated that lesions within the basal ganglia could be correlated with abnormalities of the motor system. In his description of the clinical and neuropathologic characteristics of hepatolenticular degeneration, he noted the association of lesions in the basal ganglia with abnormalities of posture and movement. Subsequently, a number of other neurological disorders have been described which show an analogous relationship of basal ganglia pathology to motor system abnormality [18]. Parkinson's disease is one of these conditions, but until about 10 years ago it has been an emigma in that the severity of the neuropathological changes seemed minor in relation to the intensity of the clinical disorder. However, the demonstration by Hornykiewicz [27, 28, 29] that there is a marked deficiency of dopamine within various components of the basal ganglia of patients with Parkinson's disease provided an indication that a basic pharmacologic abnormality underlies this disorder.

A number of neurochemical investigations have established that the basal ganglia of normal humans and animals are rich in dopamine [30, 40] and that the dopamine is located in particularly high concentrations within nerve terminals of the caudate nucleus [12, 40]. Depletion of dopamine has been considered to be the crucial biochemical abnormality in the pathogenesis of Parkinson's disease [11, 19, 31]. In rats, intraperitoneal administration of reserpine depletes dopamine from the basal ganglia and induces a syndrome characterized by akinesia and rigidity which in some respects resembles Parkinson's disease [4, 5, 8, 11, 38].

Treatment of the reserpine-induced akinesia of rats by administration of L-dopa the metabolic precursor of dopamine results in an increase in the level of dopamine in the basal ganglia and abolition of the akinesia [6, 10, 19, 20]. These findings have suggested that dopamine is involved in the chemical mediation of activity involving the caudate nucleus and possibly also other parts of the basal ganglia.

The synaptic effects of dopamine administration have been studied in a number of central nuclei. Curtis and Davis [13] showed that dopamine applied iontophoretically to the lateral geniculate nucleus of the cat suppressed the orthodromic response of single neurons to an optic nerve stimulus. Similar findings were reported from studies of cerebral cortex [34], hippocampus [26], and caudate nucleus [7]. In these studies dopamine exerted a depressive action on discharge initiated either by synaptic activation or application of L-glutamate. However, York [42]

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reported that a majority of neurons in the globus pallidus responded with an increase of firing rate to the iontophoretic application of dopamine. There have also been conflicting reports on the action of topically applied dopamine upon the activity of neurons in spinal cord. McLennan [35] reported that dopamine applied to the exposed spinal cord of the cat suppressed the monosynaptic reflex response. In a later study, McLennan [36] suggested that dopamine excites inhibitory interneurons making synaptic contact with motoneurons in spinal cord. However, other investigators have found that dopamine applied iontophoretically to various types of spinal cord neurons of the cat failed to evoke any inhibitory action on interneurons or motoneurons [13].

The above studies on the synaptic action of dopamine have been performed on anesthetized animals. In a recent investigation carried out on awake, freely moving animals, it was found that intraperitoneal administration of L-dopa heightened the amplitudes of potentials evoked by click stimuli in the caudate nucleus [15]. Intraperitoneal administration of reserpine had the reverse effect. The present investigation was initiated to study in a similar manner the effects of administering L-dopa and reserpine on evoked potentials recorded from several regions of the basal ganglia simultaneously in awake rats. This approach permitted us to evaluate the effects of administering L-dopa and reserpine upon responses recorded simultaneously from caudate nucleus (CN), globus pallidus (GP) and substantia nigra (SN), and thus to compare effects between structures and also between drugs. A barbiturate was administered for comparison, as this agent has widespread effects in the nervous system in addition to a potent influence upon the reticular activating system [14, 22, 25].

Methods

Fifty-four male albino Holtzman rats weighing 250-350 grams were used in these experiments. The animals were anesthetized with pentobarbital (50 mg/kg i. p.) and stainless steel semi-microelectrodes 60μm in diameter, insulated with diamel except at the tip, were implanted stereotaxically in the CN, GP, and SN using the atlas of König and Klippel [33]. A reference electrode was placed in the frontal sinus. The electrodes and the teflon plug to which they were attached were fixed to the skull with dental acrylic. Several days following implantation the rats were placed in an observation chamber. The Teflon plug was attached to a counter-balanced commutator which connected the electrodes to the preamplifiers. This system allowed the animals to ambulate about the cage. Click stimuli generated with electrical pulses of 0.1 msec duration were presented every 2.5 sec through a loudspeaker located 25 cm from the chamber. Paired click stimuli were presented at randomized interstimulus intervals varying from 100-1000 msec in increments of 100 msec. For each single stimulus or pair of stimuli at a single time interval, 32 successive responses were averaged on-line with a signal averaging computer (NIC 1070) and recorded with an x-y plotter.

Four groups of animals were used. In the first group of nine, paired stimuli were delivered as described above and the average acoustic evoked response was recorded. Reserpine (1.0 mg/kg i. p.) was then administered and the same procedures of stimulation and recording were performed every ten minutes post-injection. One and a half hours later, L-dopa (100 mg/kg i. p.) in aqueous suspension was administered and the same procedures of stimulation and recording were resumed every ten minutes post-injection. This group of animals was labelled the control-reserpine-dopa (CRD) group. In the second group of nine, the same procedures of stimulation and recording were followed, but these animals received L-dopa prior to reserpine. Accordingly, this group was labelled the control-dopa-reserpine (CDR) group. In a third group of 3 animals, after control recordings were taken, L-dopa (100 mg/kg) was administered. The stimulation and recording procedures described above were followed. A second dose of L-dopa (100 mg/kg) was administered and the stimulation and recording procedures were resumed. This procedure was repeated again so that the animals were treated sequentially three times

with an identical dosage of L-dopa. Nine rats were used in a fourth group to study the effects of various doses of pentobarbital on the acoustic evoked response and its neuronal recovery cycle. The same injection, stimulation and recording techniques were used in this group. Analysis of the average acoustic evoked response was carried out in the following manner. Amplitudes of the individual components of the responses were measured peak to peak and the means and standard deviations were calculated. A change in amplitude of ± 2 standard deviations was considered significant. In measurements of neural recovery cycles, the mean amplitudes of the various components of the evoked responses to the second stimulus were computed as a percentage of the corresponding components of the first response and plotted as a function of the time between stimuli.

At the conclusion of the experiments the animals were anesthetized deeply with pentobarbital and a lesion was made at the tip of each electrode by passing 50 μA of DC current for 20 sec. The brain was then perfused with a solution of 3 % potassium ferrocyanide and 3 % potassium ferricyanide, followed by 10 % formalin. Both frozen and paraffin mounted sections were used. These were cut serially at 20 μm and stained with thionin or hematoxylin-eosin. The locations of the electrode tips were identified by observing the lesions and Prussian blue spots. Data were analyzed only from those animals in which the electrode tips were located within the GP, CN and SN.

Results

Figure 1 contains potentials evoked by paired click stimuli at 600 msec. intervals recorded from the basal ganglia of an animal adapting to the test chamber. In this representative example, potentials evoked by both conditioning and test stimuli change as function of the length of time the animal is in the chamber. Responses in both GP and CN show a progressive increase of amplitude over a similar time course, whereas the responses in SN reach maximal amplitude at 30 min. In the initial 30-45 min after entering the test chamber the animals actively explored the environment, then became less active. During presentation of the click stimuli, the animals would usually orient toward the loudspeaker and remain in a fixed position until the clicks were discontinued.

Figure 2 illustrates control data from an animal after adaptation for 90 min in the test chamber. The intervals between conditioning and test stimuli are varied between 100 and 700 msec. In all 3 structures (GP, CN, SN), the amplitudes of the test respon-

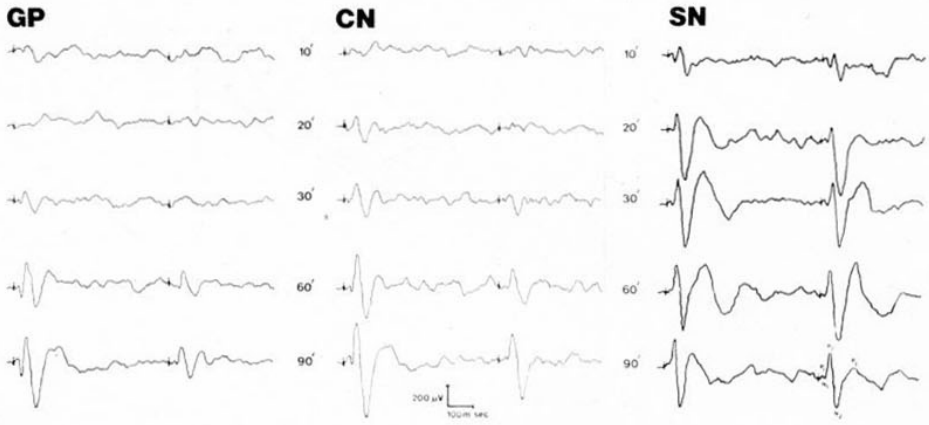


Figure 1. — *Average evoked responses to paired click stimuli in the unanesthetized rat. Recordings from globus pallidus (GP), caudate nucleus (CN), and substantia nigra (SN) taken at successive time intervals after the rat was placed in the test chamber. The interval between the paired stimuli is 600 msec. P_1-first positive wave; N_1-first negative wave; P_2-second positive wave; N_2-second negative wave; P_3-third positive wave.*

ses progressively diminish as the intervals between conditioning and test stimuli are decreased. Figure 3 presents recovery cycles for individual components (P_2, N_2, P_3) of the test responses expressed as a percentage of the amplitudes of the corresponding components of the conditioning response as a function of the interval between stimuli. Within each of the 3 structures the amplitude variations of these components follow a similar time course.

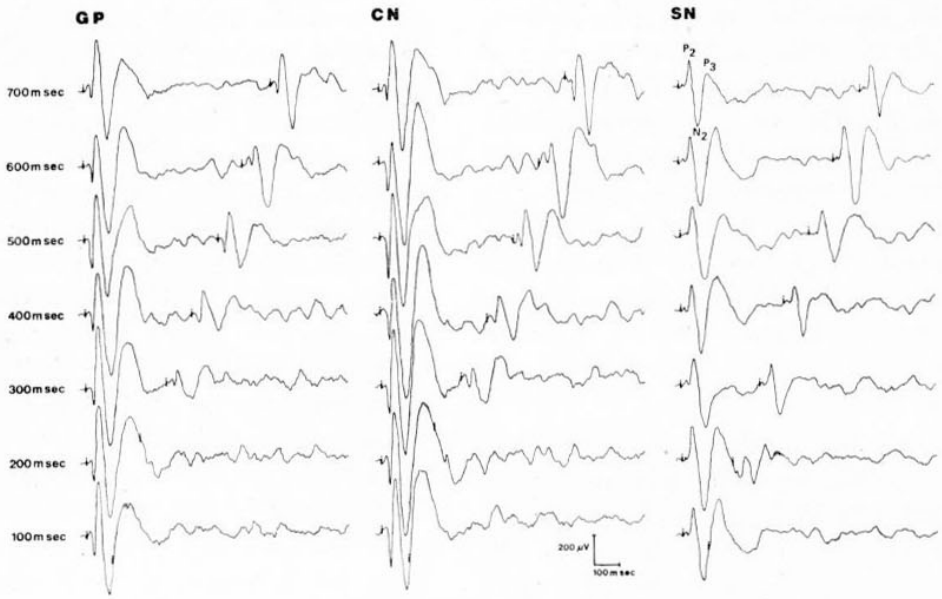


Figure 2. — *Average acoustic evoked responses to paired click stimuli at various interstimulus intervals after 90 min of adaptation in the test chamber. Recordings from globus pallidus (GP), caudate nucleus (CN) and subsatntia nigra (SN). The intervals between the paired stimuli were varied from 100-700 msec in increments at 100 msec. P_2-second positive wave; N_2-second negative wave; P_3-third positive wave.*

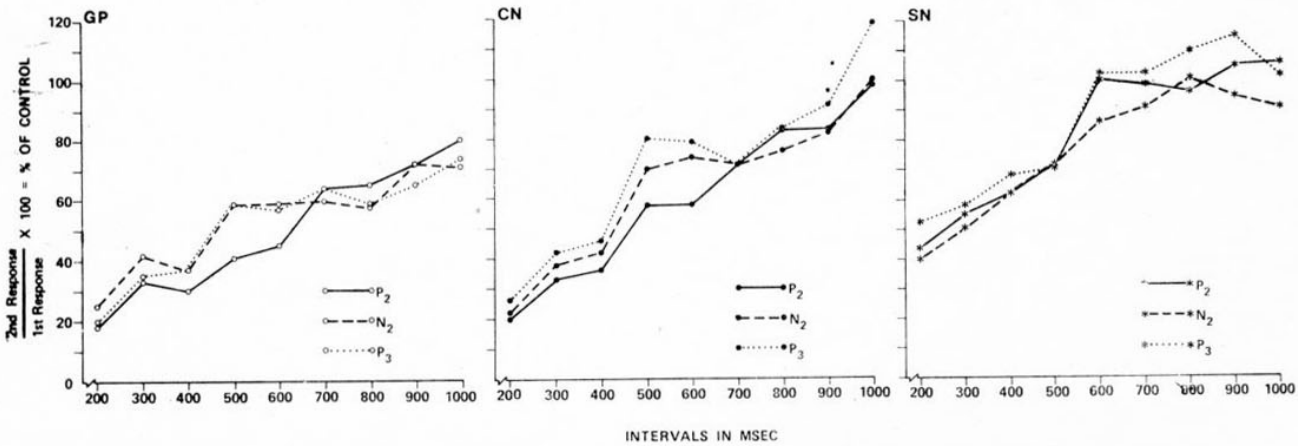


Figure 3. — *The average neuronal recovery function obtained from 18 rats under control conditions. The abscissa represents the intervals between paired stimuli in increments of —100 msec. The ordinate expresses the amplitude of a component in the test response as a percentage of the amplitudes of the corresponding component in the conditioning response. Curves are computed for each of the three late components. GP-globus pallidus; CN-caudate nucleus; SN - substantia nigra.*

Figure 4 contains potentials evoked in GP, CN, and SN prior to and at 10 min intervals following a single injection of L-dopa (100 mg/kg i. p.). An increase in the average evoked potential is evident in all three structures as early as 10 min after injection.

Figure 5 contains grouped data illustrating the effects of injecting reserpine followed by L-dopa, and of administering these agents in the reverse order, upon the amplitudes of individual components of the average evoked responses recorded from GP, CN, and SN. In this illustration the histograms depicted by heavy bars indicate the percentage of components of the evoked response showing significant changes to drug administration. The thinner bars indicate the percentage of the responsive components showing a significant increase (thin parallel lines) and decrease (solid black bars) of amplitude. The clearest effects occurs in SN (second row, Figure 5). Reserpine administration tends to decrease the amplitudes of all 3 components whereas L-dopa tends to increase them, and these effects occur regardless of the order of administration. In GP and SN (rows I and 3, respectively) a complex admixture of increase and decrease of response amplitudes occurs.

Figure 6 presents responses recorded from GP to paired click stimuli at 700 (left column) and 200 (right) msec intervals. The upper traces show the effects of administering reserpine in advance of L-dopa (CRD); the lower traces present the results of drug administration in the reverse order (CDR). In these examples both reserpine and L-dopa augment the amplitudes of the test responses. Subsequent administration of the other drug (e. g., L-dopa after reserpine) tends to leave the test response unaltered. Figure 7 contains recovery cycle curves for responses evoked in GP for both the CRD (upper row) and CDR (lower) groups. The curves were computed using individual test response components expressed as a percentage of the corresponding components of the response to the conditioning stimulus. Both drugs augment the recovery cycle over the entire range of intervals tested, regardless of the order of drug administration.

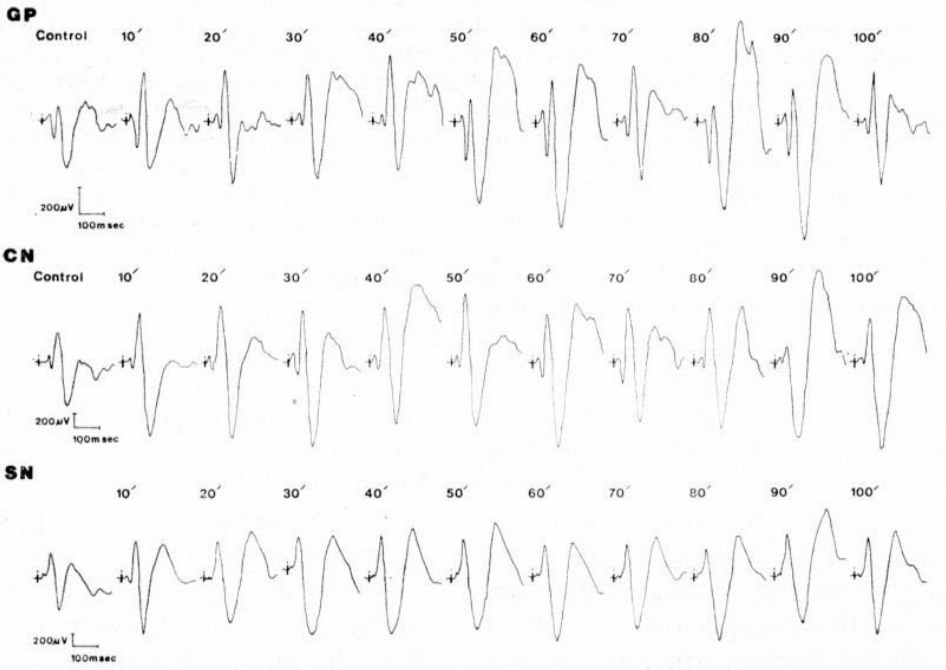


Figure 4. — *Time response effects of 100 mg/kg i. p. L-dopa on the average auditory evoked responses recorded from globus pallidus (GP), caudate nucleus (CN), and substantia nigra (SN). Recordings were taken at 10 min intervals.*

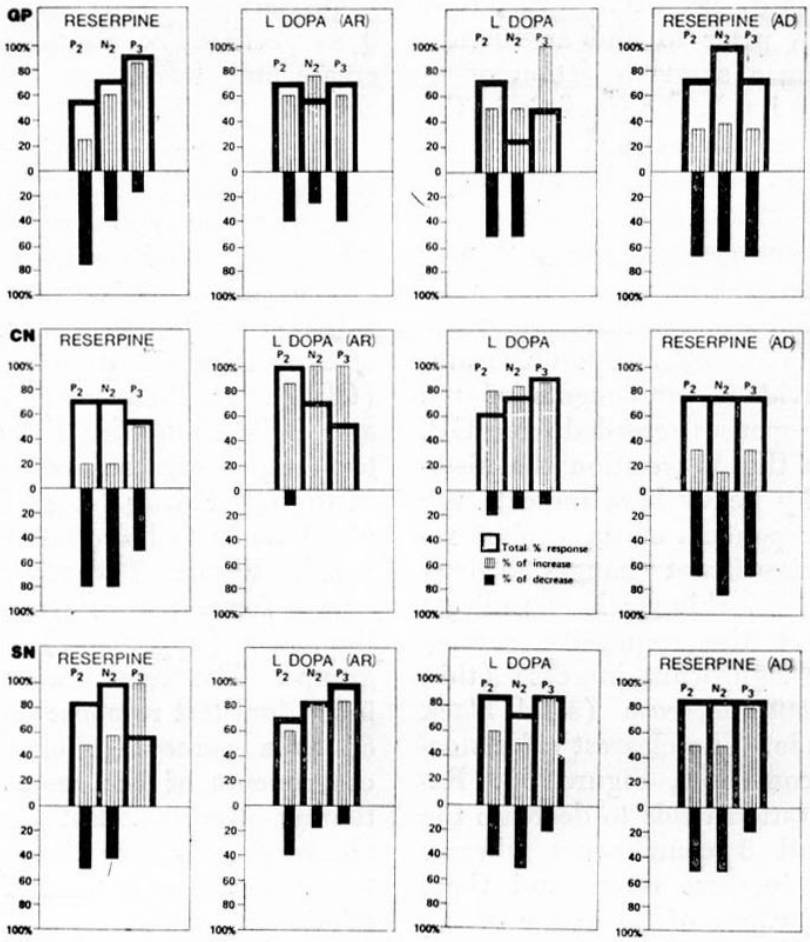


Figure 5. — *Histograms showing the total significant responsiveness (thick boxes) and the direction of the responses by increase (shaded (bars) or decrease (black bars) in amplitude compared with the control amplitude of each of the three late components (P_2, N_2, P_3) of the first responses to click stimuli. Recordings taken from globus pallidus (GP, top row), caudate nucleus (CN, middle row), and substantia nigra (SN, bottom row). The two columns on the left are based on observations in 9 rats from the control-reserpine-dopa (CRD) group and the two columns on the right on data from 9 rats in the control-dopa-reserpine (CDR) group. AR-after reserpine; AD-after L-dopa. The data in the first and third columns are expressed as a percentage of the amplitudes of the control responses; the data in the second and fourth columns are expressed as a percentage of the amplitudes recorded after administration of one of the drugs.*

Figure 8 presents responses recorded from CN to paired click stimuli at 700 (left column) and 200 (right) msec. The upper traces show the effects of administering reserpine in advance of L-dopa (CRD); the lower traces present the results of drug administration in the reverse order (CDR). The effects of these drugs upon the responses to the test stimulus were similar to those upon the responses to the conditioning stimulus (eg. Fig. 5); reserpine generally depressed whereas L-dopa generally enhanced the amplitude. These drug effects were more complex, however, when the amplitudes of the responses to the conditioning stimulus. As shown in Fig. 9, in the CRD sequence (upper row) reserpine enhanced the recovery cycle and subsequent L-dopa administration further augmented it. However, in the CDR sequence (lower row) L-dopa enhanced the recovery cycle but subsequent reserpine decreased it.

Figure 10 shows responses recorded from SN to paired click stimuli at 700 (left co-

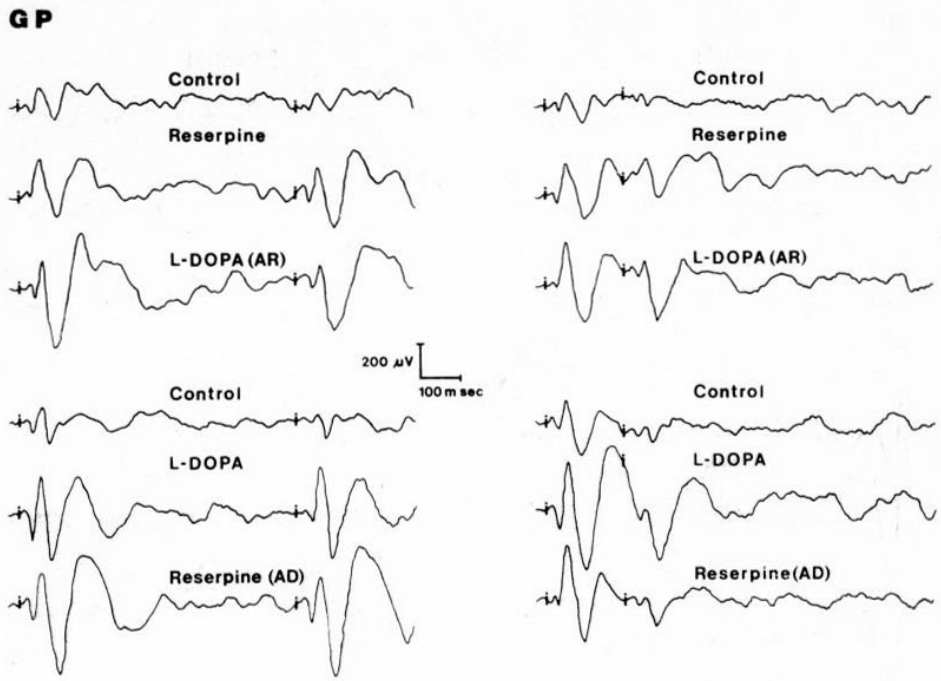


Figure 6. — *Average evoked responses recorded from globus pallidus (GP) in response to paired click stimuli. Interstimulus intervals are 700 msec (left) and 200 msec (right). The upper two sets of three traces are from a control-reserpine-dopa animal and the lower trace a control-dopa-reserpine animal.*

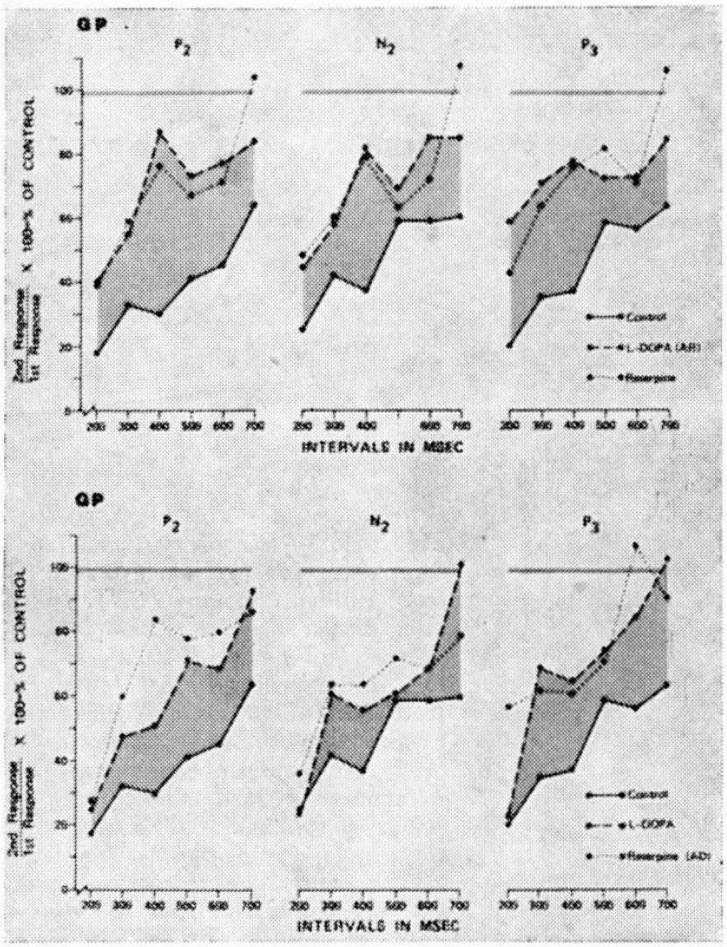


Figure 7. — *Recovery cycle curves computed for responses reorded from globus pallidus (GP). Individual curves are computed for each of the late components, P_2, N_2, P_3 for interstimulus intervals ranging from 200 to 700 msec. The ordinates express the amplitudes of the individual test response components as a percentage of the conditioning response amplitudes. The upper set of graphs are computed for 9 rats in the control-reserpine-dopa group and the lower set from the control-dopa-reserpine group. AR - after reserpine, AD - after L-dopa.*

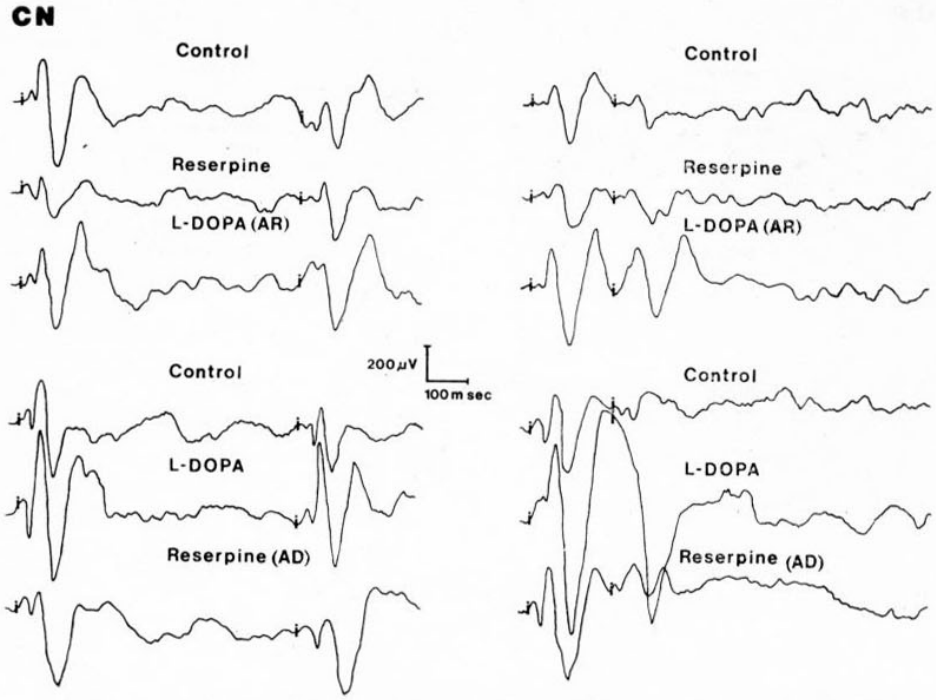


Figure 8. — *Average evoked responses recorded from caudate nucleus (CN) in response to paired click stimuli. Interstimulus intervals are 700 msec (left) and 200 msec (right). The upper two sets of three traces are from a control-reserpine-dopa animal and the lower trace a control-dopa-reserpine animal.*

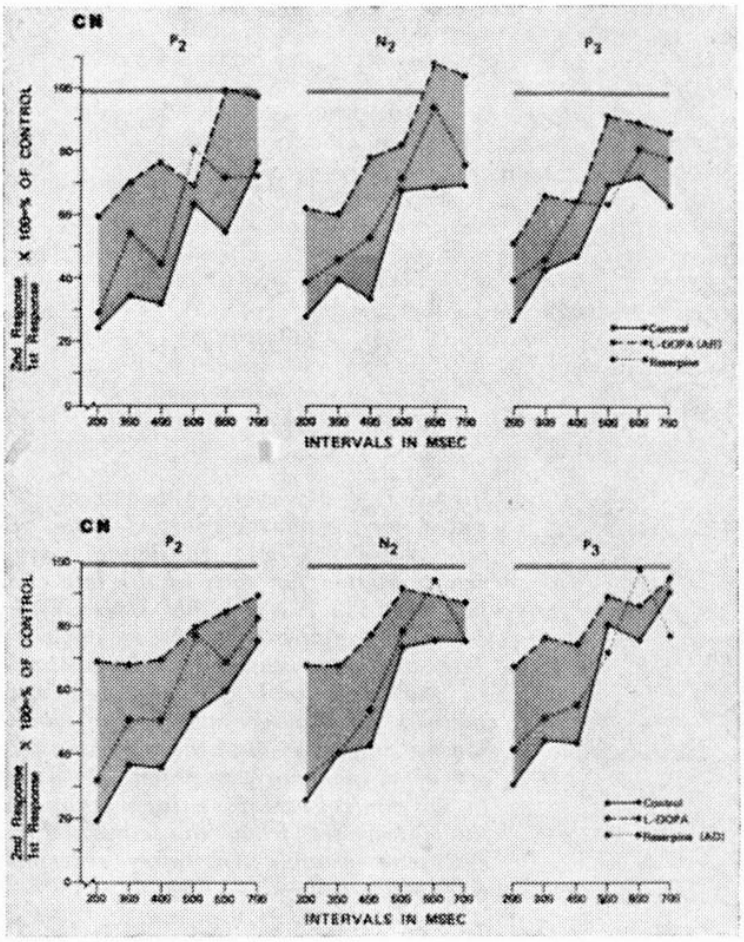


Figure 9. — *Recovery cycle curves computed for responses recorded from caudate nucleus (CN). Individual curves are computed for each of the late components P_2, N_2, P_3 for interstimulus intervals ranging from 200 to 700 msec. The ordinates express the amplitudes of the individual test response components as a percentage of the conditioning response amplitudes. The upper set of graphs are computed for 9 rats in the control-reserpine-dopa group and the lower set from the control-dopa-reserpine group. AR - after reserpine, AD - after L-dopa.*

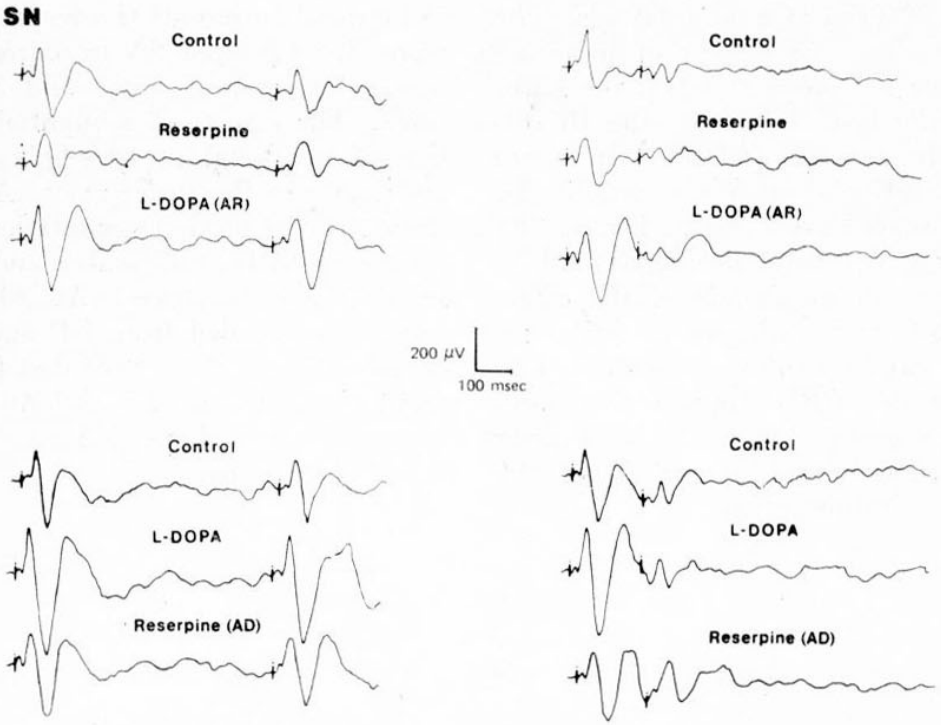


Figure 10. — *Average evoked responses recorded from substantia nigra (SN) in response to paired click stimuli. Interstimulus intervals are 700 msec (left) and 200 msec (right). The upper two sets of three traces are from a control-reserpine-dopa animal and the lower trace a control-dopa-reserpine animal.*

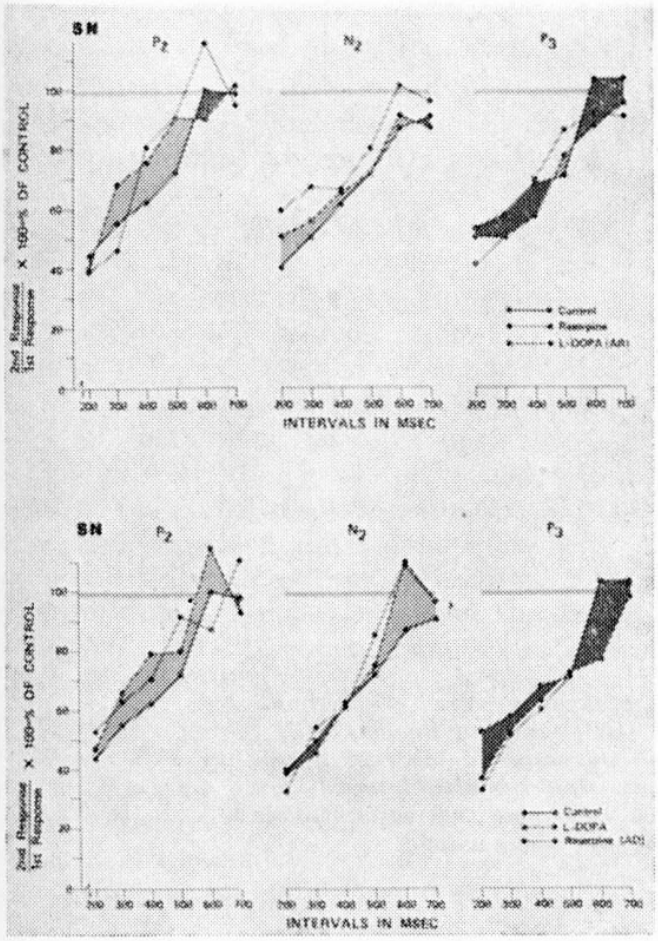


Figure 11. — *Recovery cycle curves computed for responses recorded from substantia nigra (SN). Individual curves are computed for each of the late components, P_2, N_2, P_3 for interstimulus intervals ranging from 200 to 700 msec. The ordinates express the amplitudes of the individual test response components as a percentage of the conditioning response amplitudes. The upper set of graphs are computed for 9 rats in the control-reserpine-dopa group and the lower set rom the control-dopa-reserserpine group. AR - after reserpine AD- after L-dopa.*

lumn) and 200 (right) msec intervals. The upper traces show the effects of injecting reserpine prior to L-dopa (CRD); the lower traces show the results of reversing the order of administration (CDR). In these examples the effects upon the amplitudes of the test responses are slight, but at 700 msec reserpine generally decreased and L-dopa enhanced the amplitude. Little effect occurred at 200 msec. Figure 11 shows recovery cycle curves for responses evoked in SN for both the CRD (upper row) and CDR (lower) group. The effects of drug injection were minimal, regardless of the sequence of administration.

Figure 12 presents the responses recorded from GP, CN, and SN to paired click stimuli at 700 (upper row) and 300 (lower) msec. The effects of sequential administration of nembutal in 10 mg/kg increments are shown in the lower rows. At 10 mg/kg there is a general augmentation of the responses to both conditioning and test stimuli in all three structures. At 20 mg/kg the responses recorded from GP and SN are reduced whereas those recorded from CN remain elevated. At 30 and 40 mg/kg the responses are reduced below control levels in all 3 structures.



Figure 12. — *Average responses evoked by paired click stimuli recorded from globus pallidus (GP), caudate nucleus (CN), and substantia nigra (SN) with increasing dosages of pentobarbital in 10 mg/kg increments. Interstimulus intervals are 700 msec (upper traces in each row) and 300 msec (lower traces). Recordings taken from the same animal.*

Discussion

Responses evoked by click stimuli within the basal ganglia of awake animals consisted of five components (P_1, N_1, P_2, N_2, and P_3) with long latency high amplitude, and long duration. The initial components of the response (P_1 and N_1) probably represent presynaptic activity since they show no consistent change in amplitude from either paired stimuli or drug treatments. The remaining components (P_2, N_2, P_3) probably consist of a combination of presynaptic and postsynaptic activity. These responses were large in amplitude and stable only after the animals were allowed to adapt to the test situation: at an earlier stage they were small and variable. These findings made it necessary to ascertain that response amplitudes were stable before control recordings were taken and independent variables introduced.

The findings of major interest in the present study are that the effects of reserpine and L-dopa treatment differ on potentials evoked by click stimuli in the GP, CN, and SN. Different results were also obtained from the effects of these drugs on the evoked responses and on the neuronal recovery functions. In the GP and SN a combination of increase and decrease of amplitude of the evoked responses was observed after reserpine or L-dopa injection regardless of the order of administration of the drugs; in CN the effect was mainly a depression of the responses following reserpine and an increase after L-dopa. However, the neuronal recovery function responded differently in each of these three structures. In the GP, both reserpine and L-dopa shortened the recovery time between the first and second stimulus. In the CN, with the CRD group, both reserpine and L-dopa shortened the neuronal recovery time. However, in the CDR group, L-dopa shortened the recovery time and subsequent administration of reserpine lengthened it, though the recovery cycle remained shorter than that observed in the control recording. In SN, neither reserpine nor L-dopa affected appreciably the neuronal recovery function as compared to the control recording. In contrast, pentobarbital administration affected responses in all three structures essentially equally and in the same manner.

Utilization of the Falck-Hillarp [21] fluorescence histochemical method has permitted demonstration of dopamine-containing nerve cell bodies in the substantia nigra [16], and dopamine-containing nerve terminals in the caudate nucleus and putamen [2, 9, 24]. A nigrostriatal system of dopamine-containing fibers originates in the zona compacta of the substantia nigra. Its axons traverse the lateral hypothalamus internal capsule, and globus pallidus, terminating in the caudate nucleus and putamen [1, 40]. The globus pallidus shows few monoamine-containing nerve terminals [23]. The caudate nucleus and putamen also contain nerve terminals high in serotonin concentration; the cell bodies of origin of these fibers are in the raphe nuclei [2]. Administration of reserpine depletes the nervous system of dopamine, norepinephrine, and serotonin [3, 39]. Administration of L-dopa counteracts the effects of reserpine administration [6, 10, 17, 20].

In the present study, L-dopa and reserpine administration produced consistent effects upon the amplitudes and recovery cycles of responses evoked in caudate nucleus. These findings are compatible with the observation that the caudate nucleus is an important site of termination of monoaminergic fibers [23] and with the concept that L-dopa and reserpine affect the evoked responses through alteration of the monoamine content of the caudate nucleus. In contrast, L-dopa and reserpine administration produced inconsistent effects upon the amplitudes of responses evoked in substantia nigra and globus pallidus. These findings are compatible with the observation that monoaminergic terminals are scarce in these structures [23]. Substantia nigra contains principally monoaminergic nerve cell bodies whereas globus pallidus contains chiefly fibers *en passage*. Accordingly, although effects on evoked potentials of L-dopa and reserpine administration in SN and GP may be due to alteration of monoamine concentration in these sites, it is more likely that the effects are due to actions occurring at some other related site. It is also possible that some of the effects of reserpine admin-

istration result from depletion of serotonin in these structures. This phenomenon could explain the lack of consistent reversal of reserpine effects from administration of L-dopa, since reserpine affects serotonin content but L-dopa does not [32].

The present findings indicate that in CN, L-dopa administration consistently enhances the number or intensity of neural elements responsive to clicks and also enhances the responses of these elements to a second stimulus following closely upon the first. Thus, L-dopa interferes with the occlusive or inhibitory interactions accounting for the characteristic recovery curves. The nature of this interference is opposite to that expected from previous studies on the nature of the effects of dopamine on central neurons, as determined using microiontophoretic techniques. These techniques have yielded the generalization that dopamine functions as an inhibitory neurotransmitter [7, 37]. If this is the case, the present findings of an increase of response amplitude after dopamine administration indicate that dopamine may have an inhibitory effect upon inhibitory interneurons. Alternatively, it is possible that dopamine induces excitation at some sites in the CNS and inhibition at others.

SUMMARY

Average responses to click stimuli were recorded with permanent semimicroelectrodes from the caudate nucleus (CN), globus pallidus (GP), and substantia nigra (SN) in freely behaving rats. Injection of L-dopa (100 mg/kg i. p. as an aqueous suspension) increased the amplitude of the response recorded from CN but had variable effects on the amplitudes of the responses recordad from GP and SN. Subsequent administration of reserpine (1 mg/kg i. p.) decreased the amplitude of the response in CN and had variable effects on the amplitudes of the responses recorded from GP and SN. Injection of reserpine as a first treatment reduced the amplitude of the response in CN and subsequent L-dopa administration reversed the reserpine effect. Variable effects occurred in GP and SN with this sequence of drug administration.

The neuronal recovery function obtained by paired click stimuli at various interstimulus intervals responded differently to drug administration in each of the three structures. In CN, both drugs shortened the neuronal recovery time when reserpine was give prior to L-dopa. When administered in the opposite order, L-dopa shortened the recovery time and reserpine lengthened it. In GP, both drugs shortened the recovery time and in SN neither had an appreciable effect. In contrast to the specific effects of L-dopa and reserpine, progressive pentobarbital administration altered the responses in all three structures essentially ponses in all three structures essentially equally and in the same manner.

It is concluded that the highly specific effects of L-dopa and reserpine inyection upon responses evoked in CN result from alteration of monoamine concentrations at nerve terminals in this structure. The variable effects observed in GP and SN may be due to alteration of monoamine concentrations in these sites, but it is more likely that the effects result from actions occurring at other related sites.

RESUMEN

Las respuestas promedio a los estímulos click fueron registrados con semimicroelectrodos permanentes del núcleo caudado (CN), globo pálido (GP) y la sustancia nigra (SN) en ratas de comportamiento libre.

La inyección de L-dopa (100 mg/kg. i.p. como una suspensión acuosa) aumentó la amplitud de la respuesta registrada del CN, pero tuvo efectos variables sobre las amplitudes de las respuestas registradas del GP y SN. La administración posterior de la

reserpina (1 mg/kg i. p.) disminuyó la amplitud de la respuesta en CN y tuvo efectos variables sobre las amplitudes de las respuestas registradas del GP y SN. La inyección de reserpina como un primer tratamiento redujo la amplitud de la respuesta en CN y la posterior administración de L-dopa invirtió el efecto de la reserpina. Efectos variables ocurrieron en GP y SN con esta secuencia de administración de droga.

La función de recuperación neuronal obtenida por estímulos click pares en varios intervalos de interestímulos respondieron en forma diferente a la administración de la droga en cada una de las tres estructuras. En CN, ambas drogas redujeron el tiempo de recuperación neuronal cuando la reserpina fue dada antes que L-dopa. Cuando se administró en el orden contrario, la L-dopa redujo el tiempo de recuperación y la reserpina lo prolongó. En GP, ambas drogas redujeron el tiempo de recuperación y en SN ninguna tuvo un efecto apreciable. En contraste con los efectos específicos de L-dopa y reserpina, la administración progresiva de pentobarbital alteró las respuestas en todas las estructuras en forma esencialmente igual.

Se concluye que los efectos altamente específicos de la inyección de L-dopa y reserpina sobre las respuestas evocadas en CN resultan de la alteración de las concentraciones de monoaminas en las terminaciones nerviosas en esta estructura. Los efectos variables observados en GP y SN pueden ser debidos a la alteración de las concentraciones de monoamina en estos núcleos, pero es más probable que los efectos resulten de acciones que ocurren en otros sitios relacionados.

RÉSUMÉ

La moyenne des réponses aux stimulations click furent enregistrées avec semimicroelectrodes permanentes en moyau caudé (CN), globus palidus (GP) et la substance nigra (SN) chez les rats de comportement libre.

L'injection de L-dopa (100 mg/kg. i. p. avec une suspension aqueuse) a augmenté l'amplitude de la réponse enregistrée du CN, mais a eu des effets variables sur les amplitudes des réponses enregistrées du GP et SN L'administration postrieure de la réserpine (1 mg/kg i. p.) diminua l'amplitude de la réponse en CN et ont eu des effets variables sur les amplitudes des réponses enregistrées du GP et de SN. L'injection de la reserpine comme premier traîtement, réduit l'amplitude de la réponse en CN et l'administration postérieure du L-dopa inverti l'effet de la reserpine. Des effets variables se produisirent en GP et SN avec cette sequence d'administration de drogue.

La fonction de récupération neuronal obtenue par stimulation click en divers intervales de interstimulation ont répondu en forme différentes a l'administration de la drogue en chacune des trois structures. En CN ces deux drogues réduisirent le temps de récupération neuronal lorsque la reserpine fut donnée avant la L-dopa. Lorsqu'ont l'administre dans l'ordre contraire, la L-dopa a réduit le temps de récuperation et la reserpine l'a prolongé. En GP, les deux drogues ont réduit le temps de récupération et en SN aucune eut un effet appréciable . En contraste avec les effets spécifiques de la L-dopa et reserpine, l'administration progressive de pentobarbital altère les réponses dans toutes les structures en forme essentiellement égales.

On conclue que les effets hautement spécifiques de l'injection de la L-dopa et reserpine sur les réponses évoquées en CN résultent de l'altération des concentrations des monoamines dans les terminaisons nerveuses dans cette structure. Les effets variables observés en GP et SN peuvent être dus a l'altération des concentrations de monoamine dans ces noyaux, mais il est plus probable que les effets résultent des actions dans d'autres régions en rapport.

ZUSAMMENFASSUNG

Die Durchschnittsantworten auf Click-Reize wurden mit Dauer-Semimikroelektroden des Nucleus caudatus (CN), Globus palidus (GP) und der Substantia nigra (SN) bei Ratten in freiem Verhalten registriert.

Die Injektion von L-Dopa (100 mg/kg intraperitoneal in wässeriger Suspension) erhöhte die Breite der registrierten Antwort im CN, aber hatte verschiedene Wirkungen auf die Breite der registrierten Antwort im GP und SN. Die spätere Anwendung von Reserpin (1 mg/kg i. p.) verringerte die Breite der Antwort des CN und hatte veränderliche Wirkungen auf die Breiten der registrierten Antworten des GP und SN. Die Injektion von Reserpin als erste Behandlung schränkte die Breite der Antwort des CN ein und die spätere Anwendung von L-Dopa kehrte den Effekt des Reserpin um. Veränderliche Wirkungen gab es vom GP und SN mit dieser Reihenfolge der Drogenverabreichung.

Die Funktion neuronaler Erholung erhalten durch gepaarte Click-Reize bei veränderlichen Reizintervallen erfolgte verschiedentlich auf die Drogenverabreichung in jeder der drei Strukturen. Im CN verkürzten beide Drogen die Zeit der neuronalen Wiederherstellung wenn das Reserpin vor dem L-Dopa gegeben wurde. Wenn sie in umgekehrter Reihenfolge gegeben wurden verkürzte das L-Dopa die Wiederherstellungszeit und das Reserpin verlängerte sie. Im GP verkürzten beide Drogen die Wiederherstellungszeit und im SN hatte keine eine wahrnehmbare Wirkung. Im Gegensatz zu den spezifischen Wirkungen von L-Dopa und Reserpin veranderte die progressive Anwendung von Penthobarbital die Antworten in allen Strukturen in im Wesentlichen gleicher Weise.

Man folgert, dass die hochgradig spezifischen Wirkungen der Injektion von L-Dopa und Reserpin auf die im CN hervorgerufenen Antworten Folge der Veränderung der Konzentrationen der Monoamine in den Nervenendigungen in dieser Struktur sind. Die veränderlichen Wirkungen, die im GP und SN beobachtet wurden, können Folge der Veränderung der Konzentrationen von Monoamin in diesen Kernen sein, aber es ist wahrscheinlicher, dass die Wirkungen Folgen von Vorgängen in anderen verwandten Plätzen sind.

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Antagonism of the Effects of d-Amphetamine by Amantadine and Other Stimulants, Analeptics and Anorexics in Mice*.

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Introduction

Recently we [1] reported that pretreatment of mice with amantadine blocked central effects of d-amphetamine, including motor activity, grouped toxicity and increased concentration of homovanillic acid (HVA) in the caudate nucleus.

We also found that amantadine pretreatment blocked the hyperactivity and hypothermic effects of d-amphetamine in reserpinized mice. In drug-naive mice, even when administered after amphetamine, the motor activity was reduced by amantadine [2]. From these and other considerations it was concluded that the antagonism is due to a competitive blockade at post-synaptic receptors in the brain.

The present study was conducted to ascertain whether other stimulant, analeptic and anorexic drugs could block the hyperactivity and lethal effects of d-amphetamine. Additionally, the lethal effects of d-amphetamine on aggregated and isolated mice in cages larger than previously used by other investigators were determined.

Experimental

Male albino Swiss mice (24-31g, Hilltop Labs) were used and were acclimatized for several days before use at 23 ± 1° C. The experiments were performed at this temperature. All drugs were injected intraperitoneally (i. p.) in a volume of 0.01 ml/gm body weight, and the doses were expressed as the free base.

To determine the effects of each drug a subjective screening procedure was utilized whereby the approximate lethal dose of each drug was determinad, after which declining doses were given and the animals' reactions observed. The approximate dose and time of pretreatment of each drug thus was obtained for studying the effect of each drug on the motor activity response to d-amphetamine (2 mg/kg).

Drug effects were studied by placing the mice individually in separate plastic buckets (8" high × 6" in diameter [20 × 15 cm]) and the activity measured on a modified activity meter described by Arvolo [3]. Before recording motor activity, the mice were equilibrated in the buckets for one hour. Recording time was for a duration of one hour.

The drugs tested were: amantadine hydrochloride (Symmetrel R, DuPont & Endo) *, picrotoxin (Sigma), pentylenetetrazol (Metrazol R) (Sigma), strychnine (Mallinkrodt), fenfluramine (A. H. Robins) *, theobromine (Eastman Kodak), caffeine

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(Eastman), theophylline (Calbiochem), dimeflin (Remeflin R, Rec. 7-0267, Recordati, Milano) *, 1-N-benzyl-*B*-methoxy-3-trifluormethylphenethylamine hydrochloride (related to fenfluramine) (SKF 1-39728, Smith Kline & French) *, d-amphetamine sulfate (SKF) *, amiphenazol (Daptazol R, A. & G. Nicholas, England) *, methyl-phenidate (Ritalin R, Ciba-Geigy) *, phenmetrazine (Preludin R, Ciba-Geigy) *, pipradol (Meratran R, Merrell) *, diethylpropion (Tenuate R, Merrell), doxapran hydrochloride (Stimulexin R, A. H. Robins), pyrovalerone hydrochloride (Centroton R, Wander, Bern; Dorsey), 5,5-diethyl-1-3-oxazin-2,4-dione (diethadione R, Tocen R, Lepetit, Milano), ephedrine (American Pharmaceutical), phenteramine (Wilpo R, Dorsey) * and 3-phenoxy-2-hydroxyl-1-propylmethoxamine (SAS-509, Schiapparelli, Torino) *.

Those drugs which showed inhibitory effects were studied to determine more accurately the optimum doses and times for the maximum blocking effect. The optimum doses were determined by giving the drugs in different doses at one hour (picrotoxin and pentylenetetrazol) and two hours (amantadine and fenfluramine) before d-amphetamine (2 mg/kg). For determining optimum time, mice were given the optimum dose obtained above, at different times before d-amphetamine (2 mg/kg). The toxicity of the drugs found to block the psychomotor effect of d-amphetamine then was determined.

To obtain information on the lethal effects of d-amphetamine a dose response curve was determined for isolated and aggregated conditions. Small cages (10" × 11" × 5" [25 × 18 × 13 cm]) were utilized in the isolated experiments because it was found that the cage size had no effect on isolated mice (unpublished data). However, it was observed that in the aggregate condition there was considerably more aggression and fighting in the small cages in mice injected with d-amphetamine than in the larger cages (18" × 11" × 5" [46 × 28 × 13 cm]). Therefore, for the aggregate experiments only the larger cages were used.

Mice were injected with the doses of amantadine, picrotoxin, pentylenetetrazol and fenfluramine found to exert the maximum antiamphetamine effects. The mice were aggregated five per cage and after the optimum time they were injected with 65 mg/kg d-amphetamine (LD93) and 26 mg/kg (LD60). The lethality in each group was noted at intervals over a 24 hour period. The same procedure was used in the experiments on isolated mice. Control groups receiving 0.9 % NaCl in place of the drugs and treated with same dose of d-amphetamine. were run simultaneously in all experiments.

RESULTS

Motor Activity

Drugs which had no inhibitory effect on the motor hyperactivity caused by d-amphetamine were: Caffeine (30 and 100 mg/kg), theophylline (50 mg/kg), phenteramine (10 mg/kg), doxapran (20 mg/kg), diethylpropion (20 mg/kg), phenmetrazine (20 mg/kg), pyrovalerone (20 mg/kg), pipradol (10 mg/kg) and 5,5-diethyl-1,3-oxazin-2,4-dione (20 mg/kg).

Drugs which had a small but significant inhibitory effect were: theobromine (50 and 80 mg/kg), dimefline (1-3 mg/kg), the SKF fenfluramine analogue (50 mg/kg), amiphenazole (60 mg/kg), strychnine (0.7 and 0.9 mg/kg), methylphenidate (40 mg/kg) and 3-phenoxy-2-hydroxyl-1-propylmethoxamine (60 mg/kg).

Drugs which had a marked inhibitory effect were: amantadine, picrotoxin, pentylenetetrazol and fenfluramine, as shown in Table I.

* Gifts, for which the authors are very grateful.

TABLE I

EFFECT OF AMPHETAMINE ON MOUSE MOTOR ACTIVITY
AFTER PRETREATMENT WITH OTHER DRUGS
(COMPARISON CHART)

DRUGS	DOSE* (mg/kg)	TIME* (min)	PERCENT INHIBITION	AVE. COUNTS SEM	P-VALUE
SALINE CONTROL	---	---	---	169 ± 23	---
AMPH. CONTROL	2	---	---	1252 ± 87	---
AMPHETAMINE	2	60	---	2364 ± 158	<0.001
AMANTADINE	150	120	66.7	417 ± 88	<0.001
PICROTOXIN	3	30	72.1	347 ± 30	<0.001
PENTYLENETETRAZOL	40	15	73.2	336 ± 44	<0.001
FENFLURAMINE	20	120	37.7	780 ± 75	<0.001

* From Tables II-V.

TABLE II

Effect of Picrotoxin Pretreatment On
Amphetamine-Induced* Motor Activity.

Dose Response

(Time After Injection = 15 min)

Picrotoxin Dose (mg/kg)	# Animals	Ave. Counts + SEM	n	p-Value	% Inhibit
1.0	17	848 ± 106	36	<0.010	32.4
2.0	18	654 ± 109	36	<0.001	47.8
3.0	18	233 ± 47	36	<0.001	81.4
4.0	18	347 ± 30	36	<0.001	72.3
5.0	18	384 ± 55	36	<0.001	69.4

Time Response

(Picrotoxin Dose = 3 mg/kg)

Time (Min)	# Animals	Ave. Counts + SEM	n	p-Value	% Inhibit
15	18	347 ± 30	36	<0.001	72.3
30	16	350 ± 53	36	<0.001	72.1
60	17	593 ± 85	36	<0.001	52.6
120	18	546 ± 61	36	<0.001	56.4
240	17	1311 ± 148	36	<0.50	0 (4.55%)

n = total number of amphetamine injected controls

* Amphetamine dose (2 mg/kg)

The *doses* which gave the greatest inhibition were picrotoxin (3 mg/kg), pentylenetetrazol (40 mg/kg), fenfluramine (50-60 mg/kg, with considerable tremor, convulsion and some deaths) and amantadine (100 mg/kg). The optimum *times* for administering the amphetamine after pre-treatment with the drugs given in the above doses were: picrotoxin, 15 min (72.3 % inhibition) and 30 min (72.1 %); pentylenetetrazol, 15 min (73.2 %); fenfluramine, 120 min (37.7 %); and amantadine, 120 min (80.5 %). These data are given in Table II-V.

TABLE III

Effect of Pentylenetetrazol Pretreatment
On Amphetamine-Induced* Motor Activity

Dose Response

(Time After Injection = 15 min)

Pentylene-tetrazol Dose (mg/kg)	# Ani-mals	Ave. Counts + SEM	n	p-Value	% Inhibit
20	18	636 ± 82	36	<0.001	49.3
30	18	421 ± 91	36	<0.001	66.4
40	18	336 ± 44	36	<0.001	73.2
50	18	489 ± 67	36	<0.001	61.0
60	17	700 ± 128	36	<0.001	44.2

Time Response

(Pentylenetetrazol Dose = 40 mg/kg)

Time (Min)	# Ani-mals	Ave. Counts + SEM	n	p-Value	% Inhibit
15	18	336 ± 44	36	<0.001	73.2
30	20	423 ± 66	36	<0.001	66.3
60	24	710 ± 60	36	<0.001	43.2
120	23	788 ± 111	36	<0.005	37.0
240	16	1064 ± 111	36	<0.40	15.0

n = total number of amphetamine injected controls.

* Amphetamine dose (2 mg/kg)

Amphetamine Dose - Mortality Response Curve in Aggregated Mice (Large Cages).

The lethal effects of d-amphetamine was determined in aggregated mice over a 24 hour period. Observations were made at intervals but only the 24 hour mortality rate was scored. The results are shown in Table VI. It may be seen from the table that the lethal dose for d-amphetamine is 90 mg/kg and possibly as low as 75 mg/kg. All deaths occurred within one hour after d-amphetamine administration at this dose.

Behavior patterns in the aggregated mice (large cages) were similar to those described by other investigators except for aggression. We confirmed others that marked aggression occurred in smaller cages, but we observed little aggression in the larger cages.

In the smaller cages when mice came into contact with another, they would become very aggressive and fought viciously. This did not occur in the large cage situation. The mice might have extreme tremor, stereotyped grooming and convulsions in one area of the cage but when they touched one another they would either move away or remain in contact with each other, only very occasionally fighting or displaying aggressive movements toward each other.

As shown in Table VI the LD50 of grouped mice in the large cages is somewhere between 20 and 30 mg/kg. In subsequent experiments the LD60 (26 mg/kg) was used. As the dose decreased there was more movement and excitability exhibited by the mice but again there was little aggression. For the total combined deaths at all doses,

TABLE IV

Effect of Fenfluramine Pretreatment On Amphetamine-Induced* Motor Activity

Dose Response

(Time After Injection = 120 min)

Fenfluramine Dose (mg/kg)	# Animals	Ave. Counts + SEM	n	p-Value	% Inhibit
5	18	1475 ± 116	36	<0.20	0 (+17.6)
20	26	780 ± 75	36	<0.001	37.7
30	18	501 ± 50	36	<0.001	60.0
40	18	438 ± 70	36	<0.001	65.1
50	17	360 ± 77	36	<0.001	71.3

Time Response

(Fenfluramine Dose = 20 mg/kg)

Time (Min)	# Animals	Ave. Counts + SEM	n	p-Value	% Inhibit
15					
30	18	874 ± 96	36	<0.010	30.3
60	17	927 ± 79	36	<0.025	26.0
120	26	780 ± 75	36	<0.001	37.7
240	16	1210 ± 144	36	<0.50	3.33

n = total number of amphetamine injected controls

* Amphetamine dose (2 mg/kg)

73 % died within two hours, 14 % within four hours, 6 % within six hours and 7 % between eight to twenty-four hours. The mortality-response curve, Figure I, observed with d-amphetamine in aggregated mice consists of: (a) a gradual increase between 10-40 mg/kg; (b) a slight decrease at 45 mg/kg; (c) a gradual increase between 45-55 mg/kg; (d) a slight plateau between 55-60 mg/kg; and (e) a rise to 96 % (65 mg/kg). It can be seen that the group toxicity effect occurs, but it is much smaller in the larger cages than in the small cages (our previous report and the results of others).

Amphetamine Dose Response Curve in Isolated Mice (Large Cages)

The lethal effects of d-amphetamine in isolated mice was determined as in the aggregated mice. All experiments were done in the large cages. As shown in Table VII the LD100 was 90 mg/kg and possibly as low as 75 mg/kg. Our LD100 was somewhat lower than that reported by other investigators (120 mg/kg). This probably can be attributed to strain differences. Ten mice were injected with 120 mg/kg d-amphetamine and within one hour all had died. It should be noted that the LD100 is the

same as that for aggregated mice when the very large cages are used.

There were some problems in obtaining the LD50 because of the triphasic nature of the d-amphetamine dose response curve. This phenomenon was reported previously by George and Wolf [4], by Gordocki et al.[5], by Askew [6] and by Hôhn and Lasagna [7]. L'Huillier et al [8] made specific mention of a biphasic response for methamphetamine in grouped mice. The dose mortality response curve (Figure I) observed with d-amphetamine in isolated mice consists of: (a) a gradual rise between 10-40 mg/kg; (b) a sharp rise at 45 mg/kg; (c) a drop and a slight plateau between 50-55 mg/kg; (d) an increase at 60 mg/kg; (e) a decrease at 65 mg/kg; and (f) an increase at 70 mg/kg to about 96 % deaths.

Effect of Drug Pretreatment on the Toxicity of d-Amphetamine in Aggregated Mice (Large Cages)

Contrary to our earlier study amantadine pretreatment did not afford as great a protection as we reported before [1]. This probably is due to the larger dose of d-amphetamine used in the present experiment but mostly because the small cages were used in the previous work. In the present study picrotoxin gave the best protection from a LD93 (65 mg/kg) of d-amphetamine ($p = <0.01$). The protection by picrotoxin and other drugs at this dose of amphetamine were: picrotoxin (33 %), amantadine

TABLE V

Effect of Amantadine Pretreatment On Amphetamine-Induced* Motor Activity

Dose Response

(Time After Injection = 120 min)

Amantadine Dose (mg/kg)	# Animals	Ave. Counts + SEM	n	p-Value	% Inhibit
25	18	643 ± 74	36	<0.001	48.7
50	18	540 ± 105	36	<0.001	56.9
75	18	554 ± 81	36	<0.001	55.8
100	18	244 ± 54	36	<0.001	80.5
150	17	417 ± 88	36	<0.001	66.7

Time Response

(Amantadine Dose = 150 mg/kg)

Time (Min)	# Animals	Ave. Counts + SEM	n	p-Value	% Inhibit
15	21	545 ± 71	36	<0.001	56.5
30	17	620 ± 96	36	<0.001	50.6
60	17	771 ± 87	36	<0.005	38.4
120	17	417 ± 88	36	<0.001	66.7
240	18	573 ± 108	36	<0.001	54.3

n = number of amphetamine injected controls.

* Amphetamine dose (2 mg/kg)

TABLE VI

TOXICITY OF d-AMPHETAMINE IN AGGREGATED MICE IN LARGE CAGES*

DOSE-RESPONSE CURVE

AMPHETAMINE DOSE (mg/kg)	PERCENT MORTALITY Experiment No.					
	1	2	3	4	5	AVG. SEM
100	100%	100%	100%	100%	100%	100±0%
90	100	100	100	100	100	100±0
70	100	80	80	100	100	92±5
65	100	100	100	80	100	96±4
60	80	40	80	100	100	80±11
55	60	80	80	80	100	80±6
50	60	60	100	40	80	68±10
45	60	40	80	40	80	60±9
40	80	80	80	80	20	68±12
30	100	80	100	20	20	64±16
20	20	60	20	20	80	40±13
10	40	40	0	0	20	20±9

No. of experiments = 5

No. of mice per experiment = 5 (total mice = 25)

* Cage size = 18 x 11 x 5" (46x28x13 cm.)

TABLE VII

TOXICITY OF d-AMPHETAMINE IN ISOLATED MICE IN LARGE CAGES

DOSE-RESPONSE CURVE

AMPHETAMINE DOSE (mg/kg)	PERCENT MORTALITY Experiment No.					
	1	2	3	4	5	AVG. SEM
100	100%	100%	100%	100%	100%	100±0
90	100	100	100	100	100	100±0
70	100	100	100	100	80	96±4
65	40	60	80	40	100	64±12
60	80	60	80	80	80	76±4
55	80	60	60	60	0	52±14
50	40	60	80	20	40	48±10
45	40	100	100	60	60	72±12
40	20	20	40	20	80	36±12
30	80	20	0	0	60	32±16
20	40	20	20	40	0	24±7.5
10	20	0	20	0	0	8±4.9

No. of experiments = 5

No. of mice per experiment = 5 (Total mice = 25)

FIGURE I
LETHAL EFFECTS OF AMPHETAMINE ON
ISOLATED AND AGGREGATED MICE
(LARGE CAGES)

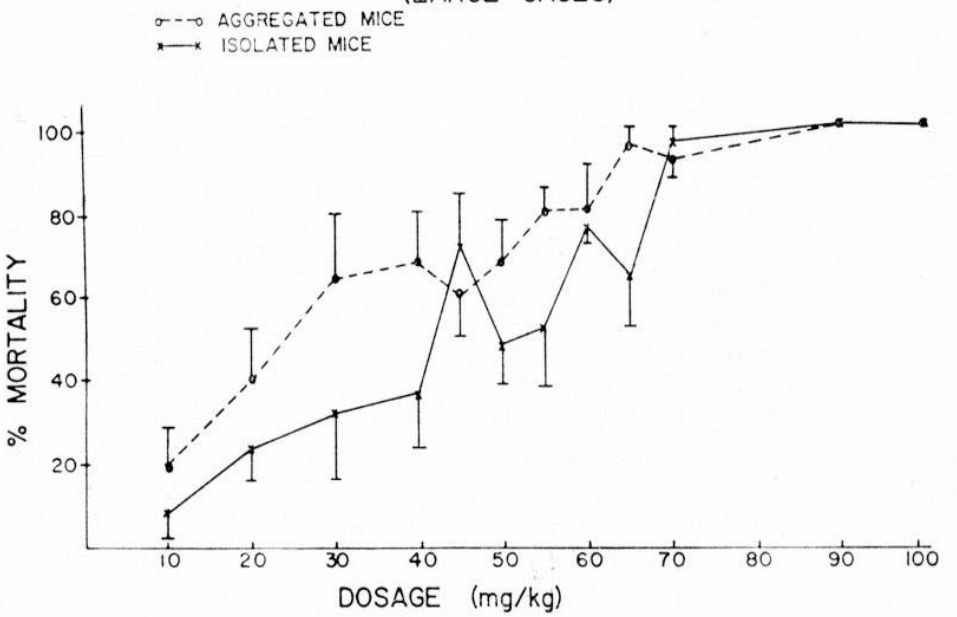


TABLE VIII

LETHAL EFFECTS OF AMPHETAMINE ON MICE

AGGREGATED MICE

LD_{93}

PRETREATMENT	% MORTALITY	n	t-VALUE	p-VALUE
SALINE	93.3±4.2	6	-----	-----
AMANTADINE (100 mg/kg)	76.7±8.0	6	1.8380	<0.100
FENFLURAMINE (20 mg/kg)	96.7±3.3	6	0.6201	>0.500
PICROTOXIN (3.0 mg/kg)	66.7±6.7	6	3.3806	<0.010
PENTYLENETETRAZOL (40 mg/kg)	83.3±8.0	6	1.1028	<0.400

AMPHETAMINE (65 mg/kg)

LD_{60}

PRETREATMENT	% MORTALITY	n	t-VALUE	p-VALUE
SALINE	60.0±7.3	6	-----	-----
AMANTADINE (100 mg/kg)	23.4±6.2	6	3.8413	<0.005
FENFLURAMINE (20 mg/kg)	40.0±8.9	6	1.7320	<0.200
PICROTOXIN (3.0 mg/kg)	46.7±6.7	6	1.3484	<0.400
PENTYLENETETRAZOL (40 mg/kg)	70.0±8.6	6	0.8885	<0.500

AMPHETAMINE (26 mg/kg)

n = number of experiments

No. of animals per experiment per cage = 1 (total = 5)

(23%), pentylenetetrazol (17%) and fenfluramine (3 %).

However, when the LD60 (26 mg/kg) was given to drug pretreated mice, amantadine gave the greatest protection (11 %) and was statistically very significant ($p = < 0.005$) as shown in Table VIII. This dose (26 mg/kg) is close to the dose (30 mg/kg) we used in our earlier report [1]. However, whereas in our earlier report (smaller cages) 30 mg/kg dose was a LD100, 26 mg/kg dose was only LD60 in the present report. The percent protection in the earlier report was 85 % and in this report it is 77 %. As shown in Table VIII picrotoxin and pentylenetetrazol gave no protection (53 %, 30 % respectively). Our observations show that fenfluramine tends to protect against amphetamine (26 mg/kg) by 60 %. This does not confirm the work of Jespersen and Bonaccorsi [9] who reported that fenfluramine (25-45 mg/kg) protected mice grouped in small cages (22 × 17 × 13 cm [9 × 7 × 5"]) against a LD75 in isolated mice. This no doubt can be explained by the very large cages we used in which the LD100 is the same as for isolated mice.

Effect of Drug Pretreatment on the Toxicity of d-Amphetamine in Isolated Mice (Small Cages)

In the LD97 experiment amantadine tended to block the lethal effects of d-amphetamine by 26.7 % in isolated mice. Even though the results were not statistically significant at the chosen level of probability it does indicate that amantadine has some tendency to block the lethal effects (LD97) of d-amphetamine in isolated mice. This can be seen in Table IX ($p = < 0.10$). As shown in Table IX, picrotoxin,

TABLE IX

LETHAL EFFECTS OF AMPHETAMINE ON MICE

ISOLATED MICE

LD_{97}

PRETREATMENT	% MORTALITY	n	t-VALUE	p-VALUE
SALINE	96.7±3.3	6	-----	-----
AMANTADINE (100 mg/kg)	73.3±11.2	6	2.0040	<0.100
FENFLURAMINE (20 mg/kg)	93.3±4.2	6	0.6201	>0.500
PICROTOXIN (3.0 mg/kg)	89.9±4.5	6	1.1951	<0.400
PENTYLENETETRAZOL (40 mg/kg)	93.3±4.2	6	0.6201	>0.500

AMPHETAMINE (70 mg/kg)

LD_{47}

PRETREATMENT	% MORTALITY	n	t-VALUE	p-VALUE
SALINE	46.7±6.7	6	-----	-----
AMANTADINE (100 mg/kg)	63.3±8.0	6	1.5971	<0.200
FENFLURAMINE (20 mg/kg)	63.3±14.9	6	1.0163	<0.400
PICROTOXIN (3.0 mg/kg)	66.7±13.3	6	1.3416	>0.200
PENTYLENETETRAZOL (40 mg/kg)	90.0±6.8	6	4.5393	<0.001

AMPHETAMINE (50 mg/kg)

n = number of experiments

No. of animals per experiment per cage = 1 (total = 5)

fenfluramine and pentylenetetrazol had no significant blocking effect. Our results show that 87.3 % of all deaths occurred within two hours after injection with d-amphetamine (70 mg/kg).

After completion of the LD97 experiment, the LD47 effects were determined and the results were somewhat unexpected. Here, none of the tested drugs gave any protection when compared with control mice (saline injected). The percent protection. as shown in Table IX, by each drug was lower than that of the control mice. However, the results were not significant except for pentylenetetrazol ($p = < 0.001$) which caused more amphetamine-induced deaths than the other drugs. Also, 47 % of all deaths (all drugs) occurred within two hours after d-amphetamine injection and 13 % at twenty-four hours.

Discussion

In 1940 Gunn and Gurd [10] first observed that amphetamine was more lethal in aggregated mice than in isolated mice. In 1946 Chance [11] investigated other factors which influenced the toxicity of amphetamine in mice. It was found that as the floor area per mouse increases, the toxicity decreased for mice confined in a group. Chance also found that if the area per mouse was kept constant (approximately 50 sq. cm.) the presence of other mice markedly increased the toxicity of amphetamine.

However, in 1960 Höhn and Lasagna [7] observed that in aggregated mice increasing the number of mice from 3 to 5 per group did not accentuate the aggregation effect and decreasing the average floor area per mouse had an inconsistent effect. Then, in 1962 Fink and Larson [12] found that an increase in the number of mice from 5 to 10 per cage (degree of aggregation) greatly increased the toxicity of amphetamine. The size of the cages (25 × 19 × 15 cm and 12.5 × 19 × 13 cm) in which the mice were confined (degree of confinement) had little influence on the toxicity of amphetamine in mice grouped 10 per cage. A decrease in cage size augmented amphetamine toxicity in mice grouped 5 per cage. We confirmed this in the present study but in our work if *much* larger cages are used the differences decreased. Swinyard et al [13] concluded that aggregation increases the toxicity of amphetamine because of "fear" or stress caused by the sudden presence of other mice, since forced inmobilized, isolated mice or aggregation decreases the convulsive threshold of pentyleneterazol. Also, Weiss et al [14] found a biphasic dose-mortality curve in isolated mice subjected to foot shock.

George and Wolf [4] concluded that LD50 values are not suitable for quantitation of amphetamine toxicity in isolated or aggregated mice. This was based on the fact that with increasing dose levels, lethality was altered in a triphasic manner; the triphasic nature of the dose lethality curve was attributed to the intrinsic pharmacological activity of amphetamine. We confirm their findings.

We conclude [1] in agreement with Jespersen and Bonaccorsi [9] that the effective drugs probably compete with amphetamine for the same central receptors. The present results strengthen this conclusion and further support our previous findings of the protecction afforded by amantadine. at least in the smaller cages. We intend to extend the amantadine work to include other, more sensitive species and as antagonist to other amphetamines including the hallucinogenic ones and amantadine analogues.

Studies are in progress to include studies on the effects of these pretreatments on the motor excitation in reserpinized mice, on the hyperthermic effect of amphetamine and on the rise in caudate HVA caused by amphetamine which we showed previously [1] to be blocked by amantadine.

SUMMARY

Of many stimulant, analeptic and anorexic drugs tested, amantadine, picrotoxin, pentylenetetrazol and fenfluranine * pretreatment significantly inhibited the motor activity effect of d-amphetamine. With a LD93 in aggregated mice picrotoxin (p=<

0.01) significantly blocked the lethal effect of d-amphetamine. Even though the results were not statistically significant ($p = < 0.10$) at the chosen level of probability, amantadine exhibited some tendency to block the lethal effect of d-amphetamine. Pentylenetetrazol and fenfluramine had no effect. However, amantadine significantly ($p = < 0.005$) blocked the effect of a LD60 of d-amphetamine, while picrotoxin, pentylenetetrazol and fenfluramine were without effect. Only amantadine, though not statistically significant ($p = < 0.10$), had some tendency to block the LD97 effect of d-amphetamine (70 mg/kg) in isolated mice. At the LD74 level none of the drugs tested blocked d-amphetamine effects (LD47 effects) in isolated mice.

* (Note added in proof). Berger et al [15] recently showed the same thing in mice but not in man [16].

SUMARIO

De los muchos estimulantes, drogas analépticas y anoréxicas ensayadas, un pretratamiento con la amantadina, la picrotoxina, el pentilenetetrasol y la fenfluramina *, inhibía en forma significativa el efecto sobre la actividad motora de la d-amfetamina. Con un LD93 en ratones agregado a la picrotoxina ($p = < 0.01$) significativamente se bloqueaba el efecto letal de la d-amfetamina. Aunque los resultados no fueron estadísticamente significativos ($p = < 0.10$) al nivel elegido de probabilidad, la amantadina exhibía alguna tendencia a bloquear el efecto letal de d-amfetamina. El pentilenetetrazol y la fenfluramina no tuvieron efecto. Sin embargo, la amantadina significativamente ($p = < 0.005$) bloqueaba el efecto de un LD60 de d-amfetamina, mientras que la picrotoxina, el pentilenetetrazol y la fenfluremina no tuvieron efecto. Solamente la amantadina, aunque en forma estadísticamente no significativa ($p = < 0.10$) tuvo alguna tendencia a bloquear el efecto LD97 de d-amfetamina (70 mg/kg) en ratones aislados. Al nivel de LD7 ninguna de las drogas ensayadas bloqueó los efectos d-amfetamina (efectos LD47) en ratones aislados.

* (Nota agregada en prueba). Berger y cols. [15] mostraron lo mismo en ratones, pero no en el hombre [16].

RÉSUMÉ

Des nombreux stimulants essayés, drogues analéptiques et anorexiques, un prétraitement avec l'amantadine, la picrotoxine, le pentilenetetrasol et la fenfluramine, inhibe en forme significative l'effect sur l'activité moteur de la d-amphetamine. Avec le LD93 sur les souris, ajouté a la picrotoxine ($p = < 0.01$) l'effet léthal de la d-amphetamine était bloqué d'une maniere significative. Malgré que les résultats ne furent pas statistiquements significatifs ($p = < 0.10$), au point de vue probabilité, l'amantadine montrait une certaine tendance a bloquer l'effet léthal de l'amphetamine. Le pentylenetetrazol et la fenfluramine n'ont pas eu d'effet. Cependant l'amantadine ($p = < 0.005$) a bloqué significativement l'effet d'un LD60 de l'amphetamine, alors que la picrotoxine, le pentylenetetrazol et la fenfluramine n'ont pas eu d'effet. Seulement l'amantadine, quoique en forme estatistiquement non significative ($p = < 0.10$) eu quelque tendance a bloquer l'effet LD97 de l'amphetamine (70 mg/kg) sur des souris isolées. Au niveau de LD74 aucune des drogues essayées n'ont bloqué les effets de l'amphetamine (Effets LD47) sur les souris isolées.

ZUSAMMENFASSUNG

Unter vielen verschiedenen stimulierenden, analeptischen und anorexischen Drogen, die als Inhibitoren der durch d-Amphetamin herrorgerufene Motoraktivität untersucht wurden, war die Vorbehandlung der Mäuse mit Amantadin, Picrotoxin, Pentyl-

enetetrazol und Fenfluramin * effektiv. Mit der LD93 in aggregierten Mäusen blockierte Picrotoxin den lethalen Effekt des d-Amphetamin significant ($p=<0.01$). Trötzdem die Ergebnisse innerhalb der gawählten Dahescheinlichkeitsgrenze nicht Significant waren ($p=<0.10$), zeigte Amantadin immerhin die Tendez den lethalen Effekt des d-Amphetamins zu hemmen Der Effekt war jedoch nicht significant ($p = < 0.10$). Jedoch mit der LD60 blockierte Amantadin den d-Amphetamin Effekt significant ($p=<$ 0.005), während Picrotoxin, Pentylenetetrazol und Fenfluramin nicht wirksam waren. Mit isolierten Mäusen zeigte nur Amantadin eine Tendanz ($p=<0.10$) die LD97 des d-Amphetamins (70 mg/kg) zu blockierten der Effekt. Mit der LD47 (50 mg/kg) war keine der untersuchten Drogen wirksam die d-Amphetamin Effekt in isolierten Mäuse zu blockieren.

* (Wahrend der Prüfung zugesetzt). Von Kurzen haben Berger et al [15] dus Selbe in Mausen aber nicha in Menschen [16] gefunden.

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Locomotor Activity and Speed of Movements in Relation to Monoamine-Acting Drugs

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A person is described as fast if he is capable of starting quickly and is able to increase the speed of his movements at any time. To be able to perform quick movements means to be able to accelerate the movements. In this respect, no difference seems to exist between the teleokinetic, W. R. Hess [22] or goal-directed movements and the locomotor movements, although the latter are probably programmed in the pallidum, Montanelli and Hassler [29], Hassler and Dieckmann [17], whereas the programming of the intended goal-directed movements is located in the primary cortical motor area. The capacity for limb acceleration and the degree of muscle tone behave reciprocally. All athletes know that muscle relaxation facilitates speed, or more exactly, limb acceleration. For example, sprinters and soccermen need to "warm up". The purpose of the massage is to loosen the muscles; cold or cramped muscles can slow down all kinds of movement. The same is true in the pathologic sphere. In diseases with decreased muscle tone, like Chorea and some cerebellar disorders, the active and the hyperkinetic movements are fast.

From observations in human beings, especially athletes, it is evident that one deliberately accelerates both the locomotor and the teleokinetic movements; but it appears that for purposes of acceleration, these movements are interdependent. It is characteristic of Parkinson patients that locomotor as well as intended movements are slowed down, and the ability to accelerate movements and to start quickly is lost, Hassler [12]. In this condition therefore, the central apparatus for acceleration of all kinds of limb movements seems to be the same. If we examine Parkinson's disease, the ability to accelerate active limb movements - locomotor as well as goal - directed ones - is lost with the development of degeneration of the (posterior) nigra neurons, Hassler [11, 12]; suggesting that the posterior sector of nigra is one central apparatus for acceleration of all kinds of movement.

The motor signs of all forms of Parkinson's syndrome including the most characteristic, i. e. movement retardation, are caused by a loss of nerve cells of the substantia nigra, Tretiakoff [32], Luksch and Spatz [28], Foix and Nicolesco [7], especially in the posterior sector, Hassler [11, 13], Greenfield and Bosanquet [8]. The Parkinson rigidity which further reduces the ability to accelerate movements is partly due to reflex contractions of so called plastic tone which is comprised of increased tonic myotatic reflexes. When we examined whether the phasic (monosynaptic) "tendon reflexes" could be reinforced and activated by a sudden, active contraction of the other extremities, it became evident that the Jendrassik manoeuver could not increase the phasic reflexes in extremities affected by Parkinson rigidity (Fig. 1). The contrary is true for the normotonic limbs of the patient, for instance in Hemi-Parkinson, Hassler [14].

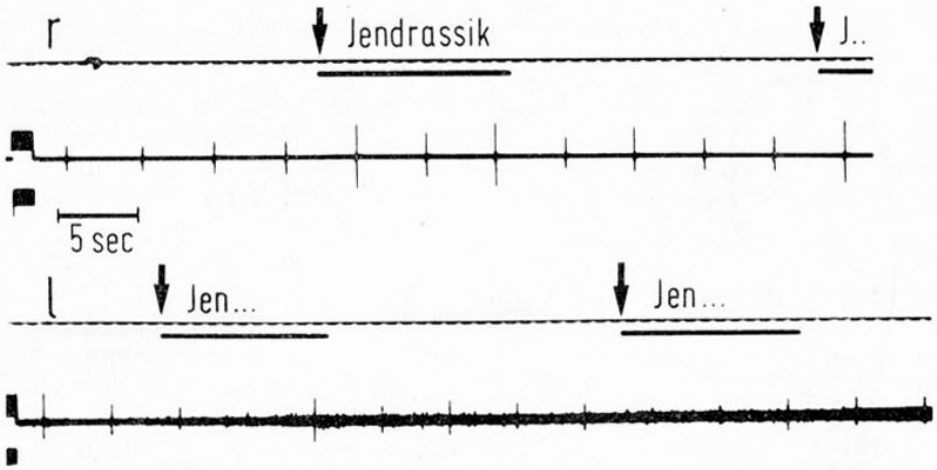


Fig. 1. — *The reflexes recorded from the left and right triceps surae muscles in a case of left-sided Hemi-Parkinsonism. During performance of the Jendrassik manoeuver, the reflex is regularly reinforced on the normal (nonrigid), right side, whereas, on the left (rigid) side, the reflex reinforcement is lacking in spite of the basic activity of the rigid muscle. The top line indicates the Jendrassik manoeuver. (After Krienitz* [27].)

To clear up the peripheral mechanism of the slowed movements of Parkinson— patients the fast and the slow muscle reflexes had to be investigated. In Parkinson patients, the phasic ankle reflexes elicited by an electrical current applied to the tibial nerve in the hollow of the knee (Fig. 2) are enhanced and provide a definite relation between the direct muscle twitch (M) and the electrically induced phasic H-reflex * (H), stimulation-strength-reflex-curve, although the tendon reflexes are not enhanced, Krienitz [27]. If in unilateral Parkinson conditions the rigidity which suppresses the intended increased speed of movements has been relieved by a stereotactic coagulation of the pallidothalamic neurons, the excitability of phasic H-reflexes - bypassing the muscle spindles - in relation to direct muscle twitches (M) are reduced and the ratio between them returns to normal. The excitability of phasic reflexes is increased in the rigid limbs of Parkinson patients although the mechanically elicited reflexes are not enhanced because of an opposing influence on the sensitivity of muscle spindle receptors themselves, after an imbalance between nigra and pyramidal influences on spinal reflex centers and γ-neurons has been established. A much more effective reflex reinforcement, however, is produced by the whole reflex arc consisting of the muscle-spindle receptor, its fusimotor innervation by γ-fibers, as well as by the anulospiral endings and their afferent fibers (1^a), which close the reflex arc on the motoneurons. This monosynaptic phasic reflex is the fastest existing reflex and in the γ-loop, it further possesses a regulating device for acceleration, whereby the monosynaptic reflex can be adjusted for different degrees of acceleration by sensitization of the anulospiral receptor. After eliminating the inhibiting influence of the pyramidal tract on the γ-efferents by stereotactic coagulations of the V. o. a and V. o. p thalamic nuclei, Hassler [16], the monophasic acceleration reflex-loop is no longer antagonized by the reflex loop of the tonic stretch reflexes and fixation reflexes, Altenburger [1], in the antagonistic muscles. The monosynaptic reflexes for rapid muscle twitches again predominate and the active movements of the Parkinson patient are accelerated postoperatively.

γ-caliber fusimotor fibers can be driven by a circumscribed stimulation of the posterior part of the substantia nigra compacta (Fig. 3), whereas an inhibition of spindle

* H-reflex is the electrically elicited monosynaptic reflex bypassing the muscle spindle receptor, so named for the physiologist who first described it, Paul Hoffmann.

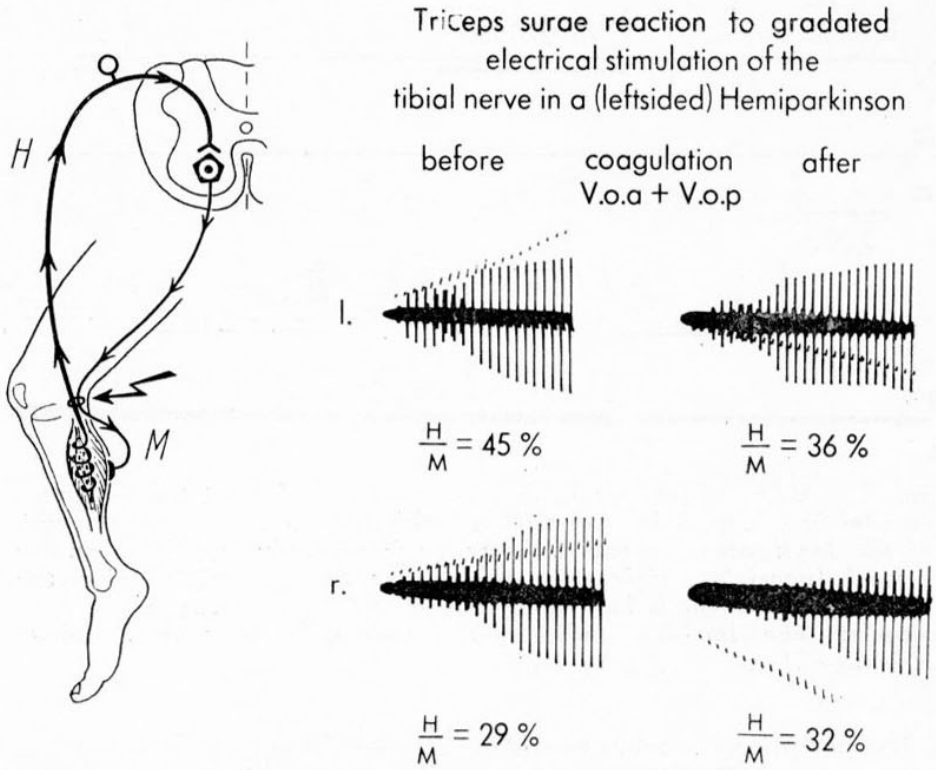


Fig. 2. — *Responses to gradated electrical stimulation of the tibial nerve — bypassing the muscle receptors — (arrow, left inset) in the hollow of the knee of a Hemi-Parkinson patient, recorded from the left and right triceps surae muscles. They first respond to the weakest stimuli with only a direct twitch, conducted through the motor fibers to the muscle. The twitching responses increase gradually as the electrical stimulus is increased. The fourth electrical stimulus to the left side elicited a small reflex response which surpassed the reflex arc. This H-reflex increases in size with the increasing strength of the stimuli, producing nothing but H-reflexes after the eighth stimulus. The relationship of H-reflexes (H) to muscle twitches (M) is 45 % in the rigid leg and 29 % in the normal leg. Following the relief of rigidity in the left extremity, a result of coagulation in the right thalamic nuclei V.o.a and V.o.p, the ratio H-M in the formerly rigid extremity of the Parkinson patient is reduced. Therefore, it may be concluded that synaptic contacts for phasic stretch reflexes are hyperexcitable in the rigid condition.* (*After Krienitz* [27].)

discharges occurs during low frequency stimulation of the anterior third of the nigra, Wagner [33], Hassler [15]. Stimulation of posterior nigra (90/sec) reinforces the responses of phasic reflexes elicited by a ramp like stretch (Fig. 4). Before the effect from the anterior nigra can be explained, it is necessary to point out that the transmitter produced in the nigra neurons is Dopamine (DA). After applying labelled noradrenalin or DA to the brain ventricles, autoradiography reveals an accumulation of labelled material in the cell bodies and dendrites of nigra cells (Fig.5[a]), Parizek *et al.* If DA is systemically administered, the simultaneously recorder single γ-fiber in filaments of the anterior roots produces an increased discharge frequency, Wagner *et al.* [34] (Fig. 5 b). If DA were the primary transmitter for the discharge of rapid neurons it could be postulated that its depletion by reserpine would suppress the rapid γ-activity. This appears to be true (Fig. 5b) and simultaneously, an increasing α-activity replaces the γ-discharges (Fig. 6). Subsequent administration of DA to one side successively reduced the γ-activity until α was suppressed, and at the same time on the other side, it slowly elicited an increase in fast γ-activity. There is a reciprocity and

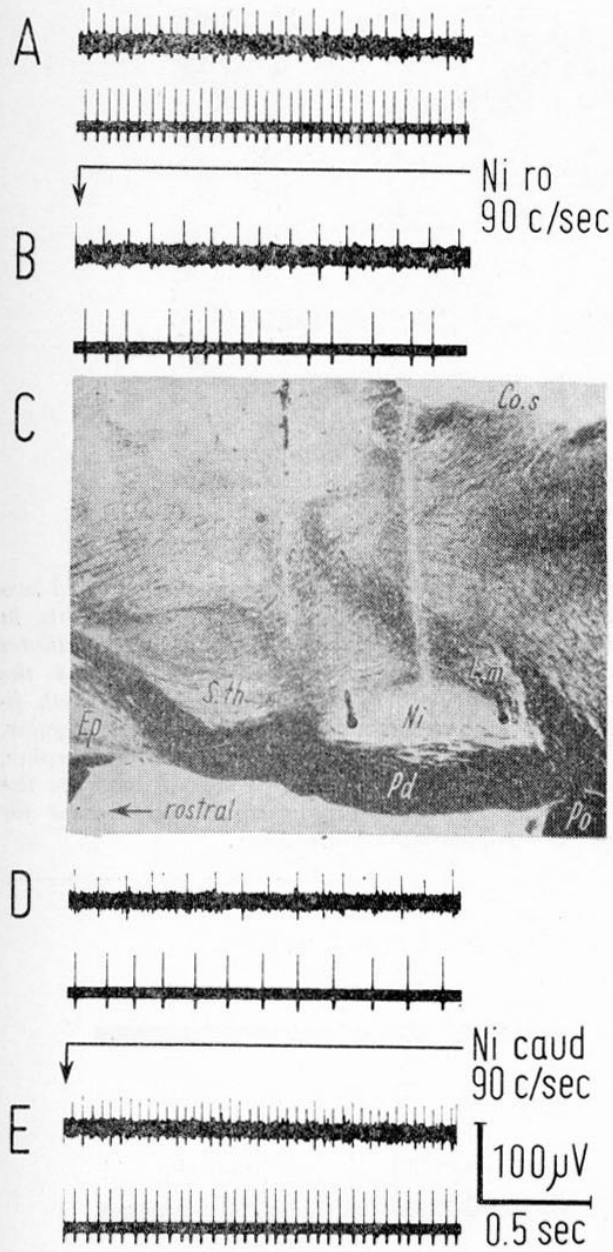


Fig. 3. — *Spike activity of sngle γ-fibers and a single Iª afferent fiber of the monosynaptic reflex arc recorded in cat from filaments of the anterior (upper line) posterior roots (lower line) respectifely, before (A, D) and during bipolar stimulation of the rostral (B) and caudal (E) parts of the substantia nigra, respectipely. The tracks of the rostral and caudal stimulation electrodes can be seen in the sagittal section of the nigra (C). The stimulation of the rostral nigra (above) results in a reduced γ-activity and an irregular and diminished Iª activity (B). The stmulation of the caudal nigra (below) results in a strongly increased frequency of γ-and Iª-discharges (E).* (*Wagner* [33])

antagonism between DA and reserpine on extensor - as well as on flexor units which is always reversible (Fig. 6). Because DA is the known transmitter of substantia nigra neurons, DA-depletion by reserpine, with the simultaneous effect of γ-suppression and α-excitation, simulates a functional loss of the substantia nigra . If the nigra is separated from the lower brainstem (Fig. 7), the same suppression of the γ- and excitation of the α-activity occurs. In the same way, the loss of nigra nerve cells, mainly in the posterior part, reduces the γ-activity and is evidenced by slow movements, inhibition in starting and inability to reinforce reflexes by the Jendrassik maneuver.

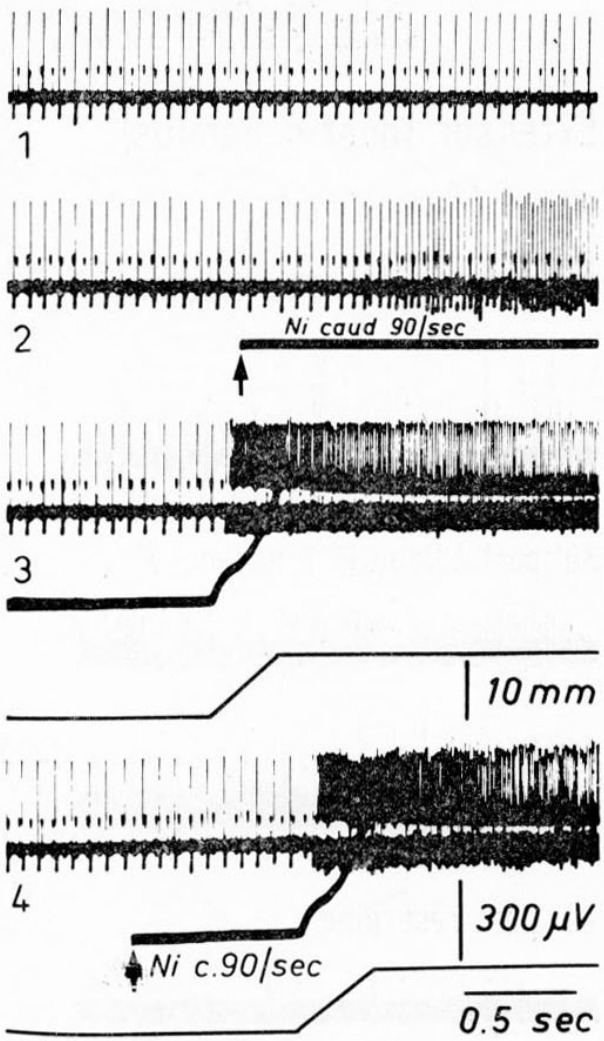


Fig. 4. — *Recordings of one Iª and one smaller unit from a filament of the posterior root L-7 in cat.* 1: *Control;* 2: *In response to* 90/*sec stimulation of the caudal substantia nigra, the activity of both units is increased after a short delay* (0.5 *sec*) ; 3: *The ramp-like stretch of the gastrocnemius muscle induces a strong activity of the Iª fibers with an initial burst;* 4: *The combination of the ramp-like muscle stretch with stimulation of the caudal substantia nigra elicits an even more enhanced response from the Iª fiber* (*Wagner and Kalmring* [35].)

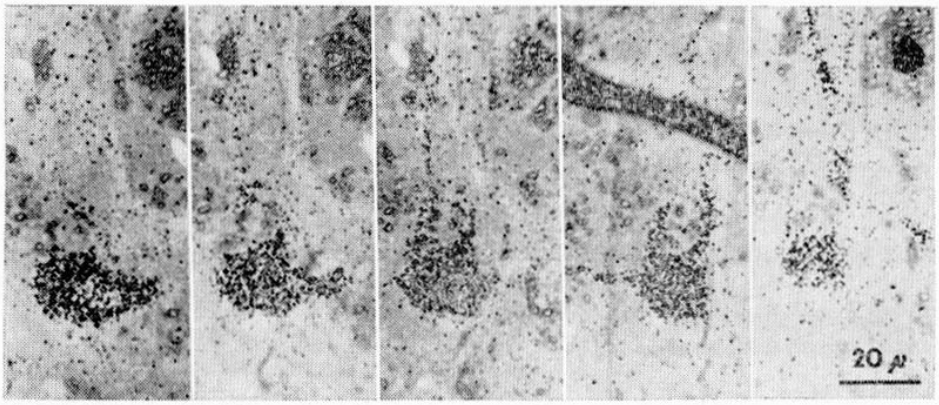


Fig. 5a. — *Serial section (1 µ) of autoradiographic preparation of a nigra nerve cell after interventricular application of ^{3}H-noradrenaline (NA). The five pictures show the same nigra cell with a high accumulation of labelled NA in a sequence. (After Parizek et al.)*

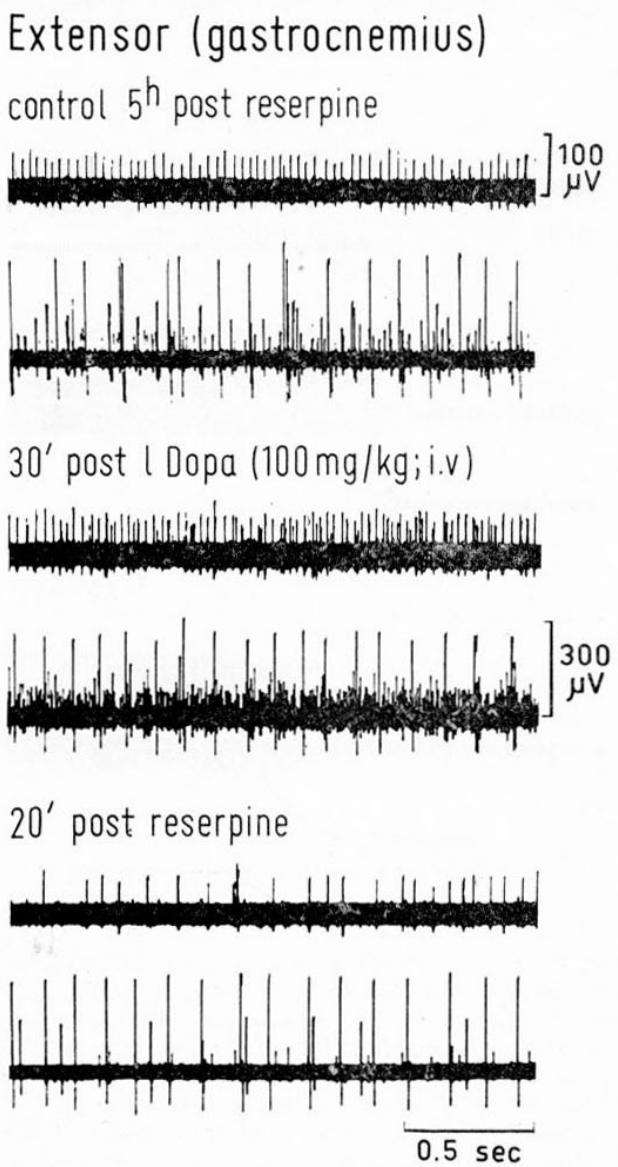


Fig. 5b. — *Recordings of two filaments separated from the anterior root of the gastrocnemius muscle of a cat which had been premedicated with 1mg/kg reserpine five hours earlier, showing two γ-units in the first filament (upper line) and two different α-units and probably three γ-units in the other filament (lower line). Thirty minutes after i. v. application of 100 mg/kg l-DOPA, the activities of γ-fibers increased greatly in both filaments and the α-activity became more regular. After another systemic application of reserpine, the γ-activity was strongly reduced whereas the α-activity remained almost unchanged except for slight irregularities (last line).*

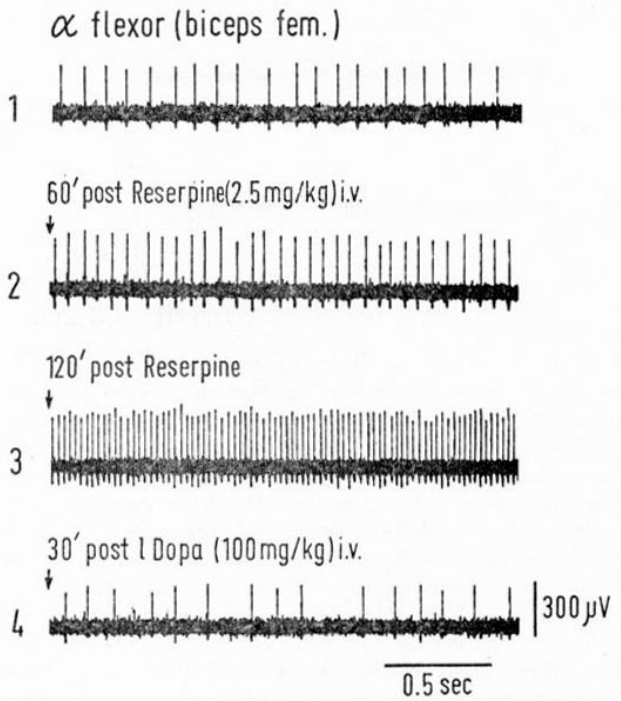


Fig. 6. — *Recorling (1) of an α-flexor unit of biceps femoris muscle 60 min after (2) i. v. application of 2.5 mg/kg reserpine showing activation which is further strongly increased in another 60 min (line 3). Thirty minutes after i. v. application of 100 mg/kg l-DOPA, the α-activity is strongly reduced and the γ-activity begins to emerge over the base line noise.*

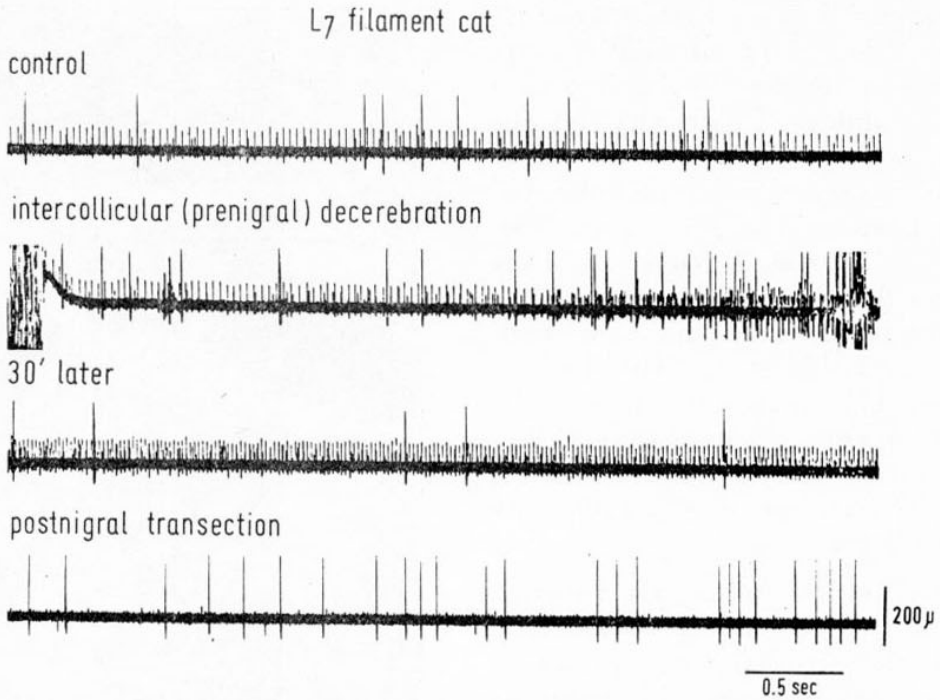


Fig. 7. — *Recordings from a thin L-7 filament (cat) shows one α-unit and at least two γ-units, the large one very regular, the smaller, irregular (1). (2) During the intercollicular decerebration which separates the nigra from all afferents descending from the forebrain, all units are active and intermingled with artifacts. Thirty minutes later the regular γ-unit fires with a higher frequency but are even more regular than before, interrupted only occasionally by an α-spike. Immediately after the postnigral transection, the γ-activity ceases and the α-activity reappears. The third line depicts γ-rigidity and the fourth, α-rgidity. (after Hassler* [16].)

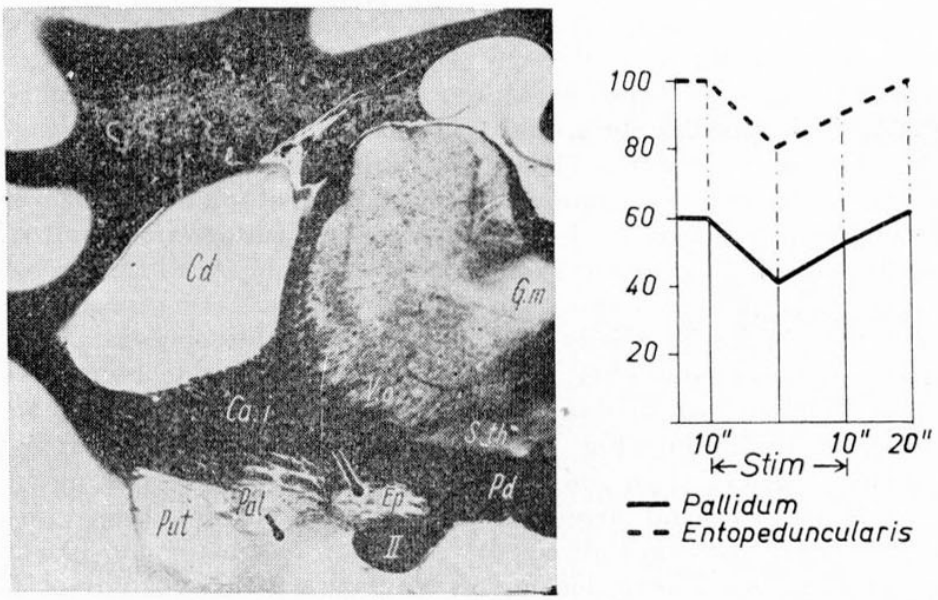


Fig. 8. — *In the sagittal section of cat basal ganglia, one electrode track reaches the entopenduncular nucleus (Ep); the other extends to the outer segment of the pallidum (Pa). The γ-unit activity drops during stimulation of each of segments of the pallidum.*

A complete parallelism exists between the effects of posterior nigra stimulation and DA application in respect to the increased γ-activity and suppressed α-activity, on one side, and the effect of functional or anatomical loss of posterior nigra neurons and reserpine application in respect to suppressed γ-activity and increased α-activity on the other side. In the clinic, too, reserpine-like drugs are able to produce Parkinson signs, mainly akinesia and rigidity. On the contrary, DA is able to produce therapeutic effects on Parkinson signs, mainly relieving rapid locomotor and other movements, and abolishing akinesia and rigidity, see Knutson and Magnusson [26].

The substantia nigra does not function in isolation; it is normally influenced and controlled by the striatum. Strionigral fibers to the pars reticulata and pars compacta seem to be GABA-ergic because the GABA concentration in the nigra is the highest in the brain and drops by nearly 2/3 after interruption of the strio-nigral fibers, Kim *et al.* [24]. After the same interruption the pleomorphic type of axodendritic synapse in the substantia nigra, Hajdu, Hassler and Bak [10] degenerates (Fig. 9). The striatal action on nigra cells is inhibitory, transmitted by GABA, as shown by Yoshida and Precht [36]. By electrical stimulation of these GABA-ergic inhibitory strio-nigral fibers in the front of the substantia nigra or in its rostral third or even during their passage through the pallidum and endopeduncular nucleus (Fig. 8), it is possible to inhibit and decrease the discharge frequency of fast γ-units in single anterior root filaments (Fig. 8). Electrical stimulation of the putamen in unanaesthetized cat, according to Hess-technique, using higher stimulation frequencies (up to 50/sec), elicits the arrest of spontaneous movements (Fig. 10a) and - using less frequent stimulation (up to 8/sec) - a delayed inhibition (Fig. 10b) or "motor ritardando", Dieckmann and Hassler [5]. Both the retardation and arrest responses concern spontaneous goal-directed movements as well as spontaneous locomotor ones. Evidently the putamen stimulations result in this slowing of movements by inhibiting the posterior part of the nigra.



Fig. 9. — *The most frequently founl type of synapse (Type I, pleomorphic) in the nigra (normal in Control "a") undergoes degeneration in "b, c" and "d" after one or two days, whereas the Type III (small, round vesicles) in "b" and Type IV (large, round vesicles) synapses in "a" are preserved. (After Hajdu et al.* [10] *and Hassler* [18].)

There is also pharmacological evidence from the putamen pertaining to the antagonistic action of DA and ACh on the speed of movements and muscle tone. The drug harmaline causes a slowing of limb movements to the point of akinesia with rigidity (Fig. 11e). Harmaline, however, acts by increasing the concentration of serotonin (5HT) and acetylcholine (ACh) with the same time course (Fig. 12) in the striatum (Kim *et al.* [25]. The criterion used in these rat studies for determining biochemical effects have always been muscle tone and speed of locomotor movements. Slow movements, whether goal-directed or locomotor, and increased muscle tone are maintained even when the augmentation of 5HT after harmaline is suppressed by an additional

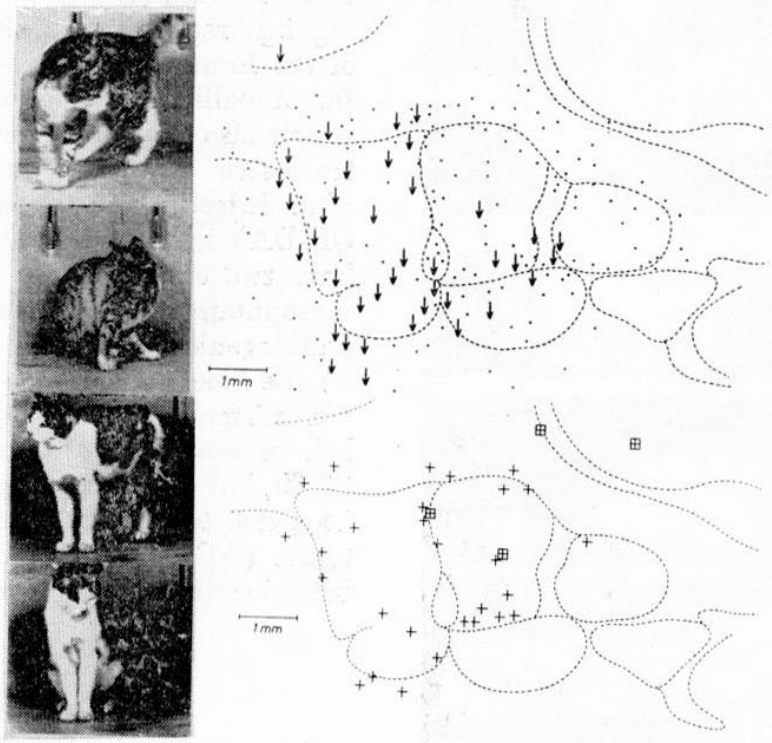


Fig. 10a. — *In the sagittal diagram of cat basal ganglia, 5.5 mm lateral to the midline, the stimulation foci marked with vertical arrows show the places from which a reaction arresting spontaneous movements (circling to the left side - upper left inset) has been elicited. Foci without arrows (points), however, failed to show any stimulus response.* Fig. 10b. — *In the same sagittal diagram all stimulated foci eliciting a delayed inhibition or motor ritardando (left inset) are indicated by +. (After Dieckmann and Hassler* [18].)

application of Chlormetamphetamine, which does not alter the ACh concentration in the putamen (Fig. 12). This harmaline action is antagonized by 1-Dopa when in combination with iproniazid, a MAO-inhibitor. An increase of striatal DA facilitates limb acceleration (Fig. 11a, b) and reduces flexor muscle tone, while an increase in striatal ACh or 5HT increases muscle tone and slows down movements. These experiments have led us to conclude that the speed of locomotor movements as well as the speed of goal-directed movements depends on the ratio of

$$\frac{\text{ACh; 5HT}}{\text{DA}}$$

The administration of 1-Dopa and a MAO-inhibitor, or of an amphetamine which prolongs the action of 1-Dopa, or of cocain or imipramine, which block the re-uptake of catecholamine transmitters, produce as a common action, an increased amount of DA acting on the postsynaptic membrane of posterior nigra neurons. The behavioral effect is an increase in the speed of teleokinetic and locomotor movements. For the teleokinetic movements, it seems probable that the acceleration effect of DA is mediated by dopaminergic neurons which descend to the spinal cord and exert two different actions (Fig. 16): 1) a facilitation of γ-neurons; 2) an inhibition of the interneurons of the tonic stretch reflexes, the elements of muscle tone which through increase produce ridigity, Hassler [12, 15, 16].

This acceleration effect on locomotor movements is probably mediated by the inhibitory action of nigra neurons on locomotor movements. The ascending nigra neurons, acting through the DA transmitter, would inhibit the neurons of the putamen which normally inhibit the pallidar neurons involved in locomotor movements to the contralateral side (Fig. 13). The nigro-striatal disinhibition of efferent pallidar systems could thus facilitate the contralateral turning movements, thereby increasing the speed of locomotor movements to the contralateral

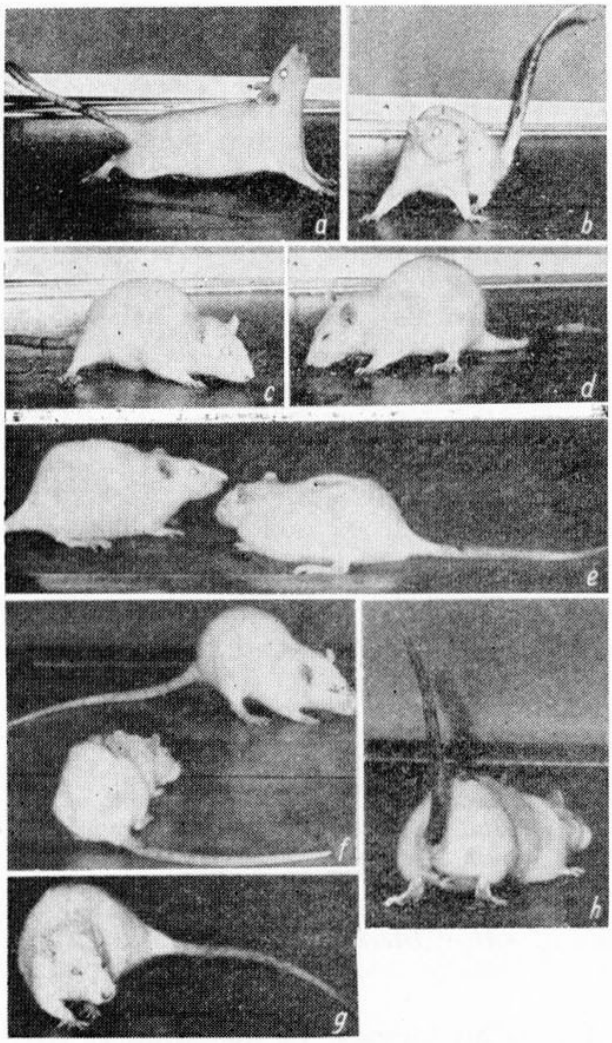


Fig. 11. — *Comparison of motor behavior of rats under the influence of drugs effecting catecholamine and acetylcholine metabolism.*
a, b: *Extended posture of legs, head and tail after application of* 100 *mg* l-*DOPA and Iproniazid; running movements are interrupted.*
c, d: *Akinesia, humpback and rigidity, with legs a bit extended after administration of reserpine* (1 *mg/kg and* 2.5 *mg/kg, respectively), following the larger dose combined with blepharospasm.*
e: *Akinesia, humpback and the feet flat on the ground with legs flexed; results of harmaline* (10 *mg/kg*). *After additional application of atropine* (*right rat*), *less rigidity and reduced humpback can be seen.*
f: *The right rat, treated with* 100 *mg/kg amantadine alone, initially shows humpback and akinesia with legs extenled to the front. The left rat additionally treated with atropine* (20 *mg/kg*) *has almost lost the humpback and its legs have become flexed.*
g: *Sixty minutes after application of amantadine* (100 *mg/kg*) *in combination with atropine, the rat has begun to circle toward the left and has its digits in an asynergic position*
h: *Forty minutes after treatment with amantadine* (100 *mg/kg*) and *atropine* (20 *mg/kg*), *the rat runs awkwardly on raised hindlegs with an erect tail.* (*After Hassler* [16], *Kim et al.* [25] *and Bak et al.* [3].)

side. Additionally applicated atropine (20 mg/kg) reduced the rigidity and the height of the humpback; this suggests that the efferent pallidar systems are cholinergic, for which also other evidence exists. The contraversive locomotor movements observed after injection of 6-hydroxy-dopamine (6-OH-DA) in cat substantia nigra, Poirier [30] have two explanations 1) the blockade of nigroputaminal dopaminergic influence on pallidogenic locomotor movements and 2) the biochemical one. When 6-OH-DA is administered to the brain ventricles, the DA content of the striatum is reduced by 25 %, but ACh is increased by 100 % (Fig. 14), due to an inhibition of acetylcholinesterase (AChE) activity (Kim [23]. In motor behavior this strong diminution of

$$\frac{\text{DA}}{\text{ACh; 5HT}}$$

ratio again corresponds to the slowed movements and rigidity combined with an extreme sympathetic tonus (piloerection and exophthalmus).

A very peculiar observation was made during the systemic application of amantadine in dosages of 100 mg/kg in rat, Bat *et al.* [3]. During the first 30-40 min the animals' movements were slow, akinetic and rigid (Fig. 11 f), corresponding to the high level of ACh found in the striatum (Fig. 15). Thereafter, however, the rat administered with amantadine began to circle towards the injected side, i. e., contralaterally (Fig. 11g, h). This delayed effect of amantadine may be an excitation of the efferent mechanism of the pallidum, the functional activity of which is locomotor circling to the contralateral side (Fig. 13), Montanelli and Hassler [29]. The latter may be explained by the increased concentration of GABA in nigra (Fig. 15) —and later in the striatum— because the enhanced inhibition of nigra may disinhibit the pallidar locomotor mechanism. The transmitter of the efferent pallidar system acting in the anterior part of the VL nucleus of the thalamus (V. o. a), in the subthalamic nucleus, and in the midbrain tegmentum, is very probably ACh (Fig. 16), suggested also by the fact that additional application of atropine to amantadine, reduces the rigidity of rats

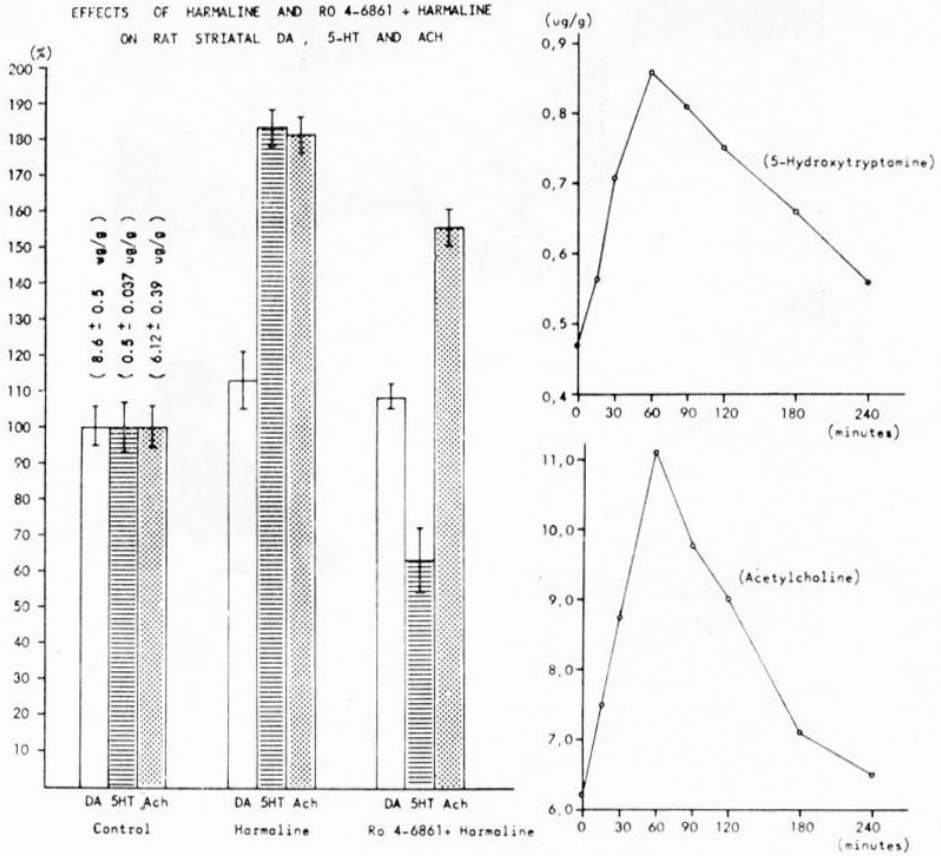


Fig. 12. — *Effects of harmaline* (10 *mg/kg*) *and harmaline combined with chlormethamphetamin* (*Ro* 4-68 61) on the content of dopamine (*DA*), *serotonin* (*5HT*) *and acetylcholine* (*ACh*) *in the rat striatum. The curves on the right side show the time course of the increase in 5HT and ACh in the striatum after application of harmaline.* (*After Kim et al.* [25].)

and the height of the humpback initially (Fig. 11 f).

GABA acts as an inhibitory transmitter on nigra neurons, decreasing muscle tone. GABA, however, is diminished in the substantia nigra after interruption of strio-nigral conections to 1/3 its former level, while the GABA concentration in the striatum remains unchanged (Table 1).

Effect of premesencephalic hemitransection on GABA and Dopamine content in substantia nigra, pallidum and striatum in Baboon (1o - 14 days p.op.)

	GABA				Dopamine			
	unop.side	op.side	%	exp.No	unop.side	op.side	%	exp.No
Sub.nigra	8.49 ± o.99	2.89 ± o.97	-66	4	1.76 ± o.32	1.45 ± o.1o	-17,5	4
N.caudatus	3.4o ± o.54	4.o8 ± o.39	+2o	4	8.o5 ± 1.4o	2.76 ± o.51	-66	4
Putamen	3.99 ± o.8o	3.83 ± o.9o	- 4	4	9.52 ± 1.5o	o.93 ± o.17	-9o	4
Pallidum	8.48 ± o.62	7.96 ± o.81	- 6	4	1.4o ± o.o9	1.13 ± o.2o	-2o	4



Fig. 13. — *The stimulation of the electrode tip Bro in the entopeduncular nucleus (Ep) resulted in a narrow circling to the left, causing the cat's head to extend over its back (modified Hess technique). The coagulation of the efferent fibers of Ep by Bru-focus gave rise to a Marchi-degeneration through H_2 and field H to H_1 bunlle terminating in the V.o.a nucleus of the thalamus. (According to Montanelli und Hassler*[29].)

During stereotactic operations on human patients we have observed another mechanism for acceleration of teleokinetic or purposive movements. When the terminal nucleus of dentatothalamic fibers: V. o. p *, in the thalamus projecting directly to the primary motor area 4γ is stimulated 25 or 50 times per second, it resulted in a speeding up of active arm movements (Fig. 17) or serial speaking, e. g., counting backwards (Fig. 17) in more than a thousand unanesthetized patients. This effect, Hassler and Riechert [20], Guiot *et al.* [9], Hassler [15], can be reproduced regularly, but only with stimuli higher than 20/sec. This increase in the rate of movement is attributed to a specific afferent facilitation at the origin of the thickest fibers of the pyramidal tract. So far, we have not been able to identify the transmitter substances of the V. o. p neurons.

It has long been known that the hormone of the thyroid gland is capable of increasing the speed of movements and even thought. It is argued that due to the hypersensitivity of the DA receptors, this special action of the thyroid hormone is mediated by catecholamines. With respect to amphetamines, it is almost certain that the prolonged action of catecholamines, mainly DA, causes their ability to increase the speed of movements.

* V. o. p is identical with the *posterior basal part* of ventrolateral nucleus (VL) of the thalamus. The coagulation of V. o. p (Fig. 18) produces relief of motor Parkinson signs, mainly of tremor at rest.

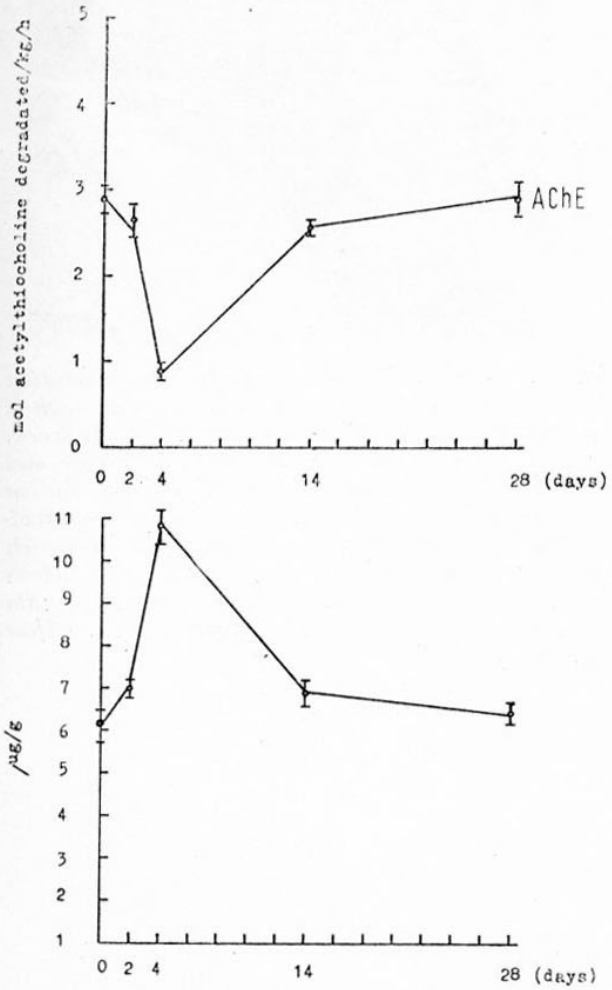


Fig. 14. — *The lower curve shows the time course of the mean values of the ACh level in the rat striatum after interventricular injection of 6-hydroxydopamine (6-OH-DA, 200 µg/dose). The upper curve of the time course of actylcholinesterase (AChE) activity is reciprocal to the ACh curve. (After Kim* [23].)

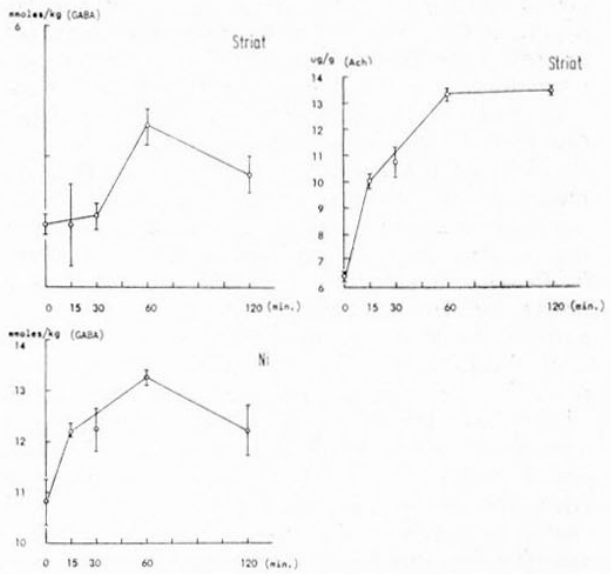


Fig. 15. — *Administration of 100 mg/kg i. p. amantadine produces an increased GABA content in substantia nigra as per the time course (lower lelft), whereas in striatum GABA increases much less. The increased ACh level in the striatum after the same dose of amantadine shows a completely different time course (upper right). (After Bak et al.* [3].)

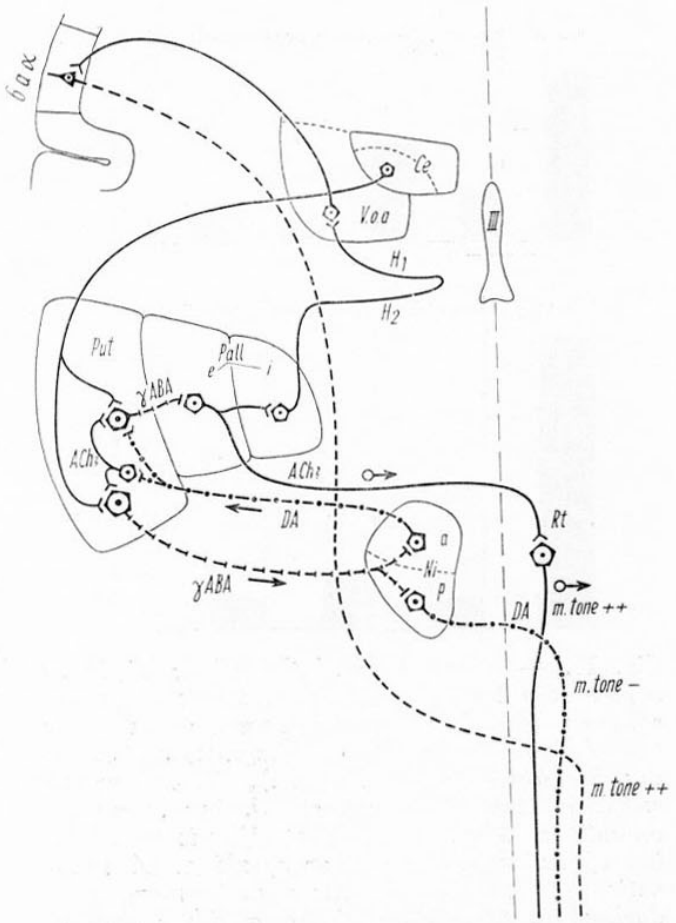


Fig. 16. — *A simplified schematic drawing of the strio-nigral connections and efferent pathways. The GABA-ergic strionigral neurons have an inhibitory action on the nerve cells of the anterior*

(Ni.a) and posterior (Ni.p) parts of substantia nigra. Whereas the posterior nigra neurons exert a probably dopaminergic inhibition on the interneurons of the tonic stretch reflexes in the spinal cord and reduce thereby the muscle tone directly, the ascending nigro-striatal neurons exert a predominately inhibitory action by dopamine transmission: 1) on the probably cholinergic small intrinsic neurons of the putamen and thereby to the GABA-ergic strio-nigral neurons, closing an inhibitory reverberating circuit; 2) directly and indirectly, to the also GABA-ergic striopallidar neurons so that the two efferent pallidar systems are disinhibited. Another action is exerted by the afferents from the centrum medianum nucleus of the thalamus to both kinds of efferent putamen neurons. This is applicable 1. to the descending pathway through the contralateral reticular formation for locomotor movements to the conralateral - and after crossing - to the ipsilateral side and for increased muscle tone, and 2. to the ascending pathway through the pallidum internum, H-fields and the thalamic nucleus V.o.a to the area 6aα of the cerebral cortex, which acts through cortico-spinal fibers on the interneurons of the tonic stretch reflexes in terms of increasing muscle tone.

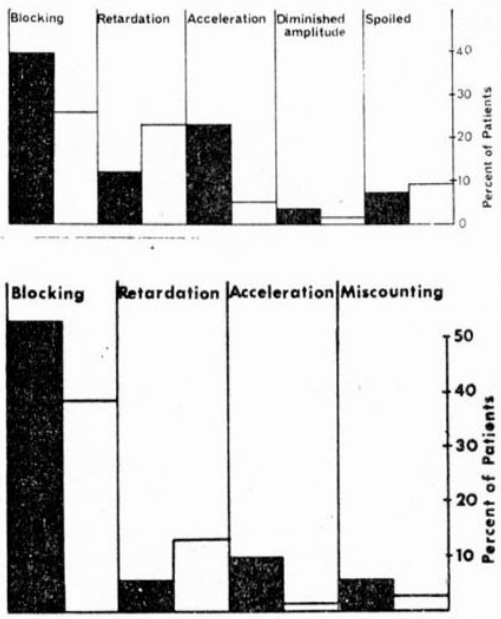


Fig. 17. — *Comparison of the effects of 10 to 50/sec stimulation of Pallidum internum (white columns) and V.o.a (black columns) on active to-and-fro movements (upper diagram) and counting backwarls (lower diagram), in 400 unanaesthetized Parkinson patients during stereotatic operations. The most frequent effect is the blocking of active movements or speaking. A retardation of active movements appears more often during the stimulation of the pallidum than of the V.o.a and to the contrary, an acceleration of active movements occurs more often during stimulation of the V·o.a (After Hassler* [15].)

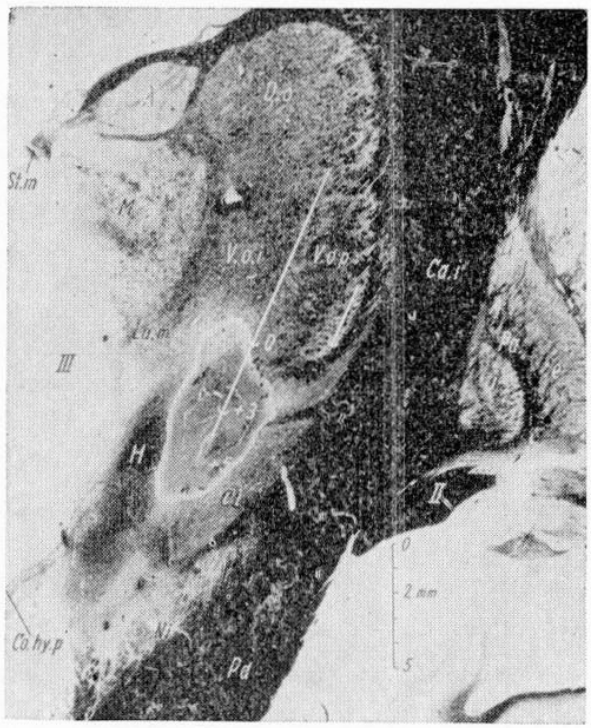


Fig. 18. — *High frequency produced coagulation focus in the base of the V.o.p nucleus with a line indicating the direction of the electrode track. By this coagulation the contralateral tremor and regidity of a postencephalitic Parkinson patient had almost been relieved. The focus also involves the Zona incerta and the H_2- bundle which form the dorsal border of the subthalamic nucleus (CL), because two coagulations, 3 and 5 mm below the target (0), hafe been performed. (After Hassler et al.* [18].)

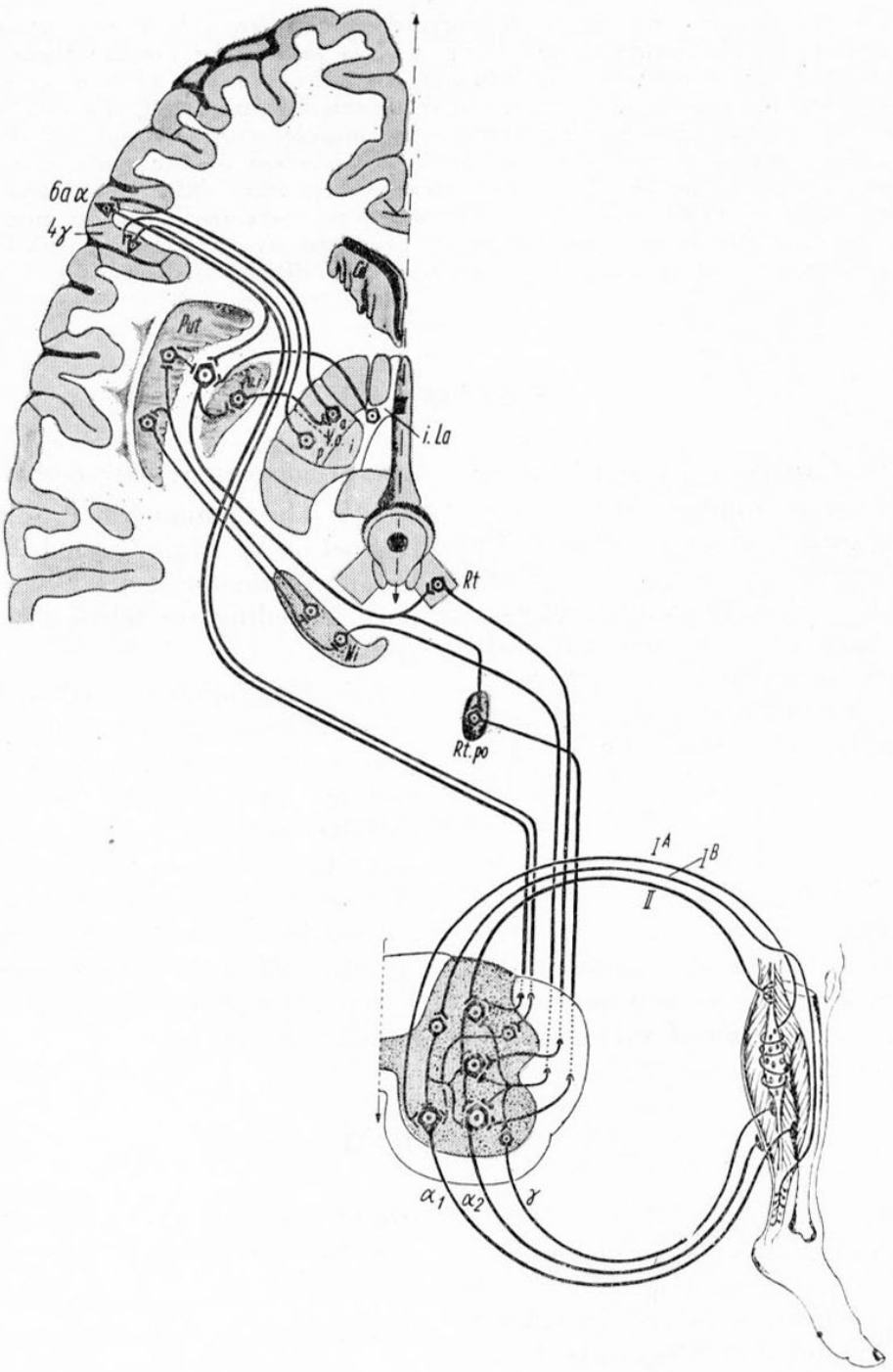


Fig. 19. — *Scheme of the peripheral and central conduction mechanisms of muscle tone and of the aceleration of movements. The tonic stretch reflexes, elicited by the seconlary endings of the muscle spindle, are conducted through the II afferents to the spinal cord and transmitted through a special set of interneurons to excite the tonic motoneurons* (α_2). *This special set of interneurons is under the inhibitory influence of descending nigra impulses. Their disinhibition by nigra lesions causes increased tonic stretch reflexes in slow-moving Parkinson cases. The reflex arc of the tonic stretch reflexes is antagonistic to the arc of the (monosynaptic) phasic reflex originating from the annulo-spiral endings on the muscle spindles which directly contact the phasic motoneurons* (a_1) *via* I^a *afferents. They are facilitated by the intrafusal innervation elicited from the posterior part of the substantia nigra by dopaminergic transmission. By facilitation of the phasic reflexes, all kinds of movements can be accelerated. The slowness of all types of movement after nigra lesions is also due to the loss of ascending inhibitory (dopaminergic) nigro-striatal influence on pallidar efferent neurons to the reticular substance in midbrain (Rt) and pons (Rt.po) both of which facilitate the arc of the tonic stretch reflex. The other efferent pallidar system runs through the internal pallidar*

segment, Forel's fields H_2, H and H_1 to the thalamic nucleus V.o.a and projects to the premotor area 6aα. The action of the latter area is facilitatory for the tonic stretch reflex arc, and thereby increases the muscle tone and the slowness of movements. By coagulating the pallidar neurons to the V.o.a or of this nucleus itself, the cortical facilitation of the tonic stretch reflexes is suppressed, the muscle tone reduced and the speed of movements increased. A non-reflectory α-rigidity independent of the tonic stretch reflexes is produced by directly descending impulses from the pontine reticular substance (Rt. po) to the tonic α-motoneurons. The complete reflectory γ-rigidity, such as that found in the rostral penigral decerebrate preparation, is produced by a release of substantia nigra from all of the descending inhibitory impulses. (Modified after Hassler [16].)

SUMMARY

The normal substantia nigra and its transmitter dopamine (DA) appear to be responsible for the normal ability to increase the speed of movements in human beings and other mammals. When dopamine action is blocked by harmaline or reserpine, the movements are slowed and muscle tone, in its reciprocal relation, increased. Biochemically, the ability to increase the speed of movements seems to depend on the ratio of

$$\frac{\text{DA}}{\text{ACh; 5HT}}$$

in the striatum.

The ability to accelerate applies to intentional (teleokinetic) as well as locomotor movements. Mediation of this increased rate of movement may occur in two ways:

1) The demonstrated, direct, descending action of nigra-formed DA on the dynamic fusimotor neurons in the anterior horn, speeding up teleokinetic movements; and

2) The demonstrated indirect, dopamine inhibition in striatum which keeps it from exerting inhibitory (GABA-ergic) action on the, probably cholinergic, efferent pallidar neurons which affect locomotor contralateral turning movements. The rate of intentional movements can also be increased by 25 and 50/sec stimulation of the specific afferents which originate in the V. o p nucleus and extend to the primary motor area 4γ.

SUMARIO

La substancia nigra normal y su transmisor la dopamina (DA) aparenta ser responsable por el incremento normal en velocidad de movimiento en seres humanos y mamíferos. Cuando está bloqueada la acción de la dopamina por harmalina o reserpina, la velocidad de movimiento disminuye y el tono muscular, en su relación recíproca, aumenta. En el aspecto bioquímico la posibilidad de aumentar la velocidad de movimientos depende de la relación

$$\frac{\text{DA}}{\text{ACh; 6HT}}$$

en el estriado. La aceleración de movimientos concierne no solamente a los movimientos intencionales (teleoquinéticos), sino también a los locomotores. Existen dos posibilidades para la mediación de esta proporción incrementada de movimiento:

1) La acción descendiente directa demostrada de la dopamina nigra-formada en las neuronas fusimotores dinámicas en el cuerno anterior, que acelera los movimientos teleoquinéticos; y 2) la inhibición dopamina indirecta demostrada en el estriado, que impide al estriado de ejercer una acción inhibidora en las neuronas probablemente colinérgicas palidales eferentes. Los últimos efectúan movimientos locomotores giratorios contralaterales. Un aumento en la rata de movimientos intencionales puede también lograrse por estimulación de 25 y 50/sec. de los aferentes específicos que se originan en el núcleo V. o. p. y se extienden hacia la zona motora primaria 4γ.

RÉSUMÉ

La substance nigra et son transmetteur la dopamine (DA) semble être responsable de l'augmentation normal dans la vélocité du mouvement chez les êtres humains et les mamifères. Quand est bloqué l'action de la dopamine par l'harmelina ou réserpina la vélocité du mouvement diminue, et le tonus musculair, dans sa relation réciproque, augmente. Dans l'aspect biochemique, la possibilité d'augmenter la vélocité des mouvements depend de la relation

$$\frac{DA}{ACh;\ 6HT}$$

dans le strié. L'accélération des mouvements intentionnels (teleoquinetique) si non aussi les locomoteurs. Il existe deux possibilités pour la mediation de cette proportion élevé du mouvement:

1) L'action descendante directe démontrée de la dopamine nigra-formada dans les neurones fusimoteurs dinamiques dans la corne anterieure, qui accélère les mouvements teleoquinetiques; et

2) l'inhibition dopamine indirecte démontrée dans le strié, qui empêche le strié d'exercer une action inhibitrice sur les neurones probablement colinérgiers palidales. Ces derniers effectuent des mouvements locomoteurs giratoirs contralateraux. Une augmentation sur le rat des mouvements intentionels peut aussi s'obtenir par stimulation de 25 et 50/sec. des afferents spécifiques qui prennent naissances dans le noyau V. o. p et s'etendent jusqu'à la zone moteur primaire 4γ.

ZUSAMMENFASSUNG

Die normale Substantia nigra und ihr Übermittler das Dopamin (DA) scheinen für die normale Zunahme der Schnelligkeit der Bewegung bei menschlichen Wesen und bei Säugetieren verantwortlich. Wenn die Wirkung des Dopamin durch Harmalin oder Reserpin blockiert ist, wird die Schnelligkeit der Bewegung kleiner und der Muskeltonus, in umgekehrtem Verhältnis zu ihr, erhöht sich. In biochemischer Sicht hängt die Möglichkeit die Schnelligkeit der Bewegungen zu erhöhen von dem Verhältnis

$$\frac{DA}{ACh;\ 6\ HT}$$

ab im Striatum. Die Beschleunigung der Bewegungen umfasst nicht nur die beabsichtigten Bewegungen (telekynetische) sondern auch die lokomotorischen. Zwei Möglichkeiten für die Vermittlung dieser Wachstumsrate von Bewegung gibt es: 1) Die gezeigte direkte herabsetzende Wirkung des nigra-geformten Dopamin in den dynamischen fusimotorischen Neuronen im Vorderhorn, welche die telekynetischen Bewegungen beschleunigt und 2) die gezeigte indirekte Dopaminbehinderung im Etriatum die das Striatum hindert eine bremsende Wirkung in den wahrscheinlich cholinergischen efferenten pallidaren Neuronen auszuüben. Der letztgenannte Effekt bewirkt kontralaterale Drehung lokomotorischer Bewegungen. Eine Erhöhung in der Rate der intentionalen Bewegungen kann auch durch 25 und 50 sec. Reizung der spezifischen Afferenten erreicht werden, die im V.O.p.-Kern beginnen und sich bis zur primären motorischen Zone 4 gamma erstrecken.

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Substantia Nigra and the Sensorimotor System

(Chemonigrectomies induced by Intrategmental Administration of the Paraquinone of 6-HYDROXY-Dopamine and 6,7-Dihydroxitryptamine in the Cat and Monkey.)

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The morphological and phylogenetical properties as well as the functional role of the substantia nigra (SN) are laden with enigmas. During mammalian development, the size of SN relative to the mesencephalon increases significantly suggesting that in higher mammals SN significantly contributes to the progressive elaboration of adaptation to the environment. The manner in which SN contributes to this adaptation is obscure.

Under the light microscope, SN may be subdivided into at least a large (p. compacta) and small (p. reticularis) celled part, but some investigators could identify numerous subunits within this nucleus [25]. Under the electronmicroscope, however, corresponding ultrastructural differences were not encountered [24, 53]. The large cells in SN contain melanin in man. This melanin is not akin to most other melanins within the nervous system and elsewhere in the body [58, 60]. It is also remarkable that only the horse and giraffe share with man this property *(high* content of melanin) of SN. Depigmentation of SN is a common corollary of parkinsonism in man, and of yellow star thistle *(centaurae solsitialis)* disease in the horse [40, 41]. Although some similarities in the symptomatology of these diseases have been described [7], parkinsonism is a disease of obscure pathomechanisms and chronic course whereas the yellow star thistle disease is an acute condition rapidly leading to death. Recently it has been recognized that cells in pars compacta contain dopamine; the nigral dopamine reaches neurons in the head of caudate nucleus (Cd) via nigrocaudate axons from cells of pars compacta [3]. These axons have been readily identifiable by fluorescence microscopic techniques. However, retrograde degeneration [39] anterograde degeneration [9, 65] electrophysiological studies [13, 14, 20 A] have provided conflicting information as to the origin of nigrocaudate axons from pars compacta [9] from pars reticularis [39]. Equally controversial issues have been the other efferent connection of SN [8–10, 38, 39]. Although there is a concensus on the connections from p. reticularis to Cd, the nigrothalamic connections are still subject to polemics [8–10, 19, 25]. Even the proponents of such connections have not provided conclusive evidence for the existence of an independent nigrothalamic projection system,

nor for nigrocaudate axons sending collaterals to the dorsal thalamus, or *vice versa*. The operational characteristics of the nigrocaudate projections are also unclarified. The nigrocaudate dopamine neurons have been suggested to exert long-axon inhibitory efects in the Cd, although the characteristics of Cd neurons upon which such inhibitory effects are exerted have not been specified. On the other hand, electrophysiological recordings from Cd neurons during SN stimulation revealed 16-20 msec latency excitatory effects [13, 14]; it has been postulated that these effects are monosynaptic (conducted via small fibers). However, intracellular recordings from Cd neurons have not been reported as showing an absence of hyperpolarization prior to the generation of such belated spike discharges. Equally important is that the reverse pathway (from Cd to SN) is also subject to controversy: intracellular recordings from neurons in SN during Cd stimulation have shown monosynaptic EPSPs [20 A]; but other studies, by strong inference, indicate that the Cd-SN pathway is inhibitory [44, 45, 62]. Taken together, these and other [1, 6, 12, 29, 33, 34 36–38, 60] observations create a perplexing picture of evolution, morphology and physiology of SN.

It is suggested that the spatial position of SN introduces formidable difficulties into the studies of SN. Figure 1 A illustrates that SN is embedded into prominent axonal systems; thus stimulation of SN is unavoidably associated with an artifact producing condition: stimulating electrodes placed inside the boundaries of SN activate, by spread of current, the perinigral, large, low-threshold axons before they do the high-threshold nigral neural elements [14, 18 20 A]. Placement of stimulating and recording electrodes or cannulae to SN through dorsal and transcerebellar approaches involves traversing a considerable mass of neural tissue. Even when the neocortex is suction-ablated (Fig. 1B) to reduce travel of microelectrodes through the nervous tissue, its distance from the quadrigeminal plate is still excessive. It is implicit that the study of SN courts artifact-prone conditions.

The scope of enquiry in this report is

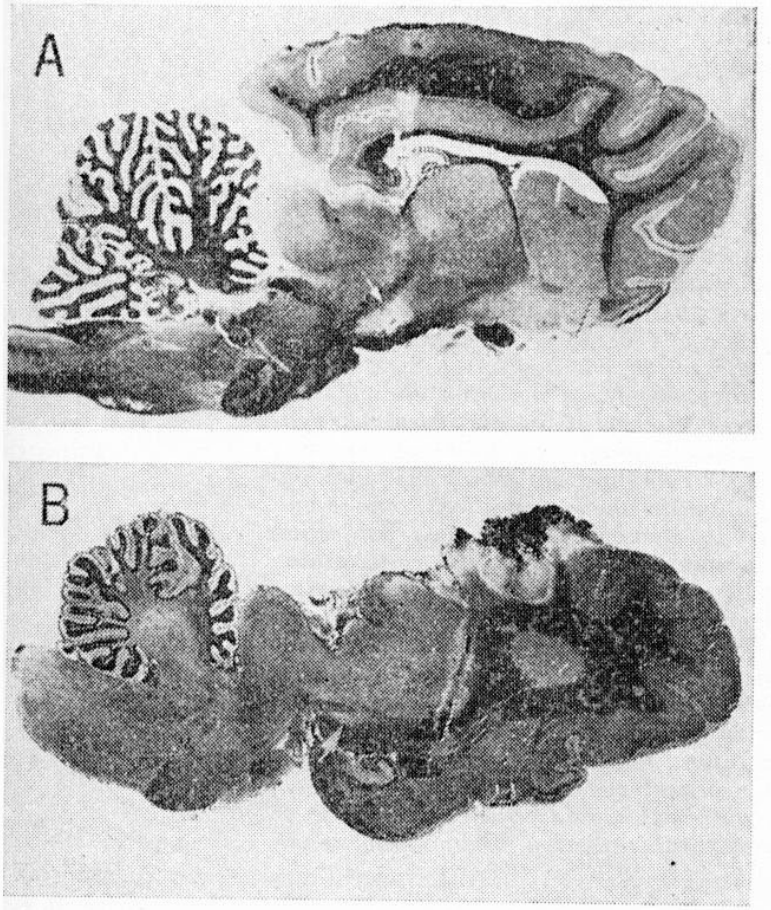


Fig. 1. — *Photomicrographs of parasagittal sections of the cat brain. Substantia nigra (white arrows) is embedded in prominent tegmental axonal systems. A_1 shows an electrode track from the surface of neocortex to SN (distance = 22 mm). In B, the neocortex overlying the dien- and mesencephalon was suction-ablated to reduce the distance of travel of recording micropipettes from the quadrigeminal plate to SN (distance = 10 mm). Further description in text. Modified from* (20A, 21).

confined to only a few of the foregoing issues. If SN is a component of the sensorimotor organization, then what is the contribution of SN to the regulation of sensorimotor activities? Further, what functional deficits exist in the integration of sensorimotor activities when SN is degenarated? Can the degeneration of SN seen in parkinsonism and yellow star thistle disease be reproduced experimental situations?

The first question will be dealt with here only briefly. (It was reported in extenso in [14].) In essence, determination of the functional role of SN calls for detailed knowledge on the functional role of Cd in the sensorimotor organization. Early studies of Mettler [39A] have established that electrical stimulation of Cd profoundly affects motor activities initiated by electrical stimulation of the motor cortex. These observations raised the question of how Cd is linked to projection systems in the core of the sensorimotor organization to systems which carry proprioceptive information from numerous sources corticopetally and motor output signals in a few pathways corticofugally [14]. It has been established that such linkage between the Cd and the proprioceptive input-motor output systems is effectuated in the dorsal thalamus [20]. Figure 2 illustrates that there is a high synaptic security in the cerebello-thalamocortico-cos-

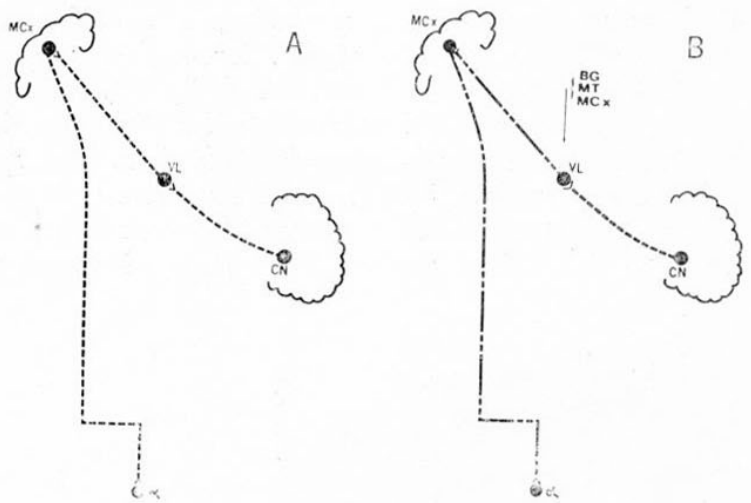


Fig. 2. — *Diagramatic illustration of patterns of activities in the cerebello-thalamocortical- corticospinal projection system. A. Eletrical stimulation of deep cerebellar nuclei elicits action potentials in BC axons which engage VL neurons* (20). *Action potentials in BC (between* 1-100 *Hz) elicit single spike discharges in VL neurons* (18, 47). *Action potentials in the thalamocortical radiation elicit EPSPs and superimposed spike discharges in corticospinal neurons* (50, 63) *whose axons impinge on alpha-motorneurons* (20). *In encèphal isolè cats and in penthrane anesthetizel squirrel monkeys, under these conditions, one-to-one synaptic relationships are demonstrable in this projection system* (20, 22). *B. Low-frequency* (8-12 *Hz) conditioning stimulation of medial thalamic nuclei, head of caudate nucleus, internal segment of globus pallidus, substantia nigra and the motor cortex elicit EPSP-IPSP sequences in the thalamic neurons interposed in this projecton systems* (14, 18-20, 21-23, 46-50). *Such evoked IPSPs gate the cerebellofugal actvities in the thalamus with resultant conversion of the tonic inputs to thalamic neurons to phasic output in the thalamocortical radiation* (20). *Patterns of evoked activities in the corticospinal tract are similar to those in the thalamocortical radiation undtr these conditions.* (20).

pinal projection system [20]. This projection system represents a large segment of the core of the sensorimotor organization: convergent proprioceptive impulses leave the cerebellum via the specific outflow system (brachium conjunctivum, BC) and through the thalamus gain access to corticospinal neurons in the motor cortex [14]. Action potentials set up by electrical stimulation of cerebellar nuclei or BC trigger single spike discharges in thalamic neurons [18, 46] whose axons engage corticospinal neurons [63]. Action potentials in the thalamocortical radiation effectively trigger spike discharges in thalamic neurons [18, 46] whose axons engage corticospinal neurons [63]. Action potentials in the thalamocortical radiation effectively trigger spike discharges in corticospinal neurons [50]; such action potentials, in turn, gain access to alpha-motorneurons [20]. Electrical stimulation [8–12] Hz of Cd alters these synaptic relationships: trains of action potentials travelling in the BC system are converted to phasic activities in the thalamocortical radiation [19, 20]; similar phasic activities are observed in close temporal relations in the corticospinal tract [20] (Fig. 2B). Thus the site of interactions between caudatofugal and cerebellofugal activities is in the dorsal thalamus. The Cd induced phasic activities in the thalamocortical radiation are resultant to the generation of relatively brief excitatory postsynaptic potentials (EPSPs) and prolonged inhibitory postsynaptic potentials (IPSPs) in the perikarya of thalamic neurons [19] which radiate to the MC (Fig. 3). This particular alteration of activities within the cerebello-cor-

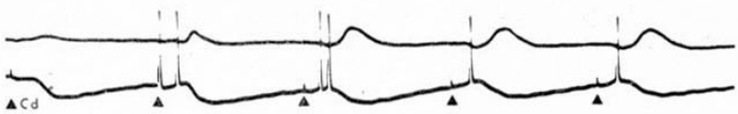


Fig. 3. — *Low-frequency (8 Hz) stimulation of the head of the caudate nucleus (at closed triangles) evoked surface activities in the motor cortex (upper trace) and a typical intracellular record from a VL neuron (lower trace). Cd stmuli generate long-latency recruiting negativities in the motor cortex and EPSP-IPSP sequences in the electrothalamogram. These data establish that there are functional conections between the Cd and the dorsal thalamus (modified from* [19]).

ticospinal projection system is the functional consequence of the Cd evoked IPSPs in thalamocortical neurons. Intracellular recordings from neurons in the thalamic reticular nucleus (nR) have revealed that stimulation of Cd [8–12] Hz generates burst discharges in these neurons [15]; these bursts in nR neurons exhibit developmental patterns and temporal properties virtually identical with the Cd evoked IPSPs in the adjacent neurons of n. ventralis lateralis (VL) (Fig. 4).

It has been intrepreted that the Cd evoked IPSPs in VL neurons are functions of the Cd evoked bursts in nR neurons [15, 22, 23, 57]. Most workers in this field seem to subscribe to this theorem [22, 48]. The basic observations are undisputed: stimulation of Cd elicits prolonged bursts in nR and IPSPs in VL neurons [15, 57]. Whether or not one accepts that there are causal relationships between the two [54], a glaring problem thrusts itself afore: inasmuch as direct Cd-thalamic projections (with the notable exception of a narrow fiber bundle [14, 35]) have not been demonstrated, how do Cd evoked action potentials reach nreuons in nR or in VL? The consensus between morphologists is that Cd projects only to both segments of globus pallidus (GP) and Sn [61]. The consensus between electrophysiologists is [14, 19, 21, 31, 62] that the dominant effect of stimulation of Cd in GP neurons is inhibitory. These imply that GP-nR and GP-VL projections (ansa lenticularis) are unlikely trajectories for Cd-dorsal thalamus projection activities [19, 33, 42]. On the other hand, intracellular recordings from neurons in SN have revealed monosynaptic EPSPs during stimulation of Cd [20A]. Further, in-

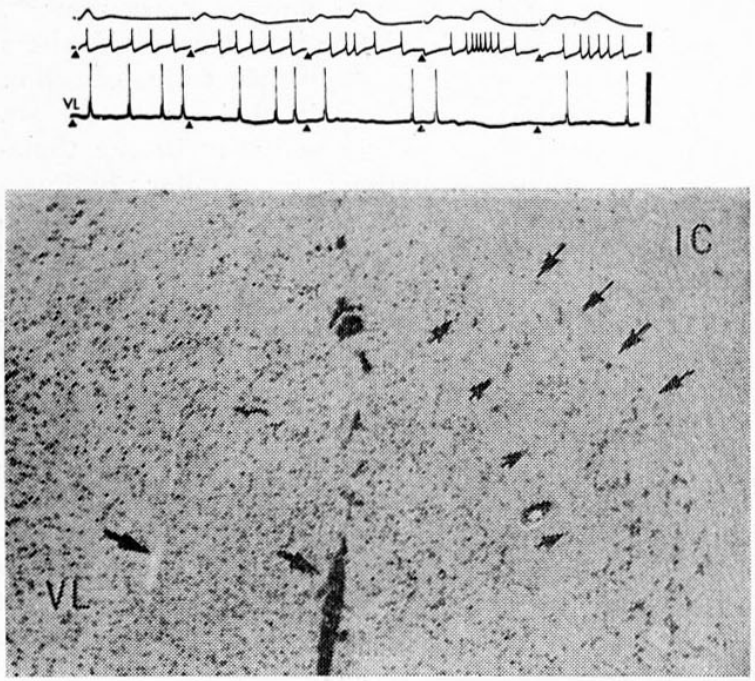


Fig. 4. — *The functional relationship between Cd evoked activities in n. reticularis thalami, n. ventralis lateralis and motor cortex. Low-frequency (8 Hz) stimulation of Cd at the closed triangles elicits 1. upper trace: double-negativities, the second of which shows recruiting characteristics, in the motor cortex (20A, 29), 2. middle trace: gradual buildup of burst discharges in the intracellular recording from a neuron in nR, and 3. lower trace: gradual buildup of IPSPs in the intracellular record from a neuron in VL. Note the similarities in developmental patterns and close temporal relations between the bursts in nR, IPSPs in VL and recruiting negativities in the cortex. The photomicrogram is a coronal section through the diencephalon. The internal capsule is at the right upper corner, nR is indicated by the series of arrows. Note the narrow diameter (300 μ) and low cellular dentity of nR. Two electrode tracks (single arrows) point at two tracks made by recording micropipettes penetrating through nR and VL (15).*

tracellular recordings from nR neurons have revealed burst discharges and from VL neurons both monosynaptic EPSPs and EPSP-IPSP sequences during stimulation of SN [15, 19]. The SN-nR and the SN-VL pathways have also been observed in anatomical studies [9, 51, 52]. Thus, these data 1. show the morphological substrates and the operational correlates of the Cd-SN and SN-dorsal thalamus pathways; 2. indicate that functional conectivity could exist between them; and 3. suggest the operation of a Cd-SN-dorsal thalamus projection system. (Fig. 5.)

The theorem advanced here relegates SN to a mere relay function. This relegation of SN to a functional role of one of inferiority is congruent with existing data [14, 16, 17, 19, 38] but also, and obviously, reflects an incomplete understanding of the function of SN. Some other established properties of SN [3], while not inconsistent with our hypothesis, cannot as yet be incorporated into it. There is a large body of evidence which indicates that SN is in the trajectory of the major discharge route of Cd, and that destruction of SN functionally is tantamount to destruction of Cd [17, 38].

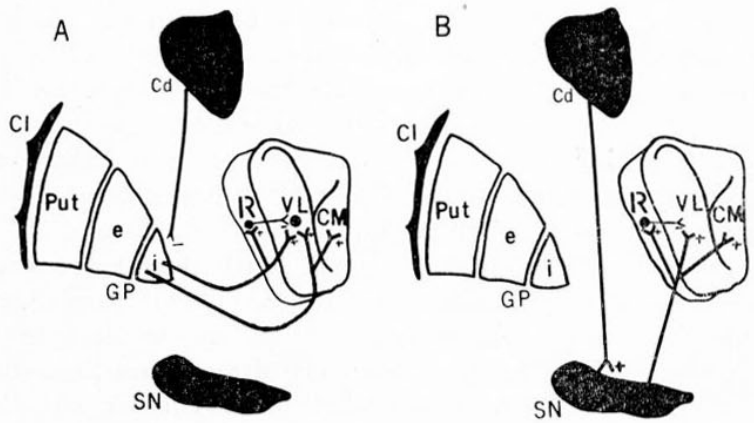


Fig. 5. — *Diagramatic illustration of the structural and functional relationships between nR neurons with axons impinging upon VL neurons and thalamopetal pathways engaged by axons of caudate neurons. Description in text.*

It is implicit in the foregoing that destruction of SN should abolish Cd evoked EPSP-IPSP sequences in VL neurons and burst discharges in nR neurons. Indeed, retrothalamic, prenigral hemitranssections of the neuraxis severely attenuated the Cd evoked inhibitory potentials in VL, leaving the Cd-VL monosynaptic [14] potentials unaffected and MC-VL excitatory potentials only slightly attenuated [22] (some of the MC-VL axons traverse through SN [22, 52]). Similar effects were observed following selective, *chemical* destruction of SN.

The introduction of chemonigrectomies in the study of function of the higher-mammalian SN [17] has had numerous advantages over the conventional fulguration technique for destruction of SN. The shape of SN is discoid in the cat and somewhat ellipsoid in the primate. The shape of fulgurated lesion is globous. Thus, the relatively narrow dorsoventral diameter of SN in the cat and in the monkey limit the size of a fulgurated lesion which could be placed into this nucleus (Fig. 6A and C) without impinging ventrally on axons in the cerebral peduncle or dorsally the BC and medial lemniscal axons in the tegmentum (Fig. 6B). Thus fulguration may produce, at best, a 30-40 % destruction of SN without encroaching on perinigral axonal systems. Remarkably, this extent of nigral damage has seldom been reported to be associated with detectable functional deficit of any sort [17,60].

Chemicals and heavy elements, like tellurium, have long been known to induce selective nigral degeneration in the mesencephalon. But such chemonigrectomies were invariably associated with selective destruction of other labeled lines in the lower brain stem and spinal cord. Six-hydroxydopamine [6]-OHDA, a compound which in the periphery was reported to selectively and reversibly destroy catecholamine containing neurons, was the first compound reported to induce a rather selective destruction in the SN when injected intraventricularly in the rodent [28]. In previous studies [17], we injected 6-OHDA *intrategmentally* in the cat; it destroyed approximately 70 % of SN without detectable tissue destruction elsewhere in the mesencephalon. The following triad of effects were observed following injection of 10 µg 6-OHDA in 10 µl volume: 1. cystic necrosis at the tip of cannula (approximately ½ cubic mm); 2. surrounding reactive infiltration; and 3. specific neural loss in SN as far as 5 mm from the site

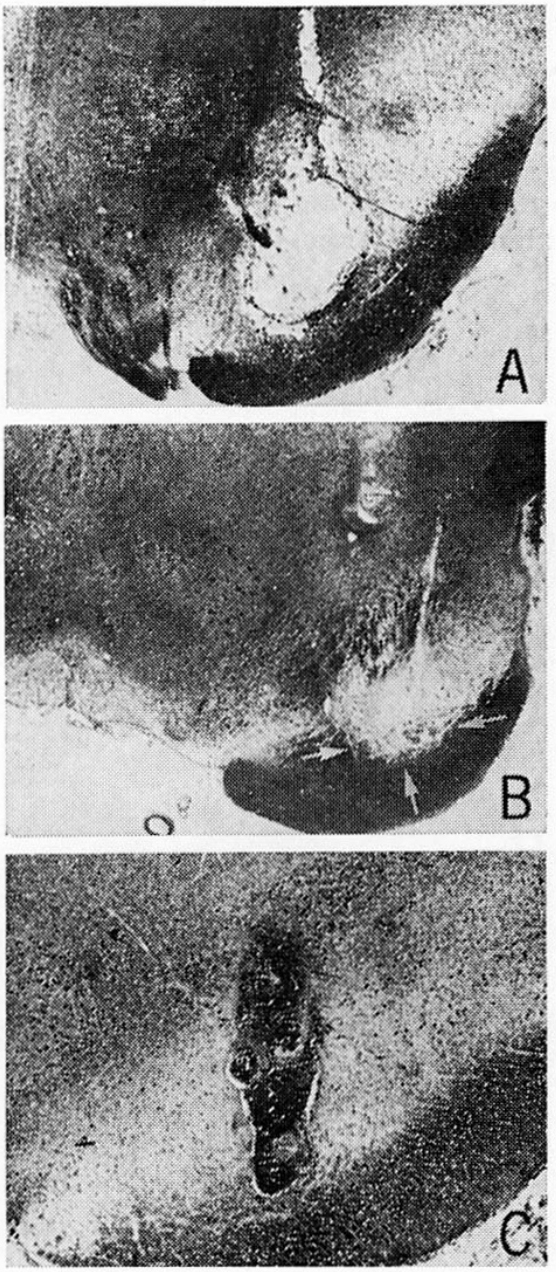


Fig. 6. — *Lesions in SN induced by fulguration. A and B: monopolar electrodes in SN against electrodes in the temporal muscle, C: concentrically bipolar electrodes in SN. The shape of SN is lentricular, whereas the shapes of fulgurated lesions are globous. The narrow dorsoventral diameter of SN sets the limit of size of fulgurated lesions which may be placed between its boundaries. A, lesion entirely within SN. B, lesion encroaches on peduncular axons (between arrows). C, cigar-shaped lesion destroys barely 15 % of nigral tissue. Further description in text.*

of injection (Fig. 7) [17]. Control injections to the Deiters nucleus induced only the local damages (1 and 2) without detectable neural or other damages in the surround. The neural damage in SN was proportional to the distance from the site of injection [17]: within 2 mm from the cystic necrosis the cell count in SN was zero or close to it; further away (3-5 mm), the cell count was 30-60 % of that of the contralateral, intact SN (Fig. 8). It is noteworthy, that SN on the injected side appeared larger than on the control (Fig. 7B). However, even if this optical phenomenon represents swell-

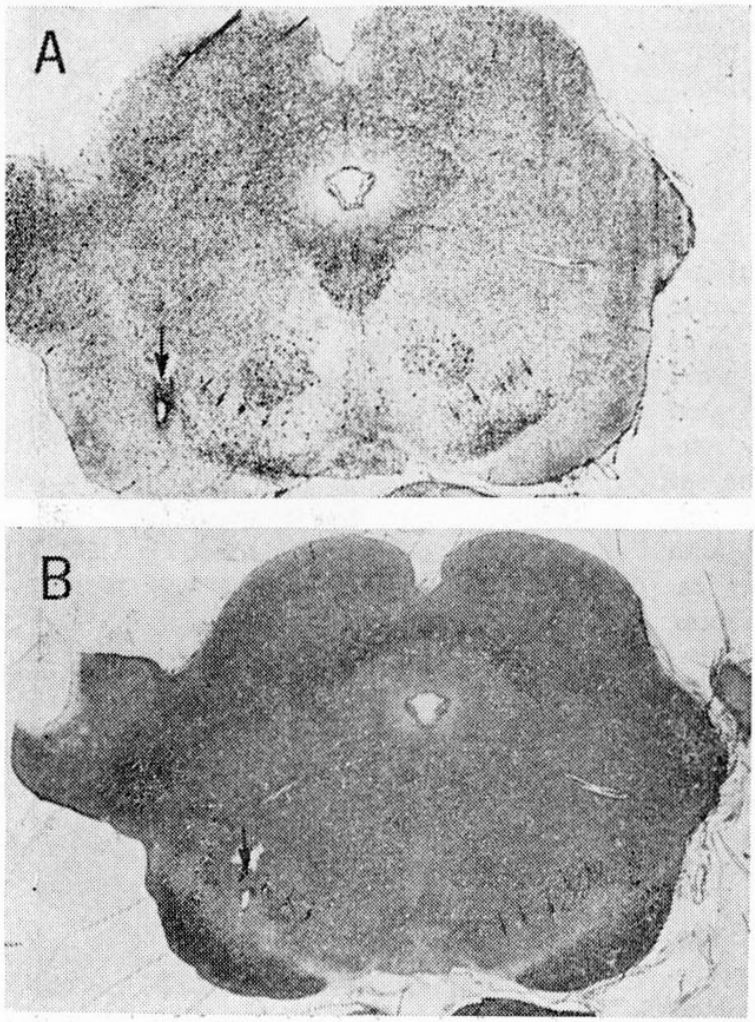


Fig. 7. — *Chemonigrectomy induced by intrategmental administration of low-concentration of 6-OHDA. A, unstained, frozen section. B, section stained with Nissl and counterstaned by Luxol fast blue. Small arrows point to SN, big arrows are superimposed on the needle tracks. A, prominent decrease in number of cells in SN on the injected (left) side. The intact, control SN is seen on the right side. B, the degenerated SN (on the left) appears larger than the control, intact SN. Further descripton in text. Modified and unpublished from* (17).

ing, thus reducing cellular density, it cannot account for the zero cell counts in extensive areas of SN. In addition, cells in various stages of decomposition were also deomonstrated. (Fig. 9.) Chemonigrectomy was effectively induced in acute electrophysiological experiments: the earliest signs of nigral damage were detected in 60-90 minutes. Time-series studies have, however, indicated that maximal cellular loss in SN is attained approximately 72 hours after intrategmental administration of the compound (Fig. 7). Follow-up studies, up to 30 days, failed to reveal additional cell count changes in SN.

The foregoing data on the effects of 6-OHDA, in consonance with numerous other studies [2, 5, 8], show that this compound has either a specific affinity to nigral cells in the mesencephalon or if penetrates mesencephalic neurons indiscriminately, it is specifically toxic to nigral neurons. A recent study by Poirier [43] however, showed different observations. He injected small volumes of highly concentrated 6-OHDA and found that the resultant tissue destruction was nonspecific. We repeated Poirier's experiments and have confirmed his observations. (Fig. 10.) Indeed, 6-OHDA in *high* concentration induced non-specific tissue da-

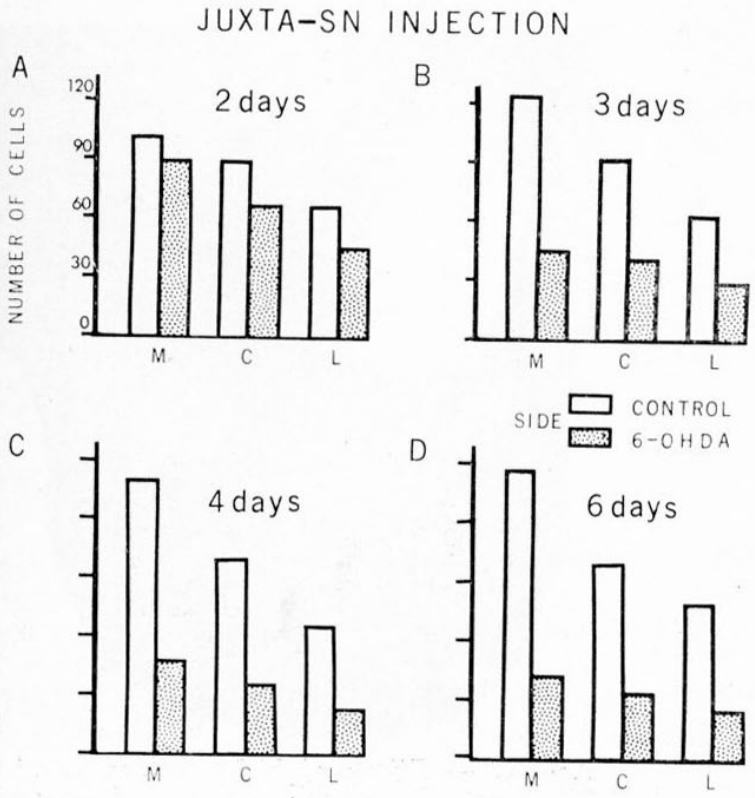


Fig. 8. — *Histograms show cell counts in SN 2, 3, 4, and 6 days after ventral tegmental administration of 6-OHDA. Empty columns indicate cell counts at the control, stiffled columns at the injeted side. M, C, L. = medial, central and lateral thirds of SN. Counts represent numers of cells seen in identical number of fields at identical sites of the injected and control sides. Counts were carried out up to 30 days, but illustrated only up to 6 days after injection. Maximal degenerations were observed at 3 days without additional changes during the remainder of the observation period.*

mage in the central nervous system everywhere we tried. In fact, in our experiments, chemopallidectomy *(vide supra)* could be attained with less capsular damage than fulguration of GP; this is because the cannula for injection has a smaller diameter than the electrode used for fulguration, and there is no peri-lesion edema following chemonigrectomy unlike after fulguration of the pallidum. Thus these data show that the 6-OHDA effects are dose dependent: low concentrations induce specific damages in the mesencephalon, high concentrations induce nonspecific neural destruction throughout the central nervous system [2, 4, 16, 26–28].

Extensive chemonigrectomies induced by 6-OHDA were associated with detectable alterations in the electrothalamograms *(vide supra)* and the sensorimotor activities *(vide infra)* of cats and monkeys. When this is compared with the localized, fulgurated lesions in SN, their superiority with respect to the study of neurobiology of SN is evident. But apart from this practicality, the question arises as to the mechanism by which 6-OHDA exerts the enumerated effects. Several suggestions have been made in attempting to account for the observations. It was noted in the periphery that 6-OHDA had specific affinity to catecholamine containing neurons [32]. Ungerstedt found that intracysternally administered 6-OHDA selectively destroyed neurons in pars compacta of SN (those which contain catecholamines) in rodents. Our findings have been at variance with these observations: intrategmentally administered 6-OHDA destroyed neurons in both pars compacta and pars reticularis of SN that is both types of neurons which do and do not contain dopamine [2, 3, 58]. (A recent report by Ungerstedt has corroborated these observations [28].)

The fact that 6-OHDA indiscriminately destroys both types of nigral neurons, requires an explanation other than that this compound has selective affinity to catecholamine cells. Saner and Thoenen suggested that 6-OHDA is oxidized to the quinone derivative inside only adrenergic neurons; the paraquinone would act as a cross-linking reagent and would tan the intraneural matter [64].

The effects of 6-OHDA on metabolism of aminoacids [5] have also been tied to the function of catecholamines as intracellular metabolic regulators. A different line of

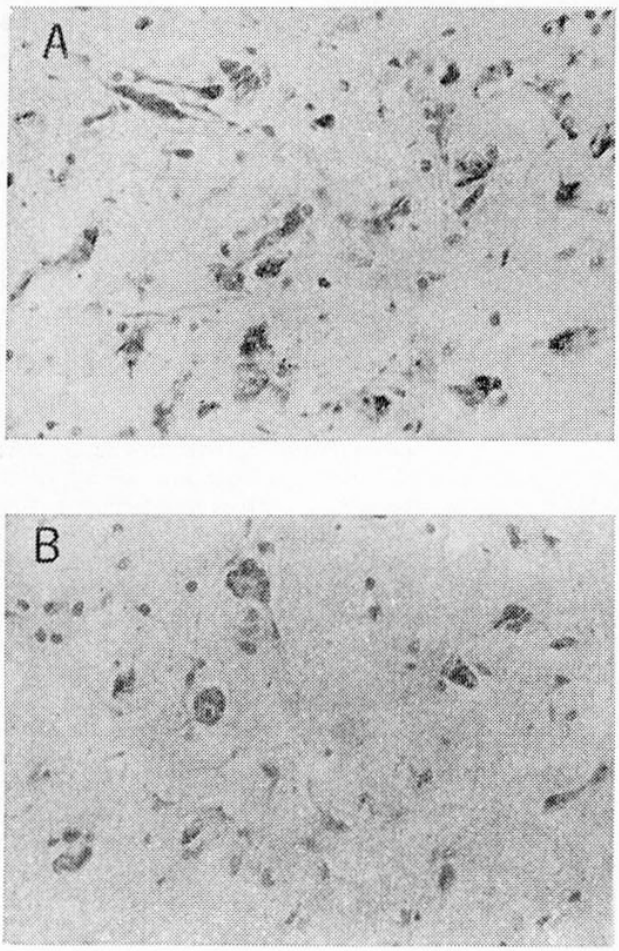


Fig. 9. — *High-pomer photomicrograms show 6-OHDA induced neuronal loss in SN. A, control, B, injected side. Central third of SN. 6-OHDA deposited into the brachium of MGB. Nissl stain.*

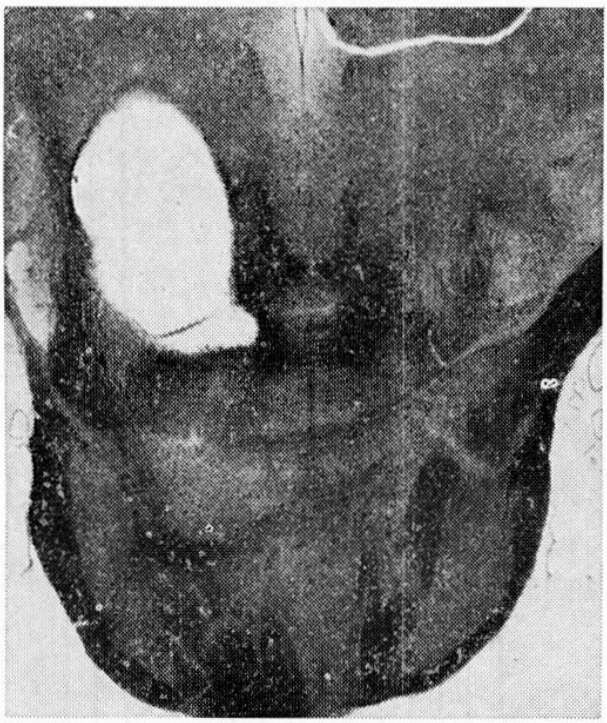


Fig. 10. — *Effects of high-concentration of 6-OHDA into the ventral tegmentum of the squirrel monkey. Huge, nonspecific lesion extends approximately equidistant to all directions from site of injection. Further description in text.*

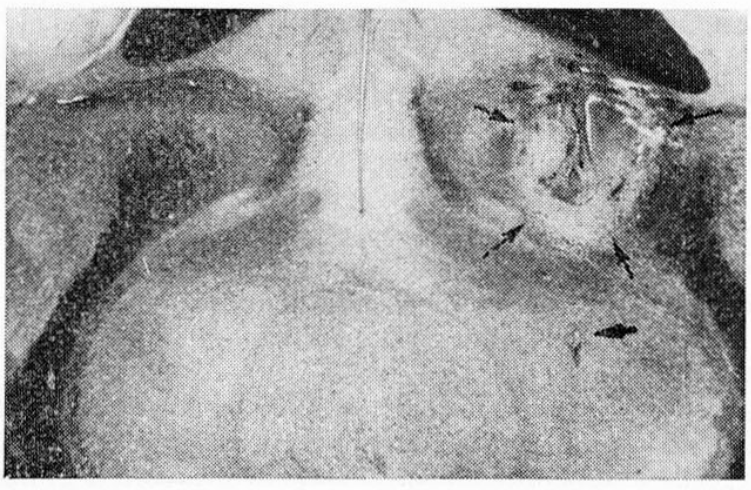


Fig. 11. — *Chemopalldectomy induced by high-conentration of 6-OHDA in the squirrel monkey. Horizontal arrow points at the needle track. The other arrows point at the destroyed pallidum. The intact lenticular nucleus is seen in the control (right) side.*

thought is, therefore, of particular interest here: it has been reported that 6-OHDA autoxidize producing superoxide radicals and a colored compound [26]. In the presence of ascorbate, the paraquinone of 6-OHDA, the colored product of such autooxidation, recycles to 6-OHDA (Fig. 12). Intracellularly, ascorbate also is an effective inhibitor

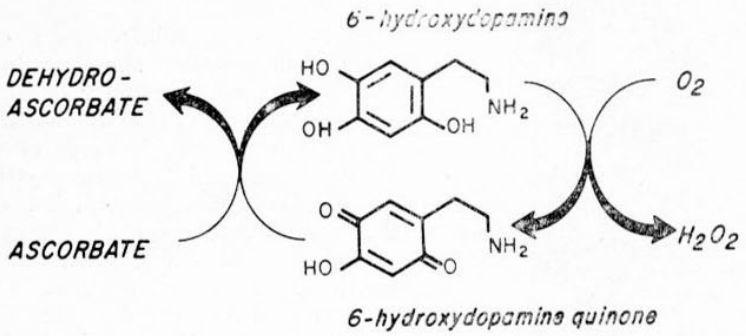


Fig. 12. — *Suggested reaction sequence for production of H_2O_2 by 6-OHDA with recycling the corresponding quinones by ascorbic acid (27). Further description in text.*

of catalase, the major enzyme which destroys H_2O_2, and thereby stimulates reactive superoxide radicals production [27]. It is tempting to consider that the neurotoxic effects of H_2O_2 account for the dose dependent neurolysis following intrategmental administration of 6-OHDA [16]. In small doses, intrategmental administration of 6-OHDA induces neurolysis only in neurons with high content of ascorbate (SN), whereas in high doses, especially when injected in solutions containing ascorbic acid, it destroys neural tissue indiscriminantely. These considerations could account for all the aforementioned experiments. This hypothesis also implies that the effect of paraquinone of 6-OHDA injected into the mesencephalon should have an effect on nigral neurons indistinguishable from that of 6-OHDA. Figure 13 illustrates that this, indeed, is the case. The time course of development of effects and the extent of nigral destruction is comparable to that of 6-OHDA (Fig. 8). It has recently been recognized [4] that another neurochemical compound, 6, 7-dihydroxytryptamine (6, 7, - DHT), may also cause chemical sympathectomy similar to that of 6-OHDA by a mechanism also similar to that of 6-OHDA [27]. The molar efficiency of 6, 7 - DHT in producing superoxide radicals is about 50 % less than that of 6-OHDA [27]. In this study 5, 6 - DHT was administered to the ventral tegmentum to regions comparable with those of 6-OHDA and paraquinone of 6-OHDA *(vide supra)*. In contrast to the latter compounds (10 µg /10µl), 6, 7 - DHT was administered in doses of 20µg/20 µl. Figure 14 illustrates that this compound was as effective in inducing selective destruction of both pars compacta and pars reticularis of SN as 6-OHDA and the paraquinone of 6-OHDA were. It is no-

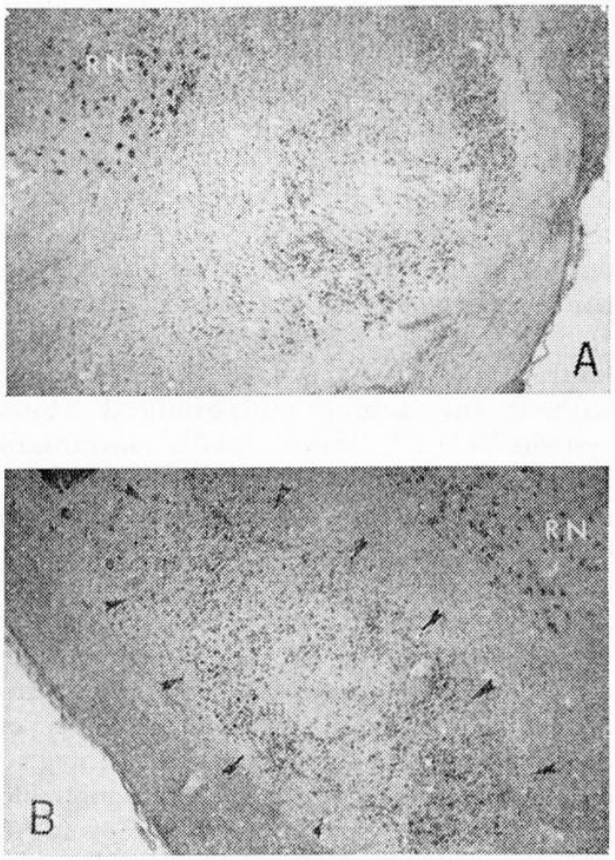


Fig. 13. — *Chemonigrectomy induced by the paraquinone of 6-OHDA in the squirrel monkey. A, injected; B, control sides. Red nucleus and peduncular axons are unaffected. Arrows in B outline the intact SN. Size of SN is smaller in A than in B.*

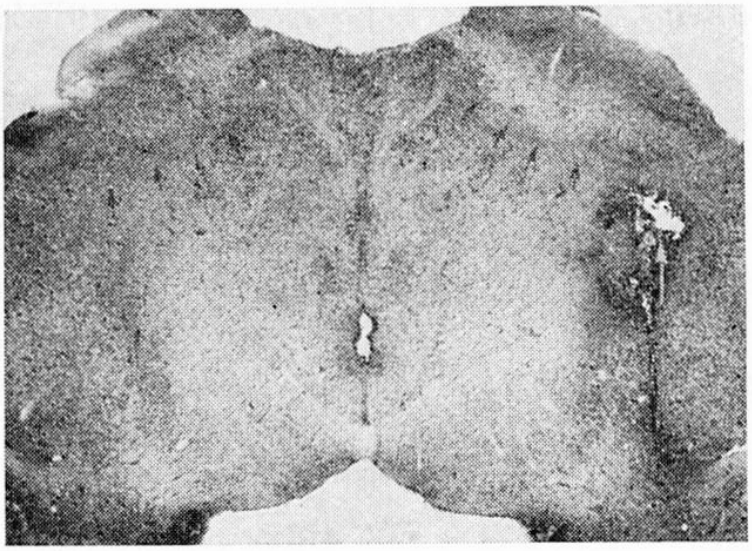


Fig. 14. — *Photomicrogram of the mesencephalon showing the effects of intrategmentally administered 6, 7 - DHT. The needle track is seen on the left side. White arrow points to the cystic necrosis at site of deposition of the compound. Neural damage is confined to SN (outlined by arrows). The degenerated SN (on the left) appears to be larger than the intact SN on the control (right) side.*

teworthy that 6, 7 - DHT induced degenerated SN also appeared to be larger than the intact SN on the control side.

The consequences of nigral destruction on the sensorimotor behavior of cats and monkeys have been dependent upon the extent of neurolysis in SN and, possibly, on the integrity of perinigral axonal systems [34, 37]. In the cat, fulgurated lesions do not destroy more than 30 % of nigral neurons without encroaching on perinigral axonal systems [16, 17, 60]. Such totally intranigral lesions fail to induce sensorimotor abnormalities in the cat, presumably because the extent of lesion does not reach the limit of physiological safety; that is, sufficient number of nigral cells remain to ensure the functional contribution of SN to the normal operation of the sensorimotor system. Since abnormal movements depend not only on damage to neural tissue but also on integrity of other critical systems [37], chemonigrectomies, which destroy up to 70 % of nigral neurons without affecting perinigral axonal systems, are commonly associated with lasting sensorimotor disabilities in the cat [14, 16, 17]. Chemonigrectomies induced by intrategmental administration of paraquinone of 6-OHDA and 5, 6-DHT were accompanied by a sensorimotor abnormality similar to that induced by 6-OHDA, namely initial transient forced circling and lasting difficulties in descending locomotion.

The role of nigral degeneration has been a long debated issue in the development of parkinson-like tremor in the monkey [34, 36–38, 59, 60]. It has been established that experimentally induced tremors following lesions into the ventromedial mesencephalic quadrant can disappear in the presence of extensive nigral cell loss [36]. In this series of experiments, tremor was not observed in chemonigrectomized monkeys. Lasting sensorimotor abnormality was observed only in 4 out of the 12 animals studied here and it consisted of an obstinate retrogression: these animals cringed against the back of their respective cages in a crouched position; when placed on a platform (Fig. 15), they rapidly moved backwards by pushing themselves with their arms. Essentially similar phenomenon was reported from cats with extensive caudate lesions [35, 38]. These observations provide further support to the theorem that, with respect to the functional consequences, extensive nigral lesions are tantamount to extensive Cd lesions [16, 17] because SN is the major relay in the discharge route of caudatofugal activities to the dorsal thalamic relays interposed between the proprioceptive input and corticospinal output systems.

The major finding in these experiments is that compounds which generate reactive superoxide radicals in mesencephalic neurons (6-OHDA, paraquinone of 6-OHDA and 5, 6-DHT) induce selective destruction of neurons in both pars compacta and pars reticularis of SN in both cats and monkeys when injected in *low* concentrations into the tegmentum. Since these compounds diffuse into all directions from the site of

tegmental injections [2], they reach neurons in the medial geniculate body, the reticular formation, red nucleus and other tegmental structures. However, structural damage has been observed only in nigral neurons [2, 17, 58]. Inasmuch as the tissue destruction is resultant to the neurotoxic effects of H_2O_2, it may be that the high content of ascorbate in nigral neurons both stimulates autoxidation of these compounds and inhibits catalase action which destroys H_2O_2.

Consequently, it may be considered that the nigral degeneration is due to the deleterious effects of locally generated H_2O_2 with inadequate catalase action also in human parkinsonism.

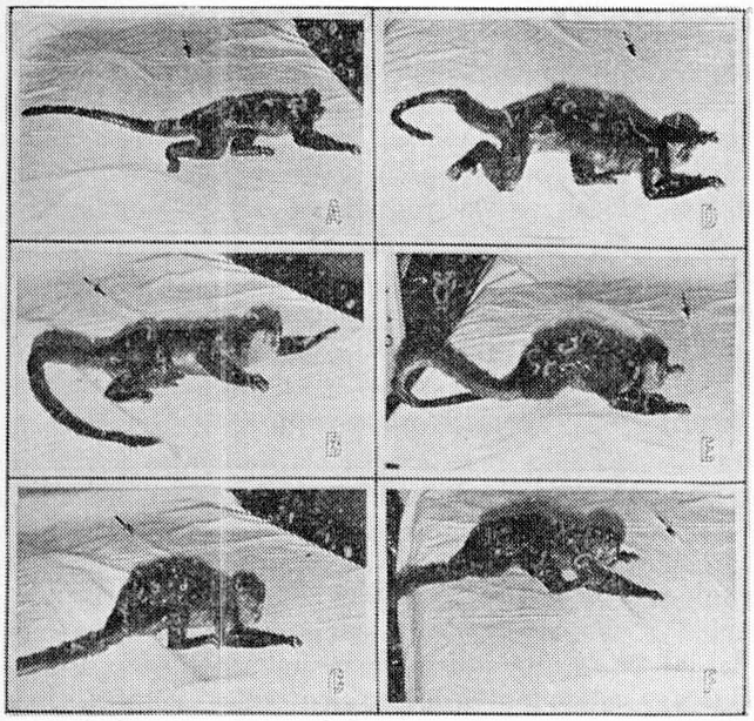


Fig. 15. — *Obstinate retrogression of a squirrel monkey chemonigrectomized by the paraquinone of 6-OHDA. Monkey, facing right, is placed on the right of the plataform in A. He pushes himself backwards. In C., he is in a crouched position. In D, proceeds backwards. In E and F, he resumes the crouched position. F, note the feet are at the level of shoulders when he reaches the left end of the platform. A crease on the sheet is indicated by black arrows to emphasize the from-right-to-left-direction of locomotion. The tail generally curves to the right, contralateral to the SN lesion.*

Acknowledgements

This work was supported, in part, by a grant from the Eric Slack-Gyr Foundation. Figures 8 and 9 represent data from the dissertation of one of us (A.I.) to be submitted as partial fulfillment of the requirements for the Ph.D. degree at N.J. Coll. Med. - J. Szabo was a Visiting Scientist from the University of Ottawa, 1973. The paraquinone of 6-OHDA was synthetized and generously provided by Dr. P. A. Wehrli, Hoffman - La Roche, Inc., Nutley, N. J. The 5, 6-DHT was synthetized and generously supplied by Dr. Albert Manian, National Institute of Mental Health, Bethesda, Md.

SUMMARY

The hodological properties, electrophysiological characteristics, and functional role of substantia nigra (SN) have not yet been established. This report reviews some of the perplexing problems in the neurobiology of SN, and presents new information on the functional attributes of SN. The data here construe that the input-output systems and synaptic mechanisms of SN indicate that this nucleus is a relay for caudato-thalamic projection activities. The nigro-thalamic axons of the caudate-SN-thalamus projection system radiate to the ventrolateral thalamus, and send axon collaterals to the dorsolateral segment of the thalamic reticular nucleus (nR). Caudatofugal activities travelling through these axons generate EPSPs in neurons in the ventrolateral thalamus, and prolonged burst discharges in neurons in nR. Cells in this segment of nR project heavily

to the ventrolateral thalamus. It is suggested that the caudate evoked bursts in nR neurons induce repetitive release of an inhibitory transmitter in the ventrolateral thalamus and, thereby, generate the prolonged IPSPs, demonstrable during low-frequency stimulation of the caudate, in ventrolateral thalamic neurons. The caudate evoked IPSPs in these cells have been shown to modulate activities in the cerebello-thalamocortical projection system, a powerful input system to corticospinal neurons. Such caudate evoked IPSPs in ventrolateral thalamic neurons are severely attenuated or abolished following ipsilateral hemisection of the mesencephalon, or after destruction of SN.

Comparison of chemical and fulgurative destruction of SN has revealed that 6-OH dopamine, its paraquinone, and 6, 7-dihydroxytryptamine produced up to 70 % cell loss in SN without damage to other mesencephalic structures, whereas fulguration produced about only 30 % cell loss. Single, fulgurated lesions, which induced more extensive cell loss in SN, also encroached on perinigral axonal systems. It is proposed that these compounds, when injected into the tegmentum, induce selective neurolysis in SN by their releasing reactive superoxide radicals.

Chemonigrectomized animals exhibited motor abnormalities qualitatively similar to those induced by extensive caudate lesions. These behavioral and the electrophysiological observations indicate that extensive, localized destruction of SN is tantamount to extensive ablations of the head of the caudate nucleus. The data are consistent with the theorem that one of the interfaces between the basal ganglia and the dorsal thalamus is established by the caudato-nigro-thalamic projection system.

RESUMEN

No se han establecido todavía las propiedades hodológicas, las características electrofisiológicas ni el papel funcional de la sustancia nigra (SN). Esta exposición pasa revista a algunos de los problemas confusos de la neurobiología de la SN, y presenta nueva información sobre las características funcionales de la SN. Los datos aquí explican que los sistemas aferentes y eferentes, y los mecanismos sinápticos de la SN indican que este núcleo es una estación para las actividades de proyección caudado-talámica. Los axones nigro-talámicos del sistema de proyección caudado-SN-tálamo, irradian hacia el tálamo ventrolateral, y envía colaterales axonales al segmento dorsolateral del núcleo reticular talámico (nR). Las actividades caudadofugales, que se orientan a través de estos axones, generan PPSE, en neuronas del tálamo ventrolateral, y prolongados brotes de descargas en neuronas en el nR. Células en este segmento del nR. proyectan grandemente en el tálamo ventrolateral. Se sugiere que los estallidos evocados del caudado en neuronas del nR, inducen la liberación repetido de una transmisión inhibidora en el tálamo ventrolateral, y con lo cual se generan prolongados PPSIs, demostrables durante la estimulación de baja frecuencia del caudado en neuronas talámicas ventrolaterales. Los PPSIs caudados evocados en estas células, han mostrado que modulan las actividades en el sistema de proyección cerebelo-tálamocortical, un potente sistema de aflujo a las neuronas corticoespinales. Tales PPSIs caudados evocados, en neuronas ventrolaterales talámicas, están fuertemente atenuados o abolidos después de la hemisección homolateral del mesencéfalo, o a continuación de la destrucción de la SN.

La comparación de la destrucción química y fulgurante de la SN ha revelado que la 6-OH dopamina, su paraquinona, y la 6, 7-dihidroxitriptamina produjo hasta 70 % de pérdida celular en la SN sin dañar otras estructuras mesencefálicas, mientras que la fulguración produjo aproximadamente sólo un 30 % de pérdida celular. Las lesiones por fulguración aisladas, que inducían una más extensiva pérdida celular en la SN, también alcanzaron sistemas axonales perinigrales. Se piensa que estos compuestos, cuando se inyectan dentro del tegmento, inducen neurolisis selectiva en la SN por su liberación de radicales superóxidos reactivos.

Los animales quimionigrectomizados exhibieron anormalidades motoras cualitativamente similares a aquellas inducidas por lesiones caudadas extensivas. Estas observaciones electrofisiológicas y de conducta indican que la destrucción extensiva localizada de la SN es equivalente a las ablaciones extensivas de la cabeza del núcleo caudado. Los datos son consistentes con la teoría de que uno de los vínculos entre los ganglios de la base y el tálamo dorsal está establecido por el sistema de proyección caudado-nigrotalámico.

RÉSUMÉ

Les propriétés hodologiques, les caractéristiques électrophysiologiques et le rôle fonctionnel de la substantia nigra (SN) n'ont pas encore été établi. Cet article passe en revue quelques problèmes controversiels concernant la neurobiologie de la SN, et présente de nouvelles données sur ses atributs fonctionnels. Les données présentées suggèrent que les systèmes input-output et les mécanismes synaptiques de la SN indiquent que ce noyau relaie les activités de projection caudato-thalamiques. Les axones nigro-thalamiques du système de projection caudato-SN-thalamus se dirigent vers le thalamus ventrolatéral, et envoient des fibres collatéraux au ségment dorsolatéral du noyau thalamique réticulé (nR). Les activités caudatofugales parcourant ces axones provoquent des EPSP dans des neurones du thalamus ventrolatéral, ainsi que des décharges de longue durée dans des neurones du nR. Les cellules de ce ségment du nR ont des projections massives vers le thalamus ventrolatéral. Nous suggérons que les décharges dans les neurones du nR provoquées par le caudé libèrent un transmetteur inhibiteur dans le thalamus ventrolatéral, ce qui explique les IPSP de longue durée dans les neurones du thalamus ventrolatéral évoqués par une stimulation de basse fréquence du caudé. Ces IPSP ont une action modulatrice sur les activités du système cerebello-thalamo-cortical, qui représente un système de input puissant vers des neurones corticospinaux. Ces IPSP dans des neurones du thalamus ventrolatéral évoqués par stimulation du caudé sont diminués ou abolis après une hémisection ipsilatérale du mésencéphale, ou après la destruction de la SN.

Une comparaison des destruction chimiques ou fulguratives de la SN a montré que la 6-OH dopamine, sa paraquinone, et la 6, 7-dihydroxytryptamine ont produit une perte de cellules jusqu'à 70 % sans destruction d'autres structures mésencéphaliques, tandis que la fulguration a produit une destruction de seulement 30 % descellules. Une lésion fulgurative qui produisait une perte de cellules SN plus massive, s'étendait aussi au système axonal perinigral. Nous proposons que l'injection de ces substances dans le tégmentum produit une neurolyse sélective dans la SN par la libération de radicaux de superoxyde réactifs.

Les animaux chémonigrectomizés présentaient des abnormalités motrices qui ressemblaient à celles produites par des lésions massives du caudé. Ces observations comportementales et électrophysiologiques indiquent que la destruction localisée, massive de la SN équivaut à une ablation massive de la tête du caudé. Ces données sont consistantes avec le téorème que une des "interface" entre les noyaux gris de la base et le thalamus dorsal est établie par le système de projection caudato-nigro- thalamique.

ZUSAMMENFASSUNG

Die Hodologie, die elektrophysiologischen Charakteristika und die funktionelle Rolle der Substantia nigra (SN) sind noch nicht vollständig geklärt. Diese Arbeit erläutert Probleme der Neurobiologie der SN und vermittelt neue Information über die funktionellen Eigenschaften dieser Struktur. Die hier mitgeteilten Ergebnisse deuten darauf hin, dass die Input-Output Systeme und die synaptischen Mechanismen der SN relais-Eigenschaften dieses Kerngebietes für Aktivitäten der caudo-thalamischen Projektion

repräsentieren. Die nigro-thalamischen Axone des Caudatus-SN-Thalamus Projektions-Systems strahlen in den ventrolateralen Thalamus ein und senden Axon-Kollateralen zum dorsolateralen Segment des Nc. reticularis thalami (nR). Caudatofugale Aktivität, die in diesen Axonen fortgeleitet wird, erzeugt EPSPs in Neuronen des ventrolateralen Thalamus und langdauernde burst-Entladungen in Neuronen des nR. Zellen dieses Segments von nR strahlen in den ventrolateralen Thalamus ein. Es wird angeregt, dass Caudatus-evozierte bursts in nR-Neuronen repetitiv Freisetzung eines inhibitorischen Transmitters im ventrolateralen Thalamus auslösen und dadurch langdauernde IPSPs in Neuronen diese Gebietes erzeugen, wie es sich bei niederfrequenter Stimulation des Caudatus zeigen lässt. Weiterhin ergab sich, dass die Caudatus-evozierten IPSPs in diesen Zellen eine modulierende Wirkund auf die Aktivität des cerebello-thalamo-kortikalen Projektionssystems hat, welches ein wichtiges Input-System für die kortikospinalen Neurone darstellt. Derartige Caudatus-evozierte IPSPs in ventrolateralen Thalamus-Neuronen werden einerseits durch ispilaterale halbseitige Durchtrennung des Mesencephalon oder andrerseits durch Destruktion des SN erheblich abgeschwächt.

Der Vergleich von chemischer und elektrischer Destruktion der SN ergab, dass 6-OH Dopamin, dessen Parachinon und 6, 7-Dihydroxytryptamin bis zu 70 % Zelluntergang in SN ohne Schädigung anderer Mittelhirn-Strukturen hervorrief, während Kauterisation nur einen Zelluntergang von etwa 30 % bewirkte. Einzelne Kauter-Läsionen, die grösseren Zellverlust in SN auslösten, griffen auf perinigrale axonale Systeme über. Als Wirkungsmechanismus der Substanzen, die nach Injektion in das Tegmentum selektive Neurolysis in der SN auslösten, wird die Freisetzung reaktiver Peroxyd-Radikale vorgeschlagen.

Chemonigrektomierte Versuchstiere entwickelten motorische Abnormalitäten, die qualitativ durch ausgedehnte Caudatus- Läsionen induzierten Veränderungen vergleichbar waren. Die elektrophysiologischen Phänomene und die Veränderungen des Verhaltens weisen darauf hin, dass ausgedehnte, lokalisierte Zerstörung der SN gleichbedeutend ist mit einer Abtragung des Nc. caudatus Kopfes. Die Ergebnisse stehen im Einklang mit dem Konzept, dass das caudato-nigro-thalamische Projektionssystem eines der Verbindungsglieder zwischen den Basalganglien und dem dorsalen Thalamus darstellt.

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Gaba Blockade, Dopamine and Schizophrenia: Experimental Activation of the Mesolimbic System

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A number of striking phenomenologic similarities between psychomotor epilepsy and schizophrenia have suggested a relationship between these disorders. Patients with schizophrenia are characterized by altered perceptions and by the preemption of consciousness by fear, suspicion, sexual preoccupation, primitive drive processes and freely rising memories linked together in an illogical, often dream-like fashion. Release of many similar sensory deceptions and primitive drive states is also regularly if transiently displayed during automatisms of psychomotor epilepsy or in response to the chomotor epilepsy or in response to the stimulating electrode of the surgeon when it is placed in amygdala and hippocampus. As in psychomotor epilepsy, EEG changes, when present in schizophrenia, are most common over the temporal lobes.

Grossman reported in 1963 a chronic behavioral disturbance in cats following prolonged seizures induced by carbachol in amygdala and associated with interictal spikes in temporal lobe and hypothalamus. Lonsbury (1971) confirmed these observations several years ago, and evidence for "downstream" alterations of electrical excitability in septum and hypothalamus following generalized seizures induced by cholinergic stimulation of amygdala bilaterally. These changes included spike activity and altered after-discharge threshold in hypothalamus and abnormal affective responses associated with spikes in midline nuclei to which amygdala projects. Changes in after discharge threshold also follow repeated or prolonged electrical stimulation of hippocampus and amygdala in both animals and man suggesting altered receptor sensitivity, enzyme induction or structural change secondary to repeated stimulation. These data have focused attention on the projection systems of temporal lobe structures, their relationship to changed affective perceptual and motor response, alterations which may relate to altered receptor site sensitivity, or to presynaptic axonal sprouting as demonstrated by Moore in the septal catecholamine system (1971).

The past twenty years have seen a revolution of schizophrenic psychoses that has important implications for these clinical and experimental observations. Introduction of phenothiazines and butyrophenones as the first relatively specific pharmacologic treatment of schizophrenic disorders has been followed by increasing evidence that the potency of these anti-psychotic agents is directly proportional to their catecholamine receptor blocking effect, thus suggesting that the neural substrate of certain psycho-

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tic states may be closely related to catecholamine excess or supersensitivity at certain central synapses.

Evidence of particular importance of dopamine synapses in schizophrenic behavior arises not only from the nearly ubiquitous occurrence of Parkinsonlike disturbances following use of potent neuroleptics, and of occasional schizophreniform psychoses following L-dopa treatment of Parkinsonism, but from more direct laboratory demonstration that neuroleptics block central dopamine receptors. This blockade is accompanied by an increase in the level of the dopamine metabolite homovanillic acid in cerebrospinal fluid and brain, apparently secondary to interference with a negative feedback loop from dopamine receptors in striatum to dopamine cells of origin in midbrain, a mechanism which normally appears to control the level of dopamine production and which is blocked by the neuroleptic.

Introduction of fluorescent methods for staining peripheral and central nervous system monoamines demonstrated that the dopamine pathway has a relatively unique CNS distribution originating in pigmented cells of substantia nigra (SN) and ventral tegmental area (VTA) ascending in medial forebrain bundle to terminate in neo and limbic striatum respectively. A third dopamine (DA) system arises in median eminence and terminates in hypophysis. In contrast, the norepinephrine (NE) pathway originates in locus coeruleus and several adjacent cell groups of the pons, also ascending in medial forebrain bundle to distribute its axons to the entire neo-cortex, thalamus, hypothalamus, septum and cerebellum. The third great monoamine system delivers serotonin (5HT) from cells o forigin located in median raphe of brain stem, to terminate in both cortex and subcortical nuclei including striatum (Fig. 1). The fact that dopamine has a relatively unique distribution to striatum, and that the most potent pharmacologic agents against schizophrenia act as dopamine antagonists has focused attention upon the striatal structures in this disorder.

Nauta has pointed out striking structural similarities between neostriatum and the dopaminergic nuclei to which the major components of the limbic system project, the nucleus accumbens, nucleus of stria terminalis and olfactory tubercle (limbic striatum). As demonstrated by Kemp and Powell (1971) the neostriatum receives fibers from the entire neocortical mantle, comprising visual, somatosensory, and association cortex, as well as the better known projections from motor areas. These fibers converge on caudoputamen in a regular topographical fashion, prefrontal regions to head, motor and sensory regions to body, and visual cortex to tail of the nucleus, only the temporal lobe remaining unrepresented. The wide input to striatum from the cortical mantle is markedly compressed at the outflow from globus pallidus from which final

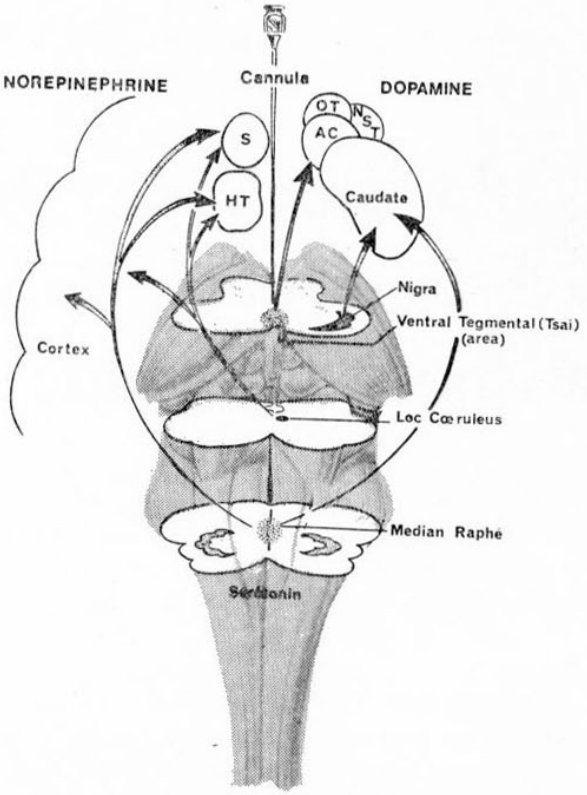


Fig. 1. — *Diagramatic representation of parallel catecholamine and indolamine systems illustrating distribution of dopaminergic terminals to caudate-putamen, nucleus accumbens (AC), olfactory tubercle (OT), and bed nucleus of stria terminalis (NST). Noradrenergic axons are distributed to cerebral cortex, hypothalamus (HT) and septum (S). Serotonin neurons from median raphe are distributed to both cortical and striatal structures, cannula in VTA marks site of bicuculline injection. Diagram based on information from Ungerstedt* (1971) *and adapted from Stevens* (1973).

pathways proceed via ventral lateral thalamus to cortex, cerebellum, and brainstem.

The limbic striatum, comprising nucleus accumbens, olfactory tubercle and nucleus of stria terminalis, is similarly placed at the junction of converging efferents from hippocampus, pyriform cortex, and amygdala respectively. Heimer and Wilson (1973) have shown that the efferent systems from the two striata via the globus pallidus and substantia innominata, respectively, also have a strikingly similar and quite unique ultrastructure. The probable projections of limbic striatum via substantia innominata to hypothalamus and frontal lobe parallel projections of globus pallidus to thalamus, brain stem and cerebellum (Wilson 1972).

These two striatal complexes might be visualized as parts of two giant fans, the larger neocortical perimeter converging with extraordinary information compression on striatum and globus pallidus; the ventral smaller fan, whose perimeter consists of limbic cortex and its specialized derivatives, streaming towards limbic striatum and thence to hypothalamus and frontal lobe via substantia innominata (Fig. 2).

Both systems share a unique DA innervation from a few thousand cells in SN and VTA respectively, the axons of which, traveling superiorly in medial forebrain bundle, terminate upon dendrites of interneurons of neo and limbic striatum and have been shown to have an influence on the level at which these neurons transmit signals from their neocortical and limbic afferent systems to final paths. The extraordinary information compression implicit in the disproportionate ratio of input to output for neo and limbic striatal structures suggests that one aspect of this information processing may be to "filter" or gate access of unwanted stimuli or percepts as well as affects, drives and memories from consciousness, a function which if defective, would seem to lie at the heart of the disturbance in schizophrenia.

In collaboration with Karen Wilson and Warren Foote at the Massachusetts General Hospital, experiments have been undertaken to explore this concept experimentally. Reasoning from the evidence of Yoshida and Precht (1971), and others that a monosinaptic inhibitory feedback system which originates from post synaptic DA receptors in caudate-putamen and descends in median forebrain bundle to terminate on DA neurons in SN is GABA coded, we have attempted to block GABA receptors at the termination of this putative feedback, namely at the presumed GABA synapse on DA cells of the midbrain tegmentum. Pharmacologic blockade has been accomplished by introducing micro amounts of the GABA blocking agent bicuculline directly into the VTA or SN or walking, freely moving cats with chronically implanted cannulas and electrodes (Fig. 1). Because nucleus accumbens shares with SN the highest con-

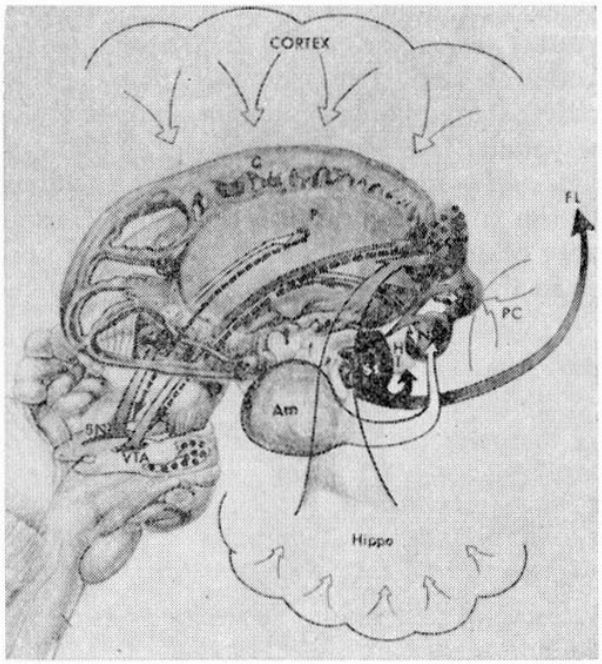


Fig. 2. — *Diagrammatic representation of fan-like confluence of neocortical structures on caudate putamen (CP), which receives dopamine axons from substantia nigra (SN). A similar confluence toward limbic striatum includes projection of amygdala (Am) to bed nucleus of stria terminalis (NST), hippocampus to nucleus accumbens (Acc), piriform cortex (PC) to olfactory tubercle (OT), and receives a separate dopamine projection ascending from the ventral tegmental area (VTA) Output from neostriatum via globus pallidus to thalamus (not shown) parallels limbic striatal efferents which exit via substantia innominata (SI) to frontal lobe (FL) and hypothalamus (HT). Stippled areas represent regions of high GAD concentration (McGeer, et al. 1971) and putative GABA feedback pathway from caudate putamen to SN and from limbc striatum to VTA. (adapted from Klinger and Gloor 1960 original drawing by W. A. J. Nauta 1972, Stevens 1973).*

centration of glutamic acid decarboxylase in the brain (McGeer et al, 1971) we have also introduced the GABA blocking agent in this nucleus in several animals. (Stevens, Wilson and Foote, 1973).

Material and Methods

Under Nembutal anesthesia adult cats weighing 2-4 kg were placed in a stereotaxic instrument and under sterile technique cannulas constructed from 21 gauge hollow needle tubing, Teflon coated to the tip and fitted with stylets, were placed through small burr holes in the right and left VTA, SN, and right nucleus accumbens (Nacc). Insulated leadoff wires soldered to the cannulas were attached to a female Cannon 15 contact connector. 0.001 inch stainless steel Teflon coated wire electrodes were placed in left Nacc, caudate nucleus, hippocampus, amygdala, lateral and medial geniculate nuclei, and soldered to the remaining contacts of the connector. Cannulas and electrodes were cemented to the skull with dental acrylic in the usual fashion for chronic use. Ten to fourteen days later electrical stimulation was carried out at each cannula site using square wave pulses of 0.5-1ms duration at 10-100 Hz in trains of 1-10 seconds with a continuous current monitor until a behavioral response or a maximum current of 1ma was achieved. To compare differences between affective responses to electrical stimulation and GABA blockade, cats were also tested for self-stimulation at the cannula sites. Several days after the completion of electrical stimulation 2.0-2.5mul of a solution of bicuculline containing 9-12mug of the alkaloid per mul and buffered to a pH of 4.4-5.0 was introduced into one both VTA cannulas in the waking cat.

Cerebral activity was recorded on a 10-channel model 78 Grass polygraph and on FM magnetic tape preceding and following introduction of the drug. Free behavior of the cats in the laboratory was carefully examined including responses to food, petting, calling, presentation of rats, company of other cats, and general exploratory activity. The initial dose of bicuculline was 16-20 mug and the quantity was then increased

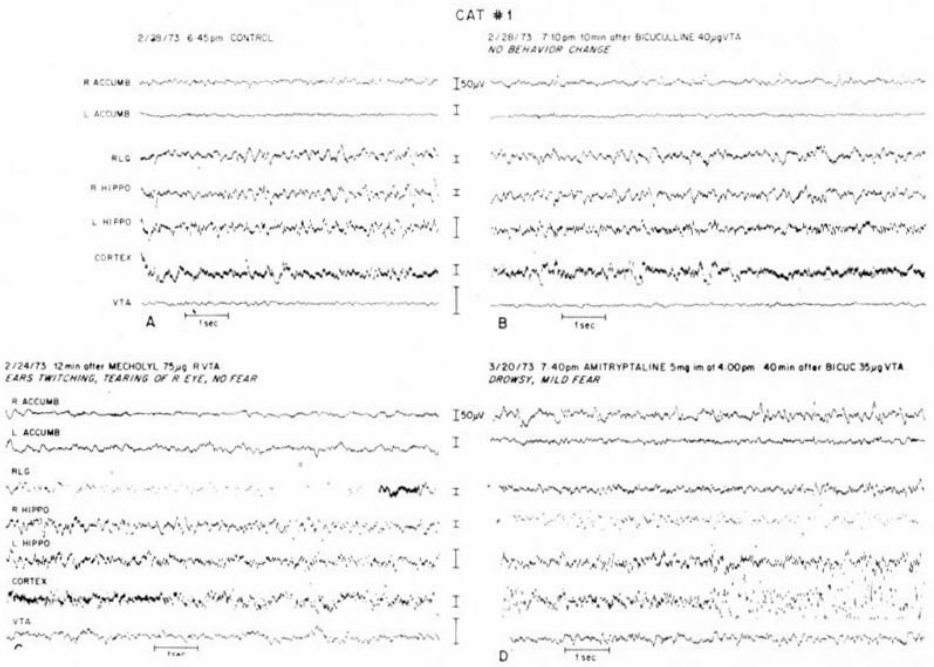


Fig. 3. — *A. control recording from normal cat with chronic implanted electrodes. B. occurrence of single monophasic spikes in* 10 *minutes after bicuculline* 40μg *in left ventral tegmental area (VTA). Cat is statuesque, fearful, staring.* C.75μg *mecholyl in VTA induces tearing of right eye, ear twitching, no affective change. D. Parenteral amitryptaline causes mild drowsing and prolongs fear and EEG reaction to* 35μg *bicuculline in VTA. RLG: right lateral geniculate Hippo: hippocampus. (from unpublished studies of Stevens, Wilson and Foote).*

by 30-50 % on subsequent injections at two-day intervals until a definite, consistent behavioral or EEG reaction was obtained (usually 20-4 μg). After establishing the "threshold" dose in this fashion and assuring its reliability after repeated trials, a similar volume of the bicuculline solvent (prepared as above but lacking the alkaloid) was injected through the same cannulas and recordings of behavior and EEG made in identical fashion. In addition to the above solutions two cats received Mecholyl (25-100 μg) two atropine (2.5 μg) in VTA and SN, and two animals received bicuculline 15 - 20 μg in right nucleus accumbens.

Following establishment of reliable behavior and/or EEG response to bicuculline at VTA and SN, animals were given the DA blocking drug haloperidol subcutaneously 2-6 hours prior to instillation of the threshold quantity of bicuculline on two successive trials two days apart. One week following the last injection of haloperidol threshold bicuculline responses were again tested and confirmed. Two days later 6-hydroxydopamine (6 - OHDA, 80 - 100 μg) in 3 μl of saline-ascorbic acid was placed into the cannulas. Two to five days later the threshold dose of bicuculline was again introduced in separate trials in VTA and SN and behavioral and electrical observations were repeated. If a reaction occurred, a second, and, if necessary, a third injection of 6-OHDA was given. Bicuculline challenge was then repeated 2 to 5 days later. Finally, when no response to bicuculline could be detected on two trials, L-Dopa 125-200mg/kg, or apomorphine 1mg/kg was administered interperitoneally and the bicuculline challenge repeated 60 minutes later. On completion of these studies the cats were deeply anesthetized with Nembutal, perfused via the carotid artery with normal saline followed by 10 % formalin and the brains removed and prepared for histological examination.

Results:

VTA Injections: Two to five minutes following introduction of threshold amounts of bicuculline in 2-4 μl of solute in VTA unilaterally or bilaterally, all animals became suddenly hypervigilant and startled in appearance. Five cats showed intense fear, crouched, stared, slunk on half bent legs along the wall, hid in corners, and cringed or backed at the approach of the investigator or in response to no apparent external stimuli. After 5-6 minutes of almost transfixed fright, cats showed bewildered glances from side to side and twitching of the ears suggestive of "hallucinations." Animals' attention could be briefly obtained by calling, but they were immediately distracted by what appeared to be an intense perceptual experience. Visual-pursuit responses were lost, as was their lively interest in catnip, food, and affection. Waxy flexibility of the limbs and statuesque stance alternated with sniffing along the ground and looking from side to side with ears twitching as though the cats were perceiving their previously familiar environment in a new way. The animals proceeded cautiously across open spaces, ignored their fellows, and failed to respond to the examiner except by cringing, retreating, and hiding in corners or behind furniture. When cats were placed in the recording box, a striking stare, episodic lateral eye movements, and ear twitching were noted. This reaction occurred in some form in all cats and in several animals on 10 or 15 separate injections of bicuculline in VTA. After 15-20 minutes the reaction subsided, following which normal, playful and often hyperaffectionate behavior returned. A periodic single spike activity appeared in accumbens and lateral geniculate nucleus coincident with the behavioral response in one animal and from VTA, medial and lateral geniculate, and nucleus accumbens (NAcc) in two cats (Fig. 2).

SN Injections: Introduction of 25-30 μg of bicuculline in pars compacta of SN induced ipsilateral circling during which animals were unable to pursue objects in the contralateral visual field. Ear twitching, intense grooming of the ipsilateral trunk and the perineum, hyperesthesia to touch over the ipsilateral side, exaggerated pleasure, or low growling were noted. Responses indicative of fear did not occur following nigral injection in any animal. Coincident

EEG disclosed spike activity not only in caudate nucleus, superior terminus of nigrostriatal system, but unexpectedly appeared first in several animals in the medial and lateral geniculate nuclei (Fig. 4). 15-20 μg bicucculine in nucleus accumbens re-

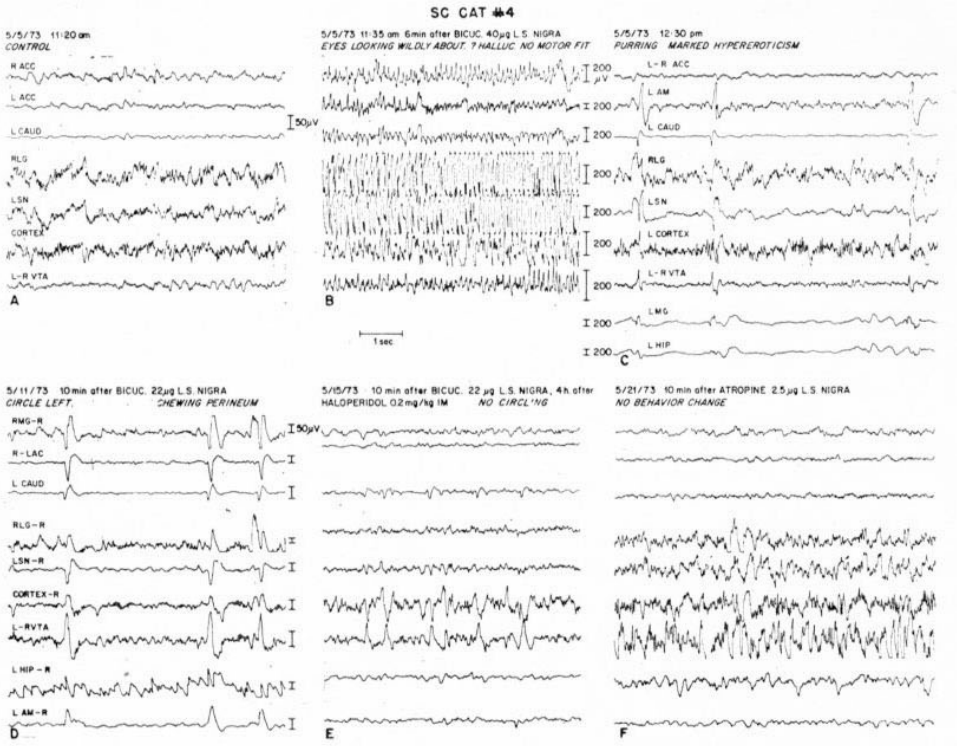


Fig. 4. — *Control, normal waking cat. B. Six minutes following injection of bicuculline 40 mcg in left substantia nigra, cat is very agitated, looking wildly about from side to side as though perceiving unusual stimuli. No motor seizure behavior. C. One hour following injection, cat demonstrates hypereroticism and purrs loudly. Spikes now appear from left amygdala, (LAM) left caudate nucleus (LCaud) right lateral geniculate (RLG); left substantia nigra (LSN), ventral tegmental area (VTA), left medial geniculate (LMG), and left hippocampus. D. 10 minutes after smaller dose of bicuculline, (22 mcg) in left substantia nigra cat circling to the left, grooms the left side and chews at the perineum as if some unusual sensation was perceived. Spike activity is apparent from all subcortical electrodes. There is no motor fit. E. Following pretreatment with haloperidol, bicuculline 22 mcg. no EEG or behavioral change. F. Atropine 2.5 mcg. in left substantia nigra causes no behavioral change.*

gularly induced severe rage and attack behavior in one animal, a reaction sufficiently aggressive to prevent simultaneous EEG recording.

Pretreatment of 0.10.2mg/wg of haloperidol prevented the behavioral responses elicited by subsequent injection of bicuculline in VTA, SN and NAcc. Mild dystonia of the head and neck was noted after bicuculline in VTA in three cats only if pretreated with haloperidol . Two to four days at cannula tips, cats became restless and following the second application of 6-OHDA hyperactive and behavioral and EEG responses to bicuculline were no longer obtained. Systemic treatment with L-Dopa (and apomorphine in one case) restored the full motor and affective response to bicuculline application at VTA and SN.

Electrical stimulation through the bared tip of the Teflon coated cannulas produced no evident affective response in VTA or nigral placements, and self-stimulation or avoidance was not obtained. Threshold behavioral responses to electrical stimulation consisted of lid closure or slight head retraction at currents of 0.7-1 ma. After-discharges were not elicited.

Histologic examination indicated that the behavioral and EEG responses noted above were closely related to accurate placements in 1-1.5 mm of the target areas were not in VTA and SN; cannulas not placed with-associated with the behaviors described.

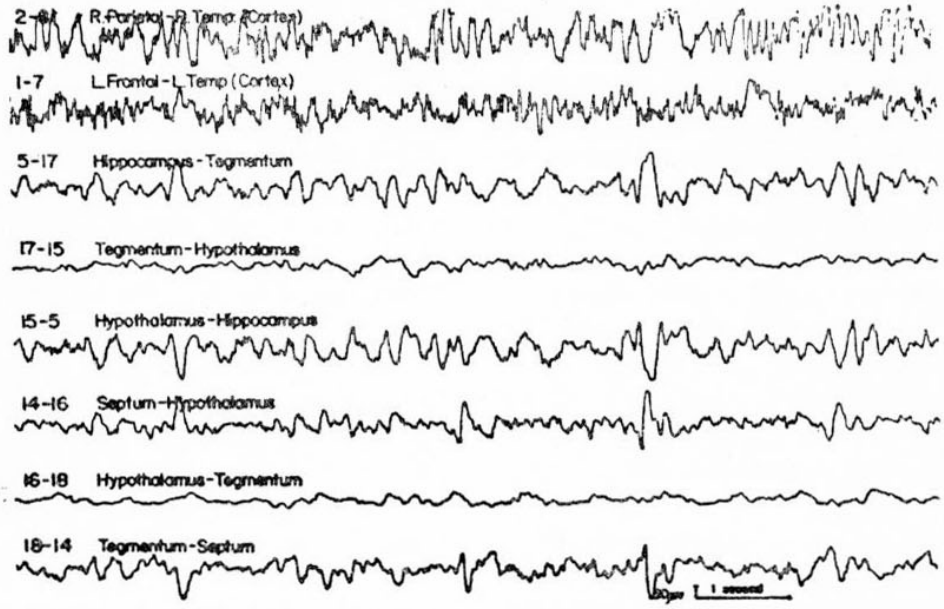


Fig. 5. — *"Septal: spikes from schizophrenic man recorded from chronic depth electrodes bear a striking resemblance to the accumbens spikes recorded in the cat (Heath 1954).*

Discussion:

The considerable reliability with which a remarkable behavioral state of fear, waxy flexibility, and evidence of "hallucinations" could be obtained repeatedly from injections of small amounts of the GABA blocking agent bicuculline unilaterally or bilaterally in ventral tegmental area of cats contrasted with the lack of affective change but pronounced ipsilateral circling or groom ing following injection of substantia nigra. Prevention of the response by the DA receptor blocking agent haloperidol or by local aplication of 6-hydroxy dopamine and potentiation by L-dopa and apomorphine are consistent with, but not concluusive evidence that the altered striatal dopamine is responsible for the behavioral electrical changes recorded. While the striking effects of dopamine of blocking and potentiating agents tend to support the hypothesis that we may be flooding limbic striatum with DA, alternative explanations exist. Thus, a large number of cells in substantia nigra and ventral tegmental areas, perhaps a majority, are not dopamine units and may also be subject to GABA inhibition and release by local bicuculline. Proof that change in DA is the crucial variable is still lacking and very necessary before the hypothesis is sustained that bicuculline blockade of GABA synapses on DA units interrupts inhibitory feedback to mesencephalon DA units, thereby altering activities subserved by limbic structures. Rather similar behavior suggesting hallucinations, and enhanced sexual activity has been reported by Jouvet (1967) and Dement (1969) in cats following 5HT suppression, a state which also fosters relative DA preponderance at the hipothesized striatal gate, and is associated with intrusion of geniculate (ponto-geniculate- occipital, PGO spikes) into the waking EEG. Spike activity recorder from lateral and medial geniculate nuclei as well as from neo and limbic striatum following GABA blockade of DA cells in waking cats, and evidence of hallucinatory and fearful behavior suggest that the geniculate nuclei may be specific focusing mechanisms for auditory and visual percepts, subject to striatal or reticular regulation. Kadobayashi (1972) has presented neurophysiologic evidence for

existence of a striatal-geniculate pathway, while Foote et al. (1973) have evidence for reciprocal serotonin innervation of lateral geniculate neurones from median raphe. EEG spike activity indicates synchronized depolarization shifts of neuronal elements, a relatively undifferentiated discharge pattern which is normally restricted in lateral geniculate and brain stem nuclei to REM sleep. Occurrence of such patterns in the waking state may underlie the striking intensity of attention displayed by the experimental animals to apparently altered visual, auditory and threatening stimuli during spike discharges. Proximity of the DA and serotonin nuclei to the site from which Lhermitte [19] described vivid hallucinations in patients with interpeduncular lesions lends clinical support to this formulation.

Preliminary evidence permits conceptualization of two parallel ascending amine systems, each containing reciprocal catecholamine/indoleamine axons: DA/5HT to striatum and NE/5HT to cortex, thalamus, hypothalamus, septum and limbic structures. These systems appear to regulate thresholds at which striatal or cortical neurones respond to the incoming stimuli mediated by cholinergic pathways. There is evidence that the catecholamine/indolamine homeostatic balance is preserved by both positive and negative feedback systems, by intrinsic reuptake mechanisms, end product inhibition, and by reciprocal displacement of transmitter on common neuronal receptors. Interference with the multiple regulatory mechanisms by experimental or pharmacologic exaltation of DA or decrease of 5HT, (e. g., by LSD, PCPA, REM deprivation, destruction of median raphe) leads to relative catecholamine preponderance, often associated with hallucinations and increased sexual behavior. Chronic amphetamine intoxication in association with dopamine-beta-hydroxylase blockade produces similar effects which are also associated with subcortical spike discharge in nucleus accumbens, olfactory tubercle, amygdala and interpeduncular region of the cat (Sudilovsky, 1973).

The normal regulatory mechanisms of central autonomic systems remain largely unknown. The close functional and anatomic relationship of central monoamine centers to sleep and arousal cycles and evidence of entrainment of these systems by light in infant mammals and lower vertebrates suggests initial dependence of central monoamine regulation on light and dark cycles. The REM sleep characteristic of infancy may be considered a relatively primitive chaotic discharge of brain stem nuclei which is gradually all but suppressed by the (initially light entrained) serotonin system which apparently supports slow-wave sleep. The intense activity of REM periods may subsequently occur only often enough and long enough to induce serotonin restoration or release. Abolition of REM periods by agents which conserve monoamines and the failure of REM rebound in acute schizophrenia and certain depressive states are congruent with such a hypothesis.

Recent studies by Wada indicate that bilateral spike-wave discharges and seizures induced by light in the baboon Papio are regularly associated with subcortical spike discharge only in median raphe, which save for pineal gland is the unique site of cerebral serotonin formation. Moreover, prefeeding Papio papio with L-tryptophane prevents the photically induced seizures in this species (and in certain myoclonic and photosensitive epilepsies in man). These observations are consistent with other evidence that diurnal fluctuations in serotonin are closely related to environmental lighting in primates and other species (Wurtman et al, 1968). We may conjecture that regulation of synthesis of serotonin by raphe neurones in the light sensitive baboon is normally more dependent on signals transduced by photo-receptors than is the case for nonphoto sensitive species. The particular photosensitivity of this primate, and that frequently found in centrencephalic epilepsy in man, could represent a selectively enhanced access of light-transduced stimuli to median raphe nuclei via accessory optic tract and median forebrain bundle, a trait developed by certain species or individuals which require photic activation for maintenance of normal serotonin activity. In support of this conjecture, it is of particular interest that Papio papio, although black faced, has white eyelids, a characteristic

perhaps developed or selected to enhance stimulation of a still photically dependent system for serotonin release or synthesis. The unnaturally great bolts of light from a stroboscope which precipitate seizure discharges from median raphe in this species would thus be not unexpected in an animal which normally requires photically transduced signals of low intensity for maintenance of adequate serotonergic activity.

These observations are relevant to the proposed, admittedly oversimplified notion of deranged catecholamine/indolamine bias at a striatal "gate" in schizophrenia. Patients with catatonic schizophrenia frequently exhibit photic-induced spike-wave activity on the EEG (Corriol and Bert, 1950; Stevens, 1970, 1973). This paroxysmal response to light is also significantly increased during adolescence in otherwise normal young women (Marcus et al, 1960). Since, as is well known, schizophrenic psychoses commonly develop during and following adolescence, the evidence of suppression of gonadotropic hormones by serotonin permits the conjeture that decline in central serotonin associated with establishment of adult gonadal function may be accompanied by a compensatory increase in the efficiency of light activation in certain individuals, perhaps by serotonin-depleted supersentitivity of raphe neurones. Under these conditions, a now lower threshold serotonin-light response may result in paroxysmal discharge of raphe units (as in Papio Papio, whose spike wave response to light, as noted, is prevented by feeding the serotonin precursor L-tryptophane).

Serotonin regulation is relatively independent of light in the adult rat and plays an unknown but probably minor role in man. However, reticular brain stem units are markedly activated during REM sleep and it seems possible that the REM state, which is much exaggerated in normal infancy, may activate monoamine systems in utero and early life, a function partially or transiently subserved by light following parturition, as has been shown for pineal serotonin and melatonin in several species (Wurtman et al., 1968). The brief periods of REM characteristic of nocturnal sleep in adult mammals could then represent cyclical reappearance of the more primitive activation mechanism for serotonin during darkness and thus permit and sustain slow wave sleep. Incomplete suppression of the intense discharge of brain stem (including geniculate) nuclei characteristic of the REM state, decreased slow wave sleep and photically induced spike-wave activity in schizophrenia might then be considered compensatory mechanisms in response to the postulated deficit in serotonin/catecholamine regulation. Finally, we may note experimental evidence of rage, irritability, hallucinatory activity and hyperexoticism in animals following depletion of serotonin (Dement 1969, Jouvet 1969). Similar symptoms and signs in schizophrenic man, including the remarkably frequent sexual paresthesias and preoccupations, may be related to disturbances in the ratio of biogenic amines which it is hypothesized, "bias" the firing threshold of neurones of the limbic striatal "gate" e. g., between amygdala and septum.

A number of mechanisms which enhance the 5HT/DA ratio centrally have found empirical use in the treatment of schizophrenia, including neuroleptic DA blockade (which coincidently augments brain stem unit activity) insulin and electric shock therapies [3]. To the extent that the foregoing conjectures and suppositions embody potentially testable hypotheses, they may stimulate experimental work which will contribute to a better understanding of the mechanisms operating in the development of schizophrenic disorders.

SUMMARY

The close relationship noted between anti-psychotic effects of neuroleptic drugs and induction of extra-pyramidal symptoms is supported by experimental evidence which indicates that increased dopamine (DA) turnover in striatum and blockade of apomorphine-induced stereotypy are closely related to the clinical efficacy of drugs used in the treatment of schizophrenia. These observations and the induction of schizo-

phreniform psychoses by DA potentiating agents such as amphetamines led to the hypothesis that overactivity or hypersensitivity of DA systems may be fundamentally concerned in the pathophysiology of schizophrenia. Of the two major DA systems, the nigrostriatal and mesolimbic pathways, our attention was drawn to the latter by Nauta because of the strategic location of its superior terminus, the *limbic striatum* (composed of nucleus of stria terminalis, nucleus accumbens septi, and olfactory tubercle) at the confluence of efferents from amygdala, hippocampus, and piriform cortex, regions notably associated with mediation of affective, visceral, perceptual, memory, and behavioral disturbances similar to those observed in schizophrenia.

A growing body of experimental evidence indicates that dopamine release in neostriatum affects the firing threshold of striatal interneurones and is in turn regulated by an inhibitory feedback loop which originates in post-synaptic receptors of caudate nucleus and descends through medial forebrain bundle to terminate at GABA-coded synapses on dopamine cells of origin in substantia nigra. The behavioral and electrophysiologic effects of blocking this putative GABA coded strio-nigral system in mesencephalon has been examined in freely moving cats with chronically implanted cannulas and electrodes. Local instillation of biculline in the ventral tegmental area, nucleus of origin of the mesolimbic dopamine system, causes a remarkable state of behavior suggesting intense fear, visual and auditory hallucinations. Introduction of the GABA blocking agent in substantia nigra causes motor and somatosensory disturbances but little affective change. Striking subcortical EEG changes were recorded. The responses are diminished or prevented by dopamine blocking agents and restored by dopamine potentiating drugs.

RESUMEN

La relación estrecha notada entre los efectos anti-sicóticos de drogas neurolépticos y la inducción de síntomas extra-piramidales es apoyada por evidencia experimental que indica que el vuelco acrecentado de dopamina (DA) en el cuerpo estriado y el bloqueo de la estereotipia inducida por la apomorfina, tienen íntima relación con la eficacia clínica de las drogas usadas en el tratamiento de la esquizofrenia. Estas observaciones y la inducción de psicosis esquizofreniformes por medio de agentes potencializadores de la DA, tales como las anfetaminas, condujo en la hipótesis de que la sobreactividad o hipersensitividad de los sistemas de DA pueden estar fundamentalmente relacionadas en la patofisiología de esquizofrenia. De los dos sistemas mayores de DA, las vías nigroestriadas y mesolímbicas, nuestra atención fue dirigida al último por Nauta, por la localización estratégica de su terminal superior, el *estriado límbico* (compuesto del núcleo de la stria terminalis, núcleo accumbens septi y tubérculo olfatorio) a la confluencia de eferentes de la amígdala, hipocampo, y corteza piriforme, regiones notablemente asociadas con el origen de disturbios afectivos, viscerales, perceptuales, de la memoria y de conducta, similares a aquellos observados en esquizofrenia.

Un cuerpo creciente de evidencia experimental indica que la liberación de dopamina en el neoestriado afecta el umbral de descarga de las interneuronas del estriado y es a su vez regulado por un ansa inhibidora de retroalimentación que se origina en receptores post-sinápticos del núcleo caudado y desciende a través del haz medial del prosencéfalo para terminar en sinapsis del código GABA, en células de dopamina originadas en la sustancia Nigra. Los efectos de conducta y electrofisiológicos del bloqueo de este sistema estrionigral con código GABA en el mesencéfalo, han sido examinados en gatos que se mueven libremente con cánulas implantadas crónicamente y electrodos. La instalación local de bicuculina en el área tegmental ventral, núcleo de origen del sistema de dopamina mesolímbico causa un cambio de conducta notable, sugiriendo intenso temor, alucina-

ciones visuales y auditivas. La introducción del agente bloqueante GABA en la sustancia nigra causa disturbios motores y somatonsensoriales, pero poco cambio afectivo. Fueron registrados pronunciados cambios subcorticales del EEG. Las respuestas fueron disminuidas o suprimidas por agentes bloqueantes de dopamina y restauradas por drogas potencializadores de dopamina.

RÉSUMÉ

La relation étroite notée entre les effets anti-phychotiques de drogues neuroleptiques et l'induction des symptomes extra-pyramidales est appuyée par l'évidence expirémentale qui indique que le tour d'augmentation de la dopamine (DA) dans le corps strié et le bloquage de la stéréotipie causé par l'apormorphine, ont une relations intime avec l'efficacité clinique des médicaments employés dans le traitement de la esquisophrénie.

Ces observations et la production de psychoses esquisophréniformes par moyens d'agents potentialisateurs de la DA, tels que les amphetamines, a conduit á l'hypothese de ce que la superactivité ou l'hypersensibilité des systemes de DA peuvent être fondamentalement relationnées dans la patophysiologie de la esquisophrenie. Des deux principaux systemes de DA, les voies nigrostriées et mesolimbiques, notre attention fut orientée a ce dernier par NAUTA, pour la localisation stratégique de sa terminaison supérieure, le *limbique-strié* (composé du noyau de la strie terminale, noyau accubenssepti et tubercule olfactif) a la confluencé des efferentes de l'agmydale hippocampe, et cortex piriforme, régions particulierement associées avec l'origine de troubles affectifs, viscerales, perceptuales, de la mémoire et de la conduite, semblables a ceux observés en esquizophrenie.

Un corps croissant d'evidence expérimentale indique, que, la liberation de Dopamine dans le neostrié affecte la limite de décharge des interneurons de (l'estrié) et est a son tour régularisé par une anse inhibitrice de retroalimentation qui s'origine en récepteurs post-sinaptiques, du noyau caudé et descend a travers du faisceau moyen du prosencephalo pour terminer en sinapsis code GABA, en cellules de dopamine originées dans la substance Nigra. Les effets de conduite et d'electrophysiologiques du bloquage de ce systeme estrionigral avec le code GABA dans le mosencephale, ont été examinés sur les chats qui, se déplacent librement avec des canules implantées en permanence et d'electrode. L'installation locale de bucuculine dans la zone tegmental ventral, noyau d'origine du systeme Dopamine mesolimbique provoque un changement de conduite notable, provoquant une intense frayeur, allucinations visuelles et auditives. L'introduction de l'agent bloquant GABA dans la substance nigra, provoque des troubles moteurs et somato-sensoriels, mais peu de changements affectif. On a constaté noté des changements prononcés subcorticales de EGG. Les réponses furent diminuées ou supprimées par agents bloquants de Dopamine et rétablis par drogues potentialisateurs de Dopamine.

ZUSAMMENFASSUNG

Der beobachtete enge Zusammenhang zwischen den antipsychotischen Wirkungen neuroleptischer Drogen und der Einsetzen extrapyramidaler Symptome wird unterstützt durch experimentelle Erfahrung, welche zeigt, dass ein vermehrter Umsatz von Dopamin (DA) im corpus striatum und die Blockierung der von Apomorphin induzierten Stereotypie in engem Zusammenhang stenen mit der klinischen Wirksamkeit der bei der Behandlung der Schizophrenie verwendeten Drogen. Diese Beobachtungen und das Auftreten von scrizophrenieartigen Psychosen mittels DA-Wirkung verstärkender Agentien, wie z. B. der Amphetamine, führten zur Hypothese, dass Über-aktivität und Hypersensibilität von DA-Systemen in einen grudsätzlichen Zu-

sammenhang mit der Pathophysiologie der Schizophrenie stehen könnten.

Von den zwei grösseren Systemen von DA, dem Nigrostriatum und den mesolimbischen Bahnen, wurde unsere Aufmerksamkeit von Nauta auf die letzteren gelenkt, wegen der strategischen Lage ihres oberen Endes, des limbischen Striatum/bestehend aus dem Kern der Stria terminalis, dem nucleus accumbens septi und den tubercula olfactoria am Zusammehfluss der efferenten Bannen aus Amygdala, Hippocampus und cortex piriformis, bekanntlich Gegenden, die in Zusammenhang mit der Vermittlung von affektiven und viszeralen Störungen stehen, solchen der warhrnehmung, des Gedächtnisses und des Verhalten, ähnlich wie sie bei der Schizophrenie beobachtet werden.

Die experimentelle Erfahrung bezeugt in zunehmendem Ausmass, dass die Freimachung von Dopamin im Neostriatum die Zündungsschwelle del Interneuronen des Striatum beeinflusst und ihrerseits geregelt wird durch eine bremsende "feed-back" Schleife, die in postsynaptischen Rezeptoren des nucleus caudatus ihren Ursprung hat und im mittleren Bündel des Prosenzephalon absteig, um in Synapsen des Codex GABA zu enden, in Dopamin Zellen, die aus der Substantia nigra stamen. Die Wirkungen auf das Verhalten und die elektrophysiologischen Wirkungen durch die Blockierung dieses Systems, Striatum-Nigra mit GABA-Kodex im Mesonzephalum, wurden bei Katzen untersucht, die sich frei bewegen mit dau-

Die lokale Instillation von Bicucullin in ernd eingesetzten Kanülen und Elektroden. die ventrale Tegmentum one, Kern, der aus dem mesolimbischen Dopamin - System stammt, verursacht eine bemerkenswerte Aenderung im Verhalten, sugeriert intensive Angst, visuelle und Gehörshalluzinationen. Die Einführung des GABA blockierenden Agens in die substantia nigra verursach motorische Störungen und somatosensoriale, aber eine geringe affektive Veränderung. Es wurden auffallende subkortikale Veränderungen im Elektroenzephalogramm registriert. Durch Dopamin blockierende Mittel wurden die Reaktionen verringert oder unterdrückt und durch Dopamin verstärkende Drogen wieder hergestellt.

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Substances Neurotropes et Comportement Sexuel du Rat Male

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Le comportement sexuel du rat mâle est profondément modifié par de nombreuses substances neurotropes. La complexité des activités copulatoires rend nécessaire l'analyse expérimentale des différentes composantes.

1º — Certaines activités sont très spécifiques, essentiellement et uniquement sexuelles: l'activité copulatoire avec ses composantes motrices (intromissions) et temporelles (latences éjaculatoires) ainsi que l'activité éjaculatoire elle-même. Toute modification intervenant directement sur ces facteurs pourra être considérée légitimement comme jouant un rôle direct sur le comportement sexuel.

2º — D'autres activités motrices, tout en étant directement associées aux éléments spécifiques du comportement sexuel ne dépendent pas cependant entièrement de lui. Ainsi l'intensité de l'activité copulatoire est étroitement liée aux facteurs précédents mais aussi à des mécanismes qui en eux-mêmes, n'intéressent pas uniquement la conduite sexuelle, en particulier les niveaux fondamentaux de vigilance du Système Nerveux Central. Les périodes réfractaires rentrent également dans ce cadre: sans réalisation sexuelle, elles n'existent pas mais leur durée n'est pas directement fonction de la conduite sexuelle elle-même.

Le schèma ci-joint représente la traduction graphique des différents éléments décrits. Ils sont normalement associés dans une séquence spatio-temporelle mais des données expérimentales prouvent qu'ils peuvent éventuellement varier quantitativement et qualitativement de façon indépendante.

Les études pharmacologiques ont montré que ces diverses composantes n'etaient pas nécessairement contrôlées par les mêmes mécanismes biochimiques. Pour la commodité de la présentation nous envisagerons les régulations pharmacologiques en fonction des grands neuromédiateurs connus.

I. Regulations adrenergiques.

Toutes les substances intervenant directement ou indirectement dans la régulation des catécholamines centrales manifestent une action sur le comportement sexuel.

a) Parmi les substances augmentant le taux des catécholamines nous avons étudié l'amphétamine, un I. M. A. O. (Iproniazide), l'adrénaline et la Nor-adrénaline.

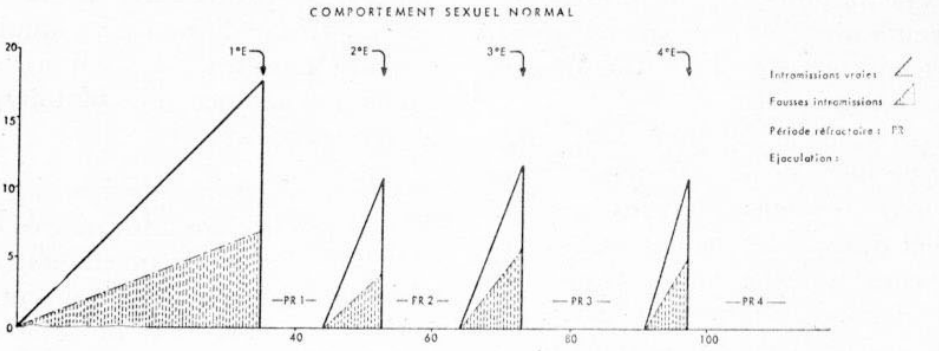
—*La Nor-adrénaline* (50 à 100 µg / kg / voie intra-péritonéale) provoque la disparition transitoire totale de tout comportement sexuel.

—*L'Adrénaline* provoque des variations différentes selon les doses: aux doses fortes (100 µg / kg / voie intra-péritonéale): disparition de tout comportement sexuel. Aux doses plus faibles (50 µg / kg), on observe une augmentation significative du nombre des éjaculations, pas de modification du nombre des intromissions ni des latences éjaculatoires ni des périodes réfractaires.

—*La d-Amphétamine* (2 mg / kg / voie intra-péritonéale) possède des effets différents selon la chronologie de son administration: l'action immédiate entraine une augmentation du nombre des éjaculations, une diminution de toutes les périodes ré-

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SCHEMA D'INTERPRETATION DES DIFFERENTES COMPOSANTES DU COMPORTEMENT SEXUEL DU RAT MALE



En abscisse sont portés les temps exprimés en minutes .
Chaque triangle représente par le côté des abscisses la latence pré-éjaculatoire et par le côté sur les ordonnées le nombre d'intromissions vraies et fausses nécessaires pour une éjaculation .

fractaires et une légère diminution du nombre des intromissions et des latences d'éjaculation. Si l'administration d'amphétamine est poursuivie pendant plusieurs jours, à partir du 5ème jour, il se produit une diminution très importante du comportement sexuel alors que l'excitation motrice reste intense.

—*L'Iproniazide* (I. M. A. O., 25 mg / kg / voie sous-cutanée) agit également différemment en administration aigue ou chronique. Après trois jours, augmentation du nombre des ejaculations, diminution du nombre des intromissions et des durées de latence pré-éjaculatoires; pas de modification des périodes réfractaires. A partir du 6ème jour, disparition du comportement sexuel chez plus de 60 % des animaux traités, les autres manifestant un comportment excessivement réduit.

b) Trois substances anti-adrénergiques ont été expérimentées: la di-hydroergotamine (D. H. T.), la dibénamine et le propranolol.

—*La di-hydroergotamine* (D. H. E.) (4 mg / kg Ip) augmente le nombre des éjaculations, diminue le nombre des intromissions et ne modifie pratiquement pas les latences et les périodes réfractaires.

—*La dibénamine* (0.6 mg / kg) augmente égalment le nombre des éjaculations diminue les latences pré-éjaculatoires et le nombre des intromissions sans modifier les périodes réfractaires.

—*Le propranolol* (3 mg / kg / voie intra-péritonéale) augmente légèrement le nombre des éjaculations et au début du comportement diminue les latences et le nombre des intromissions. Les périodes réfractaires ne sont pas modifiées.

II. Regulations cholinergiques.

Parmi les substances étudiées, nous avons retenu pour leur netteté les résultats obtenus avec la nicotine, stimulant cholinergique et l'atropine comme anti-cholinergique.

—*La nicotine* (0,60 mg / kg / voie sous-cutanée) augmente le nombre des éjaculations, raccourcit les latences pré-éjaculatoires et les périodes réfractaires. Le nombre des intromissions n'est modifié qu'au début de l'action.

—*Le sulfate d'atropine* (10 mg / rat / voie intra-péritonéale) entraine la disparition totale de toute activité sexuelle pendant la durée de son action.

III. Le rôle de la 5-hydroxytryptamine (sérotonine, 5 H.T.) a donné lieu récement à de nombreuses recherches expérimentales.

L'administration du précurseur 5 H.T.P. (30 mg / pendant 20 jours) donne des modifications chronologiquemente variables : l'action immédiate (après 1h ½) consiste en une diminution du nombre des intromissions sans modification du nombre des éjaculations ni des périodes réfractaires. Après dix à vingt jours de traitement, il se pro-

duit une augmentation très significative du nombre des éjaculations, une diminution des latences éjaculatoires, un raccourcissement des périodes réfractaires sans variation du nombre des intromissions.

La méthysergide (substance anti-sérotoninergique par blocage des récepteurs) possède des actions variables selon les doses. A la dose de 4 et 8 mg / kg, trois heures avant le test, on constate une augmentation du nombre des éjaculations sans aucune autre modification des différents paramètres comportementaux. Il faut signaler, en outre, une augmentation de l-activité générale assez peu focalisée. Aux doses supérieures (13 et 18 mg / kg) on ne constate aucune modification du comportement sexuel.

IV. Différentes substances psychotropes interviennent assez directement sur le comportement sexuel.

—*La chlorpromazine* (3 mg / jour) détermine une baisse progressive du comportement sexuel caractérisée par la diminution des éjaculations, l'augmentation du nombre des intromissions et des périodes réfractaires sans variation des latences.

—*L'acide lysergique* (L. S. D. 25), (50 µg / kg), quinze minutes avant le test, augmente très nettement le nombre des éjaculations, diminue le nombre des intromissions, des latences éjaculatoires et des périodes réfractaires.

—*La réserpine* possède des actions variables selon la dose administrée. A la dose de 250 µg /kg, le comportement sexuel se modifie progressivement au cours du traitement: augmentation des éjaculations, diminution des intromissions et des latences, pas de variation des périodes réfractaires. Aux fortes doses (600 µg / kg), après une première phase d'augmentation du comportement sexuel, il se produit une abolition totale de toute activité copulatoire, concomitante d'un effet toxique général.

—*Le sulpiride* entraine des modifications mineures du comportement sexuel: diminution du nombre des éjaculations et augmentation des latences pré-éjaculatoires et du nombre des intromissions. Ces effets sont d'ailleurs beaucoup plus nets au début du traitement qu'à partir du dixième jour d'administration du produit.

RÉSUMÉ

Ces nombreux résultats sont encore difficiles à interpréter et il n'est pas possible actuellement d'établir une corrélation stricte entre l'action d'un médiateur chimique et le comportement sexuel. Toutefois il ressort des données obtenues que le comportement sexuel dépend d'une régulation à la fois adrénergique et cholinergique. Toute exagération ou diminution de la médiation catécholaminergique, entraine des perturbations du comportement sexuel parmi lesquelles le nombre des éjaculations semble être au premier plan.

Sur le plan cholinergique, les résultats semblent plus simples pisqu'une inhibition importante de cette médiation entraine l'abolition de tout comportement, sa stimulation modérée déterminant une augmentation très importante de la conduite sexuelle. La régulation sérotoninergique reste encore difficile à définir et actuellement d'après nos données expérimentales, il semble que la 5 H. T. P. intervienne davantage comme modulateur éventuel des catécholamines ou des cholinergiques que comme agent direct. Enfin, il reste très difficile de comprendre le rôle des différentes substances psychotropes, sauf pour les substances dont on connait par ailleurs les actions sur les catécholamines ou les indol-amines et qui sont susceptibles d'intervenir sur le comportement sexuel par l'intermédiaire de leurs effets sur les mono-amines cérebrales.

RESUMEN

Esos numerosos resultados son todavía difíciles de interpretar y no es posible actualmente establecer una correlación estricta entre la acción de un mediador químico y el comportamiento sexual. Sin embargo resalta de los datos obtenidos que el com-

portamiento sexual depende de una regulación a la vez adrenérgica y colinérgica. Toda exageración o disminución de la mediación catecolaminérgica, entraña perturbaciones del comportamiento sexual entre las cuales la cantidad de eyaculaciones parece estar en el primer plano.

Sobre el plano colinérgico, los resultados parecen más sencillos ya que una inhibición importante de esa mediación entraña la abolición de todo comportamiento, su estímulo moderado determina un aumento muy importante de la conducta sexual. La regulación serotoninérgica es todavía difícil de definir y actualmente por nuestros datos experimentales, parece que la 5HTP interviene más como modulador eventual de las catecolaminas o de los colinérgicos que como agente directo. En fin, es muy difícil de comprender el rol de las distintas sustancias sicotrópicas, salvo por las sustancias de los que se conocen por otro lado las acciones sobre las catecolaminas o las indol-aminas y que son susceptibles de intervenir sobre el comportamiento sexual por intermedio de sus efectos sobre las mono-aminas cerebrales.

SUMMARY

These numerous results are still difficult to interpret and it is not possible at present to establish a strict correlation between the action of one chemical mediator and the sexual behaviour. However it is evident from the data obtained that the sexual behaviour depends on an adrenergic and at the same time cholinergic regulation. Every exaggeration or decrease of the catecholaminergic mediation causes changes of the sexual behaviour among which the number of ejaculations seems to be foremost.

On the cholinergic plane, the results seem to be more simple, seeing that an important inhibition of that mediation causes the abolition of all behaviour, its moderate stimulus determines a very important increase of the sexual behaviour. The serotoninergic regulation is still difficult to define, and at present through our experimental data, it seems that the 5 HTP comes advantageously between as an eventual modulator of the catecholamines or of the cholinergics than as a direct agent. To conclude, it is very difficult to understand the role of the different psychotropic substances of which their action on the catecholamines or the indole-amines are known, and which are susceptible to act on the sexual behaviour through the intermediary of its effects on the cerebral mono-amines.

ZUSAMMENFASSUNG

Diese zahlreichen Resultate sind noch schwierig auszulegen und es ist gegenwartig unmöglich eine sichere Verbindung zwischen einem chemischen Vermittler und dem sexuellen Verhalten aufzustellen. Auf jeden Fall geht aus den erhaltenen Daten hervor, dass das sexuelle Verhalten von einer gleichzeitigen adrenergischen und Cholinergischen Regulierung abhängt. Jede Übertreibung oder Verminderung der katecholinergischen Medikation schliesst in sich Störungen des sexuellen Verhalten, unter welchen die Menge der Ejakulationen an erster Stelle zu stehen scheint.

Im cholinergischen Bereich scheinen die Ergebnisse einfacher, schon weil eine bedeutende Unterbindung dieser Medikation das Verlöschen jeden Verhaltens mit sich bringt, ihre mässige Reizung eine bedeutende Erhöhung des sexuellen Verhalten bestimmt. Die serotoninergische Regulierung ist noch schwierig zu bestimmen und gegenwärtig scheint es auf Grund unserer experimentellen Ergebnisse, dass das 5 HTP mehr als eventueller Abstimmer der Katecholamine oder der Cholinergica eingreift als als direkter Vermittler.

Es ist am Ende sehr schwer die Rolle der verschiedenen psychotropen Substanzen zu verstehen, mit Ausnahme der Substanzen von denen man von anderwo ihre Wirkungen auf die Katecholamine oder die Indolamine kennt und die fähig sind auf das sexuelle Verhalten zu wirken mittels ihres Effektes auf die zerebralen Monoamine.

Brain Serotonin Synthesis and Sexual Behavior in Rats

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Introduction

An increased serotoninergic tone seems to have an antagonistic effect on the components of copulatory behavior in male and female rats, Meyerson [18], Malmnäs [17]. In addition, many recent reports show that para-chlorphenylalanine, a tryptophan hydroxylase inhibitor, increases sexual performances especially in male rats, Sheard [21], Tagliamonte [23] et al., Ahlenius [1] et al. We have shown that PCPA when administered neonatally can modify permanently sexual performances of rats, Hyyppä [11] et al.

Several neurochemical investigations have been designed to clarify relationships of brain serotonin function to sexual behavior and to its regulation. One of the problems in these attemps have been to measure dynamics of functional compartments of brain serotonin, Aprison and Hingtgen [2], Shields and Eccleston [22], Hyyppä et al. [12].

Many methods for estimating the rate at which the brain synthesizes serotonin has been suggested. Among them one has obvious advantages in comparison to the others: if tracer doses of radiolabeled serotonin precursor, tryptophan, are given, they do not disturb the steady state of the transmitter, and they can be administered via the physiological route mixing with the entire brain tryptophan pool, Wurtman and Fernstrom [24], Hyyppä et al. [12].

However, if turn-over rate measurements reflect the turn-over of the total serotonin rather than the free and functional pool, these methods do not necessarily provide any better correlations with behavioral changes than conventional pharmacological approaches, in which the total concentration and turn-over of serotonin are seriously altered, Aprison and Hingtgen [2], Hyyppä et al. [11].

In the present paper we introduce a new modification of serotonin turn-over measurements, which can be accepted as a "functional" parameter of brain serotonin metabolism in correlation to behavior. In the method we measure the specific activities of brain tryptophan and serotonin at very short intervals after H^3-tryptophan administration to obtain an estimate of the synthesis rate of brain serotonin. We shall present some data about its application into studies of sex behavior, as well.

Serotonin synthesis rate

Rats were decapitated at various intervals (between 3 and 30 min) after receiving L-tryptophan-H^3 (50 μcurie per 100 g). Plasma and brain tryptophan levels, serotonin levels and specific activities were measured according to Hyyppä et al. [11]. The rate at which H^3-tryptophan was converted to H^3-serotonin was calculated by dividing the brain H^3-tryptophan at that time.

The specific activity of H^3-tryptophan in plasma and brain increased very rapidly, reaching a peak value at about 10 min after

D. P. C.: Member of the Carrera del Investigador Comisión Nacional de Estudios Geo-Heliofísicos, Argentina

injection. (Figs. 1 and 2) 50 min later the specific activity of amino acid was greater in the brain than in plasma. The concentrations of endogenous tryptophan did not change during the 3-hour-period.

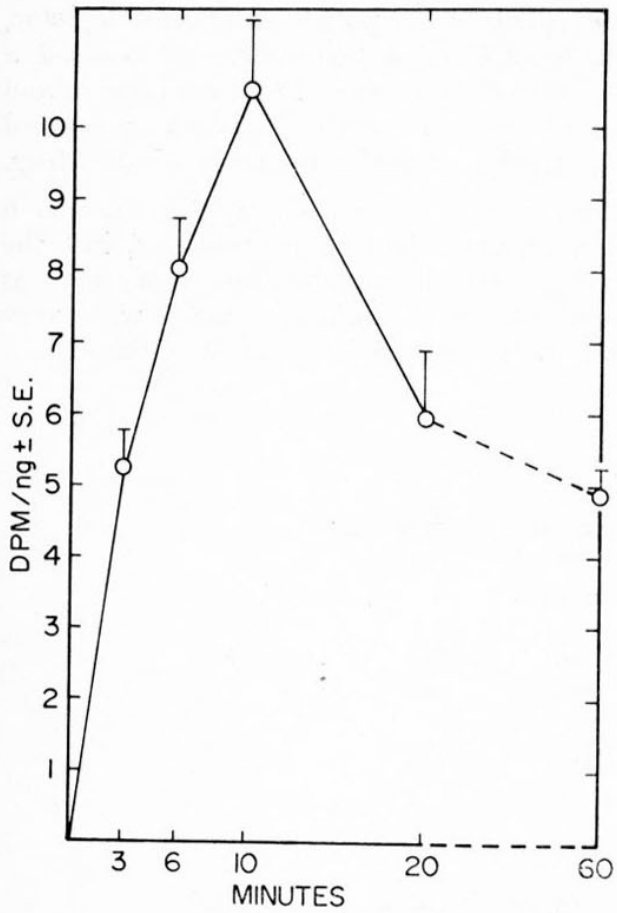


Fig. 1. — *Specific activity of H^3-tryptophane in plasma after intraperitoneal injection of H^3 tryptophane* (50 μcurie *per* 100 *g of body weight*).

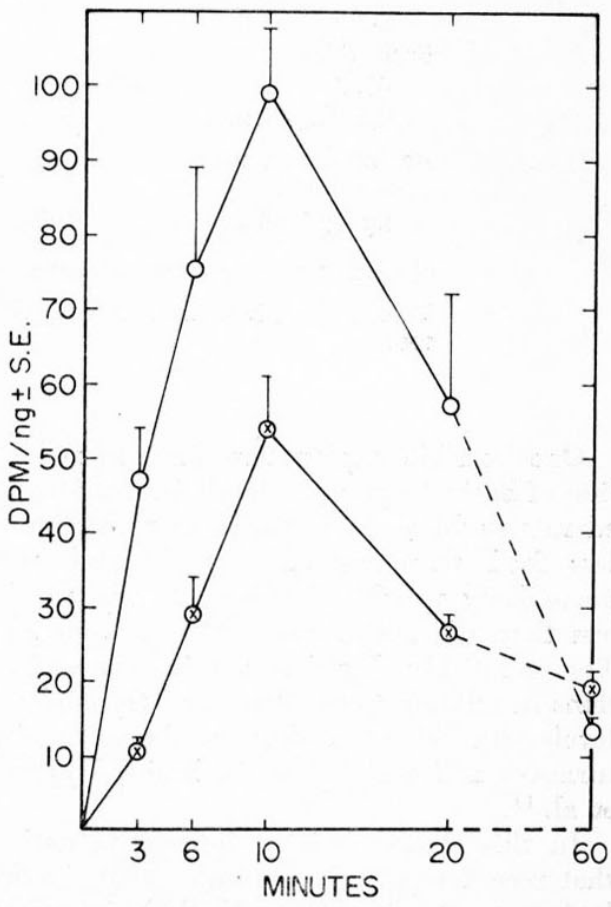


Fig. 2. — *Specific activities of H^3-tryptophane (open circles) and of H^3-serotonin (crossed circles) in brain after intraperitoneal injection H^3-triptophane* (50 μcurie *per* 100 g *of body weight*).

The specific activity of brain serotonin increased also very rapidly reaching its peak value between 10 and 20 min. (Fig. 2.)

This finding indicates that the initial accumulation of brain serotonin takes place in less than 10 minutes. That is why the following experiments have been performed in 5 minutes after the injection of radiolabeled tryptophan. (Independently very similar technique for measuring serotonin metabolism has been published by Glowinski's group, Hery et al.[9]. An interval of 7 minutes after intracisternal injection of radiolabeled tryptophan was used in their study which clearly showed daily variations in brain serotonin metabolism.)

Effect of 5,6-dihydroxytryptamine on brain serotonin synthesis

Intraventricular injection of 5,6-dihydroxytryptamine, a potent serotonin depletor, Baumgarten and Schlossberger [4], caused a significant decrease in brain tryptophan and serotonin concentrations when measured two weeks after the injection of the drug.

The specific activity of tryptophan was 6 times higher than in control rats, but the rate at which radiolabeled serotonin was accumulated (synthesis rate) was very markedly decreased as shown in table 1.

TABLE 1

Serotonin synthesis rate in brains of rats treated with 5,6-dihydroxytryptamine

	5,6-dihydroxytryptamine			Vehicle		
Brain TP						
ng/g	1510 ± 172[a]		(18)	3000 ± 210		(18)
dpm/ng/5 min	66 ± 10[a]		(9)	11 ± 1		(9)
Brain 5-HT						
ng/g	235 ± 8[a]		(18)	310 ± 0.9		(9)
dpm/ng/5 min	9.6 ± 0.7		(9)	8.2 ± 0.9		(9)
Accumulation rate of serotonin						
ng/g/5 min	6.8[a]		(8)	45.6		(8)

a) Differs from vehicle-treated controls; $p < 0.001$

Values are given as mean ± S.E. and tested according to Student's test.

One possible explanation for the reduction of brain tryptophan levels in drug-treated rats could be their tendency to consume less food than normal rats. Indeed, the mean body weight of these rats was much less than of control rats (210 vs. 300 g). The relatively high serotonin concentrations in relation to the depressed tryptophan levels can reflect a decrease in serotonin turnover and metabolism in brain, Hyyppä et al. [11].

In this respect it is of interest to notice that recent reports have shown that 5,6-dihydroxytryptamine (like PCPA) increases male sexual performances possibly by the mechanism which is mediated through brain serotonin function.

Effects of ovariectomy on brain serotonin synthesis

Female steroid treatment is known to induce estrus behavior in ovariectomized rats, Meyerson [19]. However, we did not find alterations in whole brain serotonin synthesis rates in ovariectomized rats receiving estradiol-progesterone treatment. Table 2. This finding is in agreement with similar results of Meyerson and Lewander [18]. They used pharmacological drugs to study brain serotonin synthesis or degradation rates. More direct measurements have also shown that female hormone replacement therapy does not change hypothalamic serotonin synthesis, Bapna et al. [3]. In that study radiolabel-

TABLE 2

Serotonin synthesis rate in brains of ovariectomized rats.

	Ovariectomy and hormones	Ovariectomy and vehicle
Brain TP ng/g	3500 ± 340 (11)	4100 ± 200 (11)
Brain 5-HT ng/g	620 ± 30 (11)	620 ± 25 (11)
Accumulation rate of serotonin ng/g/5 min	97 ± 24 (5)	110 ± 17 (5)

No statistically significant differences are seen between groups. Rats were injected with estradiol-benzoate and progesterone and or with vehicle.

ed tryptophan was administered into the cerebrospinal fluid through a permanent cannula in the ventricle, and hypothalamic serotonin synthesis was measured from 2 to 8 hours later by the method of Neff and his co-workers [20]. In contrast, however, Kordon and Glowinski [13] reported that the accumulation of labeled serotonin and its metabolite, 5-hydroxyindoleacetic acid, in the hypothalamus, 5 minutes after the intracisternal injection of tritiated tryptophan was significantly depressed by progesterone in ovariectomized rats. In their technique the amount of labeled tryptophan immediately after its injection can be high enough to produce an increase of serotonin synthesis, Wurtman and Fernstrom [24]. In addition, the manipulation itself can be stressful and alter the serotonin synthesis. These drawbacks of technique are avoided in our method.

Effects of castration on brain serotonin synthesis

Since the significance of androgens in the indoleaminergic regulation of sexual behavior has been established recently, Gessa et al. [7], Gawienowski and Hodgen [6], we wanted to see whether castration is able to alter brain serotonin synthesis. We did not find significant differences between castrated, testosteronized or intact male rats. However, the specific activity of brain tryptophan was lower in intact brains. Table 3.

TABLE 3

Serotonin synthesis rats in brains of castrated adult male rats

	Castrated	Castrated + Testosteronized	Intact
Plasma tryptophan ng/ml	12800 ± 1200 (3)	8000 ± 800 (4)	8700 ± 1800 (4)
dpm/ng	8.9 ± 2.2 (3)	11.8 ± 1.4 (4)	11.8 ± 2.9 (4)
Brain tryptophan ng/g	4200 ± 348 (9)	2600 ± 177 (9)	6200 ± 1060 (8)
dpm/ng	6.0 ± 1.0 (9)	8.5 ± 1.7[a] (9)	3.3 ± 0.8 (7)
Brain serotonin ng/g	267 ± 9 (9)	289 ± 20 (9)	277 ± 9 (11)
dpm/ng	2.6	2.9	2.3
Accumulation rate in 5 minutes (ng/g/5 min of serotonin)	115 ± 37 (9)	121 ± 21 (10)	196 ± 51 (7)

a) Differs from intact control; $p < 0.02$

Values are given as mean ± S.E. and tested according to analysis of variance.

Alterations in brain tryptophan levels which did not modify serotonin synthesis rates have been also observed by Bapna et al. [3], who found that tryptophan concentrations in brain can be influenced by female gonadal hormones without changes in the hypothalamic serotonin turn-over rates. In their study the turn-over rate of serotonin does not necessarily reflect the small functional pool but the total serotonin in the hypothalamus, Hyyppä et al. [11].

Effects of masculiniaztion and feminization on the brain serotonin synthesis

It has previously been shown that modifying uptake and metabolism of biogenic amines in the brain, can disturb the normal sexual development when they are given during the critical period of sexual differentiation of the central nervous system, Carraro et al. [5], Hyyppä [10], Hyyppä et al [11], Ladoski et al. [14], Lehtinen et al. [16]. From these and other observations, Ladoski and Gaziri [14], a hypothesis can be formulated according to which indoleaminergic mechanisms may play an important role in regulating the sexual differentiation of the central nervous system.

Therefore we experimentally masculinized and feminized neonatal rats, See: Harris[8]. Controls were normal females or sham-operated males. One-day-old Sprague-Dawley rats were reared in the M. I. T. vivarium with their mothers in a room where all external sensory impulses were standardized. These animals were killed at 30 days of age, and brain serotonin synthesis rates were then measured. No significant differences between groups were found among neonatally-castrated males, sham-operated males, masculinized females or intact females as far as the synthesis rate of brain serotonin. However, again differences in brain tryptophan concentrations were found between the groups : tryptophan concentrations were higher and the specific activity of tryptophan lower in the brain of castrated males and testosteronized (masculinized) females as compared to their respective controls. Table 4.

TABLE 4

Serotonin synthesis rate in brains of neonatall masculinized or feinized 30-day-old rats

	Castrated	Testosterone-nized females	Sham-oper. males	Vehicle females
Plasma TP ng/ml	10600 ± 1166 (5)	10300 ± 1750 (4)	10400 ± 1120 (5)	7500 ± 650 (4)
dpm/ng	9.8 ± 1.3 (4)	8.3 ± 0.5 (4)	10.4 ± 2.0 (4)	15.0 ± 0.7 (4)
Brain TP ng/g	4200 ± 253 (10)[a]	4800 ± 330 (9)[b]	3400 ± 126 (10)	3000 ± 221 (10)
dpm/ng	4.3 ± 0.5 (9)[c]	4.9 ± 0.5 (9)[d]	6.6 ± 0.7 (9)	6.6 ± 0.4 (10)
Brain 5-HT ng/g	335 ± 14 (10)	349 ± 8.2 (10)	344 ± 14 (10)	341 ± 12 (10)
dpm/ng	2.4 ± 0.3 (8)	2.2 ± 0.2 (8)	2.8 ± 0.3 (9)	3.0 ± 0.3 (10)
Accumulation rate of serotonin (ng/g/5 min)	176 ± 19 (8)	153 ± 19 (8)	178 ±17 (9)	166 ± 25 (10)

a) Differs from sham operated control; $p < 0.02$
b) Differs from vehicle-treated controls and sham operated males; $p < 0.001$
c) Differs from sham operated control; $p < 0.01$
d) Differs from vehicle treated controls; $p < 0.05$

Values are given as mean ± S.E. and tested according to analysis of variance.

General discussion

We present a new modification of radiochemical techniques to measure brain serotonin synthesis rate. This technique is convenient, and it is simple enough to measure brain serotonin synthesis rates in large series of experiments. Since it is known at present that neural serotonin is stored in multiple compartments, Aprison and Hingtgen [2], Shields and Eccleston [22], it is highly necessary to find methods which can measure the synthesis rate of the functional pool of serotonin. In order to avoid possible miscalculations due to the metabolism of newly synthesized H^3-serotonin we chose to take samples of brain at relatively short intervals after a pulse injection of H^3-tryptophan. Our findings suggest that time-points before 10 minutes after the injection of tryptophan provide valid data for estimating brain serotonin synthesis.

When the method was tested under experimental conditions, we found a marked change in brain tryptophan levels as well as in brain serotonin synthesis rate. However, when we validated our method for estimating whether sex hormones or gonadectomy can modify brain serotonin synthesis rates, we did not notice any significant alterations, though tryptophan levels were modified. This can be due to the possible failure of our technique or due to the fact that serotonin synthesis does not play any important role in regulation of neuroendocrine and sexual phenomena. We think that our present finding does not exclude the role of serotonin, because there are still several sources of errors in our method which must be corrected in the future: we examined serotonin synthesis between 8 and 10 am. when our animals were not eating; it is possible that diet-induced changes in serotonin synthesis, not discernable in our study, do alter the physiological activity of serotonin neurons, Hyyppä et al. [11]. On the other hand, we measured serotonin synthesis in the whole brain, and it is wellknown that there are specific serotoninergic neurons within the brain, which are located mainly in the midbrain and hypothalamus. The next step in our procedures will be to study brain serotonin synthesis rates in selective brain areas. Our unpublished data show that serotonin synthesis rate can be measured by the present method at least in two pooled hypothalami (75 mg).

In spite of certain technical limitations in our method we are of the opinion that this type of estimations really give better and more precise correlations between the functional pools of transmitters and behavioral measures.

Acknowledgement

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SUMMARY

New method for the estimation of the brain serotonin synthesis rate. In this method radioactive tryptophan is injected intraperitoneally into the rat, and the synthesis rate of the newly formed serotonin is calculated from the accumulation of the radioactive serotonin in the brain. By using this method we studied the effects of sex steroids on the metabolism of brain serotonin. Estradiol benzoate progesterone treatment is able to produce estrous behaviour in cophorectomized rats. However, we did not see changes in the rate of serotonin synthesis. Testosterone when given into newborn female rats produces permanent androgenization of the adult sexual behavior. In our study we found changes in the concentrations of brain tryptophan but the rate of serotonin synthesis was not modified. In castrated male rats testosterone did not produce alterations in the rate of brain serotonin synthesis but it did change brain tryp-

tophan concentrations. Neonatally injected p-chlorophenylalanine increases markedly adult masculine sexual activity but did not affect brain serotonin metabolism measured 15 days after neonatal injections. 5,6-dihydroxytryptamine a potent serotonin depletor, increases male sexual activity, and it decreases markedly brain serotonin synthesis in adult rats. It looks like hormones, which are known to change masculine sexual behavior, generally affect brain indoleamine metabolism, and drugs which deplete indoleamine synthesis, induce an increase in masculine sexual behavior.

RESUMEN

Nuevo método para la estimación del ritmo de síntesis de la serotonina en el cerebro. En este método se inyecta triptofan radioactivo a la rata, por vía intraperitoneal, y se calcula el ritmo de síntesis de la serotonina posteriormente formada por la acumulación de serotonina radioactiva en el cerebro.

Empleando este método estudiamos los efectos de los esteroides de sexo sobre el metabolismo de la serotonina cerebral. El tratamiento con estradiol benzoato progesterona puede producir conducta sexual en ratas coforectomizadas. No obstante, no vimos cambios en la proporción de síntesis serotonina. La testosterona dada a ratas hembras recién nacidas produce androgenización permanente en la conducta sexual adulta. En nuestro estudio, hemos encontrado cambios en las concentraciones de triptofan cerebral, pero no se modificó la proporción de la síntesis de la serotonina. En las ratas machos que fueron castradas, la testosterona no produjo alteraciones en la proporción de síntesis serotonina cerebral, pero sí cambió las concentraciones del cerebro en triptofano. La p-clorofenilalanina inyectada a los recién nacidos aumenta en forma marcada la actividad sexual masculina del adulto, pero no afecta el metabolismo de serotonina del cerebro, medida 15 días después de las inyecciones neonatales.

La 5 y 6-dihidroxitriptamina, un depletor potente de serotonina, aumenta la actividad sexual del macho, y disminuye en forma marcada la síntesis de serotonina del cerebro en ratas adultas.

Parece que hormonas reconocidas en el cambio de la conducta sexual masculina, por lo general afecta el metabolismo de indoleaminas del cerebro, y drogas que reducen la síntesis de indoleamina, inducen un aumento en la conducta sexual masculina.

RÉSUMÉ

Nouvelle méthode pour l'estimation du rythme de synthese de la serotonine sur le cerveau. Dans cette méthode, on injecte au rat du triptofan radioactif, par voie intraperitonale, et on calcule le rythme de synthese de la serotonine postérieurement fermée par l'accumulation de la serotonine radioactive dans le cerveau.

Employant cette méthode, nous étudions les effets des steroîdes du sexe sur le metabolisme de la serotonine cerebral. Le traitement avec l'estradiol benzoato progesterone peut produire un comportement sexuel chez les rats coforectomisés. Cependant, nous n'avons pas vu de changement dans la proportion de synthese serotonine. La testoterone donnée aux rats femelles nouveaux nés produit androgenisation permanente dans le comportement sexuel adulte. Dans nôtre étude, nous avons trouve des changements dans les concentrations triptofan cerebral, mais la proportion de la synthèse de la serotonine, ne s'est pas modifiée chez les rats males castrés, la testosterone n'a pas produit d'altérations dans la proportion de synthèse serotonine cérébral, mais par contre a changé les concentrations du cerveau en triptofan.

La 5 et 6-dihidroxitriptamine, dépressif puissant de serotonine, augmente l'activité sexuelle du rat mâle et diminue en forme

marquée la synthèse de la serotonine du cerveau chez les rats adultes.

Il y a aparence d'hormones connues dans le changement du comportement sexuel masculin, pour le général affecte le métabolisme de indoleamine du cerveau, et drogues qui réduisent la synthèse de l'indoleamine, produit une augmentation dans le comportement sexuel masculin.

ZUSAMMENFASSUNG

Neue Methode um den Rythmus der Synthese des Serotonin im Gehirn zu schätzen. Bei dieser Methode wird radioaktives Triptophen auf intraperitonealem Weg der Ratte injiziert und man berechnet danach den Rythmus der Serotoninsynthese durch Messung des im Gehirn gespeicherten radioaktiven Serotonin.

Durch Anwendung dieser Methode haben wir die Wirkungen der sexuellen Steroide auf den Serotoninstoffwechsel im Gehirn studiert. Die Behandlung mit Estradiolbenzoat, Progesteron kann bei ovariektomierten Ratten sexuelles Verhalten hervorrufen.

Trotzdem haben wir keine Änderung im Ausmass der Serotoninsynthese gesehen. Testosteron, weiblichen neugeborenen Ratten gegeben, verursacht eine dauernde Vermännlichung im sexuellen Verhalten der Erwachsenen. Bei unserer Untersuchung haben wir Änderungen in der Triptophankonzentration im Gehirn gefunden, aber es änderte sich nicht das Verhältnis der Serotoninsynthese.

Bei männlichen kastrierten Batten brachte Testosteron keine Änderung im Verhältnis der Serotoninsynthese im Gehirn, doch ja veränderte es die Konzentrationen von Tryptophan im Gehirn. Das p-Chlorophenylalanin, injiziert bei Neugeborenen, erhöht in deutlicher Form die sexuelle Aktivität des reifen Männchen, aber beeinflusst nicht den Stoffwechsel des Serotonin im Gehirn, gemessen 15 Tage nach der Injektion Neugeborener.

Das 5- und 6-dihidrooxytriptamin, ein starker Aufbraucher von Serotonin, erhöht die geschlechtliche Aktivität des Männchen und vermindert in deutlicher Form die Serotoninsynthese des Gehirns bei erwachsenen Ratten.

Im Allgemeinen beeinflusst der Indolaminstoffwechsel das Gehirn in einer Art Wie Hormone, von denen bekannt ist, dass sie das männliche Sexualverhalten ändern und Drogen, welche die Indolamin-Synthese verringern, verursachen eine Steigerung im männlichen Sexualverhalten.

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Regulation Biochimique des Etats de Vigilance

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Introduction.

L'approche neurochimique de la régulation des états de sommeil répond à un besoin: Comment expliquer, en effet, par la seule électrophysiologie du potentiel synaptique la durée du rebond de sommeil paradoxal (SP) qui fait suite pendant des jours ou même des semaines à sa privation sélective? Il faut bien imaginer qu'au niveau des récepteurs, ou au niveau présynaptique, il s'est produit une modification durable et que le ou les hypothétiques neurotransmetteurs entrant en jeu au cours du SP ont subi des modifications de métabolisme . La plus probable étant celle d'une augmentation de turn over. Il existe actuallement, deux grandes tendances dans la recherche des modifications biochimiques responsables du sommeil. A la premièr qui peut être qualifiée d'holistique, car elle considère le cerveau en sa totalité, s'oppose la seconde, systématique, ou régionale, qui essaie de reconnaître l'intervention de certains systèmes biochimiques à l'intérieur du cerveau.

On peut reconnaître trois directions au sein de l'approche biochimique globale du cerveau :

a) L'approche purement humorale suivie par les groupes de Bâle Monnier et al.[23] et de Boston Pappenheimer et al.[28]. Il est certain que la détermination de la structure du facteur humoral du "delta sleep" et sa prochaine synthèse marqueront une étape dans la compréhension des mécanismes du sommeil. Cette étape franchie, il sera alors nécessaire de répondre aux questions suivantes : ce facteur joue-t-il un rôle dans le sommeil physiologique équivalent à celui joué dans la synchronisation corticale provoquée par stimulation du thalamus? Est-il capable d'induire et d'augmenter de façon harmonieuse les deux états de sommeil? Quelle est son origine? Sur quel récepteur agit-il? Joue-t-il un rôle déterminant ou seulement adjuvant?

b) L'approche exclusivement pharmacologique: S'il n'existe encore aucune drogue qui soit capable d'induire une augmentation harmonieuse des deux états de sommeil chez *l'animal intact*, il est cependant possible, chez certaines préparations mésencéphaliques ou pontiques, d'induire à volonté, dans des conditions temporelles assez strictes, l'apparition du SP avec des acides gras à courte chaîne ou certaines drogues cholinergiques comme l'eserine. L'analyse de cette action rejoint l'approche régionale, comme nous le verrons plus loin.

c) Il reste enfin l'approche purement biochimique. Tel ou tel composant du cerveau (comme la pipérédine, Stepica-Klauco et al., 1974) augmente considérablement chez des animaux sacrifiés au cours du sommeil. La valeur heuristique d'un tel résultat dépend essentiellement de la situation de ce composant, soit au neveau du métabolisme nerveux, soit au niveau d'une structure nerveuse donnée.

L'approche régionale a le mérite de s'appuyer sur ces résultats récents de la neurophysiologie. Or ceux-ci ont révèlé qu'il exis-

tait une régionalisation des structures qui commandent l'éveil et le sommeil. Si une bonne partie du cerveau peut être lesée sans entraîner de modifications fondamentales du cycle veille-sommeil, il est apparu que des lésions limitées peuvent soit supprimer immédiatement ou secondairement de façon durable le sommeil lent (SL), le SP, ou les deux à la fois. Il s'ensuit donc qu'à l'intérieur de ce système de systèmes qu'est le système nerveux central, il doit exister des systèmes plus particulièrement impliqués que d'autres dans le déterminisme du sommeil. Le but de l'explication du sommeil en terme biochimique doit être ainsi de chercher à quels systèmes de neurotransmetteur (s) (ce terme étant pris au sens large) il revient d'assurer la commande des régulations des deux états de sommeil à court et à long terme. Une telle approche nécessite, on le conçoit, une connaissance précise de la localisation de ces systèmes. (Figure 1)

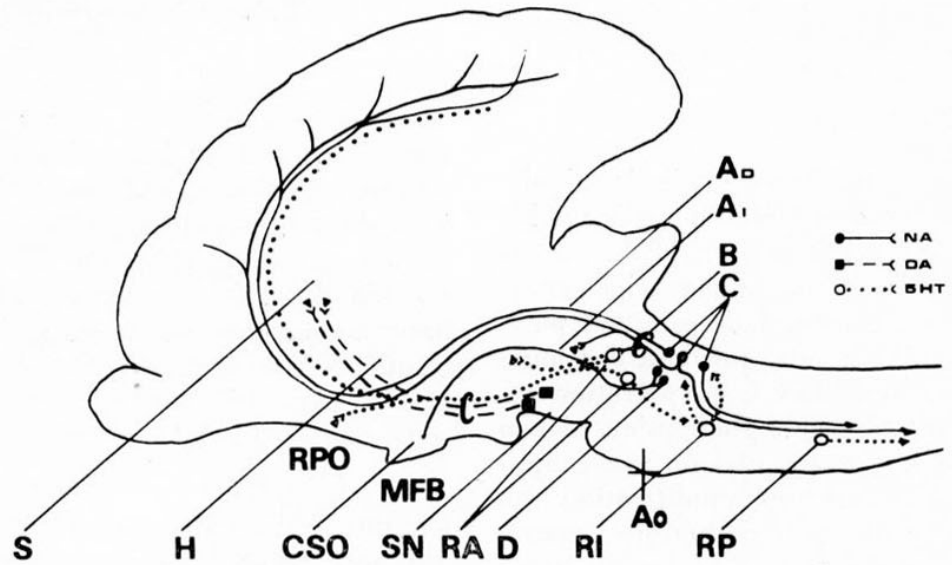


Fig. 1. — *Organisation des systèmes monoaminergiques contrôlant le cycle éveil-sommeil-sommeil paradoxal chez le chat. Sur une coupe sagittale de l'encéphale de chat, est représentée très schématiquement l'organisation possible des différents systèmes monoaminergiques mise en jeu au cours de l'alternance veille-sommeil. — En blanc; neurones sérotoninergiques (RP groupe du raphé postérieur) (noyaux Raphé pallidus et obscurus) envoyant des axones vers la moelle. — RI: groupe du raphé intermédiaire (noyaux raphé pontis et raphé magnus) envoyant des axones vers le groupe du locus coeruleus. — RA: groupe des noyaux du raphé antérieur (noyaux raphé dorsalis et raphé centralis). Ce groupe contribue à l'innervation sérotoninergique du cerveau par l'intermédiaire de fibres montant dans le faisceau médian de l'encéphale ou medial forebrain bundle (MFB). Un fort contingent de terminales sérotoninergiques se trouve situé au niveau de la région préoptique (RPO). — C: groupe du locus coeruleus et subcoeruleus (D) envoyant des axones dans le faisceau intermédiaire (Ai) décrit par Maeda. Ce faisceau croise ensuite la ligne médiane au niveau de la commissure supra optique (CSO). Le groupe antérieur du locus coeruleus envoie des axones dans le faisceau dorsal noradrénergique (A D). Il est possible que ces axones aient un contact avec le groupe antérieur du raphé. — B: lésion isthmique entraînant une hypersomnie. — SN: substantia nigra envoyant des axones jusqu'au striatum (S) par l'intermédiaire du faisceau médian du télencéphale. — H: Hypothalamus. — Ao signale le plan de référence Horsley-Clark zéro.*

Grâce à l'histochimie et l'histofluorescence, nous connaissons maintenant relativement bien la topographie des systèmes monoaminergiques cérébraux, et beaucoup moins bien celle des neurones cholinergiques. L'approche de ces systèmes est donc devenue possible. Bien sûr, ces systèmes ne constituent qu'une part minime de l'en-

semble des systèmes connus et l'on ne sait encore presque rien de l'organisation des autres transmetteurs putatifs (Gaba, histamine, glycine, etc...). Le biochimiste qui n'étudie que les systèmes monoaminergiques se trouve dans la situation de quelqu'un qui a perdu ses clefs dans une rue obscure et qui ne regarde qu'au dessous de la pâle lumière d'un réverbère, car c'est le seul endroit où il a des chances de la trouver. Le but de cette revue est de montrer que, bien qu'il persiste encore beaucoup d'obscurité dans leur mécanisme d'action, il est possible de montrer que les systèmes monoaminergiques jouent un rôle important, parfois déterminant, dans la régulation des états de sommeil.

I — La regulation monoaminergique des etats de sommeil

Pour le neurophysiologiste, le problème des relations entre les monoamines et les mécanismes du sommeil peut être abordé en essayant de répondre aux questions suivantes :

1) Quels sont les effects des modifications des neurones monoaminergiques sur le cycle éveil-sommeil? (Figure 2)

2) Quels sont les effets des altérations du cycle veille-sommeil sur l'activité des neurones monoaminergiques?

3) Quelles sont les éventuelles corrélations existant entre le sommeil et les monoamines au cours de leur variation circadienne ou ultradienne?

Les données les plus solides concernent le rôle de la sérotonine (5-HT) dans les mécanismes du sommeil et elles ont été apportées par les réponses à la première interrogation. En effet, les réponses à la deuxième question nécessitent des techniques compliquées et encore incertaines pour reconnaître avec certitude l'activité électrique des neurones monoaminergiques, et il est très probable que les privations de sommeil interfèrent avec des mécanismes non spécifiques (stress). Enfin, l'observation de variations du taux endogène des monoamines cérébrales en relation avec le sommeil, n'impliquent pas obligatoirement une relation de causalité, c'est pourquoi les réponses à la troisième question ne peuvent être que complémentaires. Pour cette raison, nous insisterons surtout sur les résultats obtenus par la première approche. Ensuite nous décrirons les interactions possibles du système sérotoninergique avec d'au-

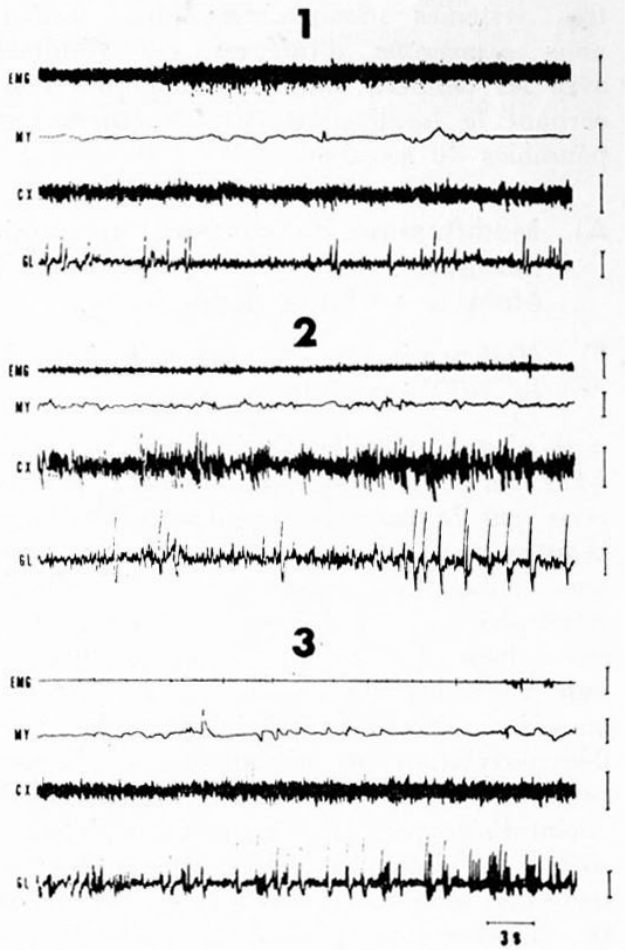


Fig. 2. — *Aspect polygraphique des états de vigilance chez le chat*:
1) *Eveil*
2) *Sommeil lent*
3) *Sommeil paradoxal*
MY Electrooculogramme
EMG Electromyogramme des muscles de la nuque.
CX Activité du cortex occipital
GL Activité au niveau des noyaux géniculés latéraux. On remarque l'existence d'une activité rapide au cours de l'éveil avec des potentiels genouillés en relation avec les mouvements oculaires, au cours du sommeil lent apparition de fuseaux et d'ondes lentes et de quelques pointes PGO, au cours du sommeil paradoxal la disparition totale de l'activité musculaire au niveau de la nuque et importante activité PGO en corrélation avec les mouvements oculaires.
Calibrage: 50 *microvolts* 3 *sec.*

tres systèmes monoaminergiques. Enfin, nous essayerons d'intégrer ces résultats avec les données neurophysiologiques concernant la localisation des structures responsables du sommeil.

A) Modification du système sérotoninergique : le cycle veille-sommeil étant la variable dépendante.

1) *Modification neuropharmacologique de la 5-HT cérébrale.*

Il n'est pas facile d'agir sur le taux de 5-HT cérébrale. En effet, la 5-HT ne traverse pas la barrière hémato-encéphalique. D'autre part, comme nous le verrons plus loin, il n'est pas certain que le 5 hydroxitryptophan (5 HTP), qui traverse la barrière hémato-encéphalique, soit le précurseur physiologique de la 5 HT. Il peut, en effet, chez l'animal intact, subir une décarboxylation au niveau des capillaires cérébraux ou au niveau des neurones catécholaminergiques. Enfin, d'autres drogues, comme la réserpine, les inhibiteurs des monoamines oxydases, et même le LSD 25 ou le méthysergide peuvent interférer avec d'autres monoamines. C'est pourquoi la démonstration, par Koe et Weismann [16] que la P. Chlorophénylalanine (PCPA) inhibait la biosynthèse de la 5 HT, a été une étape capitale dans l'étude du rôle de la 5 HT dans les mécanismes du sommeil.

—Action de la P. Chlorophénylalanine.

La PCPA inhibe la tryptophane hydroxylase au niveau du cerveau du chat comme cela est montré dans l'expérience suivante, Pujol [32], Pujol et al.[33]. Des coupes de cortex cérébral ou de tronc cérébral de chat sont incubées dans du tryptophane tritié ou dans du 5 HTP tritié et la quantité de 5 HT tritiée synthétisée est ensuite mesurée: les résultats révèlent une diminution de 90 % de la 5 HT tritiée synthétisée à partir du tryptophane tritié chez les chats qui ont été prétraités à la PCPA (comparés avec les contrôles), tandis qu'il n'y a aucune modification de la 5 HT tritiée qui est synthétisée à partir du 5 HTP tritié (Figure 3). Grâce à cette propriété très précieuse d'inhiber la première étape

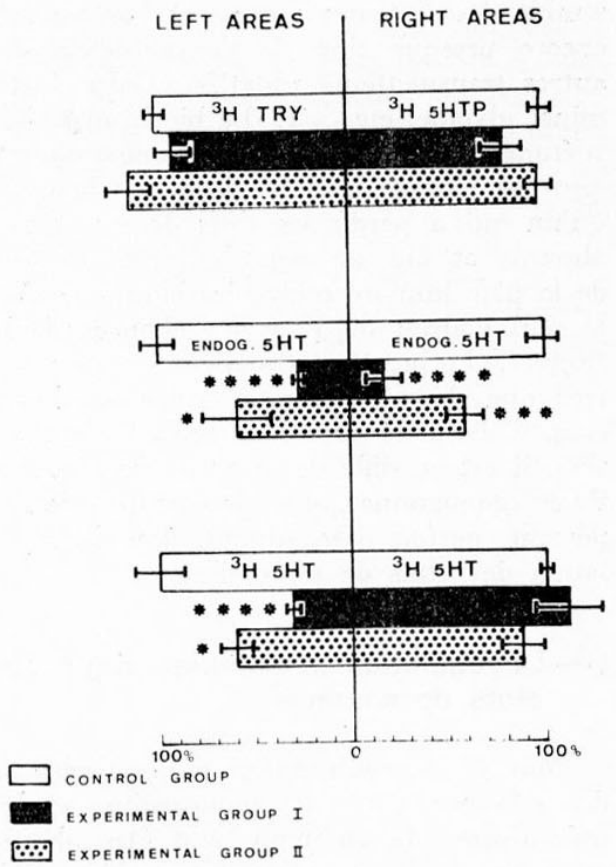


Fig. 3. — *Biosynthèse de la sérotonine après altération des neurones sérotoninergiques.*
En blanc: contrôle.
En noir: 40 heures après injection de 400 mg/kg de PCPA.
En pointillé: 8 jours après destruction subtotale du système sérotoninergique du raphé.
Des coupes de tissu cérébral ont été incubées dans du tryptophane tritié (à gauche) et dans du 5 HTP tritié (à droite), et la quantité de sérotonine tritiée a été ensuite mesurée. On remarque ainsi qu'il existe une diminution considérable de la biosynthèse de la sérotonine à partir du tryptophane chez les 2 groupes d'animaux, tandis que la biosynthèse de la sérotonine à partir du 5 HTP n'est pas significativement altérée. (D'après Pujol, 1970).

de la synthèse de la 5 HT, l'action de la PCPA sur les états de sommeil du chat a fait l'objet de très nombreuses études, Delorme et al.[9], Mouret et al.[26], Poella et al.[18], Pujol et al.[32, 33], Cohen et al.[6]. Les résultats qui sont tous concordants et facilement reproductibles peuvent être résumés de la façon suivante :

Après une injection de 400 mg/kg (intraperitonéale) de PCPA, il n'y a pas de variation du comportement ni de l'enregistrement polygraphique pendant les premiè-

res 18-24 heures. Ce fait démontre que la drogue, *par elle même*, n'a pas d'action pharmacologique au niveau du cerveau. Après 24 heures, une diminution très rapide du sommeil lent (SL) et du sommeil paradoxal (SP) se produit, et une insomnie presque totale apparaît vers la 36ème heure (Figure 5). Elle se traduit par un comportement d'éveil relativement calme, une mydriase moyenne, et une activité corticale rapide de bas voltage presque permanente, accompagnée de décharges continues de pointes PGO. Le retour du sommeil commence à s'effectuer après la 40ème heure, mais ce n'est que vers la 200ème heure que des taux de sommeil normal réapparaissent.

Après traitement par la PCPA, des corrélations très significatives ont été trouvées entre la diminution des états de sommeil et la diminution de la sérotonine cérébrale, tandis qu'il n'y a pas d'altération des catecholamines, Koella et al. [18], Pujol et al. [33], Bobillier et al. [4].

La PCPA inhibant seulement la première étape de la synthèse de la 5 HT au niveau de la tryptophane hydroxylase, la synthèse de la 5 HT est donc toujours possible à partir du 5 HTP. Il est alors possible de courcircuiter l'action de blocage de la PCPA et ainsi de reétablir la synthèse de la 5 HT en injectant du 5 HTP. Avec cette méthode, il devient alors possible de manipuler *à volonté* les états de sommeil du chat. En effet, une seule injection d'une très faible dose de DL 5 HTP (2 à 5 mg/kg) pratiquée au moment où l'insomnie a atteint son maximum (30 à 40 heures à la suite de l'administration des 400 mg/kg de PCPA) est capable de restaurer des quantités de sommeil qualitativement et quantitativement normales pendant environ 6 à 8 heures (Figure 5) Mouret et al. [26], Koella et al. [18], Jouvet [13],Pujol et al. [33]. Si des doses plus importantes de 5 HTP sont injectées (30 à 50 mg/kg), seulement une synchronisation de l'activité électrique corticale accompagnée par de la sédation réapparaît pendant les premières heures, et le sommeil paradoxal est retardé pendant 4 à 6 heures. Ces résultats suggèrent qu'après inhibition de la tryptophane hydroxylase, et en l'absence de substrat endogène, les neurones contenant de la 5 HT sont capables de synthétiser très rapidement de la 5 HT à partir de *petites* quantités de 5 HTP exogène. Cependant, il apparaît possible qu'avec des doses plus élevées, le 5 HTP exogène puisse interférer au niveau d'autres terminales avec les mécanismes normaux du sommeil paradoxal.

D'autres expériences ont montré qu'un chat qui recevait des doses de 5HTP adaptées avec des doses de PCPA qui normalement devraient induire une insomnie totale pouvait présenter des taux de sommeil normal ou même augmenté pendant au moins une semaine, Mouret et al. [26]. Ces expériences démontrent donc que les mécanismes du sommeil peuvent être manipulés en agissant "seulement" au niveau de la synthèse de la 5 HT.

2) *Modification neurophysiologique de la 5 HT cérebrale.*

Grâce au développement des techniques d'histofluorescence, les corps cellulaires contenant de la 5 HT ont été reconnus et tracés chez le rat, Dahlstrom et Fuxe [8] et chez le chat, Pin et al. [30]. La plupart d'entre eux se trouvent dans le système du raphé. On reconnaît actuellement 3 groupes : un groupe caudal situé au niveau des noyaux raphé obscurus et pallidus. Ce groupe envoie des axones descendants vers la moelle. Il ne semble pas participer aux processus du sommeil. Ce groupe intermédiaire (noyaux raphé magnus et raphé pontis) innerve la formation réticulée pontique. Le groupe rostral (noyaux centralis supérieur et raphé dorsalis) participe à l'innervation sérotoninergique du cerveau. Les axones sont concentrés dans le "medial forebrain bundle" et dans un faisceau central au niveau du tegmentum mésencéphalique. Les terminales sont situées de façon diffuse au niveau de presque toutes les régions du cerveau. La délimitation de ces groupes a permis leur approche directe par des techniques neurophysiologiques.

a) *Destruction des corps cellulaires contenant de la 5 HT au niveau du système du raphé.*

La destruction du système du raphé a

été entreprise par des méthodes stéréotaxiques chez des chats chroniquement implantés, Renault [36], Jouvet [13]. A la suite de cette opération, les animaux furent enregistrés continuellement pendant une période de 10-13 jours (cette période étant la duré critique pour la déplètion des terminales sérotoninergiques). Le 13ème jour, les chats furent sacrifiés toujours à la même heure, de façon à éviter les possibles variations circadiennes des monoamines cérébrales. Grâce à cette méthode, les informations suivantes furent obtenues: d'une part, une quantification précise des états de sommeil, obtenue grâce aux pourcentages moyens du SL et du SP pendant les 10 à 13 jours d'enregistrement, une mesure du volume de la lésion grâce au contrôle histologique du pourcentage du système du raphé détruit, et enfin, le taux des monoamines au niveau de la partie antérieure du cerveau (exprimé en pourcentage de 5 HT, 5 HIAA, noradénaline et dopamine par rapport à des chats normaux sacrifiés dans les mêmes conditions).

A la suite d'une coagulation subtotale (80-90 %) du système du raphé rostral et intermédiaire (Figure 4), un état d'éveil permanent comportemental et polygraphique s'observe au cours des 3 à 4 premiers jours. Dans la période qui suit (jusqu'à 3 semaines), le pourcentage de SL ne dépasse pas 10 à 15 % du nycthémère. Chez ces préparations, le SP n'apparaît jamais. L'injection d'une petite dose (5 mg/kg) de 5 HTP n'a aucune action sur l'éveil permanent qui suit la destruction du raphé (Figure 5). Des lésions partielles du sys-

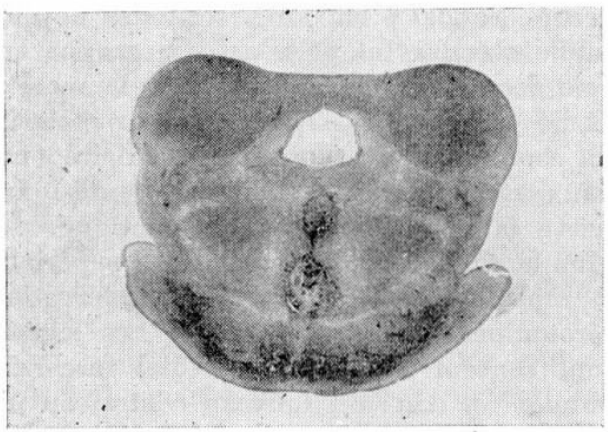


Fig. 4. — *Lésion de la partie rostrale du système du raphé (N. raphé dorsalis et centralis superior) entraînant une diminution considérable du sommeil et de la 5 HT télédiencéphalique.*

A droite: *Diminution plus rapide de la noradrénaline du cortex et du cervelet après inhibition de la synthèse par alpha méthyl tyrosine. 200 mg/kg injecté 8 heures auparavant chez des animaux dont le système rostral du raphé est détruit (Hachures) par rapport à des animaux ayant reçu des lésions de contrôle.*

(*D'après Pujol et al.*, 1973).

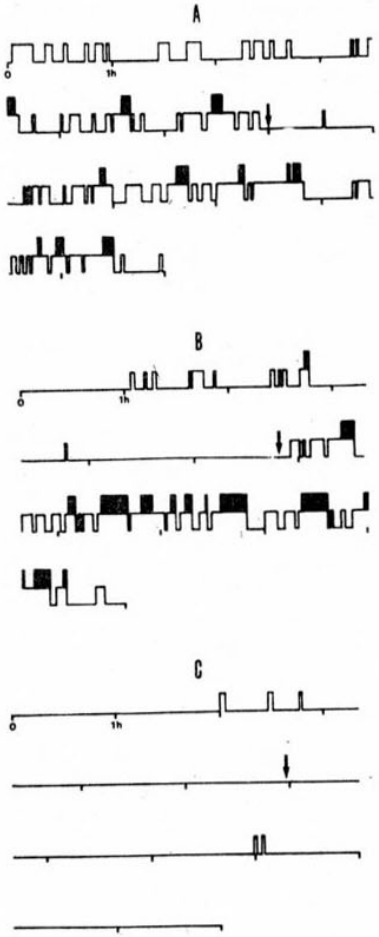


Fig. 5. — *Effet de petite dose (5 mg/kg) de DL 5HTP sur le sommeil.*

A — Animal normal. Les rectangles blancs représentent le sommeil lent et les rectangles noirs le sommeil paradoxal. Le flèche repère l'injection de 5 HTP qui a cette dose n'a pas d'effet notable.

B — Animal insomniaque ayant reçu 400 mg/kg de P. chlorophenylalanine 36 heures auparavant. L'injection de 5 HTP rétablit un sommeil normal pendant 5 heures.

C — Animal rendu totalement insomniaque par lésion de la partie rostrale du système du raphé 48 heures auparavant. L'injection de 5 HTP n'est suivie d'aucun effet.

Chaque ligne représente 3 H 30 d'enregistrement.

tème du raphé entraînent une insomnie qui est moins importante car il existe une récupération après les 2 premiers jours. Ainsi, il existe une corrélation significative entre la quantité de périkarya contenant de la 5 HT détruit et le sommeil. L'analyse biochimique du cerveau de ces préparations insomniaques a révèlé qu'il existait une diminution significative de la 5 HT et du 5 HIAA cérébral sans variation des catécholamines (NA ou DA) au niveau du télencéphale ou du diencéphale. Il existe une spécialisation des noyaux du raphé en rapport avec les états de sommeil. Ainsi, la destruction du groupe rostral s'accompagne d'une baisse significative de la 5 HT au niveau du mésencéphale et du telediencéphale. Elle entraîne également une diminution importante du SL, alors que le SP peut toujours survenir immédiatement après l'éveil (narcolapsie). La destruction des noyaux raphé pontis et magnus entraîne surtout une diminution importante et sélective du SP, sans modification notable du taux de 5 HT cérébrale (voir Table I).

1) *Métabolisme de la 5 HT chez des chats au raphé détruit.*

En incubant des coupes corticales ou de tronc cérébral dans des précurseurs marqués de la 5 HT, des informations additionnelles ont été obtenues concernant le métabolisme de la 5 HT au niveau des terminales à différents intervalles après la destruction du système du raphé, Pujol [32], Pujol et al. [33].

a) *18 heures après la lésion*, il existe une diminution de la synthèse de 5 HT tritiée à partir du tryptophane tritié et aussi une diminution du catabolisme de la 5 HT puisque le 5 HIAA tritié est diminué. Cette diminution parallèle de la synthèse et du catabolisme explique pourquoi les concentrations en 5 HT ne sont alors pas encore significativement changées. Par contre, il existe une diminution très significative (60 %) de "l'efflux spontané" in vitro de la 5 HT tritiée dans le milieu d'incubation. Ce résultat suggère qu'il doit exister également une diminution importante de la libération de 5 HT "in vivo" au niveau des terminales immédiatement après la destruction des corps cellulaires du raphé et au moment de l'insomnie maximum.

b) *10 jours après la lésion* des corps cellulaires contenant de la 5 HT, il existe une diminution importante de la 5 HT et du 5 HIAA endogène au niveau des terminales. Cette diminution est proportionnelle à la diminution de la 5 HT tritiée synthétisée in vitro à partir de tryptophane tritié. Par contre, il n'existe pas d'altération significative de la 5 HT tritiée synthétisée in vitro à partir du 5 HTP tritié. Ceci doit être expliqué par le fait que le 5 HTP peut être décarboxylé au niveau d'autres neurones probablement catécholaminergiques ou au niveau des capillaires cérébraux où se trouve l'enzyme 5 HTP-DOPA décarboxylase probablement non spécifique.

Ce dernier résultat confirme d'autres expériences qui ont montré que seul le tryptophane devait être considéré comme le précurseur physiologique de la 5 HT au niveau du cerveau, voir Moir et Eccleston [24]. Apparemment, le 5 HTP exogène à petites doses est capable d'être décarboxylé préférentiellement au niveau des neurones contenant de la 5 HT seulement lorsque le 5 HTP endogène est absent (comme cela est le cas après la PCPA).

L'insomnie déclenchée par la destruction du système du raphé a été obtenue aussi après une section sagittale du tronc cérébral (qui détruit également le système du raphé) Michel et Roffwarg [22]. Cependant, selon Mancia [20] qui a observé les mêmes résultats chez le chat et chez le singe, cette insomnie pourrait être expliquée non pas par la destruction des corps cellulaires contenant de la 5 HT du système du raphé, mais au contraire, par l'interruption de faisceaux ascendants, synchronisateurs, issus du bulbe et croisant la ligne médiane au niveau du pont. Cependant, même après section sagittale du tronc cérébral, une synchronisation corticale homolatérale peut toujours être entraînée par stimulation des nerfs vago-aortiques qui se projettent au niveau des noyaux du tractus solitaire, Puizillout et Ternaux [31]. Cette dernière expérience infirme donc l'hypothèse de Mancia. On doit admettre cependant que la destruction chirugicale des noyaux du raphé n'est pas

suffisament sélective et que d'autres neurones non sérotoninergiques pouvant jouer un rôle éventuel dans l'endormissement ont été lésés. C'est pourquoi nous avons essayé de léser sélectivement les neurones sérotoninergiques avec un "poison" sélectif, la 5, 6 hydroxytryptamine (5, 6 HT).

b) *Destruction des systèmes de terminales contenant de la 5 HT par la 5, 6 HT (Froment et al., 1974).*

Chez le rat, la 5-6 HT possède la particularité précieuse d'être captée par les terminales sérotoninergiques et de les détruire Baumgarten et al. [3]. Chez le chat, l'injection intraventriculaire de 1 mg de 5-6 HT provoque également une diminution secondaire et importante de la 5 HT, du 5 HIAA (—30 à —70 %) au niveau du cortex et de la plupart des structures sous-corticales alors qu'il n'existe pas de variation significative de la noradrénaline ou de la dopamine. Sur le plan neurophysiologique, l'injection intraventriculaire de 5-6 HT provoque un tableau immédiat de sédation accompagnée d'activation corticale et dans certains cas, de décharges continues de PGO qui surviennent au cours de l'éveil. Un tel tableau ressemble à celui qui est observé après l'injection de réserpine. Secondairement, il apparaît une diminution permanente et importante (—80 %) du stade II du sommeil (ondes lentes) et du SP. Cette diminution est étroitement corrélée avec la diminution de 5 HT et de 5 HIAA au niveau du cortex et du thalamus.

Ainsi, les résultats apportés par l'inactivation pharmacologique, chirurgicale ou toxique des systèmes sérotoninergiques sont convergents et vont dans le même sens. C'est-à-dire une diminution du sommeil. Il reste à déterminer l'organisation exacte des voies ascendantes et des systèmes terminaux présynaptiques qui entrent en jeu au cours de l'endormissement et seule la dissection fine des systèmes de projection courts et longs issus des noyaux du raphé, permettra de comprendre la hiérarchie des différentes étapes comportementales et polygraphiques qui président au sommeil.

II — Interaction possible entre les neurones serotoninergiques et les autres systèmes monoaminergiques en relation avec le cycle eveil-sommeil.

A) Interactions entre les neurones sérotoninergiques avec les neurones catécholaminergiques mis en jeu au cours de l'éveil cortical.

A côté des mécanismes cholinergiques qui dépendent de systèmes dont la topographie est mal connue, l'intervention de mécanismes catécholaminergiques dans le contrôle de l'activation tonique corticale de l'éveil, chez le chat, est suggéré par des résultats expérimentaux convergents qui peuvent être résumés de la façon suivante (voir bibliographie complète dans Jouvet, 1972):

1) L'augmentation des catécholamines cérébrales (après L-DOPA) induit une réaction d'éveil très marquée chez le chat. Cet argument pharmacologique n'est cependant pas sans critique car la L-DOPA peut provoquer une diminution de la 5 HT cérébrale.

11) L'inhibition de la synthèse des chatecholamines par l'alpha-méthyl-para-tyrosine diminue l'éveil chez le chat normal et supprime complètement l'activation corticale ainsi que le comportement d'éveil qui, normalement, fait suite à l'injection d'amphétamine.

La noradrénaline, mais pas la dopamine, semble être responsable de la réaction d'éveil cortical pour les raisons suivantes :

1) La destruction de la substantia nigra, qui diminue de plus de 90 % le taux de dopamine au niveau du striatum ne change pas de façon significative l'aspect polygraphique du cycle veille-sommeil, mais au contraire, altère considérablement le *comportement* d'éveil, Jones et al. [11].

11) La destruction du faisceau dorsal noradrénergique au niveau du mésencéphale, diminue de façon importante la noradrénaline au niveau du cortex et augmente la synchronisation corticale. Il existe alors une corrélation significative entre la diminution de l'éveil cortical et la diminution de la noradrénaline au niveau du mésencéphale et du télédiencéphale, Jones et al.[11].

1 — *Rôle inhibiteur possible des neurones sérotoninergiques sur les neurones catécholaminergiques responsables de l'éveil.*

L'augmentation de l'éveil qui suit la destruction de la partie rostrale du raphé est probablement dûe à des mécanismes catécholaminergiques comme le suggèrent les expériences suivantes:

Une injection de 200 mg/kg d'alpha-méthyl-paratyrosine (AMPT) fut donnée à des chats après destruction des noyaux raphé dorsalis et centralis à un moment où l'éveil comportemental ou polygraphique était presque permanent (2 à 6 jours après la lésion). Après l'injection, les mouvements d'éveil cessèrent, le myosis réapparût ainsi qu'une synchronisation corticale. Cet effet dura pendant environ 24 heures après lequel il y eut un retour rapide à un éveil presque total. Ainsi l'éveil entraîné par la destruction des neurones sérotoninergiques du raphé pourrait être dû à l'augmentation du "turn over" des neurones catécholaminergiques centraux. En effet, si les animaux sont sacrifiés 8 heures après l'administration d'AMPT, les concentrations de noradrénaline mesurées au niveau du cortex ou du cervelet, sont diminuées de 40 % par rapport à des animaux sans lésion ayant reçu la même dose d'AMPT (Figure 7). Cette diminution plus importante de la noradrénaline au niveau du cortex et du cervelet, après blocage de sa synthèse, suggère une augmentation du turn over du système de neurones empruntant le faisceau dorsal noradrénergique. Il est donc possible, que dans des conditions normales, les neurones sérotoninergiques puissent exercer une action inhibitrice tonique directement ou indirectement sur certains groupes des neurones contenant des catécholamines au début du sommeil.

2 — *Rôle possible inhibiteur des neurones catécholaminergiques sur les neurones sérotoninergiques.*

Ce rôle est suggéré par 2 types d'expériences :

i) *Expérience pharmacologique:* Chez le chat intact, l'inhibition de la synthèse des catécholamines par l'alpha-méthyl-paratyrosine entraîne une diminution des catécholamines cérébrales qui est accompagnée par une augmentation significative du 5 HIAA alors que la 5 HT ne varie pas. Ces données constituent un argument indirect en faveur de l'augmentation du turn over de la sérotonine. (Stein et al., 1974)

ii) *Expérience neurophysiologique:* La destruction de la partie caudale du faisceau dorsal noradrénergique au niveau de l'isthme chez le chat (Figure 6), entraîne une

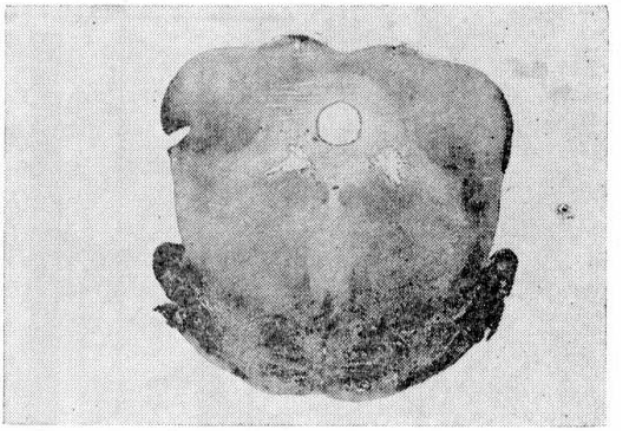


Fig. 6. — *Lésion bilatérale des faisceaux dorsaux noradrénergiques au niveau de l'isthme chez le chat. Cette lésion provoque une augmentation considérable du SP et du SL et du turn over de la sérotonine cérébrale.*
Coloration de Cresyl violet.

sypersomnie très caractéristique et passagère avec augmentation du SL et du SP pendant 3 à 8 jours. L'analyse biochimique du cerveau révèle alors une diminution de la noradrénaline au niveau du cortex et une augmentation significative du tryptophane et du 5 HIAA, Petitjean et Jouvet [29]. Tandis que chez des animaux sacrifiés 24 heures après la lésion, il existe une augmentation importante de la biosynthèse de la sérotonine à partir du tryptophane, Blondaux et al., 1973 (Figure 7). Il est probable que la destruction des fibres noradrénergiques venant de la partie antérieure du locus coeruleus supprime une inhibition tonique qui pourrait être exercée au niveau des noyaux rostraux du raphé (noyau raphé dorsalis), où de nombreuses terminales catécholaminergiques ont été remarquées, Loizou [19]. Cette destruction, en retour, aug-

menterait le "turn over" de la 5 HT comme cela est démontré par l'augmentation du 5 HIAA.

B) Interaction des neurones sérotoninergiques avec les neurones catécholaminergiques responsables du sommeil paradoxal.

A côté de mécanismes cholinergiques qui ont été revus ailleurs, Jouvet [15], l'intervention des neurones catécholaminergiques de la partie latéro-dorsale du tegmentum pontin dans les mécanismes executifs du SP est suggérée par les expériences neuropharmacologiques et neurophysiologiques suivantes (voir bibliographie complète in Jouvet.

1) Lorsque l'on injecte de la DOPA (50 mg/kg à des chats prétraités par la réserpine, le SP réapparaît beaucoup plus tôt (2 à 4 heures) que chez des animaux qui ne reçoivent pas de DOPA (24 heures). Ceci suggère que le remplissage de certains compartiments au niveau des terminales catécholaminergiques doit être une condition pour la réapparition du SP.

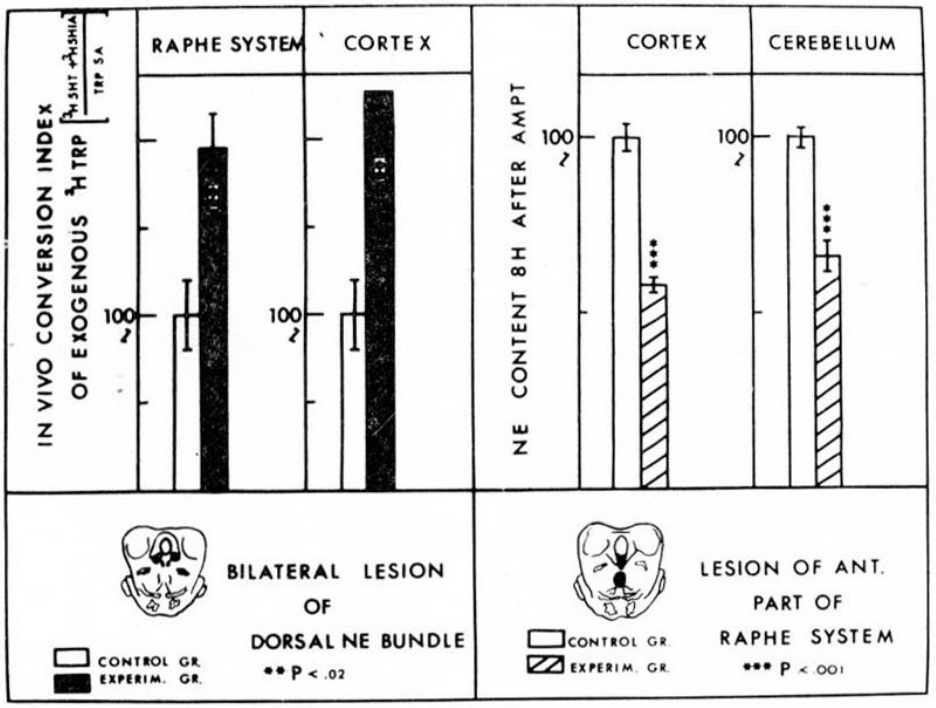


Fig. 7. — *Interactions entre les systèmes sérotoninergiques et noradrénergiques.*

A gauche: *augmentation de l'activité des neurones sérotoninergiques après lésion des faisceaux dorsaux noradrénergiques (Fig 6). La lésion est schématisée en bas. Les résultats biochimiques sont obtenus 48 heures après coagulation. La vitesse de synthèse de la 5HT est estimée en calculant l'accumulation initiale de 3H5HT et de 3H5HIAA synthétisé après que 1,5 mCi de 3H tryptophane ait été injecté 20 minutes avant le sacrifice. L'index de conversion du tryptophane est donné par le rapport*

$$\frac{3H5HT + 3H\ 5HIAA}{SA\text{-}TRP}$$

Les résultats du groupe expérimental (noir) sont exprimés en moyenne par rapport à un groupe ayant reçu une lésion de contrôle au niveau des colliculi inférieurs.

11) L'administration d'alpha - méthyl - DOPA (200 mg/kg) qui entraîne la synthèse du faux transmetteur alpha-méthyl-noradénaline supprime sélectivement le SP chez le chat pendant 12 à 16 heures et diminue l'éveil.

iii) La destruction du tiers caudal de la région du noyau locus coeruleus supprime les phénomènes d'inhibition motrice qui surviennent au cours du SP, tandis que les phénomènes ascendants, telles que les PGO et l'activité corticale rapide, sont toujours présents. Par contre, la destruction totale des deux tiers caudal du locus coeruleus et des régions immédiatement voisines des noyaux réticularis pontis, du noyau subcoeruleus, supprime tous les phénomènes centraux et périphériques du SP y compris les PGO. On peut obtenir également une suppression du SP après microinjection de 6 hydroxydopamine au niveau de la partie dorso latérale du tegmentum pontique, Buguet et al. [5].

L'hypothèse que des neurones sérotoninergiques peuvent jouer un rôle dans les mécanismes préparatoires du SP, repose sur les faits suivants :

i) Il doit exister un minimum critique de SL pour que le SP apparaisse (que ce soit après des lésions subtotales du système du raphé ou inhibition de la synthèse de la 5 HT par la PCPA). En effet, une corrélation statistique significative a été trouvée entre le pourcentage de SL et de SP tel que

$$SP = \frac{SL - 16}{-3{,}2}.$$

Cette corrélation est verifiée chez des chats qui ont été soumis à des lésions du système du raphé (avec diminution du turn over de la 5 HT) et pour des chats hypersomniaques qui ont une augmentation du turn over de la 5 HT après lésion du fasceau dorsal noradrénergique. Ainsi, un minimum de 16 % de SL quotidien (qui est à peu près le tiers du taux normal) est nécessaire pour "préparer" le SP. Puisqu'il y a quelques relations entre le pourcentage de SL et le turn over de la 5 HT, ceci suggère que toute diminution importante du turn over de la 5 HT doit supprimer ou diminuer le SP. Bien que d'autres interprétations soient possibles, cette hypothèse pourrait expliquer pourquoi les inhibiteurs des monoamines zine) qui diminuent le turn over de la 5 HT sont des drogues inhibitrices du SP.

ii) Les neurones sérotoninergiques responsables des phénomènes précurseurs du SP apparaissent être localisés au niveau du pont car la destruction des noyaux raphé pontis et magnus est suivie par une diminution importante du SP. Ainsi, il est possible que des neurones sérotoninergiques issus de ces noyaux soient responsables directement ou indirectement des mécanismes préparatoires du SP (voir Table 1).

III — Mecanismes d'action de la serotonine au cours du sommeil.

Plusieurs hypothèses sont possibles lorsqu'on considère les mécanismes pré et postsynaptiques qui entrent en jeu dans l'induction sérotoninergique du sommeil.

A) Mécanismes présynaptiques : qu'est-ce qui met en jeu les neurones sérotoninergiques?

Les mécanismes par lesquels les neurones sérotoninergiques sont activés chez le chat demeurent inconnus. Le système d'éveil apparaît infatigable puisqu'une insomnie subtotale d'au moins 2 semaines peut être obtenue après lésion du raphé. Ainsi, l'apparition du sommeil est un phénomène actif et ne peut pas s'expliquer simplement par une diminution circadienne du turn over des neurones catécholaminergiques d'éveil. On doit reconnaître que presque rien n'est connu en ce qui concerne les mécanismes qui mettent en jeu le système sérotoninergique.

Peut-être existe-t-il des synapses sérotonino-sérotoninergiques à partir du noyau paragigantesque cellularis sur le raphé puisque certaines cellules du raphé (mais pas obligatoirement des corps cellulaires contenant de la sérotonine) peuvent répondre à des administrations iontophorétiques de noradrénaline ou d'acétylcholine, Couch [7]. Ainsi, les neurones sérotoninergiques pouraient être soit sérotoniceptifs, catécholaminoceptifs et même cholinoceptifs. Alors les portes du sommeil pourraient être ouvertes par d'autres transmetteurs ou d'autres systèmes neuronaux appartenant aux structures synchronisatrices du tronc cérébral in-

férieur. Le fait que la stimulation des nerfs vago-aortiques soit toujours capable d'induire une synchronisation corticale phasique et du myosis après destruction de la partie caudale du système du raphé, ou inhibition de la synthèse de la 5 HT par la P. chlorophénylalanine, Puizillout et Ternaux [31], est une indication que des mécanismes neuroniques peuvent, dans certains cas, faire apparaître des signes EEG de sommeil, même en l'abscence probable de 5 HT au niveau des terminales. Cependant, il faut encore prouver qu'un sommeil physiologique persistant après la stimulation peut être obtenu dans ces conditions. Il est possible également que l'area postrema puisse jouer un rôle dans les mécanismes d'endormissement. Selon Koella [17], la 5 HT pourrait agir au niveau de l'area postrema comme un agent qui faciliterait ou augmenterait le "gain" dans la fonction de transfert qui serait localisée au niveau du tractus solitaire. Ceci augmenterait alors les feedback inhibiteurs entre ces noyaux et déprimerait l'éveil en augmentant les possibilités synchronisatrices de l'aire hypnogénique du thalamus. Cette hypothèse est cependant difficile a reconcilier avec le fait que la destruction du thalamus n'entraîne pas de variations quantitatives importantes des différents états de sommeil, Naquet et al. [27], Angeleri et al. [1].

A côté de mécanismes purement neurogènes, il est également possible que la mise en jeu des systèmes sérotoninergiques pourrait être facilitée par des influences humorales (au niveau des corps cellulaires ou des terminales). Parmi ces possibles influences humorales, le niveau du tryptophane sanguin pourrait jouer un rôle important puisque la tryptophane hydroxylase n'est pas un enzyme limitant. On peut aussi espérer que l'étude des mécanismes intimes agissant au niveau de l'entrée du tryptophane au niveau des synaptosomes puisse élucider certaines formes pathologiques d'insomnie ou d'hypersomnie.

B) Mécanismes postsynaptiques : où se trouvent les récepteurs sensibles à la sérotonine mis en jeu au cours de l'endormissement. (voir figure 8)

Il est probable que l'endormissement soit provoqué par la libération de 5 HT au niveau des neurones de la formation réticulée mésencéphalique et/ou des neurones contenant des catécholamines responsables de la prolongation de l'éveil cortical. Ceci expliquerait alors la persistance du comportement oculaire de sommeil chez l'animal chroniquement décortiqué ou après section haute du mésencéphale, Villablanca [40]. Ceci expliquerait également l'augmentation importante de l'éveil qui suit une section médio-pontine prétrigéminale, Batini et al. [2]. En effet, après une telle section, la plupart des structures activatrices sont situées juste en avant de la transection, tandis que la plupart des neurones du raphé sont situés en arrière. En fait, la destruction sélective du système du raphé en arrière du plan de la transection médio-pontine induit une insomnie identique, Renault [36].

Il est également possible que la libération de la 5 HT au niveau de la région préoptique joue un rôle important car la libération de 5 HT pourrait faciliter ou "moduler" les mécanismes postsynaptiques synchronisateurs qui sont situés et déclenches à partir de cette région, Sterman et Clemente [39]. Ceci expliquerait pourquoi l'injection directe de 5 HT au niveau de l'aire préoptique peut déclencher le SL, Yamaguchi et al.[42], et pourquoi le prétraitement de chats avec la PCPA supprime l'action synchronisatrice de la stimulation de l'aire préoptique, Wada et Terao [41]. L'insomnie secondaire et moyenne (comparée à l'insomnie totale et immédiate qui suit la destruction du système du raphé) qui suit la destruction de la région préoptique, McGinty et Sterman [21], pourrait également relever de la mise en jeu de mécanismes sérotoninergiques. Car, la destruction des terminales sérotoninergiques qui sont concentrée au niveau de cette région pourrait secondairement diminuer le turn over des neurones sérotoninergiques en réagissant au niveau des corps cellulaires du système du raphé.

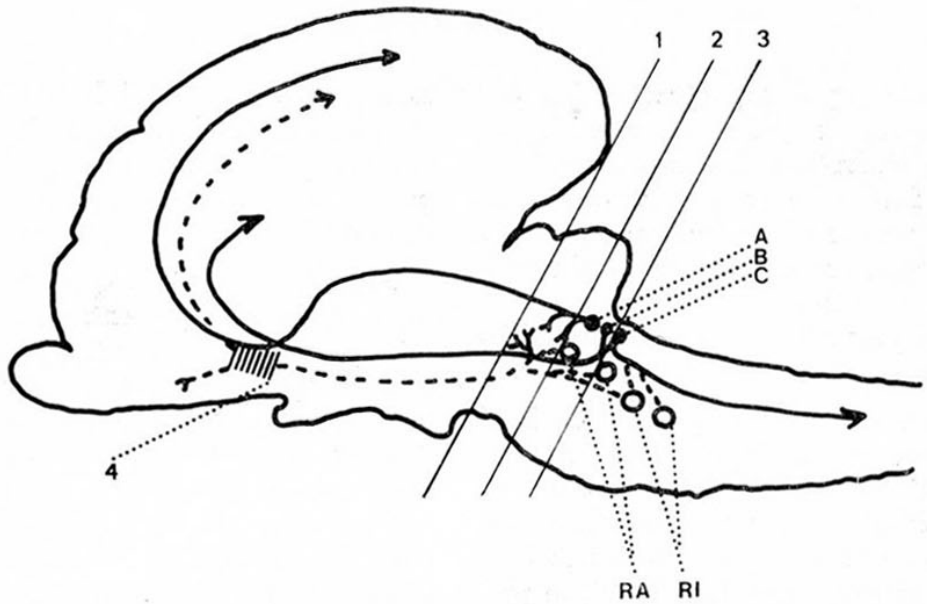


Fig. 8. — *Les systèmes NA ascendants par les faisceau NA dorsal et intermédiaire (en noir) issus du locus coeruleus (ABC) et 5-HT (en blanc et tirets) isus des groupes rostral (RA) et intermédiaire (Ri) du système du raphé sont schématisés sur une coupe sagittale du tronc cérébral (voir figure 1).*
La section 1 (ou section intercolliculaire ou "cerveau isolé") supprime l'activation corticale. Elle passe en avant des groupes NA et de la formation réticulée ponto-mésencéphalique. La récupération secondaire d'une activation corticale est attribuée à une possible régénérescence (sprouting) des faisceaux monoaminergiques ascendants. La section 2 (préparation pontique conserve du sommeil paradoxal (hypotonie musculaire périodique) car le complexe B C du locus coeruleus est situé en arrière de la section.
La section 3 (préparation médio pontique prétrigéminale) délimite en avant les neurones activateurs responsables de l'activation corticale presque permantnte (tiers rostral du locus coeruleus (A). Elle passe en avant de la majeure partie du système du raphé. Une telle section détruit également le complexe caudal du locus coeruleus (B C) et supprime la possibilité de SP.
4: lésion de la région préoptique entraînant une insomnie secondaire et réversible, peut être par effet rétrograde au niveau du système du raphé. Les systèmes nigro striatal et les systèmes issus des groupes NA du bulbe ne sont pas représentés sur cette figure.

TABLE I

Corrélations entre les lésions de chaque noyau du système du raphé, la sérotonine (5 HT) au niveau du télédiencéphale, le sommeil lent (SL) et le sommeil paradoxal (SP).

	5 HT (n=25)	SL (n=40)	SP (n=40)
N. raphe dorsalis	0,58	0,46	0,30
	xxx	xxx	NS
N. centralis sup.	0,46	0,47	0,24
	xx	xxx	NS
N. raphe pontis	0,39	0,32	0,52
	x	x	xxx
N. raphe magnus	0,006	0,37	0,48
	NS	x	xxx
N. raphe pallidus	0,10	0,29	0,29
	NS	NS	NS

(n = nombre d'animaux dans chaque groupe. Le cofficient de Bravais-Pearson a été utilisé). Il apparaît que seulement le groupe rostral (N. raphe dorsalis et centralis sup.) est responsable de l'innervation sérotoninergique du télédiencéphale et du SL, tandis que les n. raphe pontis et magnus sont responsables des mécanismes préparatoires du SP.
xxx P (0,01 xx P (0,02 x P (0,05
NS = non significatif.

RÉSUMÉ

Bien qu'aucune preuve directe n'ait encore été apportée, il existe de nombreuses données expérimentales toutes concordantes qui sont en faveur de l'hypothèse que, chez le chat, les neurones sérotoninergiques du système du raphé sont responsables du sommeil. Les résultats expérimentaux les plus convaincants peuvent être résumés de la façon suivante :

1) L'inhibition de la synthèse de la 5 HT au niveau de la tryptophane hydroxylase par la P. Chlorophénylalanine entraîne une insomnie qui est immédiatement réversible en sommeil normal par l'injection consécutive de petites doses de 5 HTP, le précurser immédiat de la 5 HT, qui courcircuite l'inhibition de la synthèse.

2) La destruction des corps cellulaires contenant de la 5 HT situés au niveau de la partie rostrale du système du raphé entraîne une insomnie. L'intensité de cette insomnie est proportionnelle avec la diminution de la 5 HT cérébrale.

3) L'inactivation des terminales sérotoninergiques par la 5-6 HT intraventriculaire entraîne une diminution du sommeil lent et du SP. Cette diminution du sommeil est proportionnelle à la diminution de la 5 HT cérébrale.

4) Il est possible que des interactions nombreuses existent entre les neurones sérotoninergiques et d'autres neurones monoaminergiques. La plupart des données obtenues jusque là chez l'animal sont en faveur de l'hypothèse que le cycle veille-sommeil est sous la régulation de deux systèmes antagonistes: le système sérotoninergique pour l'induction du sommeil et les mécanismes préparatoires du sommeil paradoxal, des neurones catécholaminergiques et cholinergiques responsables à la fois de l'éveil et du sommeil paradoxal.

Les recherches résumées dans cet article ont été effectuées grâce à l'aide de l'I. N. S. E. R. M. (U 52), du C. N. R. S. (LA 126) et la D. R. M. E. (contrat 72.108).

RESUMEN

Hay mucha evidencia concordante en favor de la hipótesis de que las neuronas serotoninérgicas de la parte rostral del sistema del Rafe, son responsables del sueño en el gato. Las evidencias más convincentes se pueden resumir de la siguiente manera:

1) La inhibición de la biosíntesis de 5 HT al nivel de la triptofano hidroxilasa por P. clorofenilalanina, induce un insomnio que es inmediatamente reversible al sueño normal con la inyección de muy pequeñas dosis de 5 HTP, el precursor inmediato de la 5 HT, que saltea la inhibición de la síntesis.

2) La destrucción de los cuerpos celulares que contienen localizados en la parte rostral del sistema del Rafe, induce un severo insomnio cuya intensidad está en correlación con el descenso de 5 HT cerebral.

3) La inactivación bioquímica de las terminales serotoninérgicas que sigue a la inyección intraventricular de 5-6 hidroxitriptamina, está acompañada por una reducción del sueño de onda lenta y del sueño paradojal. Esta reducción del sueño está en correlación con la reducción del 5 HT cerebral.

4) Pueden existir numerosas interacciones entre las neuronas serotoninérgicas y otras neuronas monoaminérgicas. La mayor parte de la información sugiere que el ciclo sueño-vigilia está regulado por dos sistemas antagónicos: el sistema serotoninérgico para el sueño de onda lenta y el mecanismo preparatorio del sueño paradojal, y las neuronas catecolaminérgicas y colinérgicas responsables tanto por la vigilia como por el sueño paradojal.

SUMMARY

There is much converging evidence which favors the hypothesis that the serotoninergic neurons of the rostral part of the Raphe system are responsible for sleep in the cat.

1) The inhibition of the biosynthesis of 5 HT at the tryptophan hydroxylase level with P. chlorophenylalanine induces an insomnia which is immediately reversible into normal sleep with the injection of very small doses of 5 HTP, the immediate precursor of 5 HT, which by-passes the inhibition of synthesis.

2) The destruction of the 5 HT containing perykaria located in the rostral part of the Raphe system induces a severe insomnia whose intensity is correlated with the decrease of cerebral 5 HT.

3) The biochemical inactivation of serotoninergic terminals which follows the intraventricular injection of 5-6 hydroxy-tryptamine is accompanied by a decrease of both Slow Wave Sleep and Paradoxical Sleep. This decrease of sleep is correlated with the decrease of cerebral 5 HT.

4) There may exist numerous interactions between 5 HT neurons and other monoaminergic neurons. Most of the data suggest that the sleep-waking cycle is under the regulation of two antagonistic systems, the serotoninergic system for Slow Wave Sleep and the priming mechanism of Paradoxical Sleep, catecholaminergic and cholinergic neurons responsible for both Waking and Paradoxical Sleep.

ZUSAMMENFASSUNG

Es bestcht übereinstimmende Evidenz zu Gunsten der Hypothese, dass die serotoninergischen Neuronen des rostralen Teils des Systems von Rafe die verantwortlichen sind beim Schlaf der Katze. Die überzeugendsten Tatsachen können auf folgende Art zusammengefasst werden:

1) Die Inhibition der Biosynthese von 5 HT auf der Basis der Hydroxylase des Tryptophans durch P. Chlorphenylamin führt zu einer Insomnie, die sofort zum normalen Schlaf umbewandelt werden kann durch die Injektion kleinster Mengen von 5 HTP, der unmittelbaren Vorstufe der 5 HT, die die Inhibition der Synthese raubt.

2) Die Zerstörung der Zellularkörper, die im rostralen Teil des Systems von Rafe lokalisiert sind, führen zu einer schweren Insomnie, deren Intensität in Relation stcht mit dem Niedergang von Gehirn-5 HT.

3) Die biochemische Investigation der serotonergischen Terminalen, die auf die intraventrikularen Injektionen von 5-6 Hydroxitriptamin folgt, wird begleitet von einer Reduktion des Schlafes von kurzer Welle und dem paradoxen Schlaf. Diese Reduktion des Schlafes ateht in Relation mit der Reduktion von Gehirn-5 HT.

4) Es können zahlreiche Zwischenreaktionen bestehen zwischen den serotoninergischen Neuronen und anderen monoaminergischen. Der grösste Teil der Information suggeriert, dass der Zyklus Schlaf-Schlaflosigkeit reguliert wird durch zwii antagonistische Systeme; das serotoninergische System für den Schlaf mit kurzer Welle und dem Mechanismus für den Schlaf mit kurzer Welle und dem Mechanismus für die Präparation des paradoxen Schlafes, und der catecholaminergischen und cholinergischen Neuronen sowohl für die Schlaflosigkeit als auch für den paradoxen Schlaf.

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Action des Substances Psychotropes Sur le Sommeil

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Il paraît intéressant de faire une synthèse des connaissances actuelles sur l'action des drogues psychotropes sur le sommeil à une époque où la consommation mondiale des produits psychoactifs ne cesse de croître, principalement celle des tranquillisants et des hypnotiques.

Nous avons délibérément écarté de cette étude les résultats de l'expérimentation animale. L'interprétation des résultats obtenus chez l'Homme reste déjà suffisamment difficile: les sujets étudiés étant tantôt des volontaires normaux, tantôt des malades mentaux avec un sommeil déjà perturbé, voire des toxicomanes.

Les paramètres le plus souvent retenus pour tester l'action d'une drogue lors d'un enregistrement polygraphique du sommeil de nuit sont la durée totale du sommeil; la latence d'apparition du sommeil après le coucher; la durée et le nombre des éveils pendant la nuit; la durée de chaque stade; le pourcentage du temps passé dans un stade donné par rapport à la durée totale du sommeil. Chez le sujet normal, on observe que la quantité de temps passé en sommeil paradoxal (S. P.) est d'environ 100 minutes par nuit avec très peu de variations interindividuelles. La latence d'apparition de la première phase paradoxale comptée à partir du début du sommeil est également considérée (cette latence est en moyenne de 90 à 110 minutes).

On analysera ici l'influence sur le sommeil des grandes familles de drogues psychotropes utilisées en clinique, groupées selon la classification de Delay, en laissant volontairement de côté les substances monoaminergiques et les stupéfiants.

L'action d'une prise unique de drogue sur une ou plusieurs nuits d'enregistrements sera comparée aux effets de l'administration au long cours.

ACTION D'UNE DOSE UNIQUE SUR UNE SEULE NUIT

Les tableaux I, II, III schématisent l'action des diverses familles de drogues sur les paramètres les plus fréquemment étudiés.

Le temps total de sommeil est rarement modifié si le produit a été testé sur des volontaires normaux car ceux-ci sont en général de jeunes adultes bons dormeurs, ce qui limite les possibilités d'une augmentation de sommeil total sous drogue. Par contre, la durée du sommeil de l'insomniaque sera augmentée par la prise d'hypnotiques de même que celle du déprimé traité aux antidépresseurs.

En fait, la latence du sommeil et le temps total de sommeil ont été très peu étudiés. Les travaux portent plutôt sur l'action sur le *sommeil paradoxal.* Les tableaux montrent que la plupart des drogues diminuent celui-ci. Certaines ne le modifient pas. Par contre, il est difficile de trouver une drogue susceptible d'augmenter le sommeil paradoxal: le réserpine semble la seule à avoir cet effet. A la dose de 1 mg per os chez l'Homme, elle potentialise le sommeil paradoxal en réduisant sa latence d'apparition et en augmentant le nombre mais non la durée des phases paradoxales. Le pourcentage de

TABLEAU I

Effet d'une dose unique de drogues psycholeptiques sur le sommeil.

DROGUES PSYCHOLEPTIQUES	TEMPS TOTAL DE SOMMEIL	LATENCE D'APPARITION DU SOMMEIL	TEMPS TOTAL DE SP	% DE SP	LATENCE DE LA 1re P.M.O.	STADE IV
BARBITURIQUES						
Pentobarbital (Nembutal)	Inchangé	Diminuée	Diminué	Diminué	Augmentée	Diminué (100 mg)
Phénobarbital (Gardénal)				Diminué	Augmentée	Diminué
Sécobarbital (Immenoctal)			Diminué	Diminué		Diminué
Amobarbital (Eunoctal) (Amopax) (Amobarbital)				Diminué	Augmentée	
HYPNOTIQUES NON BARBITURIQUES						
Glutéthimide (Doridène)			Diminué	Diminué		Diminué
Méthyprylon (Noludar)				Inchangé ou un peu diminué	Augmentée	
Méthaqualone (Toralion) (Mandrax)				Inchangé (150 mg) Diminué (300 mg)		Inchangé
Chloral				Inchangé	Inchangée	

TABLEAU II

Effet d'une dose unique de drogues psycholeptiques sur le sommeil.

DROGUES PSYCHOLEPTIQUES	TEMPS TOTAL DE SOMMEIL	LATENCE D'APPARITION DU SOMMEIL	TEMPS TOTAL DE SP	% DE SP	LATENCE DE LA 1re P.M.O.	STADE IV
TRANQUILLISANTS						
Méprobamate (Equanil) (Procalmadiol)			Diminué	Inchangé ou diminué		
Chlordiazépoxide (Librium)	Inchangé	Diminuée	Inchangé	Inchangé	Augmentée	Diminué (50 mg)
Diazépam (Valium)			Très diminué (chez le chat)	Inchangé ou un peu diminué		Diminué 10 mg
Nitrazépam (Mogadon)				Diminué	Augmentée	
Flurazépam (Dalmane)	Inchangé	Diminuée	Inchangé	Diminué (60 mg) ou Inchangé (30 mg)	Augmentée	Diminué +++
Oxazépam (Séresta)	Augmenté (chez les insomniaques)	Diminuée	Diminué		Augmentée	Diminué
NEUROLEPTIQUES						
Chlorpromazine (Largactil)	25 mg : augmenté 100 mg : inchangé		25 mg : augmenté 100 mg : diminué	25 mg : augmenté	100 mg : inchangée	Augmenté
Lévomépromazine (Nozinan)			Diminué			
Réserpine	Inchangé		Augmenté	Augmenté	Diminuée	Diminué
Halopéridol	Inchangé (étude chez le chat uniquement)			Diminué	Augmentée	Augmentation du sommeil lent

TABLEAU III

Effet d'une dose unique de drogue psychoanaleptiques.

DROGUES PSYCHOANALEPTIQUES	TEMPS TOTAL DE SOMMEIL	LATENCE DU SOMMEIL	TEMPS TOTAL DE SP	% DE SP	LATENCE DE LA 1re P.M.O.	STADE IV
AMPHÉTAMINIQUES						
d-amphétamine	Inchangé			Diminué	Augmentée	Inchangé
Méthylphénidate				Diminué	Augmentée	
Phenmétrazine				Diminué		
Diéthylpropion (Dorlon)				Diminué		
Fenfluramine (Pondéral)				Inchangé		
ANTIDÉPRESSEURS						
(1) IMAO						
Nialamide (Niamide)	Augmenté (sujet déprimé)		Diminué	Diminué	Augmentée	Inchangé
Tranylcypromine (Tylciprine)	Inchangé		Diminué		Augmentée	
(2) TRICYCLIQUES						
Imipramine (Tofranil)				Diminué	Augmentée	Inchangé ou légèrement augmenté
Désipramine (Pertofran)	Inchangé		Diminué	Diminué		Augmenté
Chlorimipramine (Anafranil)			Diminué	Diminué		
Amitriptyline (Elavil) (Laroxyl)	Inchangé	Augmentée	Diminué	Diminué		

SP est significativement accru et celui du sommeil lent est diminué, Coulter et coll. [2]. Cependant, l'opinion d'Hoffman et Domino [5] est que le SP réserpinique semble atypique.

L'action de la chlorpromazine reste encore peu claire, dépendante de la dose et des sujets. Aux doses faibles, elle potentialiserait le SP ou accélèrerait son début. Aux doses fortes, elle réduirait le SP ou le laisserait inchangé.

ETUDE DE PLUSIEURS NUITS CONSECUTIVES APRES UNE SEULE PRISE DE DROGUE

L'étude de la récupération d'un sommeil normal porte surtout sur le *retour aux valeurs de contrôle du taux de sommeil paradoxal.*

Nous avons vu que la grande majorité des drogues diminuait dans des proportions variables le SP. Celui-ci retourne à la normale, soit après une augmentation compensatrice en rebond, soit progressivement sans rebond.

Les hypnotiques, les tranquillisants, les amphétaminiques diminuent le sommeil paradoxal. Les nuits suivantes sont marquées par una *augmentation en rebond du SP.* Les antidépresseurs diminuent fortement et plus ou moins durablement le SP qui *retourne progressivement à un taux normal.* Le fait qu'il existe ou non un rebond peut s'expliquer en supposant l'intervention de deux mécanismes différents dans la réduction du sommeil paradoxal. Soit le "besoin" en sommeil paradoxal subsiste, et c'est la manifestation du SP qui est supprimée. Dans ce cas, dès qu'on laissera le SP réapparaître, il y aura récuperation rapide et presque quantitative de la "dette". Soit c'est le "besoin" en sommeil paradoxal qui est réduit et dès lors la récuperation ne comportera pas de rebond (ou alors un rebond très retardé). Les antidépresseurs IMAO ou tricycliques font partie de ce dernier groupe.

Le phénomène de rebond peut être "masqué" en particulier lorsqu'il s'agit de drogues rapidement métabolisées. L'effet suppresseur sur le SP survient dans la deuxième moitié de la nuit avec prise de drogue; l'effet est masqué si on ne tient compte que des pourcentages établis sur la nuit entière. Un tel phénomène a été constaté avec le pentobarbital, Kales et coll.[8], et également l'alcool, Rundell et coll.[12].

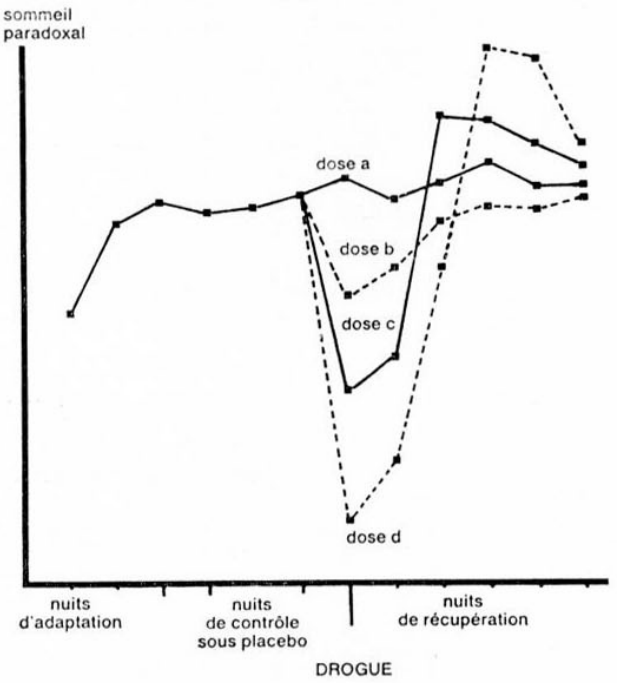


Fig. 1. — *Effet de l'admnistration d'une gamme de doses sur le SP (d'après Hartmann).*

La figure 1, d'après Hartmann [4] schématise les modifications d'un paramètre tel que le SP avec l'administration unique d'une gamme de doses. En pratique, étant donné le grand nombre d'enregistrements que nécessite une telle étude, il est difficile d'obtenir une courbe effet-dose dans le sens pharmacologique usuel. Le plus souvent, on se contente de tester l'effet d'une ou deux doses de médicaments, choisies dans la gamme utilisée en clinique.

ADMINISTRATION AU LONG COURS. DEPENDANCE ET SEVRAGE

Comme dans les paragraphes précédents, les travaux disponiblent ont surtout porté sur le SP.

Lorsqu'on administre au long cours une drogue susceptible de déprimer le SP, il se présente deux éventualités:

—tantôt il va y avoir installation d'une *tolérance,* c'est à dire que le pourcentage de SP va revenir graduellement à la nor-

male, plus ou moins rapidement selon la drogue et les sujets (quelques jours à quelques semaines). Le pattern de sommeil va rester proche de la normale tant que le patient restera sous drogue,

—tantôt on ne constatera *pas de tolérance*, l'effet suppresseur sur le SP persistera intégralment tant que durera le traitement.

—*Au sevrage*, on rencontre également deux possibilités: soit un rebond immédiat en SP, soit un rebond retardé de quelques jours ou de quelques semaines.

On peut très approximativement regrouper les drogues en deux catégories, celles associant tolérance et rebond immédiat s'opposant à celles à activité persistante et rebond retardé.

—les hypnotiques, les tranquillisants et certains amphétaminiques entraînent une tolérance plus ou moins rapide. Le sevrage est marqué par un rebond immédiat en SP.

—Les antidépresseurs (IMAO ou tricycliques) n'entraînent pas de tolérance comme le montre la figure 2 tirée des travaux de Wyatt et coll.[13], sur l'action de la phénelzine, un inhibiteur de la MAO. Le rebond en SP est retardé, apparaissant au troisième jour de sevrage avec la phénelzine, au cinquième jour avec l'imipramine, Chernik et coll.[1].

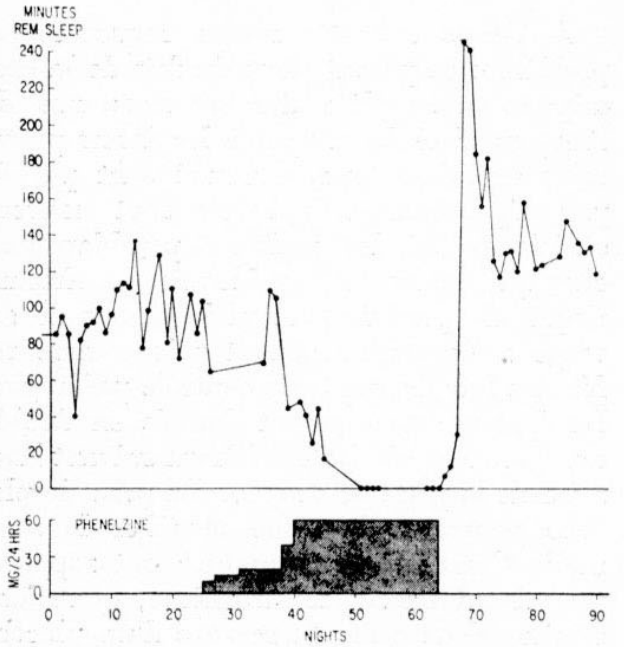


Fig. 2. — *Effet sur le SP de l'administration au long cours d'un IMAO, la phénelzine (d'après Wyatt).*

—Les neuroleptiques semblent avoir été peu étudiés sur ce point. Il ne semble pas y avoir de rebond après sept jour de chlorpromazine à 25 ou 100 mg, Lewis et Evans [6].

Cette séparation en deux types de drogues suivant leur activité au long cours et les phénomènes apparaissant au sevrage est grossièrement superposable à la notion de drogues entraînant ou non une dépendance. Les drogues capables d'entraîner une dépendance, suppriment seulement initialement le SP. Ainsi, l'amphétamine et ses dérivés (sauf la fenfluramine), les divers hypnotiques, les tranquillisants, l'alcool et les dérivés morphiniques peuvent créer une dépendance, Oswald [10]. Par contre, les antidépresseurs n'entraînent ni tolérance, ni rebond immédiat dans l'administration au long cours.

La diphénylhydantoïne et la chlorpromazine pour lesquelles il ne semble également pas exister de rebond ne conduisent pas à une dépendance.

Quand un sujet est devenu dépendant d'une drogue, il a le plus souvent un hypnogramme normal ou tout au moins une proportion normale de sommeil paradoxal, ce qui indique qu'une tolérance s'est développée. Par contre, son sommeil devient anormal au sevrage: le SP est anormalement précoce, son pourcentage est très augmenté, surtout au début de la nuit. Le sommeil est mauvais, agité avec de nombreux réveils ou passages au stade I. Les cauchemars sont nombreux chez les personnes ayant acquis une grande tolérance et une dépendance à l'égard de doses élevées d'hypnotiques. On peut constater lors du sevrage de graves symptômes: angoisse et agitation extrêmes, insomnie complète et activité onirique très vive, également pendant la veille, réalisant un tableau de délirium tremens.

Aussi Kales [7] conseille-t-il de sevrer très progressivement les sujets ayant acquis une dépendance aux hypnotiques, en diminuant d'une "dose thérapeutique" tous les quatre ou cinq jours, plutôt que tous les jours. Si nécessaire, on peut substituer progressivement une drogue ne supprimant pas le sommeil paradoxal.

Les caractéristiques du syndrôme d'abstinenence peuvent subsister pendant deux mois après le sevrage. Ce très long retour à la normale est sans commune mesure avec la rapidité du métabolisme des drogues.

Pour expliquer ce fait, Oswald [11] émet l'hypothèse de la synthèse d'une nouvelle protéîne neuronale capable de contrecarrer l'action du médicament en maintenant le sommeil aussi proche que possible de la normale pendant l'administration du produit. Si l'on arrête la drogue, cette protéîne va produire les effets inverses de l'action initiale de la drogue, puisque son action antagoniste ne sera plus contrebalancée par celle-ci.

L'effet persistera tant que cette protéîne ne sera pas catabolisée; or le cycle métabolique des protéînes cérebrales est très lent, pouvant atteindre plusieurs semaines. Cette théorie est étayée par le fait que les inhibiteurs de la synthèse des protides s'opposent à la fois à l'installation de la tolérance et aux manifestations du sevrage.

A côté des effets sur le SP, *les modifications du stade IV* doivent être étudiées dans ce chapitre. Malheureusement, très peu de travaux en font état.

La diminution du stade IV obtenue par divers hypnotiques et tranquillisants (pentobarbital, glutéthimide, flurazepam, chlordiazepoxide, diazépam) n'est en général nette qu'après deux ou trois nuits sous drogue (sauf pour le pentobarbital où ce phénomène est net dès la première nuit).

Il serait souhaitable, d'autre part, d'étudier les effets des médicaments psychotropes sur l'ensemble du nycthémère et non pas seulement sur le sommeil de nuit. Ceci permettrait, certes, d'enregistrer des phénomènes de rebond survenant pendant la sieste, mais aurait surtout l'intérêt de detecter toute baisse, même minime, du niveau de viligance. Une telle attitude pourrait peut-être réduire le nombre d'accidents de la route ou du travail survenant chez des sujets soumis à de telles médications.

Au total, pour lourde que soit l'expérimentation pour tester l'action d'une drogue sur le sommeil, il faut bien constater que notre approche reste encore superficielle, n'ayant abordé le plus souvent que les effets sur le SP sans avoir analysé le retentissement éventuel sur l'organisation propre du sommeil. Les modifications du SP sont, certes, les plus évidentes, peut-être parce que ce sommeil est plus fragile. C'est lui le premier touché (dans le sens d'une diminution) à la moindre agression: adaptation à un nouvel environnement (effet "première nuit"), température trop élevée dans la pièce, ou fièvre. De plus, les nuits dites de "mauvais sommeil" par opposition au "bon sommeil" sont celles avec un taux de SP abaissé.

Il semble donc que cette fragilité du SP soit l'explication du manque apparent de spécificité d'action des diverses drogues. Il est surprenant d'avoir à ranger dans la même catégorie des drogues aussi différentes que les hypnotiques et les amphétaminiques. Ceci peut être dû au choix de paramètres trop grossiers. Une analyse plus fine de l'organisation cyclique et des constituants phasiques du SP pourrait être un premier pas vers une meilleure compréhension des mécanismes fondamentaux du sommeil.

Au sevrage, pourcentage de stade IV remonte toujours progressivement, sans rebond.

Conclusion:

A l'issue de cette rapide revue, divers problèmes se posent, tant du fait de la description incomplète des résultats que de l'impossibilité de comparer les divers protocoles expérimentaux. Ceux-ci sont parfois peu rigoureux. Les sujets sont souvent choisis parmi les malades psychiatriques chez qui l'arrêt de la médication antérieure risque de produire des phénomènes de sevrage malencontreusement pris comme référence lors des nuits de contrôle prédrogue. La drogue est rarement donnée en double aveugle. Les résultats diffèrent suivant l'horaire de la prise de drogue. La prise de placebo pourrait elle-même modifier le sommeil: Cravens et Hartmann [3] ont rapporté un rebond en SP les troisième, quatrième et cinquième nuits de sevrage d'un placebo administré au long cours (Figure 3).

Des protocoles d'expérimentation rigoureux demanderaient de nombreuses nuits

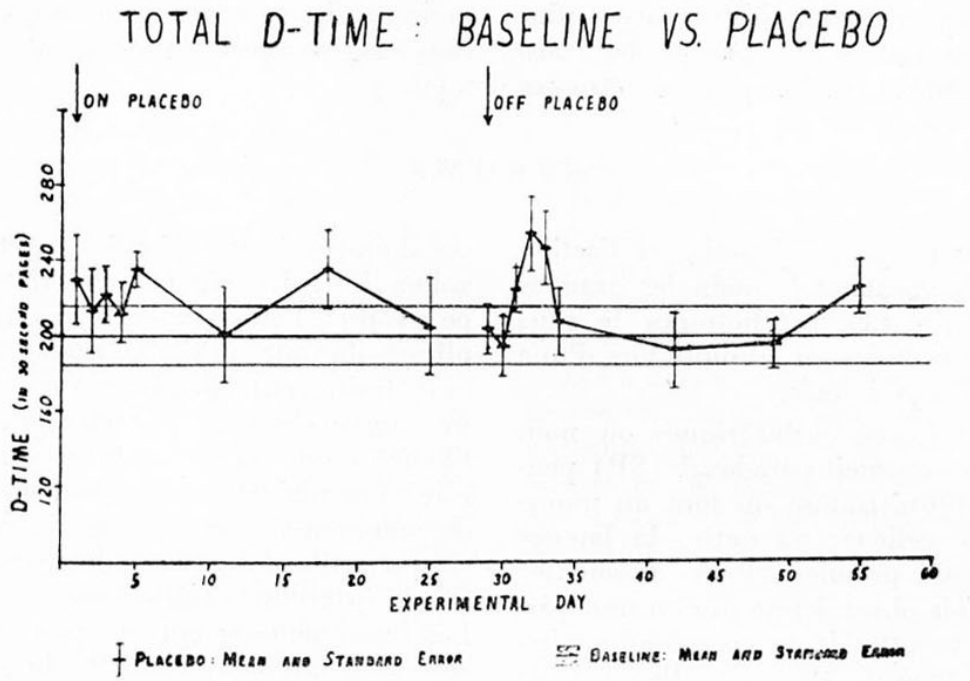


Fig. 3. — *Effet sur le SP de l'administration au long cours d'un placebo (d'après Hartmann).*

d'enregistrements, avec au moins trois nuits préliminaires d'adaptation au laboratoire.

Pour tester un hypnotique sur un insomniaque, Kales [8] conseille un protocole en 22 nuits: les nuits 1 à 4 sont consacrées à l'adaptation au laboratoire avec placebo, seules les nuits 2-3-4 étant retenues pour la mesure de la ligne de base. Les nuits 5-6 et 7 se passent au laboratoire sous drogue, pour tester l'effet à court terme de l'hypnotique dans l'induction et le maintien du sommeil. De la 8ème à la 15ème nuit, le sujet prend le médicament chez lui, sans être enregistré. Les nuits 16 à 22 se passent au laboratoire, les trois premières sous drogue, les autres sous placebo. Les enregistrements des 17ème et 18ème nuits sont seuls pris en considération pour déterminer si, après deux semaines d'administration, la drogue est encore active, ou si une tolérance s'est développée. Enfin, les nuits 19 à 22 étudient le sevrage.

Il serait souhaitable, d'autre part, d'étudier les effets des médicaments psychotropes sur l'ensemble du nycthémère et non pas seulement sur le sommeil de nuit. Ceci permettrait, certes, d'enregistrer des phénomènes de rebond survenant pendant la sieste, mais aurait surtout l'intérêt de détecter toute baisse, même minime, du niveau de viligance. Une telle attitude pourrait peut-être réduire le nombre d'accidents de la route ou du travail survenant chez des sujets soumis à de telles médications.

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ramètres trop grossiers. Une analyse plus fine de l'organisation cyclique et des constituants phasiques du SP pourrait être un premier pas vers une meilleure compréhension des mécanismes fondamentaux du sommeil.

RÉSUMÉ

Nous nous proposons d'envisager l'action qu'ont sur le sommeil humain les grandes familles de drogues psychotropes le plus couramment utilisées en clinique lors d'une administration prolongée.

Les hypnotiques, barbituriques ou non, diminuent le sommeil paradoxal (SP) pendant leur administration ou tout au moins au début de celle-ci; en outre, la latence d'apparition du premier SP est augmentée et on a parfois observé une diminution particulièrement nette de la composante phasique de ce type de sommeil. Par ailleurs le stade IV du sommeil à ondes lentes est diminué au profit de stades moins profonds La durée totale du sommeil (ST) est augmentée au début, puis revient aux valeurs initiales. A l'arrêt de la drogue, la durée du ST diminue, cependant que le SP est augmenté "en rebond". Le stade IV se normalise sans rebond. Le contenu des rêves s'appauvrit pendant la prise d'hypnotiques; lors du sevrage, on note une exacerbation de leur caractère déplaisant.

Les tranquillisants ont une action sur le sommeil assez proche de celle des hypnotiques.

Les neuroleptiques sont difficiles à étudier en administration chronique à des doses thérapeutiques chez des sujets normaux volontaires, du fait de leur effet psychotrope propre; l'étude chez le malade se complique du fait qu'il faudrait établir avant tout traitement, pendant assez longtemps, une ligne de base de sommeil. De plus, l'heure de la prise de la drogue joue un rôle. Les phénothiazines font encore l'objet de nombreuses controverses: la chlorpromazine à petite dose (25 mg) augmenterait le SP, à forte dose (100 mg) elle l'abaisserait. Les butyphénones ont été peu étudiées. La réserpine augmente le SP chez l'Homme, surtout un ou deux jours après une seule prise de 1 - 2 mg.

Les amphétaminiques particulièrement étudiés en raison de la vogue des drogues anorexiantes raccourcissent le sommeil total, diminuent le SP surtout en retardant l'apparition de la première phase de celui-ci. Le stade IV est en général diminué, parfois augmenté.

Les antidépresseurs diminuent le SP. Il ne semble pas y avoir de retard de la première phase paradoxale après une dose unique, sauf si celle-ci est massive. Lors d'une administration au long cours, le retard est manifeste.

SUMARIO

Nos hemos propuesto considerar la acción que tienen sobre el sueño humano las grandes familias de drogas sicotrópicas más corrientemente utilizadas en la clínica en ocasión de una administración prolongada.

Los hipnóticos, barbitúricos o no, disminuyen el sueño paradojal (SP) durante su administración o por lo menos al principio de él; además, la latencia de la aparición del primer SP está aumentada y a veces se ha observado una disminución particularmente neta del componente fásico de ese tipo de sueño. Por otro lado el estado IV del sueño a ondas lentas está disminuido en provecho de los estados menos profundos. La duración total del sueño (ST) está aumentada al principio, después vuelve a los valores iniciales. Al cese de la droga, la duración del ST disminuye, mientras que el SP está aumentado "en rebote". El estado IV se normaliza sin rebote. El contenido de los sueños se empobrece durante la toma de los hipnóticos. En el momento del cese del tratamiento, se nota la exacerbación de su carácter desagradable.

Los tranquilizantes tienen una acción sobre el sueño bastante cercana a la de los hipnóticos.

Los neurolépticos son difíciles de estudiar en la administración crónica a dosis terapéuticas en los sujetos voluntarios normales, del hecho de su efecto sicotrópico propio; el estudio en el enfermo se complica del hecho que faltaría establecer antes de todo tratamiento, durante bastante tiempo, una línea de base de sueño.

Además, la hora de la toma de la droga juega un papel. Las fenotiazinas son todavía objeto de numerosas controversias; la clorpromazina a pequeas dosis (25 mg) aumentaría el SP, a una dosis fuerte (100 mg) la misma bajaría. Las butifenonas han sido poco estudiadas. La reserpina aumenta el SP en el hombre, sobre todo uno o dos días después de una sola toma de 1-2 mg.

Las amfetaminas estudiadas particularmente en razón de estar en boga las drogas anorexiantes acortan el sueño total, disminuyen el SP sobre todo al retardar la aparición de la primera fase del mismo.

La etapa IV está en general disminuida, a veces aumentada.

Los antidepresores disminuyen el SP. No parece tener allí retardo de la primera fase paradojal después de una dosis única, salvo si ésta es masiva. En el momento de una administración a largo curso, el retardo queda manifiesto.

SUMMARY

It is our purpose to consider the action of the large family of the psychotropic drugs most currently used in the clinic at the moment of a prolonged administration, on the sleep.

The hypnotics, barbiturates or not, reduce paradoxal sleep (PS) during its administration at least at the commence of the same; besides the latence of the appearance of the first PS is increased and at times a particular net decrease of the phasic component of this type of sleep. On the other hand state IV of the sleep of waves is diminished in favour of the stages not so profound. The total duration of the sleep (TS) is larger at the beginning, but is reduced later on to the initial values. On leaving off drug, the duration of TS decreases, while PS is increased "in rebound". State IV normalizes without rebound. The content of the dreams gets poorer while taking hypnotics. At the moment of ceasing the treatment, there is augmentation of its disagreable character.

The tranquillizers have an action on sleep quite like that of the hypnotics.

The neuroleptics are difficult to study in the chronical administration at therapeutic doses in voluntary normal subjects, from the fact of their own psychotropic effect; the study in the sick is complicated from the fact there is need of establishing before any treatment at all, during a long time, a basical line of sleep. Also, the hour of taking the drug plays a role. The phenothiazines are still object of much controversy; the chlorpromazine at small doses (25 mg) increases the PS, at large doses (100 mg) the same decreases. The butyphenones have been studied very little. The reserpine increases the PS in man, especially one or two days after one only dosage of 1-2 mg.

The amphetaminics studied particularly due to the increase of anorexiant drugs which shorten total sleep, decrease PS especially in retarding the appearance of the first phase of the same. Stage IV is on the whole diminished, sometimes increased.

The antidepressors decrease PS. There does not seen to be a retard of the first phase paradoxal after one dose alone, except if the same is massive. At the moment of a prolonged administration the retard becomes evident.

ZUSAMMENFASSUNG

Wir haben uns vorgenommen die Wirkung zu betrachten, die die grossen Familien psychotroper Heilmittel auf den menschlichen Schlaf haben, die am Häufigsten in der Klinik für langdauernde Behandlung verwendet werden.

Die Schlafmittel, Barbiturate oder nicht, verringera den paradoxen Schlaf (SP) während ihrer Verwendung oder wenigstens am Anfang derselben. Ausserdem ist die Latenz für das Auftreten des ersten SP erhöht und manchmal hat man eine eigentümlich klare Verringerung der phasischen Komponente dieser Art des Schlafes beobachtet. Andererseits ist das Stadium IV des Schlafes von langsamen Wellen vermindert zum Vorteil weniger tiefer Stadien. Die Gesamtdauer des Schlafes (ST) ist am Anfang erhöht und kehrt dann zu den Anfangswerten zurück. Nach Absetzung des Mittels verringert sich die Dauer des ST, während der SP durch Überschiessen erhöht ist. Das Stadium IV normalisiert sich ohne überzuschiessen. Der Trauminhalt verarmt während der Verwendung der Schlafmittel. Im Augenblick des Absetzens markt man seine Verstärkung an ihrem unangenehmen Charakter.

Die Beruhigungsmittel haben eine ziemlich ähnliche Wirkung wie die der Cchlafmittel.

Die Neuroleptica sind bei den freiwilligen Normalpersonem bei chronischer Anwendung und in therapeutischen Dosen schwierig zu prüfen wegen der Tatsache ihres eitersuchung beim Kranken kompliziert sich durch die Tatsache, dass es notwendig wäre vor jeglicher Behandlung und während genügender Zeit die Grundlinie des Schafles festzustellem.

Ausserdem spielt die Uhrzeit der Einnahme des Heilmittel eine Rolle. Die Phenotyazine sind noch Objekte zahlreicher Streitigkeiten. Das Chlorpromazin in niedriger Dosierung (25 mg) erhöhe den SP, in starker Dosierung (100 mg) verringere sich dieser. Die Butiphenone wurden wenig untersuch. Das Reserpin erhöht beim Menschen den SP, vor allem 1 bis 2 Tage nach einer einzigen Gabe von 1-2 mg.
sucht wurden, weil die den Appetit verrin-

Die Amphetamine, die besomders unter-
Gesammtschlaf verkürzen und verringern;
gernden Heilmittel in Mode sind und den
Sie verkürzen den SP und vor allem wenn
sie das Auftreten der ersten Schlafphase
verzögern. Die Etappe IV ist im Allgemeinen verkürzt, machmmal erhöht.

Die den Blutdruck verringernden Mittel verringern den SP. Esscheint dort die erste Verzögzergt wird ausser wenn es eine masparadoxe Phase nach einer einizgen Dosis sive Dosis ist. Wenn eine langdauernde Behandlung erfolgt, wird die Verzögerung deutlich.

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Discussion

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L'analyse des effets sur le sommeil des psychotropes est au premier abord décevante comme la montre l'exposé précédent (Leygonie et Scherrer). Toutes les substances modifient, le plus souvent en le réduisant, le sommeil paradoxal. L'absence de spécificité de l'influence sur le sommeil de substances pharmacologiques appartenant cependant à des familles aussi différentes que les barbituriques, les amphétamines ou les antidépresseurs est-elle aussi réelle qu'il paraît? Cette question en soulève immédiatement deux autres auxquelles il sera tenté de répondre dans cet exposé.

1) Les index choisis pour étudier le sommeil ont-ils été assez sensibles pour détecter toute modification de sa composition et de son organisation?

2) La réduction du sommeil paradoxal entraînée par les différentes substances psychotropes a-t-elle la même origine? La complexité des mécanismes de mise en jeu du sommeil paradoxal, Jouvet [6], peut expliquer sa fragilité face à l'action pharmacologique: la réponse observée de réduction peut n'être que la résultante commune de modalités d'action diverses.

Nous écarterons volontairement de cette discussion des points importants comme ceux concernant les problèmes posés par la définition EEG des stades de sommeil sous agent psychotrope ou celui des modifications éventuelles de l'organisation circadienne veille-sommeil pour ne traiter que le sommeil envisagé sous l'angle de son organisation.

Nous nous proposons dans cette discussion d'apporter des arguments physiologiques à un choix préferentiel de certains indices pour l'étude des effets pharmacologiques, permettant une meilleure interprétation des résultats. Nous n'envisagerons pas non plus, faute de compétence, l'aspect pharmacologique des protocoles expérimentaux.

Comme l'exposé de Mme. Leygonie et M. Scherrer le montre, les paramètres les plus souvent utilisés dans les études pharmacologiques sont les durées totales ou relatives des différents stades et la latence d'apparition de la première phase de mouvements oculaires. Pour précieux qu'ils soient, ces indices ne permettent pas sans un contexte précis d'apprécier des changements modérés ou de les interpréter avec sécurité. En effet, chez le sujet normal le sommeil est un processus organisé, programmé. Il comporte un déroulement temporel, cyclique, précis avec enchaînement logique d'un stade à l'autre. Cette notion *d'organisation interne ou de logique interne du sommeil* est capitale car elle a des conséquences immédiates dans l'analyse même du sommeil: les différents moments du sommeil ne sont pas équivalents entre eux: par exemple, la majeure partie du sommeil lent (SL) profond (stades 3 et 4) survient dans le premier tiers de la nuit, tandis que la plupart du sommeil paradoxal (SP) est réalisé dans le dernier tiers.

La durée absolue de chaque stade de sommeil ne se modifie pas proportionnellement à la durée totale du sommeil. Les travaux de Webb et Agnew [12] et de Hartmann et coll.[5] sur les petits dormeurs (moins de 6 heures de sommeil) et les gros dormeurs (plus de 9 heures) ont montré que les différences portaient presque exclusivement sur la durée du stade 2 et sur celle du SP (Fig. 1). Valeurs absolues et même relatives de durée des stades ne peuvent être comparés qu'à longueur égale de sommeil. Peu de travaux pharmacologiques ont tenu compte de ce facteur en comparant les nuits sous pharmacologie aux nuits de contrôle. A titre d'exemple, une diminution modérée de SP, entraînée par une drogue psychotrope qui allonge la durée totale de sommeil peut être plus ou moins masquée par l'augmentation normale de ce stade en fin de nuit.

L'analyse des résultats globaux sur une nuit entière de sommeil est insuffisante. *L'analyse du déroulement temporel de la*

nuit est indispensable pour détecter des modifications d'organisation interne de ce sommeil.

Les figures 2 et 3 montrent pour le sommeil lent profond (stade 3 et 4) et pour le sommeil paradoxal l'évolution normale en fonction du temps et de l'ordre des cycles. Seules des analyses de ce type, étudiant l'évolution des différents stades au moins par tiers de nuit, permettraient de détecter une certaine dynamique de l'action pharmacologique. Le même pourcentage de sommeil d'un stade donné peut être obtenu selon la durée de l'action pharmacologique et son type, soit par une réduction modérée portant sur la nuit entière, soit par un blocage important de quelques heures suivi d'un rebond marqué en fin de nuit. Un tel effet été décrit pour le SP par Kales et coll.[7] lors de la prise de Nembutal, barbiturique à éli mination rapide. Ce rebond s'accompagne de nombreux rêves et cauchemars relatés

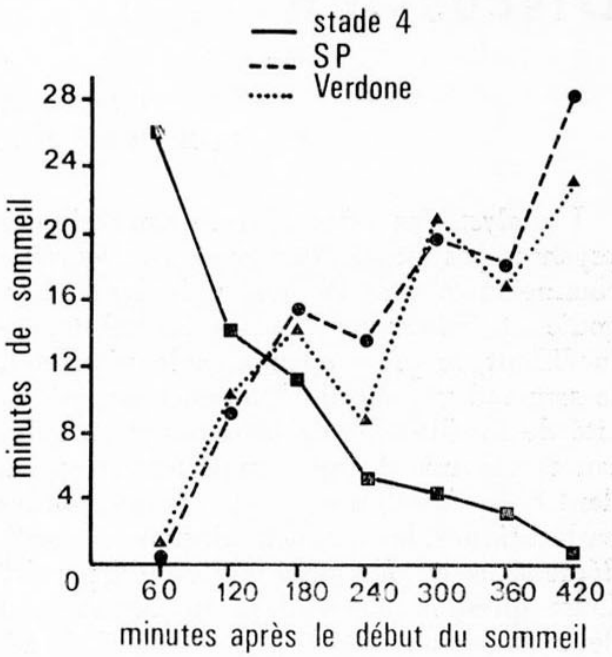


Fig. 2. — *Distributions horaires du stade 4 et du sommeil paradoxal, d'après Webb, W. B.*[11].

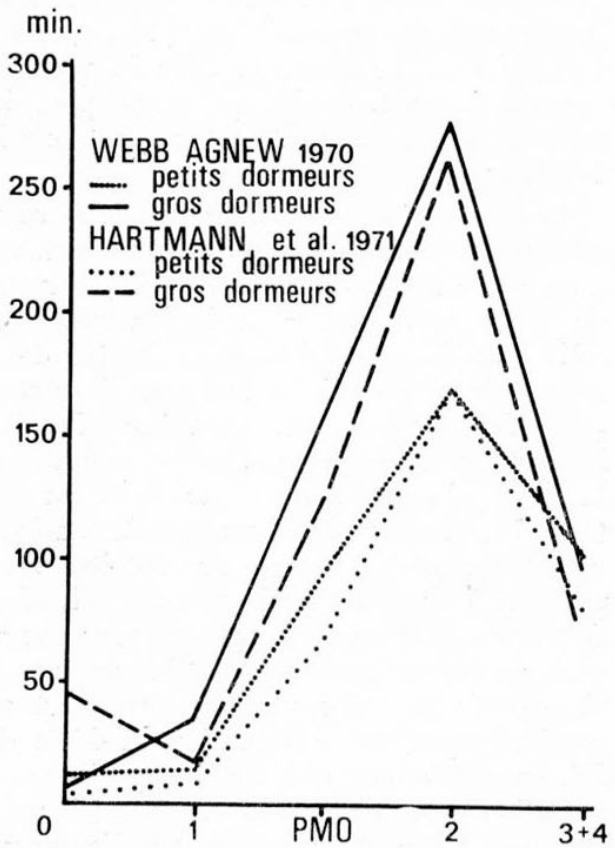


Fig. 1. — *Quantités absolues moyennes des différents stades de sommeil obtenues par Webb et Agnew*[12] *et Hartmann et coll.*[5] *pour des populations de petits dormeurs (moins de 6 heures de sommeil) et de gros dormeurs (plus de 9 heures).*

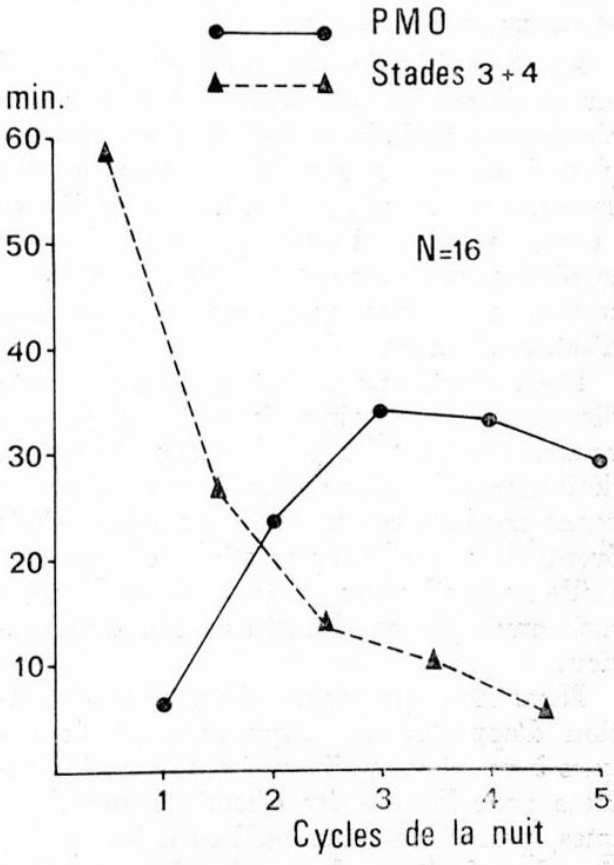


Fig. 3. — *Répartition des durées moyennes (en minutes) des stades 3 + 4 et des phases de mouvements oculaires (PMO) en fonction de l'ordre des cycles. Résultats obtenus sur 16 sujets normaux. Les cycles ont été comptés de la fin d'une PMO à la fin de la suivante.*

par les sujets, en particulier, lors des sommeils prolongés comme ceux des jours de repos.

Décrit pour le SP, le même phénomène peut parfaitement jouer pour le sommeil à ondes lentes profond. Le déplacement du SL vers la fin de la nuit serait un signe de rebond après blocage, son émiettement à travers les différents cycles témoignerait d'une action plus prolongée et plus complexe. Or de telles études sont encore exceptionnelles. Elles sont d'autant plus indispensables que de nombreux travaux ont montré la résistance du sommeil lent profond et sa plasticité lors de manipulations expérimentales (sommeil de courte durée, fragmentation du sommeil, inversion de l'horaire, privation, etc....). La sensibilité moderée ou l'absence de sensibilité du sommeil lent à la plupart des psychotropes est peut-être plus apparente que réelle. Ce point mériterait des études plus précises.

A l'inverse, les psychotropes modifient presque tous le sommeil paradoxal, en réduisant sa quantité. Ce type de sommeil survient de façon cyclique toutes les 90 minutes environ. L'expression polygraphique du SP est bien connue. Répondant à des mécanismes différents bien que liés, Jouvet [6], ses signes peuvent être classés en toniques (stade EEG de type IB - abolition du tonus musculaire) et phasiques (mouvements oculaires, myoclonies, irrégularités cardio-respiratoires). Une organisation temporelle du sommeil paradoxal, tout au long de la nuit a pu être mise en évidence chez le sujet normal, Benoit et coll. [2]. Les caractéristiques phasiques (nombre de mouvements oculaires) et toniques (durée) d'une phase de mouvements oculaires (PMO) dépendent fortement de ce qui a précédé car elles sont déterminées par le rang de cette PMO et sa latence, le rang étant le facteur prépondérant. Il a pu être montré, en outre, que l'évolution chronologique des deux composantes est différente: le facteur phasique croissant plus vite que le facteur tonique. La conséquence de cette évolution est bien connus: les premières PMO sont plus "toniques" et les dernières très riches en mouvements oculaires (Fig. 4), c'est-à-dire plus "phasiques".

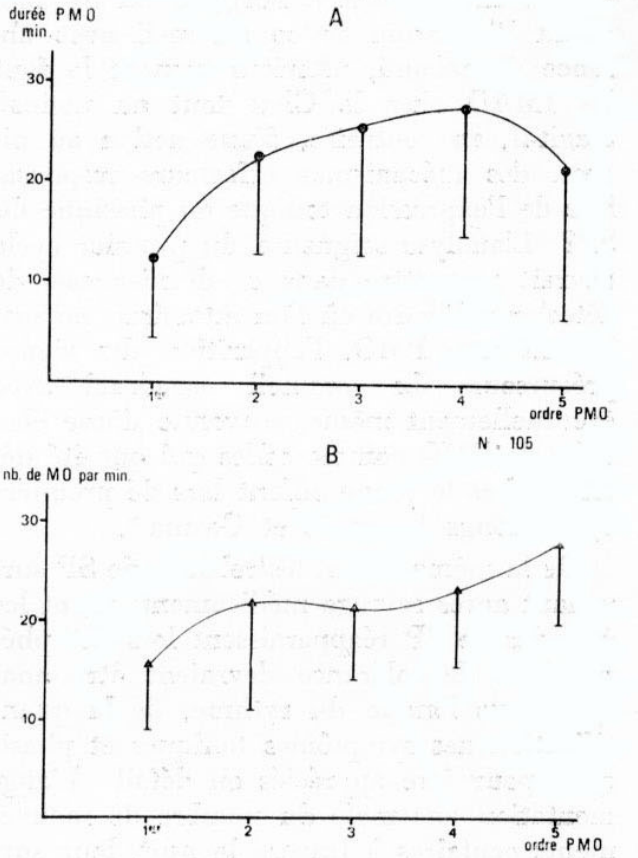


Fig. 4. — *Evolutions de la durée moyenne des PMO (en minutes) en A et de la fréquence moyenne des mouvements oculaires en B, en fonction de l'ordre des PMO. (N = 105 PMO).* La *valeur de l'écart-type est figurée par les traits verticaux.*

La sensibilité aux agents pharmacologiques des deux composantes du SP ne semblent pas la même et des dissociations toniques-phasiques ont été notées par plusieurs auteurs: avec le pentobarbital le phénobarbital, le valium ainsi qu'avec le glutethimide et la méthaqualone. Dans tous les cas, le nombre de mouvements oculaires était plus réduit que la durée des PMO. La dynamique de cette dissociation mériterait d'être analysée et apporterait peut-être des éléments de compréhension de l'action pharmacologique sousjacente.

La latence d'apparition du premier épisode de sommeil paradoxal est souvent allongée. Cet indice, à lui seul, est difficilement interprétable. S'agit-il d'une modification du rythme même de survenue des PMO que l'on devrait retrouver alors dans les cycles ultérieurs? S'agit-il d'une action

sur les mécanismes à l'origine du SP bloquant l'initiation de ce sommeil avec absence de rebond, ulterieur comme le font les IMAO chez le Chat tout au moins? S'agit-il, au contraire, d'une action au niveau des mécanismes effecteurs responsables de l'expression tonique ou phasique du SP? L'analyse soigneuse du premier cycle devrait permettre dans ce dernier cas, de détecter à l'heure où l'on attendrait normalement une PMO, l'apparition des signes précurseurs du sommeil paradoxal avec éventuellement même, survenue d'une ébauche de PMO comme celles qui ont été décrites chez le jeune enfant lors de premiers cycles longs Leygonie et Garma [8].

De la même façon, les rebonds de SP survenant après sevrage médicamenteux, et les épisodes de SP réapparaissent lors des phénomènes de tolérance devraient être analysés sous l'angle du rythme, de la quantification des symptômes toniques et phasiques pour être appréciés en détail. L'augmentation anormale du nombre de mouvements oculaires à travers la nuit, leur survenue éventuelle en dehors des épisodes de sommeil paradoxal, témoigneraient de rebonds plus importants que le seul taux de SP ne le laisse penser. De nombreux mouvements oculaires rapides associés au stade 2 ont par exemple été observés par FRAM et coll. [4] chez un sujet déprimé, traité à la L-Dopa (12,6 g/jour). Ces constatations peuvent être rapprochées de la survenue d'évènements phasiques (pointes PGO) pendant le sommeil lent chez le chat normal Thomas et Benoit [10], et de leur recrudescence après privation de SP, Peyrethon-Dusan [9], Dement [3].

On sait que la durée absolue du SP, à durée de sommeil égale, varie peu d'une nuit à l'autre. De la même façon, il est possible que le nombre de mouvements oculaires soit relativement constant pour un sujet donné, comme le suggèrent nos propres résultats. Un chiffre moyen d'environ 2000 mouvements oculaires par nuit à été trouvé chez le sujet normal par Barros-Ferreira et Bedoret [1]. L'établissement de normes quantitatives chez le sujet normal, la quantification précise de tous les élements du SP lors des nuits de contrôle, avant étude pharmacologique, devraient permettre dans les années à venir, non seulement de décrire les effets sur le SP des substances psychotropes, mais encore de les interpréter. Une sensiblilité différentielle du SP aux agents pharmacologiques pourrait bien alors se révéler.

Il est possible en outre que des travaux pharmacologiques montrent les charnières, les points critiques de la programmation du processus "sommeil", améliorant notre connaissance de cette logique elle-même et indiquant les points stratégiques où l'on peut espérer intervenir utilement pour modifier un déroulement pathologique. Une telle compréhension de l'action pharmacologique des psychotropes et tout particulièrement des substances utilisées comme hypnotiques est indispensable pour en rationaliser la prescription et améliorer la thérapeutique des troubles du sommeil.

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The Role of Monoamines in Learning and Memory Consolidation

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Previously, we reported that L-dopa treatment of Parkinson's disease patients results in improvement in cognitive, conative, memory, and perceptual functioning (1). Our studies, undertaken to investigate the role of monoamine oxidase (MAO) in the central nervous system of the goldfish, promised to serve as model for some of these L-dopa induced changes observed in parkinsonian patients. As any model, this one represents a limited number of aspects only of this problem. This limitation, however, is counter-balanced by the greater freedom of selecting parameters in the analysis of the phenomena than it is possible in studies with patients. The reason for these correlations stems from our discovery that, in this animal, not only synthesis of ribonucleic acids and proteins, but also cerebral monoamines and their metabolism seem to be tied in with the various phases of learning and information retrieval (2).

Bittermann/Agranoff test. — Our basic tool was the Bittermann/Agranoff goldfish conditioned avoidance test. The goldfish were trained in a shuttle box to avoid an electrical shock by swimming across a barrier within a specified time after onset of a light stimulus. Each trial set consisted of (1) turning on the light at the fish's end of the box for 20 seconds (2) intermittently shocking the fish for 20 seconds, and (3) complete darkness for 20 seconds. A correct response was recorded when the fish avoided a shock by crossing the barrier during the first 20 seconds. A training session consisted of each fish receiving 25-30 trials in a 30 minute interval. Each fish went through one training session every 24 hours for three to five days. In some cases the training schedule was slightly modified. For each control and for each dose of a used drug, a set of 6 animals was tested. As found in this laboratory, the logarithm of the number of errors during a training period is a linear function of the number of trials, as characterized by high correlation coefficients ($r > 0.9$) [2]. These linear relationships made it possible to define operationally various stages of the learning process (Figure I). The slope of the regressionally determined line can be considered as an indicator of the learning rate, while the consolidation ratio (CR) of the ordinate at the end of the nth training period and the intercept at the zero time of the $(n + 1)$st trial period is an indicator of the information consolidation. In controls, the consolidation ratio is approximately 1, meaning that all information is retained. Factors below 1 mean loss or information, and values above 1 may be defined as "hyperconsolidation".

The goldfish received the various agents by intracranial or intraperitoneal injections. In most cases reported here, the animals were treated by letting them swim in solutions of the particular agents.

Previously reported experiments with L-dopa. — As we previously reported [2, 3], we exposed goldfish to 10^{-4} M L-dopa and

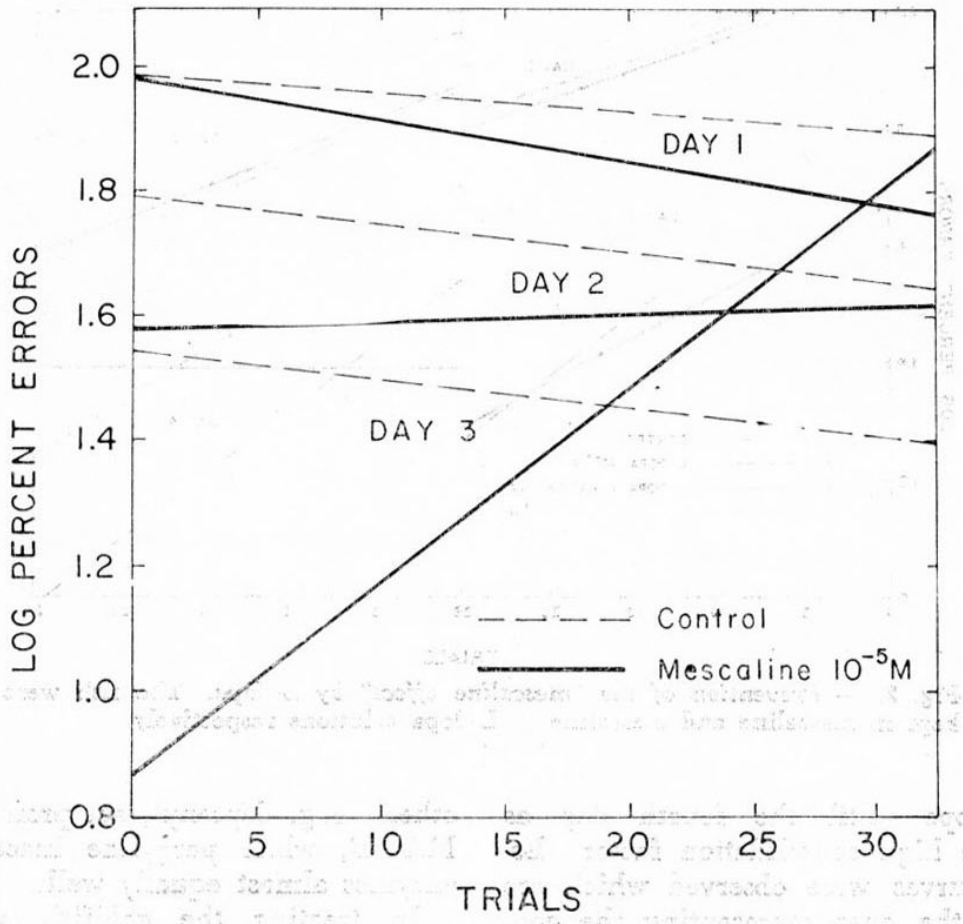


Fig. 1. — *Regression lines of results obtained for three consecutive training periods.* One set of fish served as controls, the other set was kept n 10^{-5}M mescaline.

found that this treatment accelerates the learning process. The slope can be twice as steep as that obtained for the controls. In addition, the "amnesia" produced in the fish by certain monoamine oxidase (MAO) inhibitors, can be counter-acted by the simultaneous administration of L-dopa.

Experiments with mescaline. — Recently, we exposed goldfish to the small concentration of 10^{-5} M mescaline for several days. The phenomena observed at this occasion appear to be related to dopamine or its metabolism (Figure I). One day after the first training period, the slope becomes slightly positive, and even more so during the following days. Thus, for the first time, we find that the operationally defined learning rate does not improve during the training period, but deteriorates! Equally surprising was the fact that the consolidation is much better than at any other occasion. The animals start the third, fourth and fifth days with a much better score than they ended the trial period the day before. The consolidation ratio reaches values of 5 and more. These observations are reminiscent of Seligman's concept of "learned helplessness".

Here, we do not discuss these observations in the context of possible mescaline action in fish and mammals, but rather of dopamine metabolism, as suggested by a recent report, that mescaline caused release of dopamine from the caudate nucleus of the rat (J. Coupet, 1972) [4].

Experiments with mescaline and L-dopa. If mescaline also exerts some influence on dopamine metabolism of fish, our "mescaline effect" may be reduced or prevented by the administration of L-dopa so that dopamine may better be able to compete with mescaline. This is indeed the case (Figure II). The presence of 10^{-4} M L-dopa prevented the appearance of the unusual

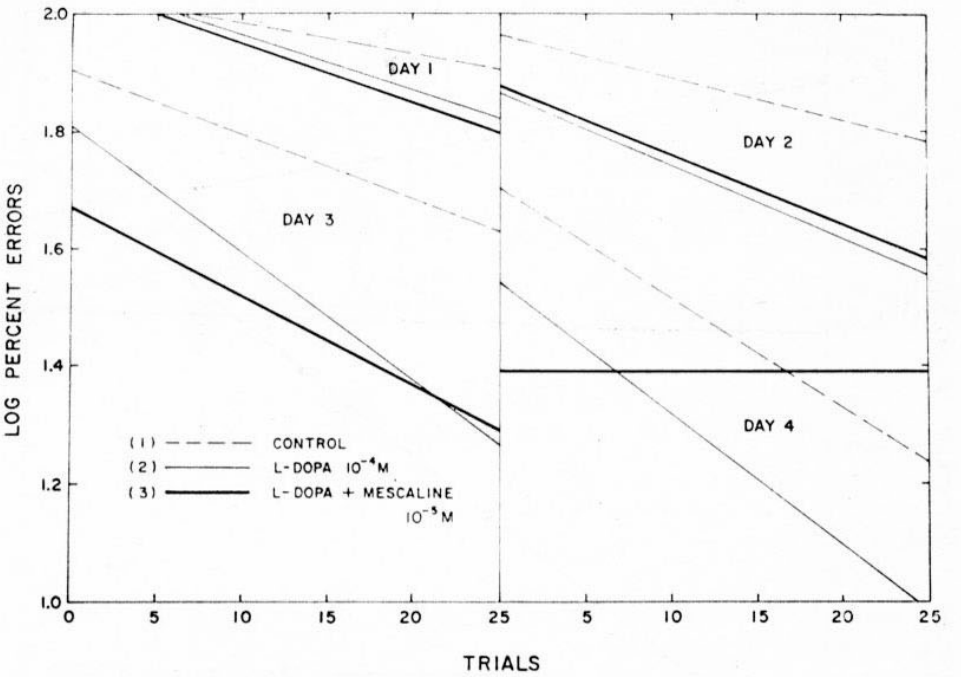


Fig. 2. — *Prevention of the "mescaline effect" by L-dopa.* The fish were kept in mescaline and mescaline + L-dopa solutions respectively.

positive slope until the fourth day as well as the high consolidation factor. Essentially, curves were observed which are similar to the ones representing the controls. Thus, L-dopa is not only capable of overcoming the amnestic influence of MAO inhibitors, but also the "mescaline effect".

Experiments with MAO inhibitors. — In preceding studies, we demonstrated that several inhibitors strongly reduced the consolidation process, so that the animals on the second and third day almost had to start from scratch with respect to learning. This type of reaction is obtained whenever the cerebral MAO is blocked by at least 90 percent and whether the inhibitors are applied by intracapsular injection or by the aqueous medium. As a consequence of this 90 percent inhibition, cerebral monoamines such as norepinephrine, and dopamine are significantly increased [2].

We have briefly to refer here to the muliplicity of MAO, in particular to the existence of MAO-A and MAO-B in the mamalian brain [5]. The former seems to inactivate neurotransmitters such as norepinephrine and serotonin, while the latter may be involved in the inactivation of phenylethylamine. Some inhibitors; e. g. clorgyline, strongly inhibit the A-enzyme, while others; e. g. deprenyl, act preferentially on MAO-B, while pargyline inactivates both enzymes almost equally well.

In treating the goldfish with strong MAO-A inhibitors, such as pargyline, Lilly 51641 or clorgyline, the phenomenon described above (Figure III) appeared. The response to the predominantly MAO-B inhibitor deprenyl was quite different. This compound, N-isopropyl-N-methyl-propynylamine, depresses the degradation of tyramine clearly more strongly than phenylethylamine (Table I). Marked reduction of MAO activity is found with 10^{-7} M deprenyl which is approximately one hundredth of a microgram of the drug, 1 per ml of "artificial pond water".

Deprenyl affects not only cerebral MAO activity, but also the behavior of the goldfish (Table II), but in a manner quite different from 5 other inhibitors. Even at 10^{-7} M solution, it increases the slope of the line representing learning function in a manner reminiscent of the action of L-dopa and even more so at higher concentrations (Table II). On the other hand, part of this high learning rate is lost, because the consolidation is less efficient. Consolidation ratios of 0.25 have been observed, meaning that at the end of a training pe-

TABLE I

INHIBITION OF GOLDFISH BRAIN MAO ACTIVITY

Degradation of Tyramine (unmoles/mg/hr) After 4 Days of Treatment

Substrate	Tyramine
Control, activity	7.1
10^{-7}M Deprenyl, inhibition	75 %
10^{-6}	99 %
10^{-5}	100 %

TABLE II

EFFECT OF DEPRENYL ON GOLDFISH BEHAVIOR

Slopes (X 10^3) Taken From Regression Lines

Days	1	2	3
Control	— 7	— 11	— 16
10^{-8}M Deprenyl	— 8	— 10	— 13
10^{-7}	— 14	— 11	— 7
10^{-6}	— 12	— 43	— 26
10^{-5}	— 16	— 28	— 43

riod the number of errors is four times less than at the beginning of the tests at the following day. Due to the steepness of the curve, however, the overall consolidation ratio is higher than in controls.

It may be of interest to note that with rats we obtained results similar to those found for goldfish, although the number of animals and tests were much smaller for the mammalian experiments. When the rats were exposed to a conditioned avoidance shuttle box testing analogous to that used for goldfish, and when more than 95 percent of the cerebral MAO (with tyramine as substrate) was reduced, the rate of learning was significantly reduced. In order to obtain this high degree of inhibition, intraperitoneal injections of pargyline as well as administration of this drug by drinking water was required.

Experiments with mescaline and MAO inhibitors. — When a substance which predominantly inhibits MAO-A (clorgyline), or MAO-B (deprenil), or one which inhibits both MAOs (pargyline) is added to the mescaline treated fish, the mescaline effect "disappears" and curves almost identical to the controls are obtained. An example is given for mescaline and deprenil (Table III).

TABLE III

EFFECT OF DEPRENYL (MAO-I) AND MESCALINE ON LEARNING RATES

Slopes of Regression Lines X 10^3

Days	1	2	3	4
Control	— 3	— 6	— 13	— 21
Deprenyl, 10^{-6}M	— 31	— 34	— 36	— 28
Mescaline, 10^{-5}M	— 0.5	+ 3	+ 10	+ 13
Depr. + Mesc.	— 11	— 10	— 13	— 32

Effect of apomorphine and fluphenazine on learning and consolidation. — Since we tentatively concluded that the dopaminergic system was involved in this learning process of the goldfish, we tested the influence of 10^{-6} M apomorphine (administered for two hours per day). This dopaminergic *agonist* produced the same responses as L-dopa and deprenyl, viz. an enhancement of the learning rate. With the dopaminergic *antagonist*, fluphenazine, the same type of curve was obtained as for mescaline. These observations are interpreted by the assumption that mescaline released dopamine which in turn was destroyed by MAO. Thus, the dopaminergic system was suffering from a transmitter deficiency.

SUMMARY and CONCLUSIONS

We infer from our results that dopamine and its metabolism is involved in the phenomena of learning, consolidation, and retrieval. Thus, this aminergic system appears to establish not only interrelationships "among primitive deeper structures commonly implicated in the control of visceral and affective functions" [6] but also in memory processes. Much work on the analysis of the enzymological and behavioral

phenomena remains to be done before a clear picture will emerge. So far, the data are consistent with the assumption that in our system mescaline is a dopamine depletor. Our information may also throw some light on the mechanism of action of mescaline on man and on some basic reactions involved in acquisition, storage, and retrieval of information. Finally, we became to believe that the goldfish test could serve as a handy model for the study of L-dopa on some cognitive functions of parkinsonian patients.

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RESUMEN Y CONCLUSIONES

Inferimos de nuestros resultados que la dopamina y su metabolismo está involucrada en el fenómeno del aprendizaje, consolidación y recuperación. De este modo, este sistema aminérgico parece establecer no sólo la inter-relación "entre estructuras primitivas más profundas comúnmente implicadas en el control de las funciones viscerales y afectivas" sino también en los procesos de la memoria. Mucha labor acerca del análisis de los procesos enzimológicos, y de la conducta queda por realizarse antes que pueda configurarse un cuadro claro de los mismos.

Hasta ahora, las informaciones son compatibles con la hipótesis de que en nuestro sistema la mescalina es un depleto de la dopamina. Nuestra información también puede arrojar alguna luz sobre el mecanismo de acción de la mescalina en el hombre y en algunas reacciones básicas involucradas en la adquisición, almacenaje y recuperación de la información. Finalmente, llegamos a creer que la prueba de los peces dorados podría servir como un modelo práctico para el estudio de la acción de la L-dopa sobre algunas funciones cognoscitivas de los pacientes parkinsonianos.

RÉSUMÉ et CONCLUSIONS

Nous faisons part de nos résultats que la dopamine et son métabolisme sont insérés dans le phénomène de l'apprentissage, consolidation et récuppération. De cette façon, ce système aminérgique paraît établir non seulement la inter-relation "entre structures primitives plus profondes communément impliquées dans le contrôle des fonctions viscerales et affectives. Si non également dans les processus de la mémoire. Beaucoup de travail au sujet des analyses des processus enzimolégiques, et du comportement reste à réaliser avant qu'il se puisse configurer un cadre claire de ceux-ci.

Jusqu'à présent, les informations sont compatibles avec l'hypothèse de ce que en nôtre système la mescaline est un dépleteur de la dopamine. Nôtre information peut également jeter une certaine lumière sur le mécanisme d'action de la mescaline dans l'homme et dans certaines réactions basiques invulcrées, dans l'acquisition enmagasináge et récupération de l'information. Finalement, nous arrivons à croire que l'essai des poissons dorés, pourrait servir comme modèle pratique pour l'étude de l'action du L-dopa sur certaines fonctions cognitives des patiens parkinsoniens.

ZUSAMMENFASSUNG und FOLGERUNGEN

Schliessen wir aus unseren Resultaten, dass die DOPAMINA und ihr Metabolismus in das Phänomen der Lehrzeit, Konsolidation und Wnedererlangung vermischt ist. Dadurch scheint dieses aminergetische System nicht nur in die "Interrelation zwischen tieferen primitiven Strukturen gemeinhin in die Kontrolle der visceralen und effektiven Punktionen" verwickelt zu sein, sondern auch in die Prozesse des Gedächt-

nisses. Viel Arbeit fär die Analyse der enzymologischen Prozesse und der Kofukta bleibt noch zu tun, bevor sich ein klares Bild davon gemacht werden kann.

Bis jetzt sind die Informationen vergleichbar mit der Hypothese, dass in unserem System das MESCALIN ein Abnutzer des DOPANINS ist. Unsere Information kann auch etwas Licht auf den Mechanismus der Aktion des MESCALINS beim Menschen werfen und auf einige basische Reaktionen beim Erwerb, Lagerung und Wiedererlangung der Information. Schliesslich kommen wir dazu zu glauben, dass die Probe bei den Goldfischen als praktisches Modell dienen kann für das Studium der Aktion der L-DOPA auf einige Funktionen erkenntlich der Parkinsonpatienten.

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L Dopa et Troubles Psychiques

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Un titre aussi peu restrictif impose une limitation volontaire du sujet a des considérations purement cliniques.

En neurologie les troubles psychiques sont des effets indésirables survenant au cours des syndromes parkinsoniens traités par la L Dopa.

Ces troubles sont maintenant bien connus et répertoriés dans leur expression clinique et leur risque de survenue.

Peut-être a-t-on moins insisté sur le rôle réel de la Dopa dans la génèse de ces troubles: rôle inducteur ou seulement révélateur chez un sujet prédisposé.

En psychiatrie les effets de la DOPA ont été étudiés sur une gamme très étendue de troubles psychiques qui se trouvent aggravés dans certains cas et améliorés dans d'autres cas. Les améliorations obtenues ne permettent cependant pas de faire entrer actuellement la DOPA au stade thérapeutique en psychiatrie. Mais les perspectives théoriques qui ont ainsi pu être ouvertes renforcent la conviction que les médiateurs du système nerveux auront bientôt leur place parmi les médicaments psychotropes.

La serotonine, ou plutot son précurseur le 5 HTP ne vient-il pas d'entrer dans la pharmacopée?

I. Les troubles psychiques au cours du traitement des syndromes parkinsoniens par la DOPA

Dès le début de l'emploi sur une large échelle de la L DOPA dans le traitement des syndromes parkinsoniens la survenue de troubles psychiques fut signalée par tous les observateurs.

L'expression clinique de ces troubles est très variée mais on reconnait que certains d'entre eux sont plus fréquents que les autres.

Il existe une discrète divergence parmi les observateurs en ce qui concerne l'appréciation quantitative du risque de survenue de ces incidents, mais une explication peut être proposée: elle concerne d'une part l'état mental antérieur du sujet, et d'autre part l'homogénéité relative des populations comparées au cours des diverses statistiques.

1. — *L'expression clinique des troubles psychiques.*

Un travail d'ensemble important fait par F. K. Goodwin [10] regroupe les constatations de 21 auteurs faites sur l'observation de 908 parkinsoniens.

—Les syndromes confusionnels sont les plus fréquents (4,4 %). Il peut s'agir soit d'une confusion mentale pure, soit de l'adjonction d'un élément délirant en général hallucinatoire soit encore d'un tableau confuso démentiel surtout si une détérioriation intellectuelle préexistait à l'administration du traitement.

Ces épisodes confusionels aigus surviennent en règle en début de traitement et imposent l'arrêt de celui-ci; ils sont alors vite résolutifs. Dans les cas de syndrome confuso démentiel on a signalé des évolutions irréversibles et définitives vers une détérioration mentale.

—Des phases dépressives n'atteignent jamais une intensité mélancolique (4,2 %) sont rapportées. P. Rondot [16] signale de tels épisodes surtout au cours des traitements de longue durée alors que la DOPA a entrainé une amélioration indiscutable du syndrome parkinsonien?

L'élément thymique n'est pas toujours au premier plan mais il existe une indifférence avec perte de l'initiative et ralentissement de l'activité. Une modification de la posologie ou le recours aux psycho analeptiques permettent en généralals de supprimer ces incidents.

—Une hyperactivité est notée dans 3,6 % des cas. Elle s'accompagne souvent d'une légère note hypomaniaque avec euphorie et ludisme.

Damasio [7] insiste sur la sensation de bien être ressentie par les patients avec stimulation de l'attention et de la curiosité. Il décrit cet état comme "l'énervement ressenti à la veille d'un grand voyage: on est content mais nerveux"...

—Des épisodes délirants purs, sans élément confusionel sont possibles (3,6 % des cas). Ces bouffées délirantes aigues ne surviennent jamais sur une personnalité indemne d'antécédent psychiatrique. Le mécanisme du délire est essentiellement à base d'hallucinations visuelles et l'anxiété est toujours importante.

—Des états maniaques francs (1,5 %) obligeant à arrêter le traitement ont été signalés, mais ils sont tout à fait exceptionnels et ne se voient jamais en l'absence d'antécédent identique.

—Une stimulation sexuelle est observée dans 0,9 % des cas, quel que soit le sexe du sujet, et consiste essentiellement en une augmentation de l'appétit sexuel.

—Enfin, Goodwin [10] retrouve 1,5 % de troubles qualifiés "divers" et qui regroupent essentiellement une insomnie et des bouffées anxieuses.

D'autres auteurs ont insisté sur l'insomnie et l'anxiété qu'ils semblent avoir retrouvé avec une bien plus grande fréquence.

Martin [12] rapporte 60 % d'insomnies, associées ou non à des états dépressifs.

P. Castaigne et coll. [5] signale des bouffées anxieuses apparaissant brusquement à heure fixe dans la journée et nécéssitant le recours aux anxiolytiques qui les font en général céder rapidement.

2. — *L'aspect quantitatif des troubles psychiques.*

La fréquence de survenue des troubles psychiques est assez diversement appréciée selon les auteurs.

Il faut dire que les lots de malades à comparer sont bien rarement homogènes.

Cheifetz [6] par exemple sur 34 malades traités ne rapporte aucune manifestation mentale mais ceci... après avoir exclu tous ceux qui avaient des antécédents psychiatriques.

D'une façon générale cependant les chiffres sont assez voisins.

Goodwin [10] dans sa statistique portant sur 908 cas rapporte 20 % de troubles psychiques. R. Douvoisin [9] en trouve 16 % sur 116 cas.

Holzer, J. et Beck, H. rapporteurs d'une étude coopérative réunissant 44 centres (Deuxième colloque L DOPA - Rabat 20 mai 1972) signalent 285 cas de troubles psychiques sur 1036 patients observés, soit 27,5 % en fréquence globale.

P. Castaigne et coll. (1972) reprenant les observations de 110 patients traités depuis plus d'un an rapportent 13,6 % de troubles psychiatriques.

Ainsi les variations entre les auteurs sont finalement minimes, la fréquence absolue de survenue des troubles étant grossièrement de 20 %.

L'entrée dans la rubrique "troubles psychiques" de manifestations mineures que certains négligent peut expliquer les differences constatées.

Tous les observateurs s'accordent à reconnaitre que la survenue de manifestations psychiques se voit surtout en début de traitement. Le risque est maximum pendant les 3 premiers mois (17 %), puis il diminue rapidement et devient très minime au dela du 10ème. mois.

Enfin, comme nous le reverrons, le risque de survenue de troubles psychiques est en grande partie conditionné par l'existence ou l'abscence d'antécédent psychiatrique chez le malade traité.

3. — *Incidence des troubles psychiques sur le traitement.*

Les troubles psychiques n'arrivent qu'en 3e. position parmi les effets secondaires de la L DOPA.

Les plus fréquents (65 %) étant les troubles digestifs, suivis par l'apparition de mouvements anormaux (43,9 %).

Mais les troubles psychiques représentent la cause la plus fréquente d'arrêt du traitement lié à une intolerance.

D'après l'enquête multicentrique de J. Holzer et H. Beck l'apparition de troubles psychiques a déterminé l'arrêt du traitement dans 24 % des cas, la réduction de la posologie dans 33 % des cas et l'absence de toute modification de la thérapeutique dans 43 % des cas.

Parmi les troubles psychiques signalés, certains entrainent dans tous les cas l'arrêt du traitement; il s'agit des syndromes confusionnels, des bouffées délirantes et des états démentiels.

Par contre les épisodes hypomaniaques peuvent céder à une simple diminution de la posologie et les états dépressifs et anxieux nécessitent le plus souvent la seule adjonction d'un correcteur thymo-analeptique ou anxiolytique.

4. — *Responsabilité réelle de la L DOPA dans l'apparition des troubles psychiques.*

Si l'on considère la fréquence des troubles psychiques chez le parkinsonien non traité ou utilisant des médicaments autres que la L DOPA on est amené à se poser la question de la responsabilité réelle de la L DOPA dans la génèse des troubles.

En d'autres termes la L DOPA agit-elle comme inducteur de troubles psychiques ou simplement comme révélateur sur un terrain prédisposé?

J. Holzer et H. Beck retrouvent dans 59 % des cas des antécédents psychiatriques chez des sujets ayant presenté des troubles psychiques sous L DOPA et dans 25 % des cas les antécédents sont identiques dans leur nature aux troubles survenus en cours de traitement.

R. Fau, R. Chateau et coll. rapportaient au cours du 2è. colloque Larodopa à Rabat en 1972 leurs résultats portant sur une étude systematique de l'état psychique de 80 parkinsoniens.

D'emblée 50 % d'entre eux avaient dans leurs antécédents des troubles mentaux patents: état confusionnel, état délirant, mélancolie, détérioration intellectuelle.

Sur les 50 % restant (soit 40 malades) une étude plus minutieuse ne pu retenir que 13 patients strictement "normaux", les 27 autres malades ayant un état thymique particulier caractérisé par une tendance à l'aboulie et à l'apragmatisme en dehors de tout élément dépressif.

Niebla, A. Devic, M. et Aimard, G.[16] arrivent à des résultats analogues au cours d'une étude portant sur 110 parkinsoniens chez qui ils étudièrent la fréquence des troubles psychiques en dehors de tout traitement par la L DOPA.

Ces auteurs retrouvent 42 % de complications psychiques dont 74 % d'épisodes dépressifs pouvant parfois inaugurer la maladie de Parkinson.

De tels arguments militent en faveur d'une conception "neuro-psychiatrique" de la maladie de Parkinson et tempèrent la responsabilité réelle de la L DOPA dans la génèse des troubles psychiques.

II. La L DOPA en psychiatrie

L'activité psychotrope de la L DOPA ne pouvait manquer d'attirer l'attention des psychiatres.

En effet un corps qui produit ou réactive des troubles psychiques chez les parkinsoniens présente déjà un intérêt; en outre la place de la DOPA dans le métabolisme de l'adrénaline laissait espérer une action sur l'humeur pour les partisans de la théorie adrénergique de la dépression. Aussi de nombreux chercheurs ont utilisé la DOPA dans des entités psychiatriques très diverses.

1. — *Les effets de la L DOPA sur certains troubles psychiques.*

a) troubles de l'humeur.

Les résultats publiés ne procèdent ni d'une méthodologie rigoureuse, ni de lot de malades comparables, aussi les contradictions apparentes ne manquent pas.

La plupart des observations sont recueillies chez des parkinsoniens, ce qui apporte une note particulière aux résultats.

— Dans les dépressions, Barbeau [2] a pu faire le point de la façon suivante: seules les formes sévères de dépressions endogènes réagissent favorablement à la DOPA.

Le groupe des dépressions, même si l'expression clinique est identique, recouvre des entités biochimiques différentes. D'ailleurs des produits très divers: 5 HTP, tryptophane... peuvent améliorer des syndromes dépressifs. Barbeau suggère aussi que dans les dépressions la noradrénaline pourrait avoir sous sa dépendance l'humeur, alors que la dopamine stimulerait la motricité qui est toujours ralentie chez le déprimé.

— Des épisodes maniaques ont pu être induits par la L DOPA. Messiha [13] a pu démontrer qu'il existait une augmentation de l'élimination urinaire de dopamine au cours de l'accès maniaque, et que cette excrétion diminue avec la normalisation de l'humeur. Si l'expansion de l'humeur est fréquente chez les parkinsoniens sous DOPA, depuis la discrète euphorie jusqu'à l'accès maniaque franc, la survenue de manie chez des déprimés est diversement commentée selon les observateurs.

Bunney [4] lie les effets à la posologie employée, et trouve à la L DOPA une activité bipolaire en fonction des doses. Certains auteurs pensent qu'un épisode maniaque ne peut se voir chez un déprimé sous DOPA que dans la mesure où celui-ci a déjà présenté un épisode analogue dans ses antécédents.

Enfin Murphy [14] dans une étude rigoureuse confirme le rôle de la DOPA comme inducteur d'épisode maniaque uniquement dans des cas de psychose maniaco dépressive bipolaire.

b) L DOPA et schizophrénie.

La simple étude biochimique de la L DOPA pouvait laisser présager une activité chez les schizophrènes.

En effet, la "tache rose" retrouvée dans l'urine des schizophrènes par Friedhoff et Van Winckle en 1962 contient du 3-4 dimethoxyphenylethylamine. Ce corps est en fait une molécule de dopamine dont deux groupements oxydriles ont été substitués par deux groupements CH_3. L'adjonction d'un troisième radical CH_3 aboutirait à la constitution de la mescaline dont chacun sait les propriétés hallucinatoires.

Barbeau pense qu'à de très fortes doses la L DOPA peut induire des tableaux rappelant la schizophrénie: stéréotypies, délire paranoïde, hallucinations, et même un syndrome cataleptique.

Yaryura-Tobias [17] attribue à la L DOPA le rôle d'un producteur de modèle biochimique de psychose, et voit dans ce corps un outil métabolique pour l'étude de la schizophrénie.

Tous les auteurs s'accordent à reconnaitre que la L DOPA aggrave les schizophrènes délirants en stimulant leur délire actuel ou en réactivant un délire ancien.

La création "de novo" d'une symptomatologie psychotique (comme le font les amphétamines) demeure une question sans réponse à ce jour. Un auteur américain la formulait d'une façon imagée: "la DOPA peut-elle changer le disque ou se borne t-elle à augmenter le son?"

Une étude très récente de Angrist apporte des arguments de poids pour confirmer ces observations. Cet auteur s'est proposé de vérifier le rôle possible des mécanismes dopaminergiques dans certaines psychoses. Dix schizophrènes, chez qui les neuroleptiques avaient été arrêtes depuis une semaine, ont reçu des doses de L DOPA variant de 3 à 6 g par jour. L'étude du comportement de ces patients a mis en évidence une aggravation chez les dix malades dont 3 cas de stimulation et d'excitation non spécifique, et 7 cas de stimulation avec aggravation des symptomes pré existants ou apparition d'une nouvelle symptomatologie (délirante en particulier).

L'auteur pense, avec Goodwin [11] que l'hyperactivité est liée à l'action de la dopamine qui augmente les catecholamines cérebrales et en accelère le turnover. Il avance enfin l'hypothèse que les neuroleptiques sensibilisent les sujets aux effets de la DOPA en bloquiant les récepteurs dopaminergiques et centraux et en augmentant le turnover de la dopamine.

c) L DOPA et stimulation de la sexualité.

La stimulation de la sexualité par la DOPA n'a pas manqué de retenir l'attention des chercheurs.

Goodwin [11] y voit à la fois le rôle de la dopamine sur les catécholamines cérébrales qu'elle augmente mais aussi la participation d'un syndrome hypomaniaque.

En fait l'excitation sexuelle s'observe souvent en dehors de toute stimulation de l'humeur. Elle se traduit par une restauration ou une augmentation de la libido avec un appétit sexuel accru.

Diverses études ont été entreprises sur des patients impuissants, celle de Benkert [3] est la plus importante. Les effets de la DOPA furent étudiés sur 8 patients pendant 12 semaines. Chez tous furent notés: une augmentation des érections spontanées nocturnes, una augmentation de l'intensité des érections au cours des rapports sexuels dont cependant aucun ne pu être mené à son terme, enfin une augmentation générale de la libido avec une fréquence accrue des rêves érotiques.

Ces effets commencèrent à s'estomper vers la 8e. semaine et les patients retrouvèrent leur état antérieur, malgré le maintien des doses de DOPA, vers la 12e. semaine.

2. — *Place de la L DOPA parmi les psychotropes.*

Devant des effets psychiques aussi nombreux, qu'ils soient indésirables ou pouvant avoir un intérêt thérapeutique, se pose la question de la place de la DOPA parmi les médicaments psychotropes.

Comment peut-on situer les effets de la DOPA par rapport aux grandes classes thérapeutiques de médicaments utilisés en psychiatrie?

Une étude française récente (Deniker et Zarifian[8]) a tenté d'y répondre. Les auteurs ont procédé à un essai pilote sur 37 patients représentant des catégories nosologiques diverses et comprenant des schizophrènes délirants ou à forme déficitaire, des dépressions, des névroses psychasthéniques et hypocondriaques et enfin des impuissances sexuelles non organiques. La posologie fut de 1,5 g par jour en moyenne, sans dépasser 2,5/jour et la durée d'observation s'étendit de 1 à 8 mois.

Les effets sur l'humeur furent de deux ordres: soit aucune modification, soit amélioration de l'humeur. Il n'y eut aucun effet dépresseur de l'humeur ni d'aggravation d'un état dépressif existant.

Par contre chez trois mélancoliques vrais il y eut un rétablissement franc, net et rapide (moins de 15 jours) de l'humeur avec dans tous les cas un bref passage hypomaniaque vers le 8e. jour.

Les autres effets notés furent les suivants:

Une aggravation quasi générale de l'anxiété a été observée avec une exacerbation très importante dans 5 cas. Dans la plupart des cas le recours aux anxiolytiques s'est avéré nécessaire.

L'activité fut stimulée chez tous les patients. Tous les intermédiaires se sont trouvés réalisés entre la simple augmentation de l'activité habituelle avec sensation de bien être, et l'hyperactivité idéatoire, verbale et gestuelle ayant un caractère hypomaniaque.

Parallèlement à cette hyperactivité la vigilance était stimulée avec une tendance à l'insomnie d'endormissement cédant facilement à de petites doses d'hypnotiques.

L'activité onirique s'est trouvée accrue avec une fréquence certaine des thèmes érotiques ou terrifiants.

L'activité onirique s'est trouvé accrue avec une fréquence certaine des thèmes érotiques ou terrifiants.

L'activité sexuelle fut stimulée dans de nombreux cas (simple augmentation de la libido) et un des cinq impuissants retrouva une activité sexuelle normale.

Enfin une action notable sur l'asthénie fut retrouvée en particulier chez les névroses psychasthéniques.

RÉSUMÉ

Tous ces effets peuvent être regroupés de la façon suivante:

—l'action stimulante de la DOPA permet de la placer parmi les psychoanaleptiques;

—l'existence d'inversion de l'humeur au cours de melancolie —qui définit les anti dépresseurs vrais— autorise à rapprocher la DOPA des thymoanaleptiques.

—la potentialisation de l'anxiété, la stimulation de la vigilance, la facilitation de l'activité idéatoire et motrice, l'efficacité sur l'asthénie son des caractères communs aux nooanaleptiques, et en particullier aux amphétamines.

—la DOPA ne semble présenter aucun des caractères cliniques des neuroleptiques en dehors de la création de mouvements anormaux que l'on pourrait comparer aux dyskinésies tardives dues aux neuroleptiques.

Mais malgré ce caractère joint à ses propriétés stimulantes, la DOPA ne saurait être rapprochée des neuroleptiques desinhibiteurs;

—l'action stimulante sur la sexualité est a l'opposé des manifestations inhibitrices habituelles des anti dépresseurs et des neuroleptiques.

Ainsi la DOPA est une substance psychotrope qui trouve son champ d'action aux confins des antidépresseurs et des substances à action amphétaminique.

Si l'action thérapeutique de la DOPA en neurologie est actuellement parfaitement précisée, il est un peu tôt pour fixer les limites des applications de la L DOPA en psychiatrie.

Cependant toutes les constatations concernant la "Dopa et les troubles psychiques" relance l'intérêt des médiateurs du système nerveux au point de rencontre des préoccupations de la neurologie et de la psychiatrie.

RESUMEN

Todos esos efectos pueden ser agrupados de la siguiente manera:

—la acción estimulante de la DOPA permite situarla entre los psicoanalépticos;

—la existencia de la inversión del humor en el curso de la melancolía —que define los anti-depresores verdaderos— autoriza a aproximar a la L-Dopa a los timoanalépticos;

—la potencialización de la ansiedad, el estímulo de la vigilancia, la facilitación de la actividad ideatoria y motora, la eficacia sobre la astenia son caracteres comunes a los no analépticos, y en particular, a las anfetaminas.

—La Dopa no parece presentar ninguno de los caracteres clínicos de los neurolépticos fuera de la creación de movimientos anormales que podríamos comparar a las disquinesias tardías debido a los neurolépticos.

Pero a pesar de ese carácter junto con sus propiedades estimulantes, la Dopa no podría ser aproximada a los neurolépticos desinhibidores;

—la acción estimulante sobre la sexualidad es la opuesta a las manifestaciones inhibidoras habituales de los anti-depresores y de los neurolépticos.

Así la Dopa es una sustancia psicotrópica que encuentra su campo de acción en los confines de los antidepresores y de las sustancias con acción anfetamínica.

Si la acción terapéutica de la Dopa en la neurología está en la actualidad perfectamente precisada, es un poco temprano fijar los límites de las aplicaciones de la L-Dopa en la psiquiatra.

Mientras tanto, todas las constataciones concernientes a la "Dopa y los problemas psíquicos" estimula el interés de los mediadores del sistema nervioso al punto de reunir las preocupaciones de la neurología y de la psiquiatría.

SUMMARY

All these effects may be grouped as follows:

—the stimulant action of Dopa allows it to be placed among the psychoanaleptics;

—the existence of the inversion of humor in the course of melancholy —which defines the true anti-depressors— allows the Dopa to be approached to the thymoanaleptics;

—the potentialisation of anxiety, the stimulation of vigilance, the facilitation of thought and movement, the efficacy on asthenia are characteristics common to the non-analeptics, and particularly, to the amphetamines;

—the Dopa does not seem to present any of the clinical characteristics of the neuroleptics outside of the creation of abnormal movements which we can compare with the late dyskinesias due to the neuroleptics;

But notwithstanding that characteristic together with its stimulating properties, the Dopa was not approached to the neuroleptic disinhibitors;

—the stimulating action on sexuality is opposed to the habitual inhibitory manifestations of the anti-depressors and of the neuroleptics.

Thus the Dopa is a psychotropic substance which finds its sphere of action in the confines of the antidepressors and of the substances with amphetaminic action.

If the therapeutic action of the Dopa in neurology is perfectly precised at present, it is a bit soon to fix the limits of the applications of the L-Dopa in psychiatry.

Meanwhile, all the proofs concerning the "Dopa and the psychic problems" strengthen the interest of the mediators of the nervous system to the point of reuniting the preoccupations of neurology and psychiatry.

ZUSAMMENFASSUNG

Alle diese Wirkungen können in folgender Weise grupiert werden:

—die stimulierende Aktion des DOPA erlaubt es unter die Psychoanaleptica einuteilen;

—der Umstand, dass es ein Umschlagen der Stimmung im Verlauf der Melancholie erreicht —das was die wirklichen Antidepressoren kennzeichnet— erlaubt das L-DOPA in die Nähe der Thymoleptica zu stellen;

—die Vervielfachung der Spannung, der Anspr on der Wachsamkeit, die Förderung der geistigen und motorischen Aktivität, die Wirksamkeit gegen Asthenie sind Eigenschaften, die die Nicht-Analeptica, besenders das Amphetamin gemeinsam haben.

—Das DOPA scheint nicht eine einzige der klinischen Eigenschaften der Neuroleptica zu haben mit Ausnahme des Hervorrufen abnormaler Bewegungen, die wir mit den Spät-Dyskinesieen der Neuroleptica vergleichen könnten.

Aber trotz dieser Eigenart zusammen mit seinen stimulierenden Eigenschaften, pflegte man das DOPA nicht mit den enthemmenden Neuroleptica zussammenzubringen;

—die stimulierende Wirkung auf die Sexualität ist entgegengesetzt zu den gewöhnlich lähmenden Erscheinungen durch Antidepressoren und Neuroleptica.

So ist das DOPA eine psychotrope Substanz, die ihr Aktionsfeld findet im Grenzgebiet der Antidepressoren und der Neuroleptica. Wenn die therapeutische Wirkung des DOPA in der Neurologie gegenwärtig genau umrissen ist, so ist es etwas vorzeitig die Grenzen der Anwendungen des L-DOPA in der Psychiatrie zu bestimmen.

Inzwischen wecken alle Feststellungen, die sich auf das "DOPA und psychische Probleme" beziehen, das Interresse an den Vermittlern des Nervensystem so sehr, dass sich die Besorgnisse von Neurologie und Psychiatrie vereinen.

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Withdrawal of the Paradoxal Sleep by the Clomipramine, Electrophysiological, Histochemical and Biochemical Study

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Most of the tricyclic antidepressants provoke a decrease of the paradoxal sleep in man, whether it be after one dose alone as during the course of a prolonged treatment. That effect has been obtained by the Imipramine,Toyoda [27], the Amitriptiline, Hartman [17], the Desimipramine, Zung 1969, while the Trimipramine and the Iprindole do not have much effect, Dunleavy et al [12]. After a prolonged administration of Amitriptiline, when the treatment is stopped it is followed by an increase of the paradoxal sleep, Wyatt and Snyder [29]. As a consequence of the suppressing action of the clomipramine on rapid sleep, this drug has been praised in the treatment of Narcolepsia-Cataplexy with good results, Passouant et al. [23].

The mechanism of action of the tricyclical antidepressants seem to be linked with the changes of the cerebral metabolism of the monoamines whose role in the different kinds of sleep has been pointed out many times. In order to determine these facts we have studied the effects of clomipramine on man's sleep and also on an animal on the histochemistry and biochemistry of the cerebral monoamines.

I. — EFFECTS OF THE CLOMIPRAMINE ON MAN'S SLEEP

Clomipramine has been given in doses of 25 to 200 mg., whether during a short period covering 4 days, or during a long period covering 15 to 27 days in different normal, narcoleptic or depressed people. Some night poli-graphic registrations have been practised during the treatment, such as the electro-encephalogram, the eye movements, the electromyogram, and the breath and heart frequency, but also during 3 days before commencing, under placebo and during several days after its interruption. In some cases, telemetric registrations have been made during the day, while the patients have been submitted to several psychological tests in order to see the variations of the attention, the memory and affection.

A) Normal Subjects

Seven voluntary students 20 to 25 years old, 5 of the masculine sex and 2 of the feminine sex have been studied during three nights under placebo. The clomipramine has been given for 4 days in progressive doses which go from 25 to 175 mg. The subjects have been followed during 3 nights after receiving the medication and exceptionally by one of them on the 8th and 26th night.

1. *Effects on the rapid sleep and the movement of the eyes.*— As from the first night a total or nearly complete suppression of the rapid sleep was obtained in all the subjects with a dosis of 25 to 75 mg of clomipramine.

During the 4 days of observation, the

clomipramine has been increased progressively from 50 to 100 mg in 4 subjects, 125 mg in another 2 and 175 mg in the last. The rate of rapid sleep has varied from 0 to 4 %, except for one subject who, notwithstanding a dosis of 125 mg of clomipramine has presented a rate of 12 %. During the 4th night the rapid sleep was null in six of the seven subjects and with a very low rate (1,25 %) in the last who had received a larger dosis (175 mg) (Fig. 1).

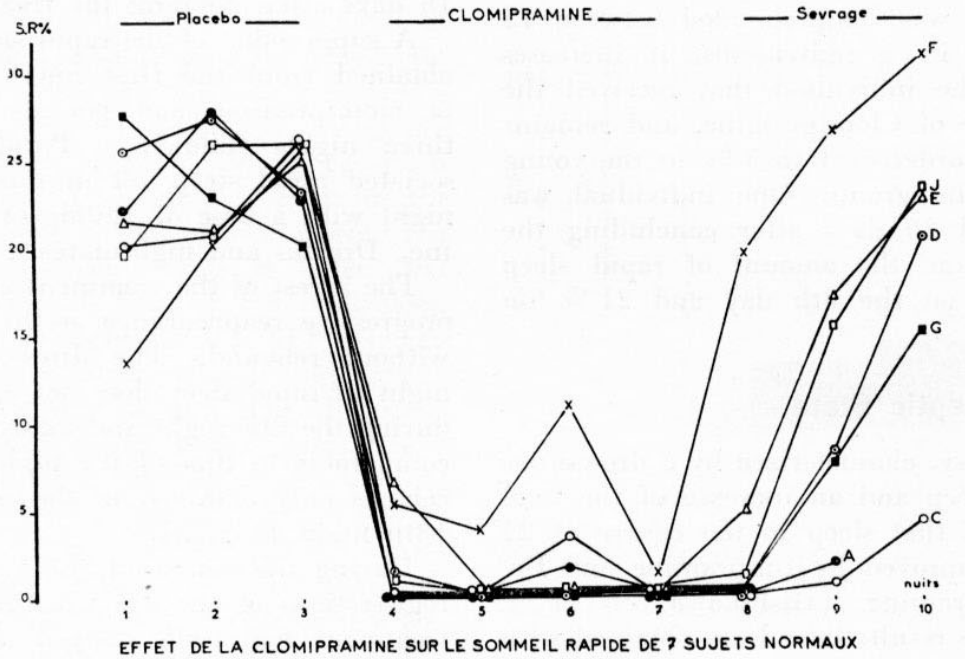


Fig. 1. — *Suppression of rapid sleep in 7 normal persons with individual variations. Percentage of rapid sleep related to the total sleep in the course of 3 nights under placebo, 4 nights under clomipramine and 3 nights after the arrest of the clomipramine.*

Notwithstanding the suppression of the rapid sleep, periods with movements of the eyes come episodically at the end of the night. At the moment these are produced the tone of the muscles is not modified and the electroencephalographic activity is that of the rapid sleep or of the slow sleep. The ocular movements are not very frequent but they increase in the course of the succeeding nights under the clomipramine. They commence 4 to 6 hours after falling asleep, they may be organized into cycles and may be associated with short periods of rapid sleep.

2. *Effects on slow sleep.*— State Nº 1, not modified during the first night, increases later on, and may correspond to 13 % of total sleep. It is reproduced periodically during the night. Notwithstanding this relief of sleep, no periods of insomnia have been observed although the clomipramine has been taken at the end of the day and at the moment of lying down.

State 2 is increased as from the first night, going in one individual from 57 % (under placebo) to 65 % after 25 mg of clomipramine and in another from 48 % (under placebo) to 80 % after 75 mg.

States 3 and 4 come at the beginning of the night, its duration is shortened and state 4 may be suppressed during the last two nights.

3. *Effects on the muscular tone and the movements.*— The muscular tone is reinforced as from the very first night, it does not suffer any change by the production of rapid movements of the eyes, but it decreases at the moment of stage 4.

Brief muscular shakes, with a flexion of the superior limbs, more rarely of the lower limbs, are produced during the night and they are precise two hours after falling asleep. They are associated in stage 2 of

the slow sleep and they may provoke brief episodes of stage 1.

4. *The arrest of the Clomipramine.*— Rapid sleep reappears progressively with different variations according to the individual. On the third day after concluding the treatment the total duration of the rapid sleep was comprehended between 15 and 22 % in 4 individuals, it increases 31 % in the individual that received the largest dose of Clomipramine, and remains low in the order of 4 to 5 % in the young ladies of the group. One individual was seen 8 and 26 days after concluding the treatment and the amount of rapid sleep was 32 % on the 8th day and 21 % on the 26th.

B) Narcoleptic State

Narcolepsy, characterized by a drowsiness of rapid sleep and an increase of the total duration of that sleep in the course of 24 hours is improved by Imipramine and Demethylimipramine (Hishikawa et al. [18]. Comparable results have been obtained with Clomipramine, Passouant and Baldy-Moulinier [21]. They are precise on cataplexy, Passouant et al. [22], less neat on the accesses of sleep which remain but they correspond then to a slow sleep.

After 3 nights under placebo the clomipramine has been given during 4 days increasing the doses from 25 to 100mg to a narcoleptic person whose sleep during the night has been followed during a period of 18 days after stopping the treatment.

A suppression of the rapid sleep has been obtained from the first night with 25mg of clomipramine and persists during the three nights following. Periods of "dissociated rapid sleep" occur during the 4th night with a dose of 100mg of clomipramine. Dreams and nightmares disappear.

The arrest of the treatment causes a very progressive reappearance of the rapid sleep without rebound. The drowsiness of the night in rapid sleep does not appear except during the 8th night and most of this sleep comparable to that of the night under placebo is only obtained in the course of the 18th night (Fig. 2).

During the course of the two telemetric registrations of the day practised when the treatment had been stopped, an access of slow sleep (State 1 and 2) is followed after the meal.

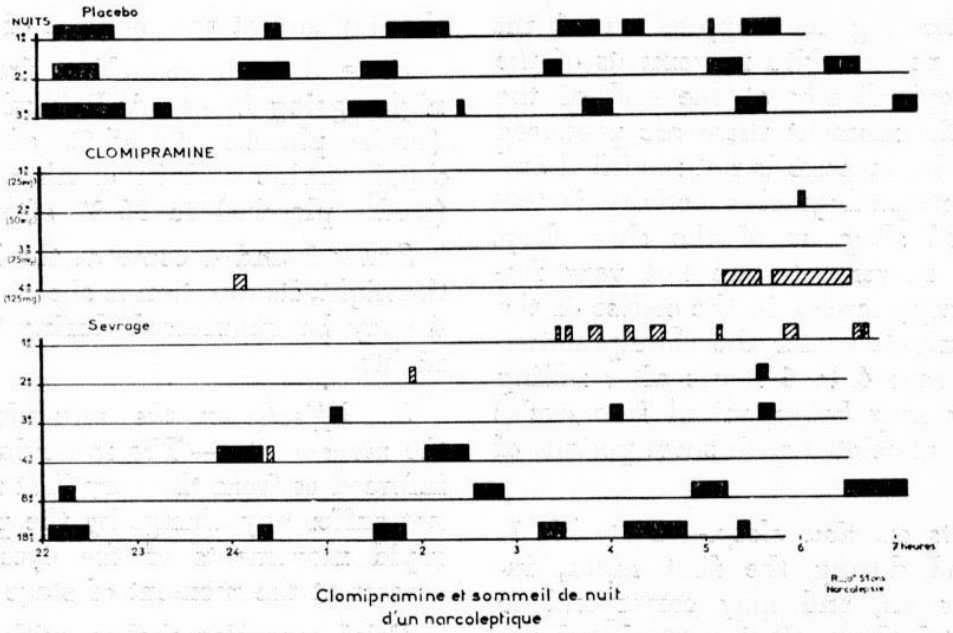


Fig. 2. — *Diagram of the night sleep with indications of rapid sleep (black) and of the dissociated rapid sleep (broken line) in a narcoleptic person in the course of 3 nights under placebo, 4 under clomipramine and 6 after the arrest of the clomipramine.*

C) Depressive State

A long term study lasting from 25 to 50 days has been made on 3 depressed patients.

The first, 52 years old, with a neurotic depression has been followed during 18 nights. The examinations under placebo show in course of the third night 20 % of rapid sleep, and absence of state 4 and not many awakenings (42 mm total). The Clomipramine given during 16 days in progressive doses of 25 to 100mg cause an entire suppression of rapid sleep from the very first night and that persists during ten nights. Rapid sleep reappears after that and corresponds to 5 % of the total sleep during the 16th night. Periods of "dissociated sleep" appear during the 7th night, they are not very frequent and they disappear later on. State 4 remains null and state 3 decreased. The time awake during the night important (170 mins.) with 25 mg of Clomipramine, it is attenuated inmediately after and disappears in the course of the 10th night while there is an improvement in the behavior.

The arrest of the treatment studied during two nights is associated with a progressive increase of the rapid sleep: 10,3 % and 14,7 % with a persistance in the delay of the appearance of the first rapid sleep (143 mins.). The profound slow sleep (state 4) does not appear (Fig. 3).

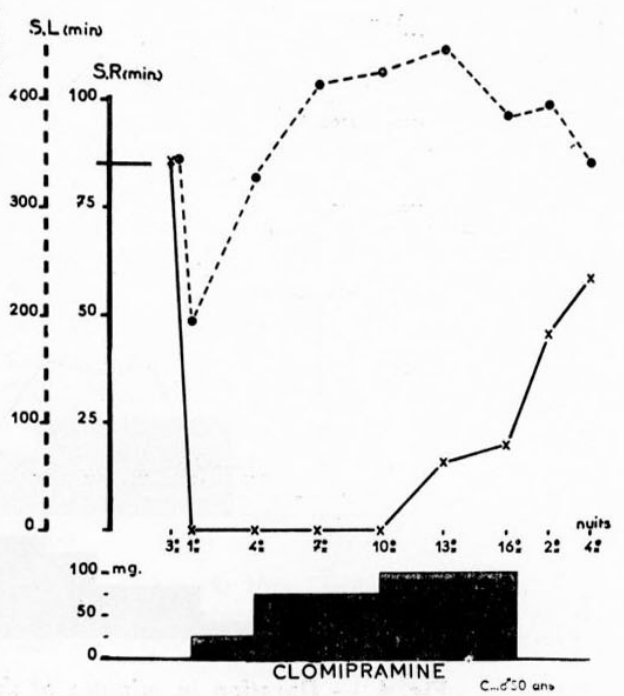


Fig. 3. — *Duration in minutes of the rapid sleep (straight line) and of the slow sleep (dotted line) in the course of a 3rd night under placebo, of 16 nights under clomipramine and 4 nights after arrest (depressed patient). The horizontal line corresponds to the middle duration of the rapid sleep. Total suppression of rapid sleep during 10 days, augmentation of the rapid sleep without rebound after the arrest of the clomipramine.*

The second individual of 55 years of age, presents a depressive state with a psychastenic background having needed many visits to the psychiatrists. The examinations under placebo, effected a month after the arrest of the treatment by I. M. A. O. show the persistance of a rebound of rapid sleep which corresponds to 33,09 % of total sleep with a very short latency (10 mins) of the first rapid sleep. The Clomipramine has been given during 27 days increasing progressively the doses from 25 to 200mg. As from the first night the rapid sleep is suppressed with 25mg and this total supression is maintained during 4 nights. As from the 7th night rapid sleep oscillates between 4,57 % and 12,98 % of total sleep, these variations being in connection with the increase of the dosis. The latency of the first rapid sleep is comprehended between 90 mins. and 398 mins. and this variation depends also on the dosis of Clomipramine. State 2 of the slow sleep is netly increased: from 37,82 % under placebo; it varies between 50 and 65 % under Clomipramine. The same occurs with state 1 which is of 4 % under placebo and oscillates between 7 and 28 % under Clomipramine. State 4 is diminished and corresponds to 5 % of the total sleep.

The arrest of the treatment studied during 15 days shows a progressive increase of the rapid sleep and a rebound (33,75 %) as from the 4th day that is maintained during 15 days (Fig. 4). The improvement of the humor comes as from the end of the first week and has continued notwithstanding the increase of the rapid sleep which has followed the arrest of the Clomipramine. The bad ideas, the pessimism, the intelectual and motrice inertia are very much improved. The nightmares which occurred daily and even causing the individual to

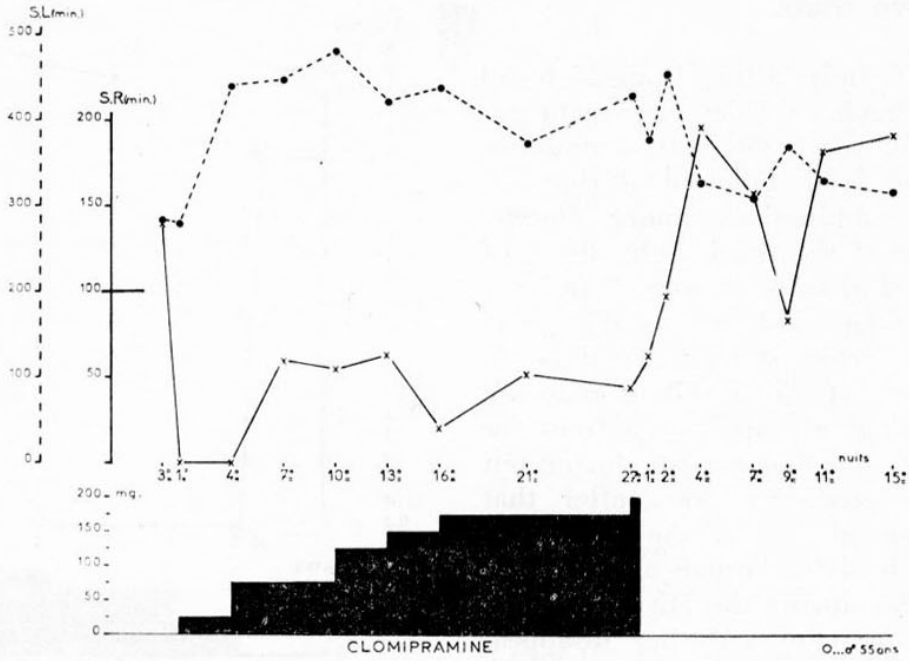


Fig. 4. — *Duration in minutes of the rapid sleep (straight line) and of the slow sleep (dotted line) in the course of a 3rd night under placebo of 27 nights under clomipramine and 15 nights under arrest (depressed patient). The horizontal line corresponds to the middle duration of the rapid sleep in that person. Total suppression of the rapid sleep during 4 days. Rebound of the rapid sleep after the arrest of the clomipramine.*

fall out of his bed have disappeared and the remembrance of dreams have not reappeared, very inprecise, except on the 4th day after the arrest of the treatment.

The third individual, a lady 45 years old presents a neurotic depression associated with insomnia. The examinations under placebo (4 nights) show insomnia with a delay of drowsiness, many times wakening in the course of the night and a total sleep which varies from 3 to 5 hours. The Clomipramine at a dosis of 25mg with a night meal causes a complete supression of rapid sleep that with an increase to 50 and later on to 75mg will be maintained during 15 days. Insomnia is improved during the first 4 nights, afterwards the duration of sleep increases till it reaches 6 to 7 hours. The periods of "dissociated rapid sleep" appear in the course of the 4th night, afterwards they become more and more numerous and they come a short time after falling asleep. State 4 is null.

The arrest of the treatment, followed during a period of 6 days is associated with the reappearance of rapid sleep which at the moment of the 6th night corresponds to 26,3 % of total sleep and translates a slight rebound, with an important increase of the movements of the eyes. Insomnia remains reduced and state 4 reappears (Fig. 5).

II. — THE EFFECTS OF THE CLOMIPRAMINE ON THE CEREBRAL MONOAMINES IN ANIMALS

Clomipramine (3 mg/kg I. M. whether in one injection alone, whether in a double injection with an interval of 12 hours) produces in the cat a suppression of rapid sleep during 2 to 4 days, without any change of behavior except for an attitude of sleep, corresponding to an improvement of the slow sleep (above 80 % the first 3 days). The reappearance of rapid sleep is progressive without rebound. The normal percentage of the three states of wakefulness is found once more on the 6th day, Baldy-Moulinier et al [4].

This effect is connected with the action of the antidepressors on the cerebral monoamines. Imipramine blockades the recapture of the catecholamines through the nervous terminals within the peripheral neu-

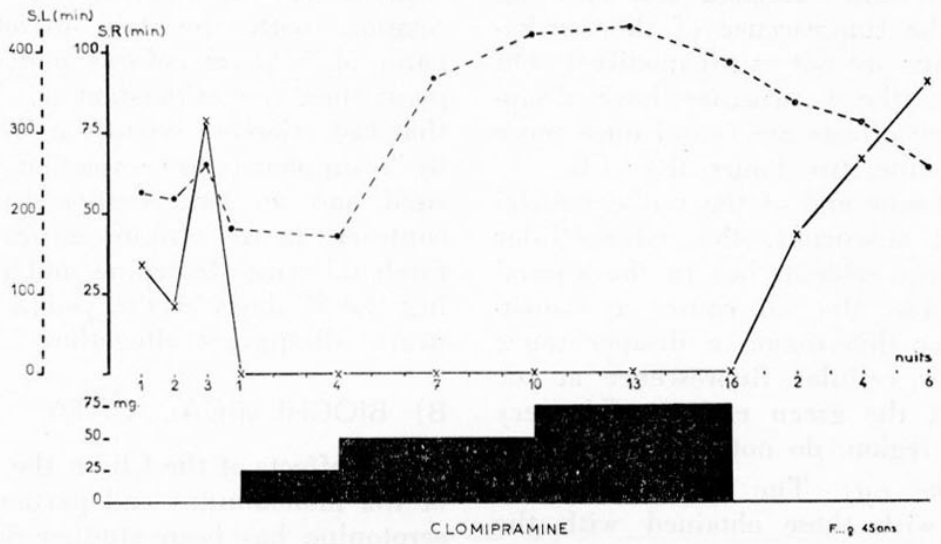


Fig. 5. — *Duration in minutes of the rapid sleep (straight line) and of the slow sleep (dotted line) in the course of 3 nights under placebo, of 16 nights under clomipramine and 6 nights after arrest (depressed patient). Total suppression of the rapid sleep during 10 days. Slight rebound of the rapid sleep on the 6th night after arrest of the clomipramine.*

rons, Axelrod et al. [3] and within those of the cerebral trunk, Glowinski et al. [16]. The other tricyclical derivatives seem to have a selectivity of action on the different types of neurons with monoamines, Carlsson [7]: the recapture of the catecholamines is preferently blockaded by the secondary tricyclics or monomethylated, that of the serotonin by the tertiary derivatives or dimethylated of which Clomipramine is one of the most active.

The blockade of the recapture of the serotonin may be sometimes placed in evidence by the histofluorescence, Carlsson et al. [8]. It also gives room to the biochemical changes, Meek and Werdinius [19].

A) HISTO-CHEMICAL DATA

The effects of Clomipramine on the histofluorescence of the neurons with monoamines has been studied on 24 kittens and 81 rats, Dumas et al [11]. The animals, of which some had been treated beforehand with Nialamide or Reserpine - Nialamide were killed by beheading from ½ hour to 4 hours after the administration of one only dose of Cli (25 mg/kg) or after 10 days of prolonged treatment with Cli (25 mg/kg/day), all the brains were prepared in view of an examination in histofluorescence following the technique of Falk and Owman [14] or of Olson and Ungersteadt [20].

1) *Effects of Cli on the neurons with catecholamines (C A)*

On the rat and the kitten treated only with Cli, there are no changes of the different cellular groups CA. On the animals treated before-hand by Nialamide-Cli, we unconstantly observe a certain extracellular diffusion of the fluorescence above all net within the region of the pigmentosus parabrachialis nucleus (group A 10 of Dalstrom and Fuxe [10]), while the other neurons with D A or N A as their diencephalic and mesencephalic terminals remain intact.

2) *Effects of the Cli on the neurons with Serotonin*

a) *on the kittens* We constantly observe important changes of the cellular and extra-cellular yellow fluorescence. They exist within the very animal submitted to the sole action of the Cli, but they are, however, more precise after the Nialamide or the Nialamide-Reserpine.

The middle mesencephalic nuclei of the raphe (centralis superior and dorsal) present a very weak yellow fluorescence due

to an extra-cellular difusion and to a reduction of the fluorescence of the perikarion; the axons are not much modified. On the contrary, the varicosities have disappeared. These effects are found once more exactly the same, two hours after Cli.

At the extreme end of the raphe (nuclei pallidus and obscurus), the extra-cellular difusion is less evident, but in the animal with Nialamide, the Cli causes a vanishment and for this reason a disappearance of the yellow cellular fluorescence at the moment that the green ends at CA very rich in that region, do not change.

b) *on the rat:* The results are most comparable with those obtained with the kitten. However, they are not evidence sufficient that only certain animals treated beforehand with Reserpine or Reserpine-Nialamide at the moment that in the individuals submitted to the Cli alone, the modifications are insignificant.

In the middle part of the raphe (N. dorsalis, B7), there exists in about half of the cases, an extra-cellular difusion and a reduction of the cellular fluorescence. In the other cases, there only exists a diminution of the intensity of the fluorescence of the perikarion. In the caudal region (raphe pallidus B1), the same effects are noted, but more constantly. After the Nialamide, the Cli causes thus after half an hour and an hour, an extra-cellular difusion of yellow fluorescence at the moment the green ends are not modified.

These different histochemical alterations vary in function of the time and the animal treated of acute or chronic way. After one only dose of Cli, the extra-cellular diffusion and the reduction of the neuronal fluorescence noted from the first half hour increases in the first and second hour. On the other hand, at the fourth hour, the extra-neuronal diffusion is attenuated, but the reduction of the neuronal fluorescence is determinad. At this moment very frequently there is nothing but a thin halo of yellow fluorescence around the nucleus. In the animal treated with Cli of prolonged way and Nialamide, this last aspect is never observed, but only a global reduction and a loosening of the cellular fluorescence. This aspect does not seem due to the long time spent before the animals were sacrificed in relation with the last injection of Cli (around 7 hours before) and does not explain then the exhaustion of the effects of that last injection because it is not modified by a supplementary injection of Cli practised half an hour before death. On the contrary, in the chronic animal treated beforehand with Reserpine and notwithstanding the Nialamide, the yellow fluorescence nearly disappears altogether.

B) BIOCHEMICAL DATA

The effects of the Cli on the biochemistry of the monoamines and particularly of the serotonine has been studied on 20 lots of 10 rats, whether without any previous treatment, whether submitted to a first treatment with Nialamide, Pons et al [24]. The global rate of the cerebral monoamines has been determined at different times after one only injection of the drug or after a treatment of 10 days (25 mg/kg/day), following the spectrofluorimetric methods of Euler and Lishajko [13] by the Nor-adrenaline, of Fleming [15] by the Dopamine, and of Bogdanski [6] by the serotonine. The rate of 5 HIAA after probenecide (following a technique derived from that of Meek and Werdenius [19] has been evaluated by the method of Contractor [9].

1) *The global rate of the different cerebral monoamines* is not modified significantly after Clomipramine whether acute, whether in a treatment of 10 days.

2) *The global rate of 5 HIAA of the brain* is significantly reduced in 30 % after Clomipramine, whether in one dose alone (½ hour, 1 hour, 2 hours after the injection), whether after a prolonged treatment during 10 days at the moment the rate of 6)the cerebral serotonine is not modified (Fig. 6).

3) *After probenicide* that blocks the cerebral afflux of 5 HIAA, the speed of accumulation of 5 HIAA in the brain is detained by an acute administration of Cli. On the other hand, the speed of accumulation of 5 HIAA is not modified after the prolonged administration of Cli even when the global rate of 5 HT is comparable to that

MODIFICATIONS DE FLUORESCENCE
APRES CLI

	CA			5 HT		
	EC	C	T	EC	C	T
1°) - Cli 25 mg/kg						
Chatons						
1/2 h	+			++	-	---
1 et 2 h	±			+++	--	---
Rats (+ N ou RN)						
1/2 h	+			++	--	--
1 et 2 h	±	-		+++	--	---
4 h					---	---
2°) - Cli 25 mg/kg						
10 jours				+	-	-
+ R					---	---
+ Cli 1/2 h	±	+		+	-	-

EC : diffusion extra-cellulaire ; C : fluorescence cellulaire ; T : terminales.

TABLE. — *Modifications of the fluorescence after clomipramine* (1) *Immediate effect on the kitten and rat* (2) *Delayed effect* (10 *days*) *in the rat.*

of the animal placebo, but the reduction of the rate of 5 HIAA is larger than in the placebo.

These data show that the action of the Cli is different in an acute or in a chronic administration. After one only dose, there exists a reduction of the turnover of serotonine. After a prolonged treatment, the turnover of the serotonine is not modified, but only the global rate of 5 HIAA is reduced.

DISCUSSION

I. — THE SUPPRESSION OF RAPID SLEEP WITH CLI

The modifications of the paradoxal sleep with the Clomipramine ought to be situated in three different periods: the immediate effect, the effect of a prolonged treatment, and the effect due to the arrest of the Clomipramine.

Immediate effect: Clomipramine, with a dose of 25 mg when going to bed, causes a complete suppression of the rapid sleep in a normal individual, the narcolepticed, the depressed and in the cat. This result, compared with the effects of other tricyclics on the rapid sleep, makes of the Clomipramine the most powerful substance to suppress the rapid sleep. This immediate effect is also very different from that of I. M. A. O. which cause a suppression of rapid sleep after a delay of 10 to 15 days, Akindele et al. [1].

The privations of rapid sleep which may have a duration of 15 days, do not cause reactions of the behavior and particularly hallucinatory reactions during the day. A comparative study which we have made between the privation of rapid sleep by awakening and the privation of rapid sleep with clomipramine on a group of normal people has not shown us but slight variations determined by the tests of learning, of memory and of attention. The people who are deprived of rapid sleep by being awakened are slightly hyper-active, those deprived of rapid sleep by clomipramine are slightly hypo-reactive.

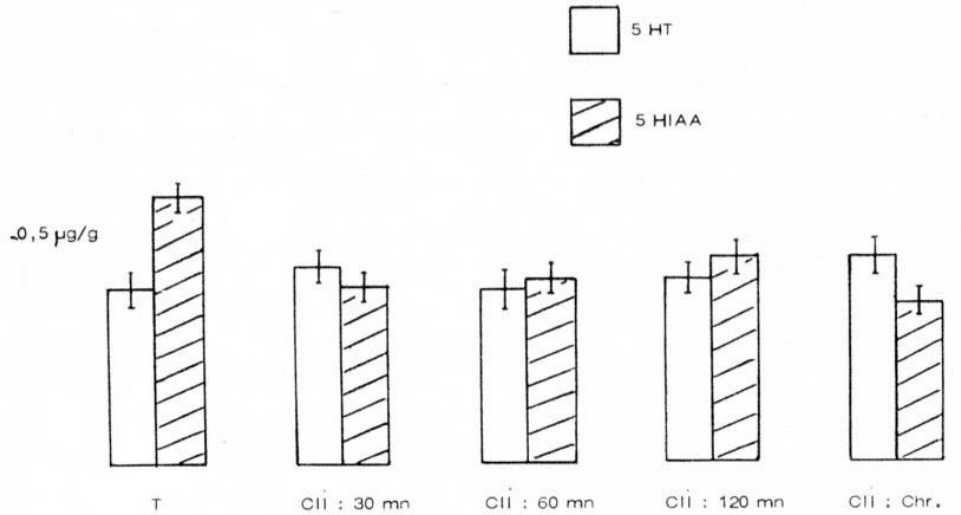


Fig. 6. — *Modification of the* 5 *HT and of the* 5 *HIAA after immediate effect* (30 mn, 60 mn, 120 mn) *and slow* (10 *days*) *of the clomipramine - T; witness.*

Effect of the prolonged treatment: the act of taking clomipramine during a period over 2 weeks is followed by the reappearance of rapid sleep, the rate of which, in the conditions of our study, remains below 50%. On the other hand, the latency of the first rapid sleep remains very long and has varied from 118 minutes to 398 minutes, at the moment that it is normally from 50 to 100 minutes.

This phenomenon of tolerance, found with the other tricyclics may result in a rate of rapid sleep near to the normal with the amitriptiline, Wyatt and Snyder [29]. On the contrary it would be absent with the I. M. A. O. and the total suppressions of the rapid sleep have been obtained for as a year with the phenelzine by doses comprehended between 60 and 90 mg. per day, Wyatt et al. [28].

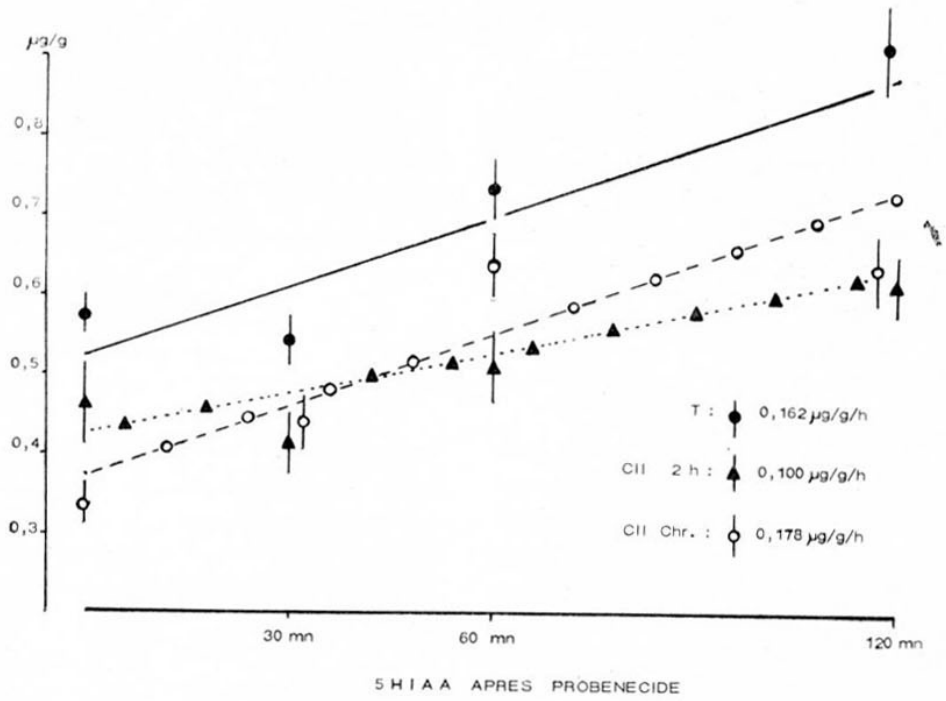
Arrest of the Clomipramine: the interruption in the taking of clomipramine is followed by an increase of rapid sleep, of the progressive installation and of which the importance seems to depend on the duration of the treatment, of the doses used and of the individual reactions.

At the time some studies were made on 7 normal individuals during a short period of time a rebound of rapid sleep has been identified 3 days after detaining the treatment, in the individual who received the largest dose (175 mg on the 4th day) and 8 days after detaining the treatment in another individual treated during 27 days with doses which are progressive from 25 to 200 mg. This improvement remained 15 days after arresting the treatment.

Notwithstanding the discordances of some of our results, as the absence of rebound 18 days after arresting the treatment with clomipramine in a narcoleptic person treated during 4 days, we may anticipate that the arresting of the clomipramine is followed by increase of rapid sleep which may remain many weeks after prolonged treatments. The abscence of rebound of rapid sleep after the imipramine and the amitryptilene found by Hartman [17] in the course of short termed studies must be related as some of our results, to the brief duration of the administration of the medicine. The long termed studies have by other means shown a rebound of rapid sleep with all the tricyclics which modify this sleep, Dunleavy and coll. [12], Wyatt and Snyder [26].

II. — THE PRIVATION OF PARADOXAL SLEEP AND THE BLOCKADE OF THE RECAPTURE OF SEROTONINE WITH THE CLI

The action of the Cli on rapid sleep is worthy of being placed on the same level as its effect with the biogenic amines and particularly the serotonine, the recapture



Fiy. 7. — *Modification of the speed of accumulation of* 5 *HIAA under probenicide, after clomipramines withess;* (————) ; *immediate effect* (.... ▲ ....) *Delayed effect* (- - - O - - -).

of which is very effectively blockaded but the consequences of which are different following the way of acute or chronic administration.

After a short period of administration of Cli, the suppression of rapid sleep is complete both in man and in the animal during 24 to 48 hours. At the same time we notice precociously an extra-neuronal accumulation of serotonine, after an important reduction of the cellular fluorescence and varicosities. Although the global cerebral rate of the serotonine is not much modified, there exists a reduction of the rate of 5 HIAA and a diminution of the speed of accumulation of that metabolite after probenecide, Meek and Werdinius [16], Pons et al. [24], translating a lasting reduction of the rate of renewal of the serotonine, Schubert et al. [26]. The latter may be also linked, after Belin and Pujol [5], with an inhibition of the incorporation of the predecessors of the cerebral monoamines, tyrosine and tryptophane. In the sense of the monoaminergic theory of sleep proposed by Jouvet, and of the role of 5 HIAA in the production of rapid sleep, the elective privation of this type of sleep would be related to the descent of the cerebral rate of this metabolite.

After a prolonged treatment, the suppression of the paradoxal sleep is not always complete and its reappearance is possible although its proportion remains below normal. In the animal, the prolonged treatment does not cause but some modifications not very important of the histofluorescence. The reappearance of rapid sleep could depend therefore on the rate of renewal of the serotonine. Shildkraut et al. [25] have shown that the imipramine in a prolonged administration causes a reduction of the endogenous NA at the moment that the rate of the marked NA increases progressively. In the same conditions, Alpers and Himwich [2] have observed a reduction of the synthesis of the serotonine, as also a diminution of 5 HIAA. With the clomipramine, this diminution of 5 HIAA is notorious but the speed of degradation of the serotonine does not seem to be modified, Pons et al.[24]. The reappearance of the rapid sleep may from that moment depend on the return to normal of the rate of renewal of the serotonine even when the rate of 5 HIAA remains feeble.

SUMMARY AND CONCLUSIONS

The immediate and complete suppressive action of the paradoxal sleep after small doses of clomipramine in a normal, narcoleptic or depressed man, as in the animal is linked with the modifications of the metabolism of the serotonine. At the time of prolonged treatments rapid sleep reappears with a variable delay, but with a rate always inferior to 50 % of the normal rate. The histochemical and biochemical data related to the synthesis and the degradation of the serotonine may render account of these facts.

RESUMEN Y CONCLUSIONES

La acción supresiva y total del sueño paradojal después de la clomipramina a dosis débiles en el hombre normal, narcoléptico o deprimido, así como en el animal, está ligado a las modificaciones del metabolismo de la serotonina. En los tratamientos prolongados, el sueño rápido reaparece con un plazo variable, pero a un nivel inferior en 50 p. 100 de lo normal.

Los datos histoquímicos y bioquímicos en relación con la síntesis y la degradación de la serotonina pueden dar cuenta de estos hechos.

RÉSUMÉ ET CONCLUSIONS

L'action suppressive immédiate et totale du sommeil paradoxal après clomipramine à doses faibles chez l'homme normal, narcoleptique ou déprimé, ainsi que chez l'animal est liée aux modifications du métabolisme de la sérotonine. Lors de traitements prolongés, le sommeil rapide réapparait avec un délai variable, mais à un taux toujours inférieur à 50 p. 100 de la normale. Les données histochimiques et biochimiques portant sur la synthèse et la dégradation de la sérotonine peuvent rendre compte de ces faits.

ZUSAMMENFASSUNG UND FOLGERUNGEN

Die suppresive und totale Aktion des paradopalen Schlafes nach Chlomipramin in schwacher Dosis beim normalen Mensch, narkoleptisch oder deprimiert, ebenso wie beim Tier, ist an die Modifikationen des Metabolismus des Serotonins gebunden. Bei den prolongierten Behandlungen kommt der Schlaf nach verschiedenen Zeiten zurück, aber mit einem um 50 % niedrigeren Niveau gegenüber dem Normalen.

Die histochemischen und biochemischen Daten in Relation mit der Synthese und der Degradation des Serotonins können über diese Tatsachen Kenntnis geben.

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p-Bromo-methamphetamine (V-III) induced improvement of learning ability in rats

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In recent years we have analyzed the correlation between chemical structure and pharmacological activity of amphetamines (Knoll [14], Knoll et al. [20, 21, 22, 24]) Their performance-increasing effect in different behavioral tests has been known for a long time (cf. Essman [9]), and their biochemical actions have been variously analyzed (cf. Costa and Garattini [7]). We have extensively studied the structure-activity relationships of amphetamines on processing and retention of information in rats. We aimed to develop new derivatives with a more selective action on the central nervous system than that of amphetamine or methamphetamine.

Amphetamine and methamphetamine as prototypes of derivatives with mixed catecholaminergic and serotonergic effects.

Figure 1 illustrates that amphetamine in lower doses improves and in higher doses

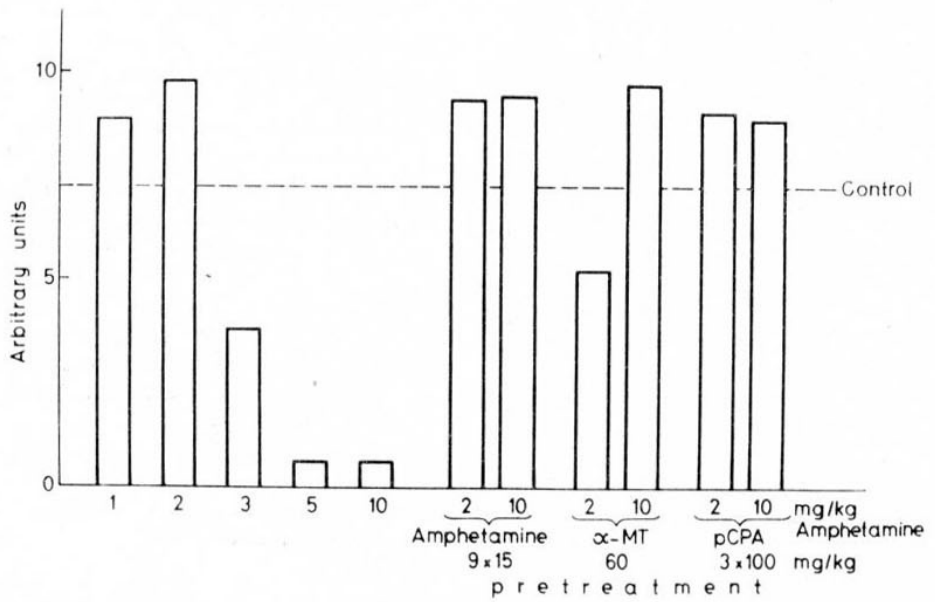


Fig. 1. — *Inhibitory effect of high doses of amphetamine on the modified jumping test (Knoll and Knoll, 1964) and its absence in animals pretreated with amphetamine, α-MT, or pCPA. Amphetamine administered subcutaneously 30 min before measurement. Ten rats in each group. Pretreatments: (a) daily 15 mg/kg amphetamine for 9 days. Last injection 24 hrs before measurement. (b) 60 mg/kg α-MT subcutaneously 4 hrs before measurement. (c) daily 100 mg/kg pCPA subcutaneously for 3 days. Last injection 24 hrs before measurement.*

disturbs the rats' performance in a simple escape test. The figure further demonstrates that the disturbing effect of the higher doses of amphetamine can be antagonized by both α - methylparatyrosine (α-MT) and parachlorophenylalanine, (pCPA), pretreatment and that tolerance to this effect, but not to the stimulatory one, develops in animals treated for some days with amphetamine.

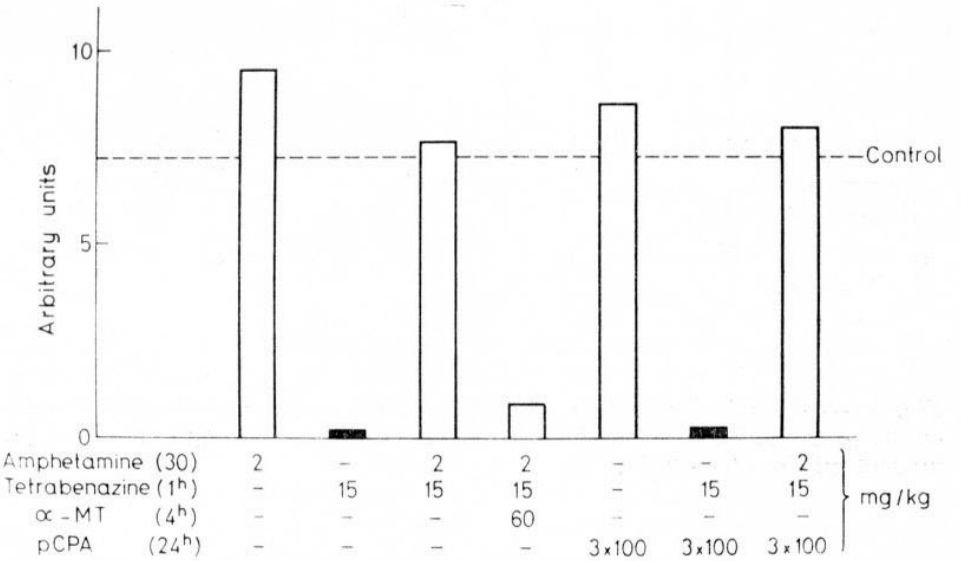


Fig. 2. — *The influence of α - MT and pCPA on the tetrabenazine antagonistic effect of amphetamine on the modified jumping test. All drugs administered subcutaneously. Numbers in parantheses indicate the time elapsed between drug administration and the beginning of measurement. Ten rats in each group.*

Data shown in figure 2, on the other hand, furnish evidence that the psychostimulant effect of amphetamine shown by its ability to inhibit the tranquillizing effect of tetrabenazine can be antagonized by α - MT but not by pCPA. Methamphetamine in all tests acts like amphetamine. From detailed analysis of the mechanism of the dual effect of amphetamine and methamphetamine we concluded that these drugs stimulate performance in low or medium doses by increasing the catecholaminergic tone, but that after administration of higher doses increasing activity of the serotonergic system counteracts the catecholaminergic effects and a disturbance of the animal's performance becomes preponderant. As the scheme in figure 3 shows, in the case of these amphetamines the serotonergic tone-increasing effect is indirect and can be blocked by either pCPA or α - MT.

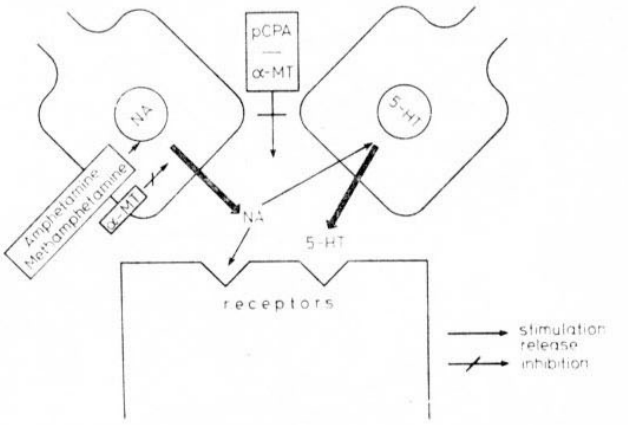
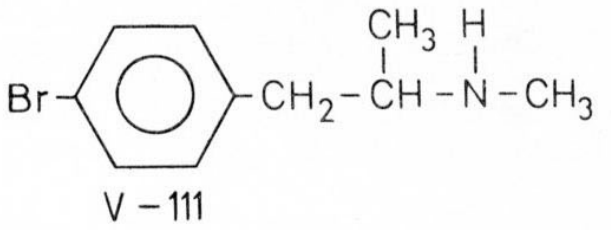


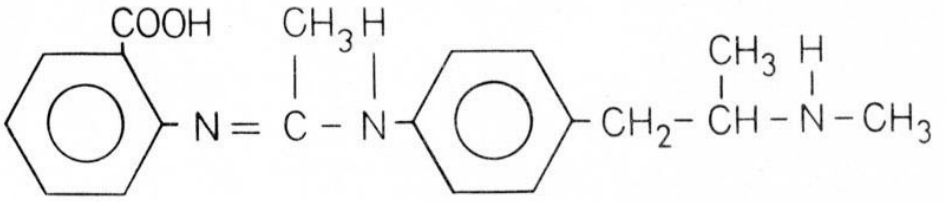
Fig. 3. — *Scheme of a possible mechanism of action of amphetamine and methamphetamine ion the catecholaminergic and serotonergic systems.*

Development of "catecholaminergic" and "serotonergic" amphetamines.

Considering that the dose-dependent dual effect of amphetamine and methamphetamine is a consequence of their mixed actions on the catecholaminergic and serotonergic system, we tried to synthesize amphetamines acting more selectively on one of the two systems. We learned that proper substitutions at the paraposition fulfill the requirements set. Figure 4 shows the struc-



V - 111



I - 1703

Fig. 4. — *Chemical structure of para—bromo—methamphetamine* (*V*—111) *and* N_1*—O—carboxy—phenyl—*N_2*—p—* A2*—methyl—aminopropy—*1—) *phenylacetamidine* (*I*—1703).

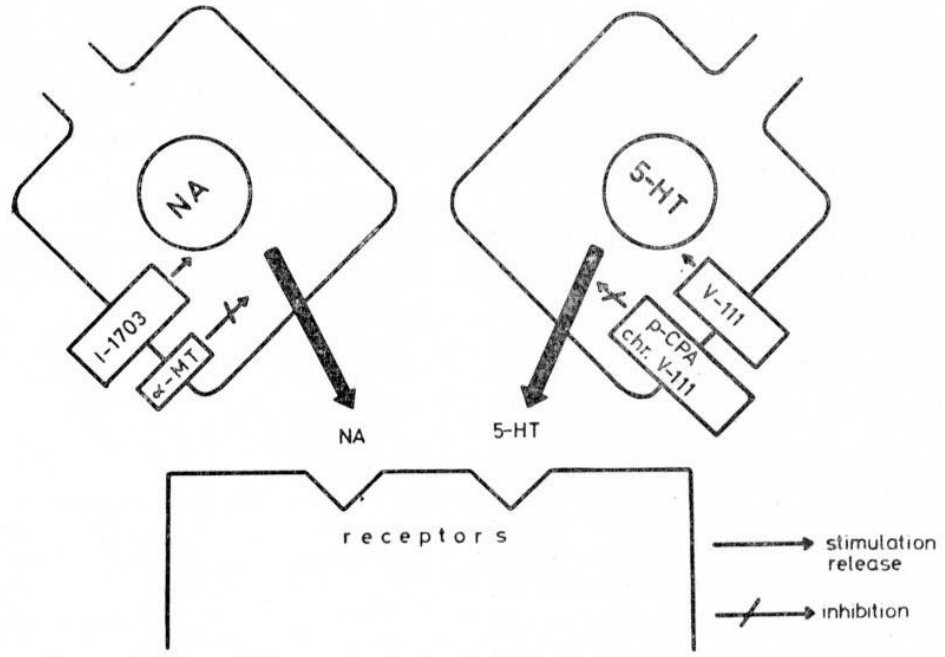


Fig. 5. — *Scheme of a possible mode of action of I*—1703 *and V*—111.

ture of two new methamphetamine derivatives, selected from a large number of compounds we synthesized as more selective in their activity than the parent compound.

Figure 5 shows schematically the site of action of these compound. By comparing this scheme with the one in figure 3 one can see the differences between the effects of methamphetamine and its new derivatives.

Figure 6 shows that in the modified jumping test (Knoll and Knoll [18]) para-bromo-methamphetamine, V-111, which 1 h after the administration in low or high doses increases the serotonergic tone, only inhibits the animal's performance. On the other hand, N_1-O-carboxyphenyl-N_2-p-(2-methyl-amino-propyl-1-) -phenylacetamidine I-1703, which acts more selectively on the catecholaminergic system, stimulates performance even in high dose ranges.

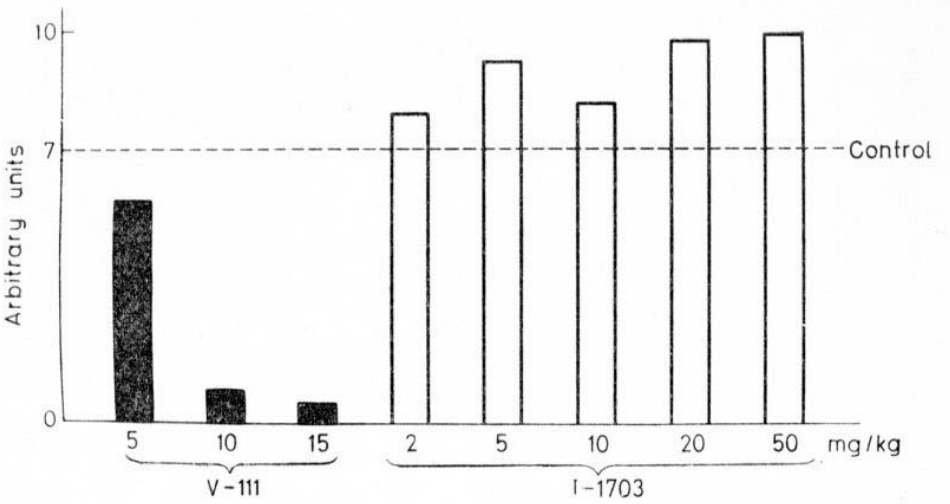


Fig. 6. — *Effects of V—111 and I—1703 in the modified jumping test. Onset of measurement* v *h after the subcutaneous administration of the drugs. Ten rats in each group.*

I-1703 is as potent in antagonizing the tranquillizing effect of reserpine, tetrabenazine, and phenothiazines as amphetamine, and this effect can be blocked by α - MT but not by pCPA. No tolerance develops to the stimulatory effect of the compound.

"Psychotomimetic-like" effects following the acute administration of V-111.

In all the applied behavioural tests performed on rats mice and cats, acute treatment with V-111 caused a significant disturbance of the higher nerve functions which closely resembled the effect of psychotomimetics. Figure 7 and 8 present a typical example of the psychic disturbance developed following acute dosage of V-111. It appears from the plotted date that the dose-response relationship established with this amphetamine derivative in rats closely resembles those found with the commonly known hallucinogenic substances LSD, mescaline or diethyltryptamine. In animal experiments the compound shows 1/10 of the activity of LSD its efficiency being of the order of magnitude of psilocybine, and diethyltryptamine. As it can be gathered

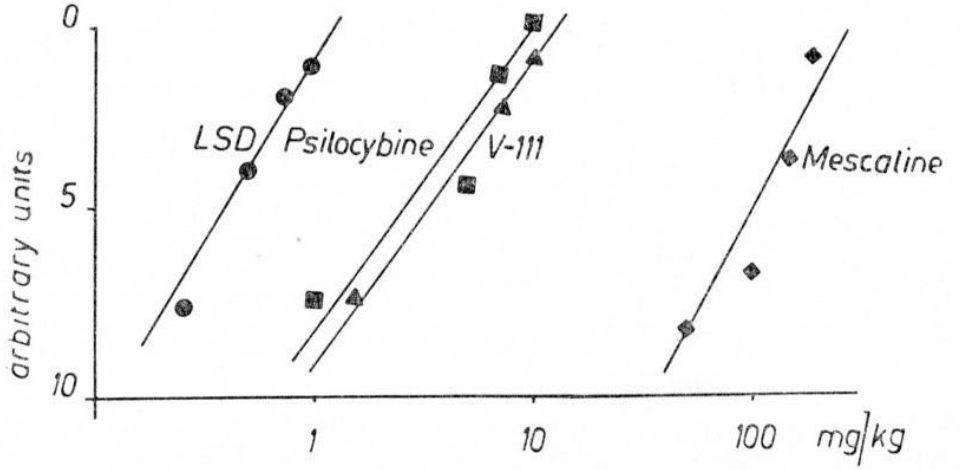


Fig. 7. — *Inhibition of an unconditioned escape reaction in rats by LSD tartrate, psilocybin, mescaline sulphate and V—111. Modified jumping test. All drugs were administered subcutaneously. Measurements performed 5 min after LSD and 30 min after the other drugs.*

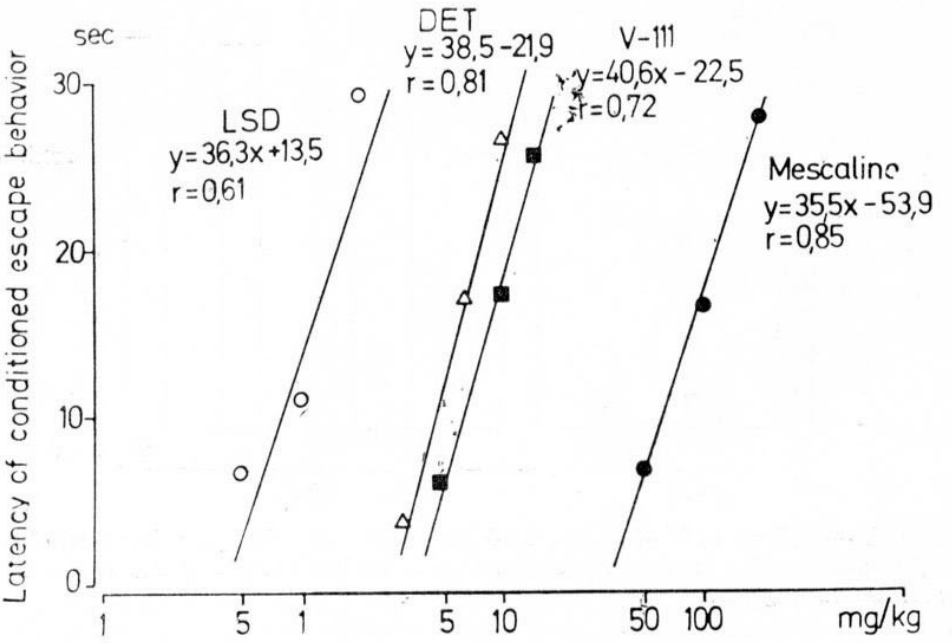


Fig. 8. — *Prolongation of a conditioned escape reaction in rats by LSD tartrate, diethyltryptamine (DET), mescaline sulphate and V—111, as estimated by the jumping test (Knoll and Knoll, 1958; Knoll, 1959) 30 min, 1, 2, 3, 4, and 6 hours after subcutaneous administration of the drugs. The peak effect observed during the hour period taken into consideration.*

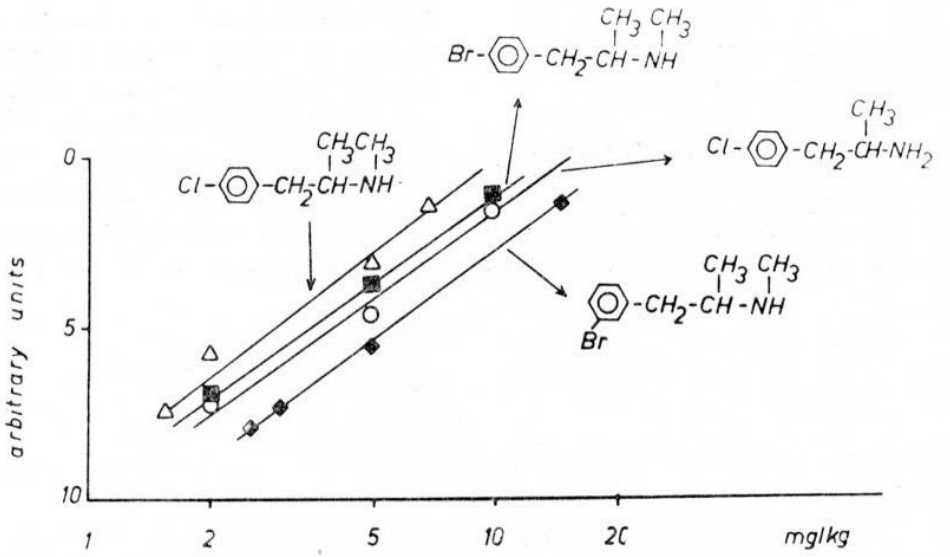


Fig. 9. — *The dose dependent inhibition of an unconditioned reaction by halogenated methamphetamines in the rat. Modified jumping test. Amphetamines were administered subcutaneously 30 min prior to measurement.*

from Fig. 9 the para- and meta- halogenated homologues of amphetamine and methamphetamine were found to elicit a similar type of central effect.

Studying the effect of V-111, we found (Knoll [14], Knoll and Vizi [22, 23], Knoll et al. [25, 26]) that the disturbances of psychic functions observed in acute experiments ceased completely on readministration of the effective dose. In fact, in the course of prolonged treatment significant psychoenergizing action could be observed. Fig. 10 displays the development of high grade tolerance in rats chronically treated with

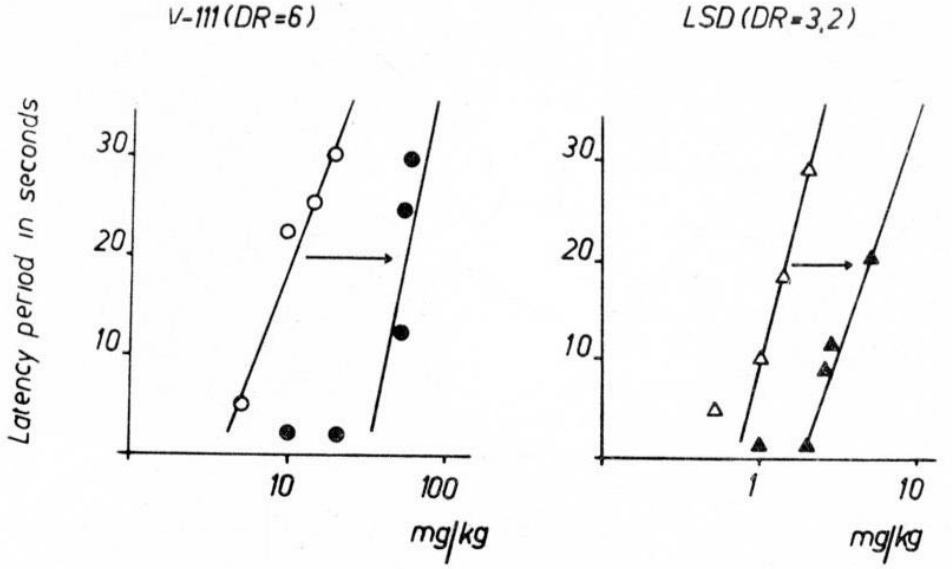


Fig. 10. — *Development of tolerance to V—111 and LSD tartrate in rats pretreated with 10 mg/kg of V—111 daily for 210 days, as estimated in the jumping test. Calculated dose ratio values are given. All drugs were administered subcutaneously.*

V-111. It can be seen that a considerable loss of potency occurs and a significant grade of cross tolerance develops to LSD. The same phenomenon was registered in cats.

The observation (Knoll [14], Knoll and Vizi [22]), that p-chloro-phenylalamine, (p-CPA), pretreatment strongly inhibits the action of V-111 and LSD and that α - methyl-paratyrosine, α - MT, fails to influence the effect of these compounds was of a decisive importance from the point of view of our interpretation of the mechanism of action. A similar correlation between p-CPA and bufotenin was observed by Winocur et al. [42]. Considering that p-CPA pretreatment, i.e. inhibition of 5-HT synthesis (Koe and Weissman [29]), antagonizes the effect of V-111 and LSD completely and α - MT pretreatment, i.e. the inhibition of noradrenaline synthesis fails to exert this effect, it appears evident that both LSD and V-111 produce psychic disturbances by increasing the serotonergic tone in the brain of the rat. The development of cross tolerance between V-111 and LSD is a further and essential proof of similarities in the mode of action of the two compounds.

The daily pretreatment of rats with V-111 for 7-30 days inhibited not only the effects of V-111, mescaline and LSD but also psychic disturbance seen after the administration of high amphetamine and methamphetamine doses. Tolerance developed only to the LSD - like effects of amphetamines while the catecholaminergic effects of these compounds were maintained or even increased. A strong inhibition of the effect of high amphetamine and methamphetamine doses could be observed following pretreatment of p-CPA however, while the effect of V-111 was uneffected by α - MT the V-111 like action of large amphetamine and methamphetamine doses was completely inhibited by this substance. This fact supports our suggestion that in the case of amphetamine and methamphetamine the increase of the 5-HT tone is somehow mediated through the catecholaminergic system as visualized in Fig. 3. Fig. 11 presents a scheme comparing the sites of action of amphetamine, methamphetamine and V-111, respectively, derived from the above described experiences. The scheme offers an easy survey of the pharmacological actions of the amphetamines compared. Up to a medium dose level amphetamine or methamphetamine exerts its psychostimulant effect by a rather selective increase of the catecholaminergic tone. This effect can be inhibited by α - MT, but is uninfluenced by p-CPA. Similar results have been observed by Rech and Stolk concerning p-CPA and methamphetamine. Large

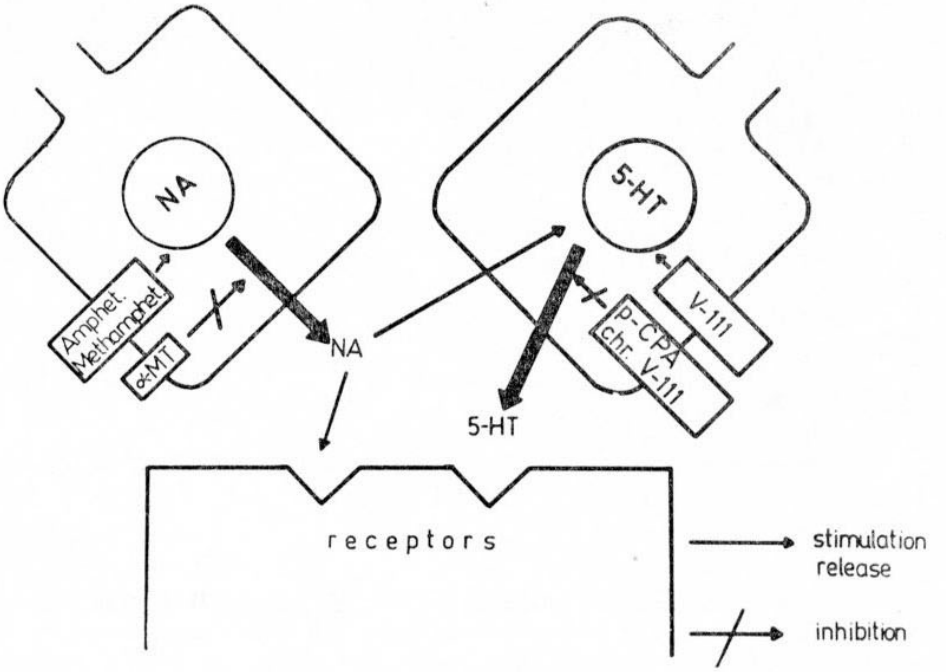


Fig. 11. — *Comparison of the presumed sites of action of amphetamine and V*—111.

doses of amphetamine or methamphetamine seem to increase the 5-HT tone indirectly through excessive release of catecholamines from the intraneuronal stores, i.e. the net effect in animals resembles that of V-111 and LSD. This action can be inhibited by α - MT and p-CPA but it fails to occur in animals pretreated with V-111.

Energized state of the CNS persisting after chronic administration of V-111.

According to the scheme in Fig. 11 the acute effect of V-111 becomes manifested in a selective increase of 5-HT tone which in turn leads to the development of the characteristic disturbances of the CNS. It is not seen from the scheme, however, that the disturbing effect ceases on repeated administration of V-111 and in that case V-111, LSD, as well as large doses of amphetamine and methamphetamine fail to produce an increase of the serotonergic tone, indeed, a characteristic energized state of the CNS persisting after discontinuation of the treatment ensues. This energized state differs essentially from the acute psychostimulatory action of amphetamine. On simple observation of these animals no signs of excitation could be detected. There was no sign of the stereotyped behaviour, sniffing, licking and biting (Randrup et al. [36], Munkwad and Randrup [37]), mainly attributed to an increase in the dopaminergic tone and no change in the effect of tranquillizers was to be observed. As an example Fig. 12 shows that in animals chronically pretreated with V-111, the effect of tetrabenazine is unchanged. In otherwise normally behaving animals the presence of this energizing effect can be readily demonstrated by measuring the processing and retention of information in the rat. For the evaluation of drugs improving the processing and retention of information in the rat we developed two rapid screening tests.

Screening Test I. The rat is put in a glass cylinder 30 cm in height open at both ends standing on a metal grid which delivers electric shocks of 110 V. The only way of escape is jumping to the rimmed opening of the top. The animal has to find the solution within 2 sec. The procedure is repeated 10 times with 5-sec intervals. The electric shock is combined with a shrill ringing of a bell, serving as a conditioning stimulus. After 10 trials with electric shock the conditioned

escape response is checked 10 times with 5 sec intervals. The response is taken as positive if the animal jumps to the rim within 30 sec. The evaluation of the animal's ability to find the solution is as follows: absent = inability to solve the problem, slight = some positive unconditioned reactions, no sign of conditioned response; medium = all trials with electric shock are successful, appearance of conditioned responses; excellent = all trials with electric shock successful, firm conditioned response.

Screening Test II. The rat has to jump from a hot plate of 60°C; otherwise the setup is the same as in the other test. 30 trials with the unconditioned stimulus and 10 trials from a cold plate are checked at 5-sec intervals.

The response is considered positive if the animal escapes from the hot plate within 2 sec and from the cold plate within 30 sec. No special conditioned stimulus is used. The evaluation of the problem-solving ability of the animals in this test is as follows: absent = inability to find the solution; good = animal escapes from the hot plate but no sign of conditioned response; excellent = firm conditioned response.

The probability of differences in performance was calculated by the x^2 test. The various probabilities (p) were taken from R. A. Fisher's Statistical Methods for Research Workers.

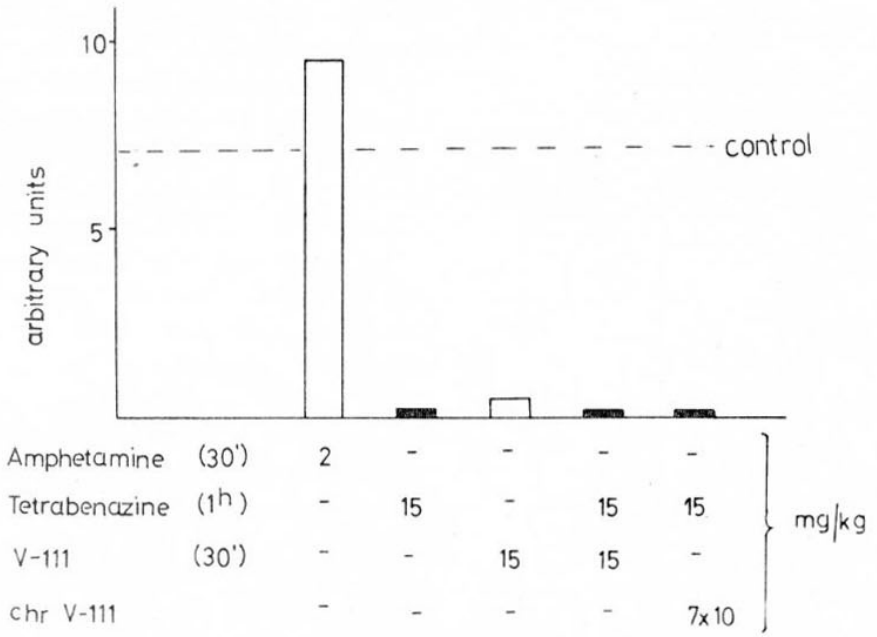


Fig. 12. — *Unchanged effect of tetrabenazine in animals treated with V—111. All drugs administered subcutaneously. Numbers in brackets indicate time elapsed between drug administration and the beginning of measurement.*

The controls in figures 13 and 14 show the distribution of 200 and 100 naive Wistar rats, respectively, according to their performance in screening tests I and II. As can be seen, some animals found the solution in a very short time, some could not do so, and some fell between the two extremes. The experimental circunstances in screening test II are especially apt for the evaluation of drugs enhancing information processing because 80 % of the naive Wistar rats cannot find the solution within the time given.

Figure 13 shows that in screening test I the efficiency of Wistar and Eprague-Dawley CFY rats do not differ from each other but the R-Amsterdam R/A strain seems to be less efficient. In screening test II the differences between the three strains are conspicuous (Fig. 14).

Figure 15 shows the improvement of the performance in Wistar rats treated with

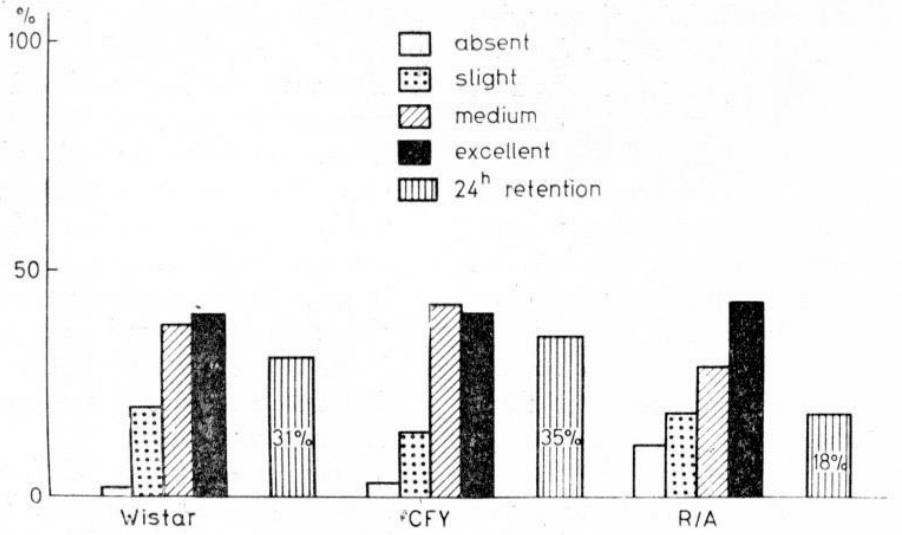


Fig. 13. — *Performance of Wistar, CFY and R/A rats in screening test I. 40 rats in each group.*

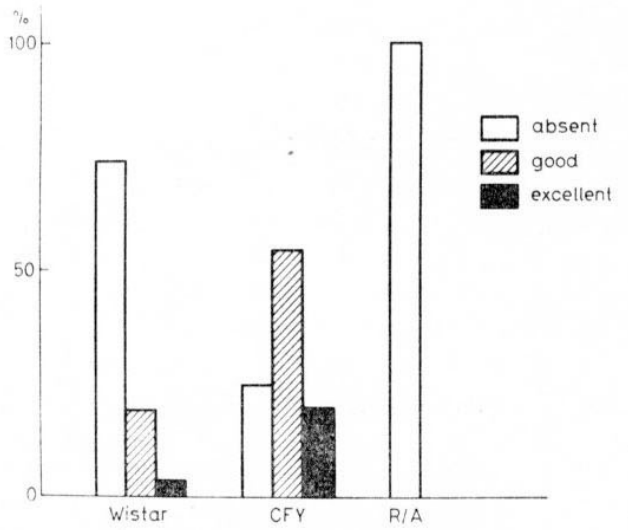


Fig. 14. — *Performance of Wistar, CFY and R/A rats in screening test II. 40 rats in each group.*

I-1703, acute administration, $x^2 = 10.2$; $p < 0.05$, and V-111, given chronically, $x^2 = 47{,}5$; $p < 0.001$, in screening test I.

Figure 16 shows the comparison between the effects of amphetamine and I-1703 in screening test II. A moderate increase in performance after acute administration of both I-1703 and amphetamine can be seen in this test. The pretreatment of the rats daily with 5 mg/kg I-1703 for a week does not improve the performance of the rats, $p > 0.05$. In this test a more pronounced effect can be achieved by decreasing the serotonergic tone, either by chronic administration of V-111 or by pCPA pretreatment. The effects of pCPA and chronic administration of V-111 are compared. In our experimental conditions pCPA pretreatment improved the performance. Similar results have also been reported by others (Campbell et al. [6], Stevens [40], Tenen [41]). The effect of V-111 is more pronounced. The difference was significant, $x^2 = 105.8$; $p < 0.001$. Some combinative effects are also demonstrated. Best results were found with the combination of V-111 and orotic acid which, as a precursor of RNA synthesis, improved retention (Matthies et al. [35]). The difference in performance between the animals treated with orotic acid and V-111 plus orotic acid was statistically significant $x^2 = 51{,}8$; $p < 0.001$, although orotic acid by itself also improved performance, $x^2 = 10.5$; $p < 0.05$). Similar results were obtained when the rats were tested two weeks later. It is interesting to note that pCPA pretreatment failed to potentiate the effect of orotic acid on performance in both conditions.

Figure 17 shows the effect of some parasympathetic drugs and that of strychnine. At the first trial only scopolamine and atropine exerted a positive effect on the performance of naive animals (fig. 17 A, but on the second trial neostigmine, scopolamine, atropine and strychnine pretreatment significantly improved retention (fig. 17 B).

The modulation of learning and retention in a highly positive manner by appro-

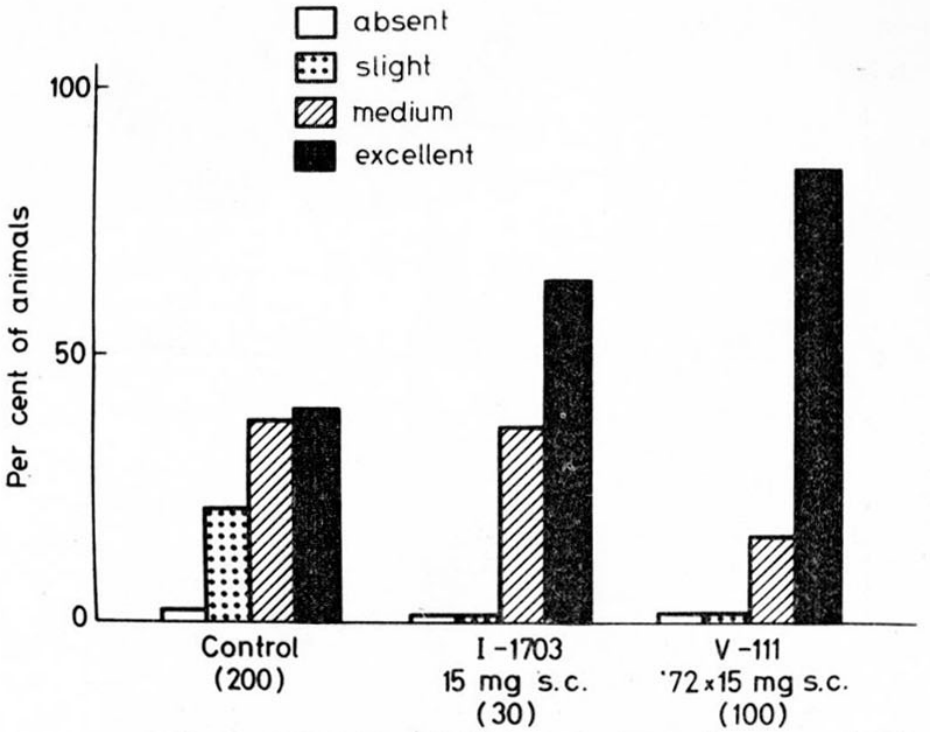


Fig. 15. — *Effects of I—1703 and V—111 on the performance of Wistar rats in screening test I. Number of animals in parantheses. Onset of measurement 30 min after the administration of I—1703 (15mg/kg) and after the last injection of V—111 (15 mg/kg daily for 72 days). Significance (X^2—test), control vs. I—1703 = $p < 0.05$; control vs. V—111 treated group: $p < 0.001$.*

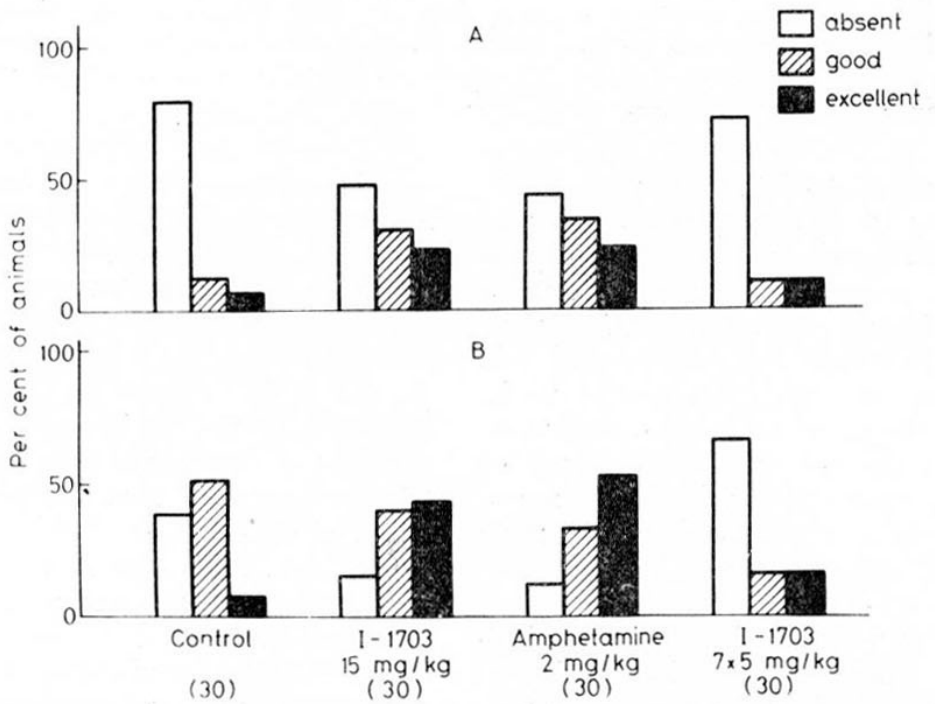


Fig. 16. — *Effect of amphetamine and I—1703 on the performance of Wistar rats in screening test II. Number of animals in parentheses. All drugs were administered subcutaneously.* A *Onset of measurement 30 min after the injection of 2mg/kg amphetamine and 15mg/kg I—1703, respectively, and 24 hrs after the last injection of 5mg/kg I—1703. Significance (X^2—test), control vs. I—1703: $p < 0.01$; control vs. amphetamine: $p < 0.01$; control vs. I—1703 (7x5 mg/kg—treated group): $p > 0.05$.* B *Second trial 2weeks later. Significance (X^2—test), control vs. 1703; control vs. amphetamine: $p < 0.01$; control vs. I—1703 (7x5 mg/kg): $p < 0.05$.*

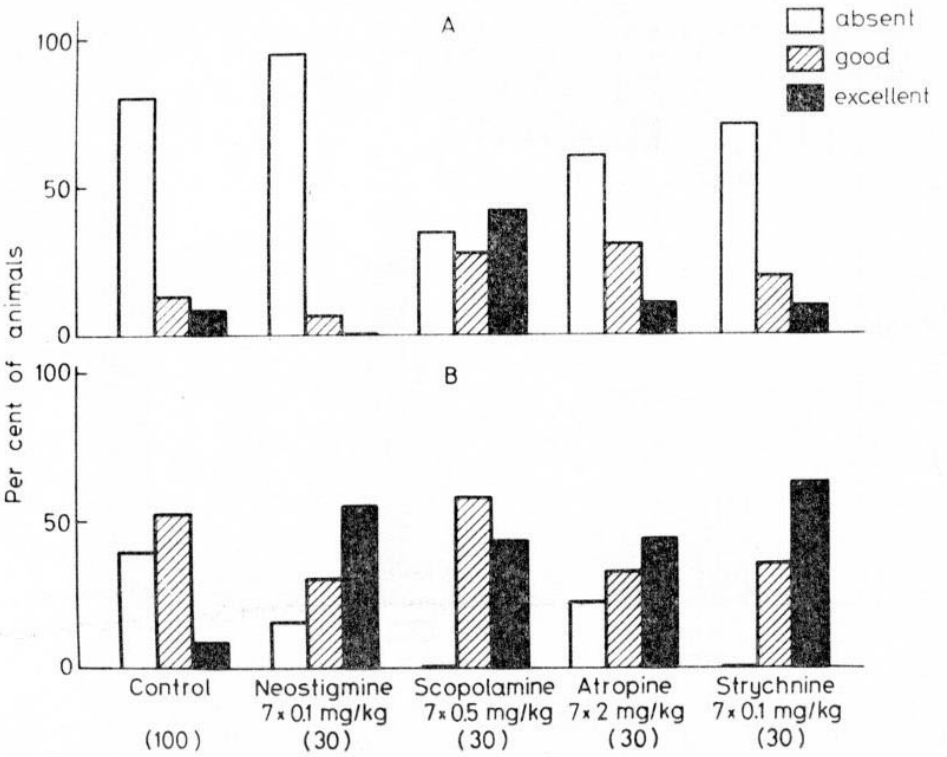


Fig. 17. — *Effect of parasympathetic drugs and strychnine on the performance of Wistar rats in screening test II. Number of animals in parantheses. Drugs injected subcutaneously.* A *Onset of measurements always* 24 *hrs after the last injection. Significance* (X^2*—test*), *control vs. neostigmine*: $p > 0.05$; *control vs. scopolamine*: $p < 0.01$; *control vs. atropine*: $p < 0.01$; *control vs. strychnine-treated group*: $p > 0.05$. B *Second trial* 2 *weeks later. Significance* (X^2*—test*), *conirol vs. neostigmine*: $p < 0.01$; *control vs. Scipolamine*: $p < 0.01$; *control vs. atropine*: $p < 0.01$; *control vs. strychnine—treated group*: $p < 0.01$.

priate pretreatment of the rats with V-111 is convincing when one compares the performance of animals in a long-term experiment. The animals were trained once a week for 10 weeks and the changes were recorded. The Wistar group reached full efficiency by the 9th experimental week, whereas all the CFY rats could escape within 2 sec on the 3rd week. The group of Wistar rats pretreated with V-111 for a month showed a dramatic change in their efficiency in the test, surpassing the CFY controls.

The role of 5-HT level in learning ability of mice was emphasized by Wooley [43]. The characteristic behavioral effects of V-111 suggested that not the level but the outflow of 5-HT in the brain plays a crucial role in the learning ability of rats. The processing of information is impaired when 5-HT outflow is increased (immediate effect of the first dose of V-111) and enormously enhanced when the outflow of this amine is strongly decreased (chronic administration of V-111). This conclusion is in fact in good agreement with the findings that LSD, psilocybin, and DMT, which directly stimulate the 5-HT receptors (Andén et al. [2, 3, 4]), impair the behavioral performance in the rat like V-111 (Knoll [14], Knoll et al. [21, 26]), and that there is a cross tolerance between these drugs (Knoll and and Vizi [23], Knoll et al. [21]).

Our data from the new amphetamines which we synthesized suggest that the catecholaminergic and serotonergic systems antagonistically modulate the processing and retention of information in the rat. One might assume that when the animal is put in the experimental situation both the serotonergic and catecholaminergic systems are nonspecifically activated. The balance of this activation might be responsible for the individual differences in the per-

formance of the naive animals. A rat with an excess of the catecholaminergic tone would be successful in finding the way for escape and another one with a dominance of the serotonergic system would turn out to be "dull". This working hypothesis satisfactorily explains why the pretreatment of animals with amphetamines that selectively increase noradrenaline outflow in the brain e. g. I-1703 and those which lead to a long-lasting decrease in the 5-HT outflow e. g. chronic administration of V-111, improve the processing and retention of information.

Effects of V-111 *on brain serotonin metabolism.*

The brain 5-HT level of rats is decreased by V-111 (Knoll and Magiar [19, 20, 21], Knoll et al. [22], Leonard and Shallice [32, 33]). The time course of the effect of 15 mg/kg V-111 is illustrated in Fig. 18. It is considered essentially important that no change occurs in the 5-HT level during the first two hours, during the second 2 hour period the decrease reaches its maximum(5-HT concentration is reduced to half of the control value) and, as it can be seen from the figure, no change occurs in the subsequent 96 hours. Fig. 19 shows that the decrease in the 5-HT level produced by 15 mg/kg

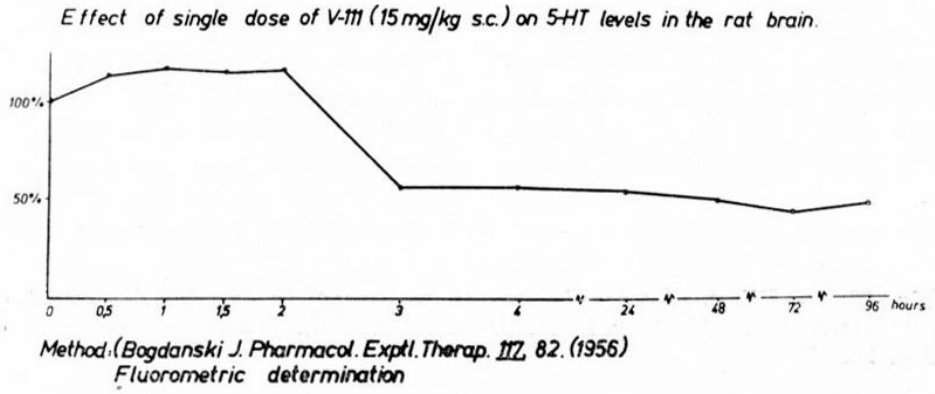


Fig. 18. — *Effect of single doses of V—111 (15 mg/kg s. c.) on 5 HT levels in the rat brain. Estimated by fluorometric method (Bogdanski, 1956/n=5.*

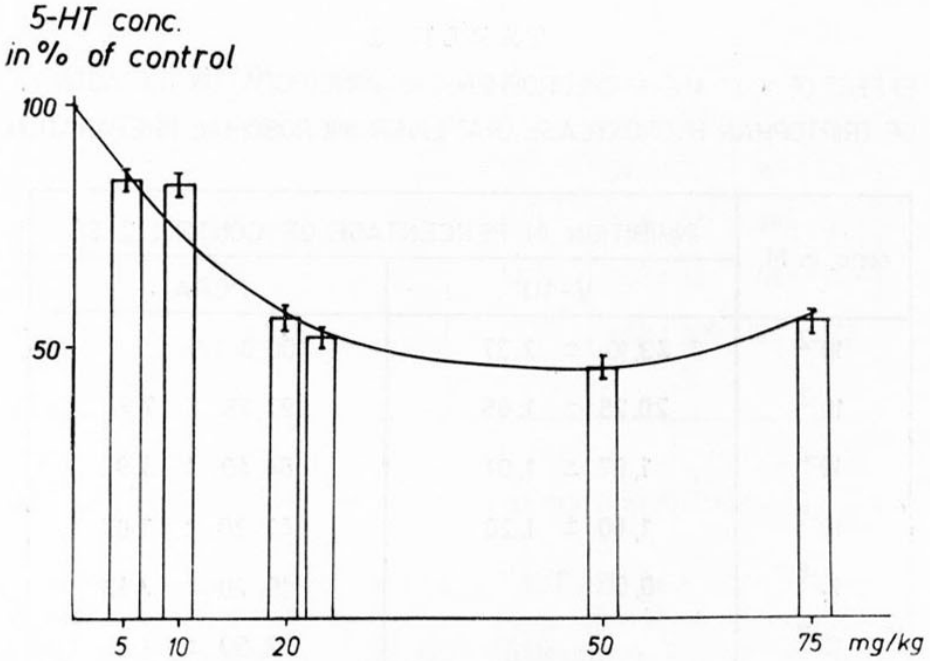


Fig. 19. — *Changes of the rat brain 5 HT level 24 hrs after s. c. administration of different doses of V—111. Mean ± S. E. Method as specified at Fig. 28.*

V-111, ED_{100} in the commonly used tests, cannot be further enhanced by the application of excessively high doses (25 to 75 mg/kg). Fig. 20 proves that this critical reduction of the 5-HT level can also be obtained with prolonged administration of

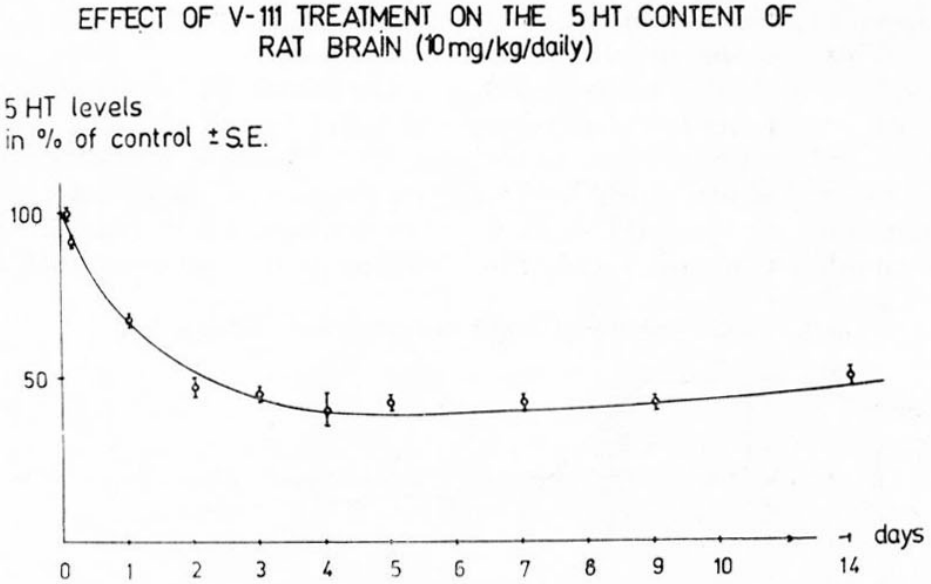


Fig. 20. — *Effect of Chronic V—111 treatment on the 5 HT content of rat brain* (10 *mg/kg/day s. c.*). *Mean* * ± *S. E. Method as specified at* Fig. 28.

lower daily doses, hence it constitutes a maximum effect. A further reduction of the 5-HT level in V-111 pretreated animals can be effectuated with reserpine or p-CPA, respectively. The results suggest that V-111 might produce a loss of 5-HT only in a well defined store holding about 50 per cent of the total quantity. The store holding the remaining 50 per cent of the substance is not influenced.

As it appears from the comparison with p-CPA, Table 1, V-111 does not inhibit the synthesis of 5-HT. Neither does it affect 5-HT decarboxylation. The circumstance

TABLE 1

EFFECT OF V-111 AND P-CHLOROPHENYLALANINE(PCPA) ON THE ACTIVITY OF TRIPTOPHAN HYDROXYLASE (RAT LIVER MICROSOMAL PREPARATION)

conc. in M.	INHIBITION IN PERCENTAGE OF CONTROL ± SE	
	V-111	PCPA
10^{-2}	43,10 ± 2,37	100,0
10^{-3}	20,25 ± 1,95	92,75 ± 7,28
10^{-4}	1,67 ± 1,01	64,40 ± 3,92
10^{-5}	1,60 ± 1,20	42,20 ± 3,92
10^{-6}	0,0	19,20 ± 2,13
10^{-7}		3,50 ± 1,21

Measurement of enzyme activity according to Fuller. (Life Sci. Vol. 4, 1. 1965)

that even large doses of V-111 do not influence triptophane hydroxylase activity of the liver in vitro does not necessarily exclude the inhibition of the brain enzyme by the compounds. Still it appears more likely that another mechanism of action (inhibition of uptake, release of 5-HT, or both) can be made responsible for the acute effects.

The psychic disturbance caused by V-111 is not a consequence of the decreased 5-HT level in the brain because, as shown by Fig. 18, the reduction of the 5-HT level occurs only after the two hours following s.c. administration, whereas the effect of V-111 appears as soon as 15 minutes following injection and reaches its maximum level within one hour. Thus the possibility remains that the observed effect is the result of an increase in the intraneuronal free 5-HT concentration which ensues following enhanced release or inhibited uptake of the compound or from the combination of these two effects.

The effect of V-111 on the uptake of 5-HT-^{14}C by the tissues was studied in vivo in mice. Pretreatment with V-111 reduces the 5-HT-^{14}C concentration of blood, heart, lungs and spleen tissues. 5-HT does not penetrate the bloodbrain barrier thus the low 5-HT activity measured in the brain might be attributed to the uptake in the wall of the vessels and to blood contamination of the brain tissue. In contrast to the uptake of 5-HT-^{14}C, the uptake of noradrenaline 3 (NA-^{3}H) is not influence (with the exception of the heart) by pretreatment with V-111. Interpreting these data it should be considered that 5-HT is taken up by the blood plataletes into specific storage sites for this amine, but in the organs examined the possibility of 5-HT uptake into catecholamine and other unspecific stores cannot be excluded.

The effect of V-111 on the uptake of 5-HT-^{3}H and NA-^{3}H in the CNS was tested in synaptosoms prepared from the brain of treated and untreated rats, using in vivo and in vitro conditions. The results of these experiments are visualized in Table 2 which

TABLE 2

EFFECT OF V-111 ON THE UPTAKE OF 5-HT-^{3}H AND NA-^{3}H INTO RAT BRAIN SYNAPTOSOMES

in vivo experiments			in vitro experiments		
V-111 mg/kg s.c. 1 hour before decapitation	5-HT-^{3}H	NA-^{3}H	V-111 conc in M	5-HT-^{3}H	NA-^{3}H
7,5	40,8 ± 4,13	29,0 ± 6,29	10^{-8}	14,2 ± 4,7	0
			10^{-7}	28,2 ± 1,1	8,7 ± 3,1
15	48,2 ± 2,69	46,6 ± 9,90	10^{-6}	50,6 ± 6,5	38,8 ± 6,2
			10^{-5}	75,2 ± 1,5	68,8 ± 1,1
30	55,7 ± 7,51	61,7 ± 5,51	10^{-4}	80,8 ± 0,29	79,0 ± 1,03

Inhibition in percentage ± S.E. (n>10)

Applied method: Snyder and Coyle. J.Pharmacol.Exptl.Therap.(Vol.165.78.1969)

shows that in animals pretreated with V-111 both 5-HT-^{3}H and NA-^{3}H uptake is reduced, with lower doses (7,5 mg/kg), however, inhibition of 5-HT-^{3}H uptake is more explicit. Table 2 also shows the inhibition of 5-HT-^{3}H and NA-^{3}H uptake by synaptosoms of untreated rats in the presence of different V-111 concentrations. Here again uptake of 5-HT is more strongly inhibited by lower concentrations of V-111. Table 3

reveals that V-111 is a more potent inhibitor of the uptake of 5-HT-^{3}H and NA-^{3}H in brain synaptosomes than imipramine and desipramine (DMI).

Table 4 contains the V-111 concentrations producing 50 per cent inhibition of 5 HT uptake using 5-HT-^{3}H and NA-^{3}H as substrates. Inhibition produced by V-111 on

TABLE 3

Comparison of the effect of V-111, imipramine and desmethylimipramine (DMI) on the uptake of 5-HT-^{3}H and NA-^{3}H into rat brain synaptosomes.

in vivo experiments			in vitro experiments			
Compounds 30 mg/kg i.p.	5-HT-^{3}H	NA-^{3}H	Compounds	Conc. M.	5-HT-^{3}H	NA-^{3}H
V-111	55,7	61,7	V-111	10^{-6}	50,6	38,8
				10^{-5}	75,2	68,8
				10^{-4}	80,8	79,0
Imipramine	39,7	25,7	DMI	10^{-6}	14,5	19,6
				10^{-5}	47,3	35,7
DMI	15,5	9,5		10^{-4}	79,5	73,8

Inhibition in percentage.

Applied method: Snyder and Coyle (J. Pharmacol. Exptl. Therap. Vol. 165, 78, 1969.)

TABLE 4

ID_{50} values of V-111 on the uptake of 5HT-^{3}H and NA-^{3}H.

	brain slices		*synaptosomal preparation*	
	5-HT-^{3}H	*NA-^{3}H*	*5-HT-^{3}H*	*NA-^{3}H*
in vitro	*2,6.10^{-6}M*	*1,3.10^{-6}M (DMI 1,66.10^{-7}M)*	*10^{-6}M (DMI 1,4.10^{-5}M)*	*2,1.10^{-6}M (DMI 10^{-5}M)*
in vivo	*10 mg/kg*	*5 mg/kg*	*15 mg/kg (DMI 50 mg/kg i.p. 33,7%)*	*15-20 mg/kg (DMI 50 mg/kg i.p. 36,0%)*

the uptake of 5-HT by rat brain synaptosomal preparations was compared to that of brain cortical slices of mice. In brain cortex slices of the mouse, V-111, caused a stronger inhibition of the NA-^{3}H uptake, while in rat brain synaptosoms the uptake of 5-HT-^{3}H was more strongly inhibited. The figures in brackets represent some ID_{50} values of DMI. They indicate that DMI known to be the most potent inhibitor of NA-^{3}H uptake on the nerve membrane, lags behind V-111 regarding intensity of both in vitro and in vivo effects.

Enzyme-kinetic studies were performed to test the inhibitory effect of V-111 on the uptake of 5-HT-^{3}H in the presence of four substrate concentrations. The 5 minute uptake of 5-HT was measured in the absence

and in the presence of 10^{-6}M concentration of V-111. Representation of the 5 minutes experimental values according to Lineweaver and Burk (1934) shows the inhibition to be competitive as the value ($8{,}3.10^{-8}$M) of the synaptosomal uptake was increased ($2{,}8.10^{-7}$M) by a 10^{-6}M concentration of V-111 (fig. 21). The inhibition of 5-HT-^{3}H by microsomal fractions added in different concentrations was measured both in the presence and absence of V-111.

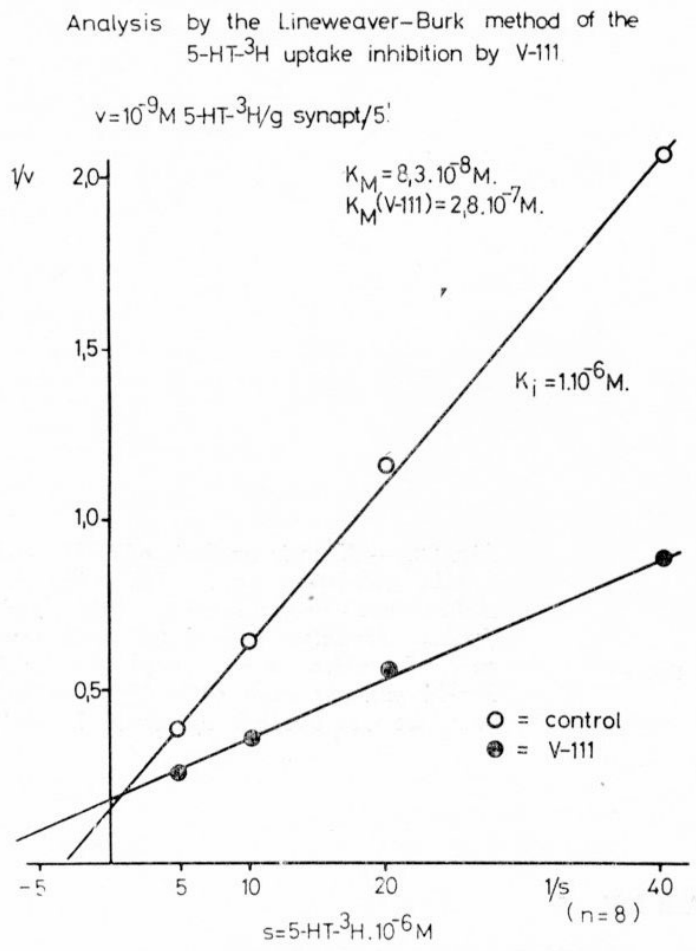


Fig. 21. — *Kinetic analysis of* 5 *HT—*^{3}*H uptake inhibition by V—*111 *using the Lineweaver —Burk technique* (1934). *Synaptosomal fraction was incubated for* 5 *min with* 4 *different concentrations of* 5 *HT—*^{3}*H* (0.025—0,2 *nM*) *in the presence and absence of* 10^{-6}*M of* V—111.

The two lines in Fig. 22 are seen to meet in the origo indicating again the competitive, reversible nature of inhibition.

These in vitro experiments of 5 minute duration showed the inhibition of 5-H-^{3}H uptake by V-111 to be reversible, however, following s. c. administration of a single dose (15 mg/kg) of V-111 the uptake of 5-HT-^{3}H and NA-^{3}H was inhibited for an extremely long period indicating an irreversible damage of the uptake process. Table 5 shows that the inhibition of NA-^{3}H uptake ceased only after two weeks, 5-HT-^{3}H uptake was not completely restored even by the end of this period. The most plausible interpretation of the enzyme-kinetical results is that the development of irreversible lesions of the uptake mechanism takes time. The rapidity of the irreversible inhibition of the uptake process in vivo appears to exclude the possibility of this effect being produced by a metabolite of V-111. The prompt and potent inhibition of the intraneuronal uptake of the continually synthetized 5-HT by V-111 leading to an increased serotonergic tone seems to be in causal relationship with the psychic disturbances elicited by V-111 in naive animals.

The irreversible nature of this inhibition on the other hand offers a good explanation for the development of tolerance to V-111. As it was shown a single pharmacologically fully active dose of V-111 causes a maximal (50 per cent) and long lasting inhibition of 5-HT uptake. Thus it seems to be logic that repeated doses cannot further increase

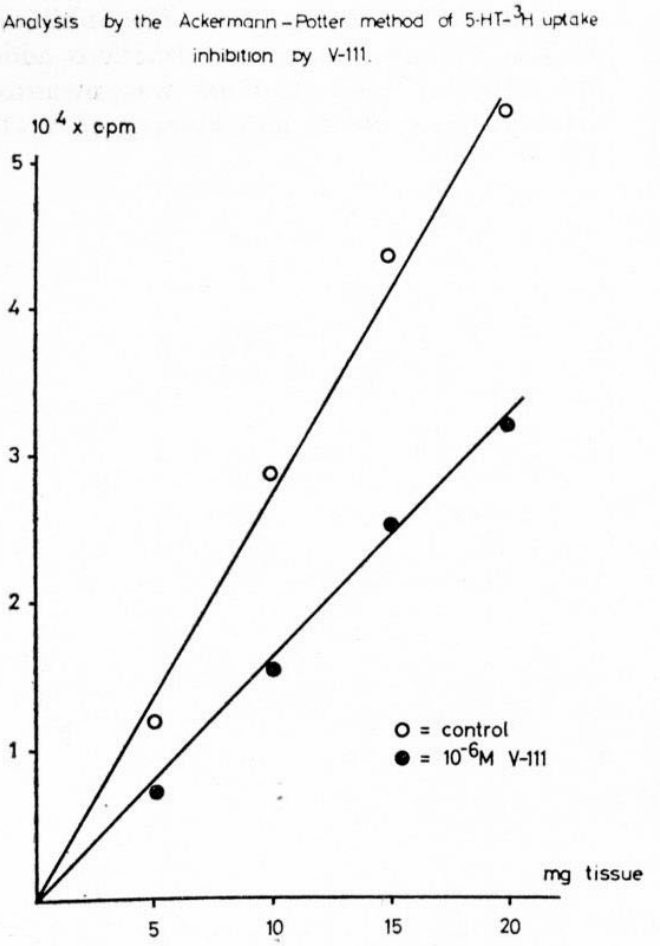


Fig. 22. — *Kinetic analysis of 5 HT—^{3}H uptake inhibition by V—111 using the Ackermann - Potter method* (1949). *Different concentrations of the synaptosomal fractions were incubated with 10^{-7}M concentration of 5HT-^{3}H in the presence and absence of 10^{-6}M V—111.*

TABLE 5

Duration of uptake inhibition after single injection of 15mg/kg V-111 s c
(Rat brain synaptosomes)

Time	5-HT-^{3}H	NA-^{3}H
1/2 hour	42,1	38,8
1 day	53,2	47,1
2 days	43,4	24,1
3 ↓	49,7	22,3
4 ↓	55,5	32,2
1 week	50,7	23,3
2 weeks	30,0	0,0
3 – • –	0,0	0,0

Inhibition in percentage (average, n=3)

the serotonergic tone by the same mechanism.

Metabolic experiments in rats furnished further strong evidence to the inhibition of intraneuronal 5-HT uptake by V-111. The compound is highly potent in increasing the O_2-consumption in rats. This action appears to be only partly of serotonergic origin as its total inhibition occurs only after pretreatment with p-CPA and α-MT. Nevertheless, the serotonergic component plays a substantial role in it. The metabolism of untreated animals is influenced by 5-HTP only to minimal degree but as seen in Fig. 23, in animals pretreated chronically with

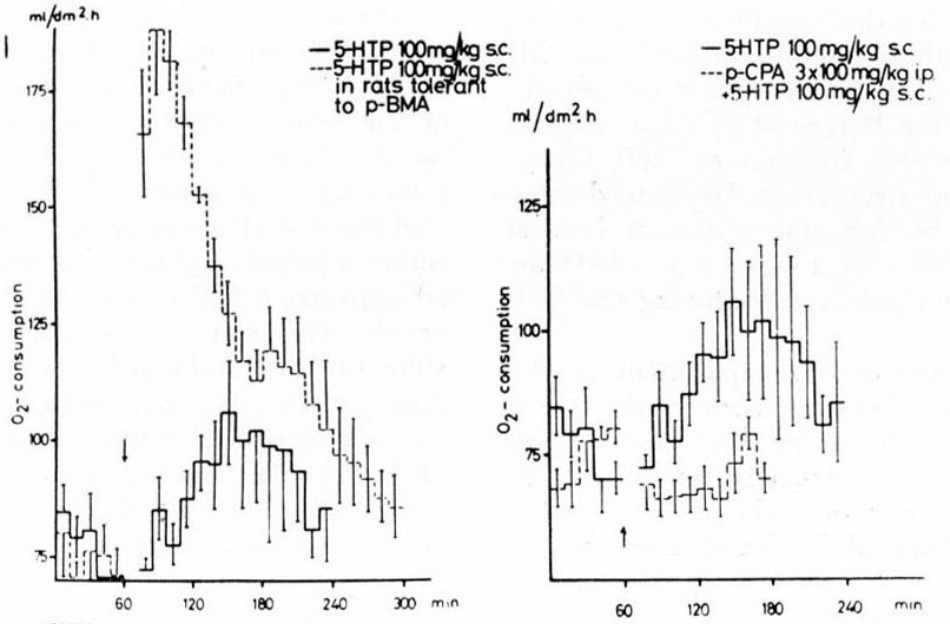


Fig. 23. — *Enhancement of the 5—HTP induced increase 0_2— consumption of rats tolerant to V*—111.
5—HTP = *5 hydroxytryptamine*
p C P A = *p—chlorophenylalanine*
p—BMA — *p—bromo—methamphetamine*

V-111, injection of 5-HTP produced usually strong increase in O -consumption. This phenomenon too is satisfactorily explained by the irreversible inhibition of the uptake of intraneuronally freshly formed 5-HT by V-111.

Besides the inhibitory effect of V-111 on the uptake of 5-HT, the enhanced release of 5-HT from the stores may also be involved in the acute effect of the compound. The development of tolerance could be attributed to the complete depletion of a V-111 sensitive compartment storing half of the quantity of brain 5-HT and the replenishing of this store is blocked because of irreversible inhibition of the uptake mechanism. As indicated by the experimental results presented in Fig. 24 the release of 5-HT may also be involved in the psychic disturbance caused by V-111. As indicated

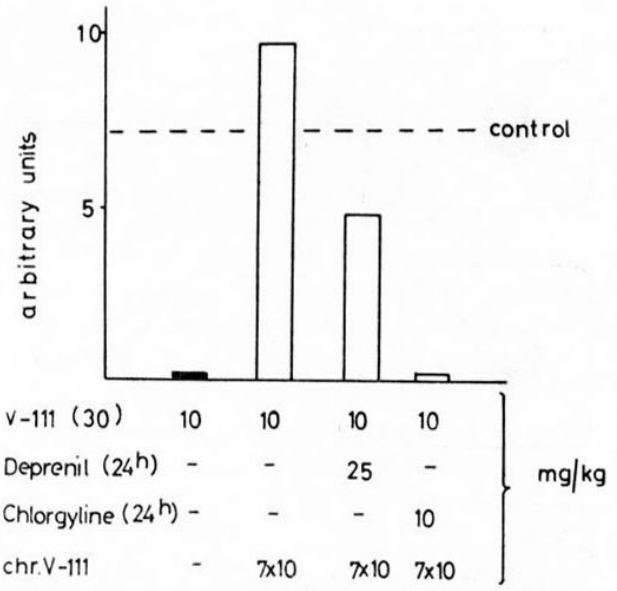


Fig. 24. — *The effect of monoamineoxidase inhibitors in rats tolerant to V*—111. *All drugs were injected subcutaneously.*

by the figure, one week pretreatment of the animals with V-111 induces a significant grade of tolerance and the activity of the compound is not restored by s. c. injection of 25 mg/kg Deprenil. Treatment with 10 mg/kg clorgyline, Johnston [12], however, restores the activity of V-111. Deprenil the first selective MAO inhibitor, developed by us in 1965 (Knoll et al.[15]) inhibits much more potently the metabolism of benzylamine than that of serotonin Knoll and Magyar [20] and is up to now the most selective inhibitor of the B type of MAO as supported by the recent findings of Neff Clorgyline, a similar structure to Deprenil developed in 1968 by Johnston proved to be a selective inhibitor of the A type MAO and is much more potent in restoring the 5-HT stores.

On the basis of our experiments, V-111 might be considered as a more selective serotonergic amphetamine derivative. It appears to be an extremely useful tool for studying the role of 5-HT tone in various functions of the CNS. Based on our present knowledge, we outlined the mechanism of action of the compound in the scheme presented in Fig. 25. Part "A" of the scheme represents the state of intraneuronal 5-HT metabolism in untreated animals. Part "B" shows the changes produced by the first dose of V-111. In our concept, as a result of the prompt inhibition of the uptake of continuously freshly synthetized 5-HT and of its gradual release from extragranular stores, the intraneuronal concentration of 5-HT is significantly increased. Part "C" of the scheme displays the effect produced by the first doses of V-111 a few hours following administration. During that period the V-111 sensitive serotonin stores become depleted, uptake is inhibited, the intraneuronal 5-HT concentration is still elevated. This state is thought to be responsible for the prolonged effect of the first dose. Part "D" represents the stabilized state developed after repeated administration of V-111. In that energized state the initially active doses of V-111 fail to elicit an effect. An explanation of it could be found

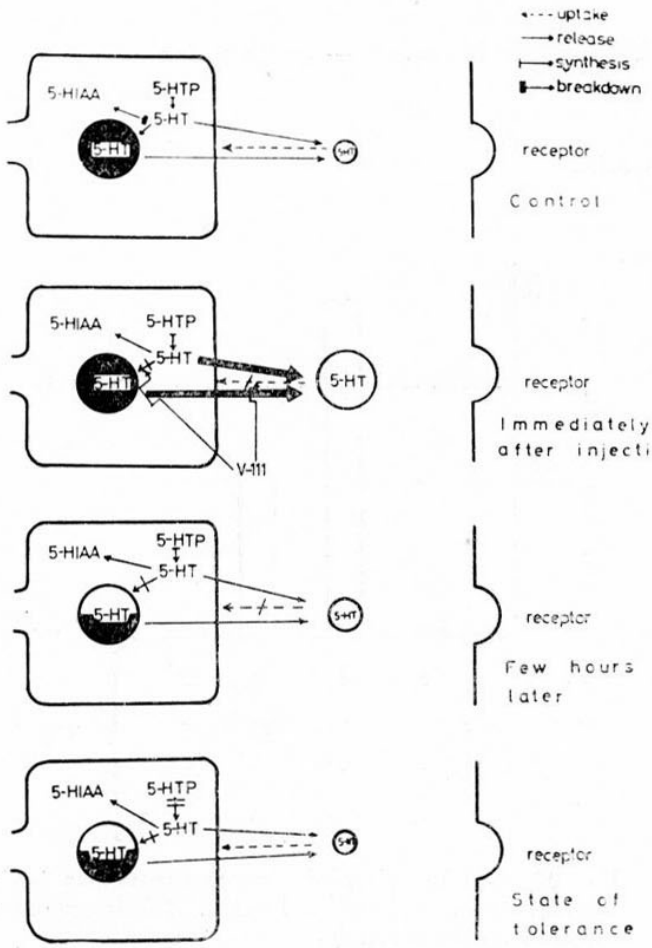


Fig. 25. — *Proposed states of the 5 HT system in the brain of various points of time following V—111 administration.*

in the following: the uptake of 5-HT is still lastingly inhibited, the serotonin store sensitive to the compound are almost completely depleted, at the same time 5-HT synthesis adapted to the lasting change proceeds at a lower rate and leads to the development of a new state of equilibrium. As a result of this the intraneuronal concentration of free 5-HT is restored to the starting level.

From the changes represented in the scheme, changes of 5-HT level and inhibition of 5-HT uptake could be proved directly, the inhibition of brain 5-HT synthesis, though literary data refering to experiments performed with p-chloro-amphetamine (Sanders-Bush and Sulser[38–39]) appear to support our hypothesis, needs detailed investigations.

Further proves supporting the hypothesis that the catecholaminergic and serotonergic systems antagonistically modulate the processing and retention of information in the rat.

It is well known, that 5-HT neurons in the rat brain are concentrated in the midbrain raphe and appropriate lesions of the median and dorsal raphe lead to significant decrease in the 5-HT content of the forebrain (Dahlström and Fuxe[8], Andén et al.[4] Jouvet et al.[13], Kostowski and Giacalone[30], Kostowski et al.[31], Giacalone and Kostowski[10]). Table 6 shows our own results which in good agreement with literary data prove that 3 weeks after the combined lesioning of the nucleus medianus and dorsalis raphis, the 5-HT content of the forebrain decreases exactly to the same level caused by chronic treatment with V-111. Fig. 26 demonstrates that in the animals with lesions of midbrain raphe the same improvement in the processing and retention of information was found as in the animals treated chronically with V-111 ($x^2 = 14{,}268$ $p < 0{,}01$). On the other hand, rats with lesion of the substantia nigra (SN) on one side, which leads to a decrease in the dopamine level of the striatum (Gumulka et al., 1970) seem to show an impairment in their performance (see fig. 26) but the difference is not significant ($x^2 = 3{,}666$ $p > 0{,}05$).

The detailed analysis of the role of dopaminergic and noradrenergic systems in the processing and retention of information using our tests is now in progress.

TABLE 6

CHANGES IN FOREBRAIN 5HT LEVEL AFTER LESIONS OF MIDBRAIN RAPHE

N° of RATS	EXPERIMENTAL LESION	FOREBRAIN 5HT	HISTOLOGY
9	Sham lesion 3 week	− 1,5 %	
6	Lesion MR° 1 week	-19,3 %	+
6	Lesion MR 3 week	-18,6 %	+
6	Lesion DR°° 3 week	-38,3 %	+
12	Lesion MR+DR 3 week	-45,6%	+
20	V-111 30×15 mg/kg	-45 %	

o = nucleus medianus raphis

oo = nucleus dorsalis raphis

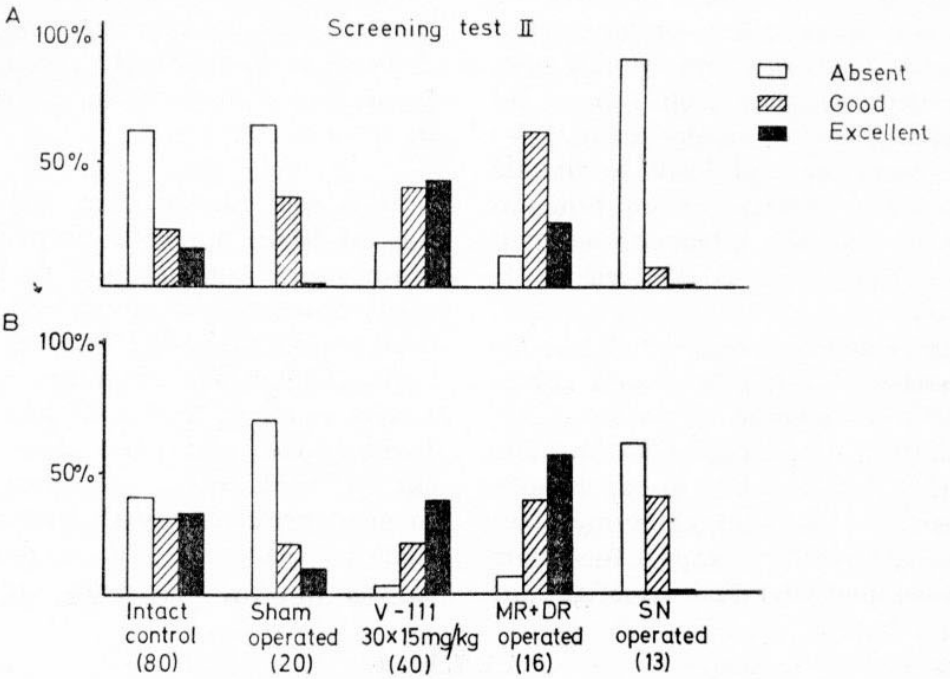


Fig. 26. — *Comparison of the effect of V—111 and combined lesioning of the midbrain raphe and substantia nigra, respectively, in screening test II. Number of animals in parentheses. V—111 was administered subcutaneously.* A *Onset of measurement 24 hrs after the last injection of V—111 and 3 weeks after sham operation or lesioning.* B *Second trial 2 weeks later. Significance (X^2—test) intact control vs. V—111: $p < 0.01$; intact control vs. MR + DR operateds $p < 0.001$; sham operated vs. V—111: $p < 0.0L$; sham operated vs. MR + DR operateds $p < 0.0L$; sham operated vs. SN operateds $p > 0.05$. MR = nucleus medianus raphis. DR = nucleus dorsalis raphis. SN = substantia nigra.*

SUMMARY

In small and medium doses amphetamine and methamphetamine enhance chatecholaminergic tone, in high doses the serotonergic tone is dominant. Structure-activity relationships were studied in order to synthesize more selective amphetamines. Among the new methamphetamine derivatives N_1- O -carboxy-phenyl-N_2-2-2-methyl-aminopropyl-1-phenylacetamidine (I-1703) is a more selective catecholaminergic amphetamine that even in high doses does not influence the serotonergic tone in the brain.

Para-bromo-methamphetamine (V-111) is a selective serotonergic amphetamine which by long-lasting inhibition of the intraneuronal 5-HT uptake first increases and afterwards decreases serotonergic tone in the brain. Daily treatment of the rats with V-111 for weeks results in a 50 % decrease of the 5-HT content of the brain accompanied by an energized state of the CNS, without any sign of amphetamine-like stimulation (stereotyped behavior, increased motility, resistance to tranquillizers, etc.). Even the administration of subtoxic doses of V-111 do not lead to further decrease in the 5-HT content of the brain tissue.

We analysed the site of action of V-111 and demonstrated that the lesion of nucleus medianus raphis (MR) and of nucleus dorsalis raphis (DR) in the rat's brain results a long-lasting 45,6 % fall in the 5-HT content of the forebrain. The lesioned rats showed the same improvement in their learning and retention performances than rats treated chronically with V-111.

Our studies with the newly synthesized amphetamines led us to the conclusion that the catecholaminergic and serotonergic systems antagonistically modulate the learning ability of rats. Pharmacologically-induced increase of the catecholaminergic tone and

more favorably a long-lasting decrease in serotonergic tone improves the learning and retention performances in the rat.

V-111 a new amphetamine derivative with a highly selective biochemical action on the serotonergic system of the midbrain is a useful tool for the analysis of the role of 5-HT in the higher nervous activity of the rats.

RESUMEN

En dosis pequeñas y medianas, la anfetamina y metamfetamina aumentan la actividad catecolaminérgica, en altas dosis la actividad serotominérgica es dominante. Fueron estudiadas las relaciones de la actividad-estructura a fin de sintetizar derivados anfetamínicos más selectivos. Entre los nuevos derivados el N_1-O-carboxi-fenil-N_2-2-2-metilaminoprofil-1-fenilacetamidina (I-17 03) es una anfetamina catecolaminérgica selectiva que aún en altas dosis no influye el tono serotoninérgico en el cerebro. Parabromo-metamfetamina (V-111) es una anfetamina serotoninérgica selectiva que por inhibición de larga duración del 5-HT intraneuronal, primeramente aumenta y luego disminuye el tono serotoninérgico en el cerebro. El tratamiento diario con V-111 en las ratas durante semanas resulta en una disminución del 50 % del contenido de 5-HT del cerebro acompañado con un estado energético del CNS, sin que ninguna señal de estimulación de amfetamina esté presente, conducta estereotipada, motilidad mayor, resistencia a los tranquilizantes, etc. Aún la administración de dosis subtóxicas de V-111 no conducen a una disminución adicional en el contenido 5-HT del tejido cerebral.

Hemos analizado el lugar de acción de V-111 y demostrado que la lesión del núcleo mediano del rafe (MR) y del núcleo dorsal del rafe (DR) en el cerebro de una rata resulta en una caída de 45,6 % por mucho tiempo en el contenido 5-HT del cerebro anterior. Las ratas lesionadas mostraban la misma mejoría en su aprendizaje y la retención que las crónicamente tratadas con V-111.

Nuestros estudios con las amfeminas recientemente sintetizados nos llevaron a la conclusión de que los sistemas catecolaminérgicos y serotoninérgicos controlan con cierto antagonismo la habilidad de las ratas de aprender. El aumento inducido farmacológicamente del tono catecolaminérgico y más favorablemente una disminución duradera del tono serotoninérgico mejora el aprendizaje y la retención de la rata.

La V-111 es un nuevo derivado de amfetamina con una selectiva acción bioquímica en el sistema serotoninérgico del mesencéfalo y es un instrumento útil para el análisis del papel del 5-HT en la actividad del sistema nervioso central de las ratas.

RÉSUMÉ

Amphétamine à doses faibles ou moyennes augmente l'activité catécholaminergique, à dose fortes l'activité sérotoninergique est dominante. Des correlations activité-structurales on été étudiées afin de synthétiser des dérives amphétaminiques plus sélectifs. Parmi ces dérives nouveaux la N_1-O-carboxy - phenyl-N_2-2-2-methylaminopropyl-1-phenylacetamide (I-1703) est une amphétamine catécholaminergique sélective, qui n'influence pas l'activité sérotoninergique du cerveau même à doses fortes.

La p-bromo-methamphétamine (V-111) est une amphétamine sérotoninergique, selective, qui, inhibant la récapture neuronale de la sérotonine, augmente puis déprime l'activité sérotoninergique cérebrale. Chez des rats, traités à V-111 tous les jours pendant plusieures semaines, une décroissance de la concentration de la sérotonine cérebrale de 50 % et un état énergétique du système nerveux central se presente sans que des symptomes de la simulation d'amphétamine s'apparessaient stéreotypie, moti-

lité accrue, résistance au tranquillisants, etc. Même l'administration des doses subtoxiques ne fait pas décroitre le taux de sérotonine du cerveau plus que 50 % de valeur de témoins.

Nous avons étudié le lieu d'effet de V-111 et démontré que la lésion du noyau médial du raphé (MR) et du noyau dorsal du raphé (DR) des cerveaux des rats produit une baisse durable de la concentration de la sérotonine du telencéphale. Ces rats lésionés ont montré la même amelioration d'apprentissage et de retention, que des rats traités a V-111.

Nos études considerant les dérivés amphétaminiques nouveaux nous a amené à concluire que les systèmes catécholaminergique et sérotoninergique contrôlent d'une façon antagonistique la capacité d'apprentissage des rats, L'augmentation de l'activité catécholaminergique, mieux encore la décroissance durable de l'activité sérotoninergique induites pharmacologiquement causent l'amellioration d'apprentissage et de retention.

La V-111 est un dérivé d'amphétamine d'un effet biochimique sélectif sur le système sérotoninergique de mesencéphalon, donc ce produit est un moyen util à étudier le rôle de la sérotonine dans l'activité du système nerveux central de rat.

ZUSAMMENFASSUNG

Durch kleine und mittelgrosse Dosen von Amphetamin und Methamphetamin wird der watecholaminergische Tonus gesteigert, bei grossen Dosen dominiert der serotonergische Tonus, Zwecks Synthese der Amphetaminderivate mit selektiveren Wirkung werden die usammenhänge zwischen Struktur und Wirkung untersucht. Unter den neuen Amphetaminderivaten stellt N_1-O-carboxyphenyl - N_2-2-2-methylaminopropyl-1-phenylaminopropyl-1-phenylacetamidine (I-1703) ein selektiver wirkendes katecholaminerges Amphetamin dar, durch das der Serotonergtonus des Gehirns such in grösseren Dosen nicht beeinträchtigt wird. p-Brom-methamphetamin (V-111) ist ein selektiv serotonergisch wirkendes Amphetamin, durch das der serotonesgische Tonus des Gehirns zunächst vorübergehend gesteigert, sodann langdauernd vermindert wird. Eine bei Ratten über mehrere Wochen hindurch täglich durchgeführte Behandlung mit V-111 führte zu eine 50 % - ige Verminderung des 5-HT Gehaltes im Gehirn, die durch einen energisierten Zustand des Zentralnervensystems begleitet wurde, ohne die Symptome eines amphetaminartig stimulierten Zustands (stereotypes Verhalten, gesteigerte Motilität, Resistenz gegenüber Tranquilizer unsw.). Auch durch subtoxische Dosen von V-111 wurde keine weitere Verminderung des 5-HT-Gehalts der Gehirngewebe bewirkt.

Der Angriffspunkt von V-111 im Gehirn wurde ebenfalls untersuch und es wurde nachgewiesen, dass eine Läsion des Nucleus medianus raphis (MR) und Nucleus dorsalis raphis (DR) im Rattenhirn zu einer 45,6 % - igen nachhaltigen Verminderung des 5-HT-Gehalts des Vonderhirns führt. Die Erlernungsfähigkeit der lädierten Ratten steigerte sich im selben Grade, wie die der mit V-111 chronisch behandelten Tiere.

Anhand der Untersuchungen mit den neuen Amphetaminderiwaten konnte jene Konsequenz gezogen werden, dass durch das watecholaminergische und serotonergische System die Erlernungsfähigkeit der Ratten antamonistisch beeinflusst wird. Die auf pharmakologischem Wege erfolgte Erhöhung des katecholaminergischen Tonus, oder noch vielmehr die nachhaltige Verminderung des serotonergischen Tonus führt zu einer Steigerung der Erlernungsfähigkeit der Ratten.

Das neue Amphetaminderivat, V-111 stellt infolge seiner auf das serotonergische System des Mittelhirns ausgeübten äusserst selektiven Wirkung ein nützliches Mittel im Studium der Rolle von 5-HT in der höheren Nerventätigkeit der Ratte dar.

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Neuropsychological Findings in Parkinson's Disease: a Comparison Between various Test During Long-Term Levodopa Therapy

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Introduction

Modern psychological evaluation methods were not available to Parkinson in 1817 when he wrote "The senses and intellect being uninjured" [41]. Until the 1950' most clinicians were convinced that Parkinson's disease is not associated with intellectual impairment. However, a few papers stated the contrary. In 1882, Ball [3] wrote: "I would willingly say that a slight degree of intellectual disturbance is almost the rule in this disease". Ionesco-Sisesti et al. [25] also wrote in 1938: "Nous nous sommes demandés souvent si le ralentissement psychique des parkinsoniens est simplement un effet de la bradykinésie indiscutable de ces malades, ou s'il n'est pas un état réel". They used for this study the Rorschach technique and the skin-galvanic reflex, demonstrating in parkinsonian patients a hyporeactivity of sub-cortical centers, a lowered skin galvanic response with increase in latency, smaller galvanic deflections and a rapid return to normal.

In order to have an objective measurement of the intellectual deficit in post-encephalitic parkinsonian patients, compared to normal subjects, three tests were used by the above authors [25, 26]: a perceptive- intellectual test, an attention test and a memory retention test. They found a marked decrease in associative processes, an impossibility to acquire new facts, a shortening of the attention span and a decrease in recent memory. Their conclusion was that the slowness in thinking processes (bradyphrenia) is independent of the motor deficit (bradykinesia). Recent studies confirmed this point of view [17, 57]. However modern neuropsychological testing in parkinsonian patients effectively started with the paper of Nyssen and Wens in 1948 [40]. Literature from the last 25 years has been extensively reviewed in Ricklan's book [46].

In parkinsonian patients as such, mental disorders have been divided as follows [51]:

i) preexisting mental disorders such as manic depressive personality, unrelated to the disease or its treatment;
ii) reactive states related to the disease;
iii) toxic states directly related to the treatment;
iv) transient disturbances of paroxysmal character as for example confusion during oculogyric crisis;
v) gradual mental deterioration concomitant with the progressive Parkinson's state and primarily due to the cerebral atherosclerosis.

In our state of knowledge, three groups of parkinsonian patients should be considered in any neuropsychological evaluation:

i) untreated patients;
ii) parkinsonians receiving classical anticholinergic or antihistaminic medication, and
iii) patients treated with L-DOPA or with L-DOPA and peripheral decarboxylase inhibitors.

It should be remembered that the use of anticholinergic drugs can sometimes lead to toxic impairment of mental functions.

In untreated parkinsonian patients psychological tests showed conflicting results [20, 32, 40, 45, 48, 49, 54]. Some authors [54] did not find any significant differences in performance scores on cognitive tests between parkinsonian and agematched arthritic patients. More recently Levita and Ricklan [32] failed to find differences between parkinsonian and cardiac patients on testing visual-motor, perceptual and cognitive functions.

Evidence of a general deterioration of mental functions has been found by Selby [52] in 16 % of his cases and there was a significant correlation with ventricular enlargement demonstrated by pneumoencephalography, dementia being related to arteriosclerotic or senile changes. According to Kral and Dorken [31], impairment of intelligence may be considered dependent upon lesions of the cortex rather than upon involvement of basal ganglia structures.

However for many years it has been known that a decrease in intellectual ability can be observed in a fair proportion of patients with Parkinson's disease, occasionally leading to actual dementia [2, 3, 22, 32, 33, 38, 47, 53]. There is also evidence that this mental deterioration in highest integrative functions is more closely associated with the symptom akinesia [48, 51] and the late onset of Parkinson's disease [21]. Previous studies from our laboratory have attempted a quantification of the psychomotor components of akinesia [28] and have delineated a significant impairment in the ability to elaborate a motor pattern or plan of action. This impairment was more evident with progressive complexity of the puzzle test utilized. The presence of akinesia is probably the single most important factor in a rapid progression of the illness. Indeed, Hoehn and Yahr [24] demonstrated that 40 % of the akineto-rigid patients are invalid within five years, while fewer than 10 % of those whose first symptom was tremor reached this stage after the same period. With this background it was of great interest that along with a more or less specific anti-akinetic effect [4, 89], levodopa therapy has been observed to produce intellectual "awakening" or alerting [1, 12, 19, 36, 37] and occasionally improved thinking capacity. Some authors have even reported improvement in learning ability, auditory perception and immediate memory functions as measured by verbal I. Q. and performance I. Q. scores [1, 10, 11, 37–39]. This improvement appeared to be greatest in tests measuring perceptual organization such as block designs and object assembly [34, 35, 39]. Although, as noted by Klaiber et al. [30], even within this test specialization, only the simple tasks were modified and the more complex procedures involving a sequence of actions or taking a decision, remained essentially unchanged. Ricklan [45, 46], however, still maintains that an increase in behavioral activation or arousal is responsible for the observed increments in test scores of intellectual functions following short and long-range Levodopa therapy.

With more long-term use of Levodopa, many authors [4, 5, 36] are becoming aware of a subtle mental change occurring in many patients on chronic Levodopa therapy but apparently not correlated to the degree of physical impairment. This motor psychological dissociation is potencially very important [17, 57]. Patients outwardly intellectually bright, mobile, well oriented and not depressed, perform at a definitely low level on tasks involving constructive and perceptual organization. It is far from clear, at this time, whether this change is the result of the chronic Levodopa therapy, or the unmasking through motor improvement of the natural progression of the mental component of Parkinson's disease. Our study was designed to attempt an answer to this crucial question.

MATERIAL, SUBJECTS AND METHODS

In the design of such a study one must stress the importance of proper control

groups, including age and scolarity matched non neurological subjects, and a similarly matched group of parkinsonian patients not receiving Levodopa. This double control has most often been absent from the reported studies. Moreover, because of the fatiguability factor, most evident in akinetic patient, it is important that the total duration of the test period not be too long, while still giving the maximum of information with the most sensitive (e. g. most disturbed) tests.

Recent publications on this subject have mainly employed the Wechsler Adult Intelligence Score (WAIS) battery of tests, or variants thereof, to evaluate intellectual functioning [17, 32, 39]. Our own results indicate that it is of some interest to compare intellectual ability with performance (as graded by dexterity tests) and to include a measurement of attention, a heretofore neglected component, before drawing definitive conclusions.

In the present study, we applied the following tests: the Kohs block design with its 17 sub-tests [59], the K-T attention test [58], the Purdue Pegboard and the Porteus Maze test [42]. Kohs Block Design test offered the desired flexibility and ease of handling with progressively more complex tasks (in fact, 17 sub-tests) which would permit the proper grading of each patient along a wide scale of possible achievements (from 1 to 131). The Block Design test [59] seems to involve one's ability to perceive and analize spatial-perceptual patterns. It requires the ability to analyze both the pattern and its component parts. It involves gross motor functions and a perceptual conceptual quality. The K-T attention test [58] is a test of "barrage" and, like other attention tests, has three evaluation parameters: time of performance, errors and omissions. On a sheet of paper each of two columns has 20 lines with 17 signs for each line, i. e., a total of 340 signs for each column. The column on the left contains errors, while the column on the right is the correct one. The patient has to cross out as fast as possible each sign that does not correspond to the column on the right side. The performance is timed for each minute. We think that this test is more complex than the Zazzo test because it requires a permanent shifting from one pattern to another.

On the Purdue Pegboard the number of pegs placed with the right, left or both hands in 30 seconds has been noted using a stopwatch. Evaluation and scoring for the Porteus Maze test were done with the most recent revision of the test [43]. Further examinations involved application of the extension series which was previously shown to eliminate practice effects and yield identical means and standard deviation as the Vineland Revision on retesting [42]. Testing was begun with the test age 5 instead of 7. If the subject failed at age 5 and 6, testing was discontinued and a test age of 4 was assigned. Only the mental age scores have been evaluated.

A total of 99 subjects were studied in an identical manner. The subjects were divided into 5 sub-groups, each serving as a control for the others, and matched for age and educational level:

Group 1:

Consists of 40 normal control subjects who were all spouses or age matched relatives of parkinsonian patients coming to the clinic. This sort of control permits an approximation of educational and socio-economic background, as illustrated in *Table 1.*

Group 2:

Consists of 14 patients with Parkinson's disease who, like the others, were referred to us for Levodopa therapy, but who were treated with conventional (antihistaminic or anticholinergic) or non-DOPA experimental drugs (Amantadine HCl). The decision to treat or not to treat with Levodopa was made by the treating neurologist independently from the neuropsychologist. This decision was usually based on the predominance of non-akinetic symptoms, especially tremor. These 14 patients were generally less affected in overall motor performance than the other study groups; this was not due to a shorter average duration of illness (see *Table 1)*, but rather to the lesser importance of akinesia.

TABLE 1 — **STUDY GROUPS DESCRIPTION**

GROUP		AGE	SEX	EDUCATION	Length of the Illness
1	Controls (40 subjects)	65.8 ± 1.4 years	20 M 20 F	7.97 ± 0.55 years	
2	"Classic" medication (No DOPA) 14 patients	57.28 ± 1.65 years	6 M 8 F	10.85 ± 1.02 years	10.42 ± 2.16 years
3	DOPA + Ro 4-4602 33 patients	60.67 ± 1.42 years	20 M 13 F	10.30 ± 0.65 years	8.75 ± 0.61 years
4	DOPA alone 12 patients	58.08 ± 2.40 years	9 M 3 F	11.67 ± 1.36 years	9.58 ± 1.24 years

TABLE 2 — **RESULTS**

			K - T			PURDUE PEGBOARD				PORTEUS
Group	*Examination*	*Kohs*	*Time (sec.)*	*Errors*	*Omission*	*Right*	*Left*	*Bilateral*	*Total*	*Mental Age*
1 CONTROLS	I Time 0	92.95 ± 2.76	532.42 ± 33.19	3.0 ± 0.83	15.05 ± 1.89	14.20 ± 0.55	15.35 ± 0.50	21.12 ± 0.66	50.17 ± 1.55	15.46 ± 0.27
	II 1 year	92.12 ± 2.64	539.02 ± 33.60	3.02 ± 0.76	16.05 ± 1.63	14.57 ± 0.47	14.95 ± 0.50	20.72 ± 0.59	50.65 ± 1.52	15.52 ± 0.25
2 NO DOPA	I Time 0	55.86 ± 6.44	639.07 ± 46.63	5.14 ± 1.11	26.86 ± 4.94	11.07 ± 0.80	9.43 ± 0.81	12.64 ± 0.87	33.19 ± 1.87	13.54 ± 0.73
	II 1 year	49.93 ± 6.92	658.71 ± 52.04	4.86 ± 0.94	27.85 ± 5.39	10.42 ± 0.86	10.21 ± 0.88	13.07 ± 1.26	33.71 ± 2.70	13.71 ±

TABLE 2 (continued) — **RESULTS**

			K - T			PURDUE PEGBOARD				PORTEUS
Group	*Examination*	*Kohs*	*Time (sec.)*	*Errors*	*Omission*	*Right*	*Left*	*Bilateral*	*T o t a l*	*Mental Age*
3 DOPA + Ro 4	I Time 0	32.67 ± 3.99	1.054.00 ± 57.76	5.51 ± 0.52	37.67 ± 2.78	7.60 ± 0.51	7.45 ± 0.51	9.21 ± 0.49	24.30 ± 1.36	11.77 ± 0.55
	II 2 months	56.36 ± 4.66	807.00 ± 46.58	4.87 ± 0.47	28.36 ± 2.64	9.06 ± 0.50	9.00 ± 0.52	11.78 ± 0.63	29.96 ± 1.47	13.31 ± 0.53
	III 6 months	52.00 ± 4.67	820.06 ± 44.58	5.15 ± 0.56	28.36 ± 2.62	9.33 ± 0.56	9.39 ± 0.63	11.84 ± 0.63	30.30 ± 1.60	13.10 ± 0.55
	IV 1 year	46.02 ± 4.70	851.60 ± 46.69	5.09 ± 0.63	29.81 ± 2.72	9.33 ± 0.53	9.06 ± 0.50	11.90 ± 0.67	30.78 ± 1.54	13.04 ± 0.55
4 DOPA ALONE	I 24 months	59.08 ± 9.41	755.75 ± 60.48	4.67 ± 0.99	31.08 ± 5.93	10.33 ± 0.84	9.92 ± 0.81	12.00 ± 1.01	32.25 ± 2.47	13.75 ± 0.82
	II 30 months	55.67 ± 8.97	760.08 ± 64.23	3.92 ± 0.72	31.91 ± 5.26	9.58 ± 0.63	9.83 ± 0.87	11.91 ± 0.86	31.17 ± 2.04	13.7 ± 0.77
	III 36 months	52.17 ± 9.14	755.17 ± 65.76	3.92 ± 1.09	30.17 ± 5.54	9.25 ± 0.69	10.42 ± 0.76	11.58 ± 1.06	31.42 ± 2.20	13.58 ± 0.79

Group 3:

Consists of 33 patients with Parkinson's disease who were treated with Levodopa in combination with the peripheral decarboxylase inhibitor Ro 4-4602 according to the schedule previously described [8, 9]. The average dosages once a therapeutic plateau had been reached, were 600 mg. of Levodopa and 150-200 mg. of Ro 4-4602 daily administered in divided doses [8].

Group 4:

Consists of 12 parkinsonian patients who had been treated for over 2 years with Levodopa alone. Mean daily dosage of Levodopa was 3.8 g.

For all series repeated tests were carried out according to the following schedule:

—in group 1 and 2: at time 0 and after 12 months of therapy;

—in group 3: at time 0, 2 months, 6 months and 12 months of therapy *(Table 2)*;

—in group 4: at 24, 30 and 36 months of therapy;

Each patient was first evaluated clinically by a neurologist for highest integrative functions. All cases of overt dementia were eliminated outright from the study. Otherwise patients were chosen in a consecutive fashion. Performance evaluation as already described [17, 18] was then carried out. On another day all the psychological tests listed above were administered, always by the same room. There were no significant differences between the different parameters (age, education and duration of illness) in the groups under study *(Table 1)*.

RESULTS

Our results *(Table 2)* indicate that:

1) Controls had significantly better ($P < 0.01$) performance than parkinsonian patients for all tests used;

2) In the Kohs Block Design test there were no significant differences between the examinations for group 1 at times 0 and 1 year (mean score at time 0: 92.9 ± 2.8). In group 2 there was a slight decrease ($P < 0.05$) in results over the same period. However there was a significant improvement ($P < 0.01$) in group 3 after 2 months of treatment (score from 32.7 ± 4.0 to 56.4 ± 4.7). From 2 months to one year there was a slow gradual, and significant ($P < 0.05$), decrease (to mean score values of 46.0 ± 4.7); in group 4 there was a slow gradual, but non significant decrease between the first examination (perfomed at 24 months) and the third examination (at 36 months), i. e. from a score of 59.08 ± 9.41 to 52.17 ± 9.14;

3) In the K-T Attention test the qualitative pattern of performance remained unchanged in all three patients groups; all parkinsonian patients had significantly ($P < 0.01$) increased error and omission scores as well as lenghthened test times when compared to age-matched control subjects. The only change brought about by Levodopa was a significant ($P < 0.01$) shortening of the time required to perform the special tasks after 2 months of treatment, a result which was maintained in all subsequent observations to one year. Errors and omissions were not modified either by time or by Levodopa in any of the four groups;

4) It is of great interest that despite significant improvements in motor performance in patients from group 3 mainly at 2 months, the Porteus results were not significantly modified (from a mean score of 11.77 ± 0.55 at base line to a best score of 13.3 ± 0.5). Similarly in groups 1, 2 and 4 the results of the Porteus test did not change significantly over a period of one year;

5) With the Purdue Pegboard test, the only significant modification was found at time 2 months in group 3 (from a mean score of 24.3 ± 1.4 to 30.0 ± 1.5). However after this initial improvement there was no deterioration over 1 year of treatment (mean score at one year 30.8 ± 1.5). Similarly the test remained totally unchanged in groups 1 and 2 after one year. In group 4 (DOPA alone) generally the performances were better than those of the DOPA and Ro 4-4602 group, but the following factors have to be taken in consideration:

i) all patients unable to perform a single test from our series (i. e. 15 patients) were disregarded from the present study;

ii) this combined treatment group has not been tested at time 0 (before treatment);

iii) the level of education of this group was higher, but not significantly so when compared to other groups. All these reasons can provide an explanation for the relative high degree of performance of this group, performances similar to those of group 3 after some months of treatment.

DISCUSSION

These studies delineate a few important observations. First, all the above procedures were sensitive enough to differentiate between control subjects and parkinsonian patients, but the most specific deficit was found with the Kohs Block Design test.

When we chose the Kohs Block Design test [13] for our study this was on the one hand in agreement with the modern concepts on the cortico-subcortical circuits underlying human behaviour [14] and, on the other hand, with some previous findings showing some disorders in the integration of body scheme [48] or in the "apraxic area" [28] in akinetic parkinsonian patients. The other tests in our battery have been chosen in order to get general neuropsychological information.

Experimental findings have shown that the caudate nucleus is part of a neural system which plays a role in the retention of learning behaviour [23, 29]. The similarity between some disorders of visuo-spacial and visuo-motor tasks in frontal and parkinsonian subjects are well-known [44, 55, 56].

Taking into account the neurophysiological circuits between the caudate and the prefrontal and parietal lobes [15, 27, 50] the Kohs Block Design test appears to be the most sensitive test in detecting psychological disorders in parkinsonian patients. Our battery thus appears more discriminating than the WAIS test alone. At no time, even with optimal therapeutic levels of Levodopa sufficient to significantly improve motor performance, were we able to obtain a result within normal values on the Kohs test in any of our patients. Secondly, in all groups of parkinsonian patients, despite continued improvement on motor tasks even after one year, there was a slow gradual decrease in some mental performance measurements. This was not evident with the Porteus or K-T tests, which remained essentially unchanged after one year despite a mild (non significant) improvement at 2 months in group 3. This confirms results obtained by others with the WAIS [10, 37]. However the decrease was clear and significant in the Kohs Block Design results, probably indicating more impairment in perceptual organization than in cognitive function. The improvement on Kohs Block Design could not be accounted for by an improvement of manual agility of fine motor coordination because normal and psychiatric patients perform as well on these tests with one hand as they do with both hands.

In the most recent studies on this subject, Loranger et al [35] using the WAIS, stated that: "It seems that the parkinsonian's greatest difficulty is in comprehending and analyzing novel or unfamiliar stimuli". They reexamined their patients with the WAIS after five to thirteen months treatment with 4 to 8 g. of Levodopa daily. The greatest improvement was in the function most impaired before treatment, i. e. perceptual organization. On the other hand, they observed that patients with lower pretreatment I. Q. improved more than those with high I. Q.'s. Violon et al. [57] found that the attention tests (test of Zazzo) are not influenced by L-DOPA therapy. Their patients performed definitely worse with the Kohs Block Design tests. They also observed "l'absence de corrélation notable entre les modifications aux épreuves motrices d'une part, psychologiques d'autre part" . Our results are in partial agreement with their findings. It is thus evident that despite sustained motor improvement with Levodopa over a one year period, there is mounting evidence for progression of the disease process to other cortical as well as subcortical structures [13, 16]. Preliminary results in some of our patients at 2 to 5 years of treatment indicate that the slope of the

decrease in intellectual function continues unabatted at the same rate as that observed in akinetic patients treated without Levodopa.

In our "no-DOPA" group, there was a slight decrease in the performance over one year probably consonant with a progression of the disease process. In our DOPA and Ro 4-4602 group, it is noteworthy that none of the patients with low pretreatment scores ever returned to a performance within the normal range. It is also important to note that in the same group, in spite of a continuous improvement on dexterity tests, the performances at Kohs Block Design and Porteus tests tend to return slowly to pretreatment levels. For the L-DOPA and Ro 4-4602 group, despite amelioration in the time factor in the K-T test, there was no significant improvement for omissions and errors, thus the qualitative aspect of the performance remains definitely impaired. Our data for group 3 are generally in agreement with some previous findings [1, 11, 12, 38, 39] showing an improvement in motor performance in parkinsonian patients after several weeks on L-DOPA therapy.

Thus our last conclusion would be that Levodopa *per se* does not seem to be involved in the intellectual changes observed after long-term treatment even if it is a major contributing factor to long-term side effects such as *akinesia paradoxica* [6, 7]. Progression of the primary disease process in Parkinson's disease is not stopped by Levodopa, a treatment method resulting in symptomatic long-term relief of akinesia [4, 6, 7].

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SUMMARY

99 subjects, controls and parkinsonian patients, were evaluated with the 17 subtests of the Kohs Block Design test, the labyrinths of Porteus, the K-T attention test and finally the Purdue Pegboard test. All parkinsonian subjects performed below normal on all tests before and even after treatment with L-DOPA.

There is initially a clear-cut improvement in performance after 2 or 3 months of treatment, but gradually the performance scores decrease towards pre-treatment levels. The authors conclude that this decrease is due to progression of the disease rather than to loss of efficacy of L-DOPA.

RESUMEN

99 personas, controles y pacientes con parkinsonismo, fueron evaluados mediante los 17 sub-tests del test de Kohs, los laberintos de Porteus, el test de la atención "K-T", y finalmente el test de Purdue. Todos los pacientes parkinsonianos, tratados o no con la L-DOPA, tuvieron un comportamiento inferior al normal.

Inicialmente, durante los 2 ó 3 primeros meses de tratamiento hubo una evidente mejoría en el estado general, pero gradualmente esta mejoría fue disminuyendo hasta llegar al nivel del período del pre-tratamiento. Los autores concluyen que dicha disminución, es más bien debido a la progresión de la enfermedad que a la pérdida de eficacia de la L-DOPA.

RÉSUMÉ

99 sujets, contrôles ou patients parkinsoniens, furent évalués par les 17 sous-tests du test de Kohs, les labyrinthes de Porteus, le test d'attention "K-T" et finalment le test de Purdue. Tous les sujets parkinsoniens eurent une performance inférieure à la normale avant et même après traitement par la L-DOPA.

Au début, il y a amélioration nette dans la performance après 2 ou 3 mois de thérapie, mais graduellement le score de performance diminue vers le niveau pré-traitement. Les auteurs concluent que cette diminution est le résultat de la progression sous-jacente de la maladie plutôt que due à une perte d'efficacité de la L-DOPA.

ZUSAMMENFASSUNG

Bei insgesamt 99 Kontrollpersonen und Parkinsonpatienten wurde der 17 sub-test des "Kohs Block Design test", der K-T aufmerksamkeitstest, der labyrinthtest von Porteus und schliesslich der Purdue Pegboard test geprüft. Alle patienten mit Parkinson'scher Krankheit wiesen sowohl vor wie nach Behandlung mit L-DOPA.

Initial fand sich eine deutliche besserung der resultate, die indessen allmählich auf den Zustand vor der behandlung zurückfield. Die autoren schliessen daraus, dall dieses absinken eher durch die progression der krankheit als durch eine mangelnde wirksamkeit von L-DOPA bedingt ist.

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Neurotropic Drugs and Epilepsy

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Advances in neuropharmacology have greatly increased our knowledge of neurotropic drugs, some of which may enhance and others lessen convulsive susceptibility. We live in a drug age in which a high percentage of people are taking neurotropic agents of one type or another, and patients, including epileptics, frequently are on several agents, some of which increase their susceptibility. It is important, therefore, that the physician be fully aware of all drugs that his epileptic patients are taking.

The principal stimulants used therapeutically are the amphetamines, the psychic stimulants, such as ritalin, and other more rarely used agents, such as nikethamide (Coramine^R), strychnine and pentylenetetrazol (Metrazol^R). Experimental evidence has shown that reserpine and chlorpromazine lower the threshold to seizures and some uncontrolled clinical evidence would be consistent with this possibility (Fink and Swinyard [4],). Another drug, commonly used socially, is alcohol. During the period of withdrawal, after excessive use of alcohol, seizure susceptibility is greatly increased. Studies have shown that this is due to a transient hypoglycemia, magnesium deficiency and respiratory alkalosis, all of which develop about 4-12 hours after the cessation of drinking. In addition, such dietary stimulants as caffeine, used in coffee and soft drinks, may also be harmful if used to excess. The effect of the "pill" has been much debated and it is true that estrogens exaggerate seizure susceptibility. However, as usually used, the pill contains both estrogens and progesterons, and its effect on seizure susceptibility is slight or nil.

Modern clinical pharmacology has demonstrated another type of drug action, which is even more dangerous because it frequently is not suspected. One drug may alter the absorption, distribution, metabolism and excretion of another and thus result in either excessive or inadequate concentrations of it. Such drug interactions in the case of neurotropic drugs that may affect epilepsy are very complex and have not been fully worked out. However, the principal mechanisms involved are known and some of the principal effects produced can be outlined.

The absorption of antiepileptics, as in the case of other drugs, is dependent upon its pKa and lipid solubility, the pH of the media in which the drugs are dissolved and the concentration of the drug. For drugs that have a low lipid solubility, their pKa values and the pH of the stomach and intestines constitute important factors which determine their absorption. For example, most anticonvulsants are absorbed from the gastro-intestinal tract by passive diffusion in a nonionized form. Phenobarbital with a pKa value of 7.3 is rapidly absorbed from the gastric juice at a pH of about 2.0. It is almost all in the nonionized form at this pH and is soluble to some extent in gastric juice. Local changes of gastric pH, however, would modify this. In the small intestines, phenobarbital is absorbed more slowly, since at the intestinal pH of 7-8 only about 50 % of it is in a nonionized form.

Diphenylhydantoin, on the other hand, is very insoluble in gastric juice and is mainly absorbed in the duodenum, where at a pH of 7-7.5 it is more highly ionized and consequently more soluble in intestinal fluid.

Although other mechanisms, such as the malabsorption syndrome and disorders of

the gastro-intestinal system, may influence the absorption of neurotropic drugs, it should be emphasized that dietary or other factors that alter the acid-base balance may, also, modify the absorption of drugs.

The principal factors influencing the distribution of centrally acting neurotropic drugs are protein binding and their blood-brain barrier permeability. Still another factor which can modify the distribution of neurotropic drugs is the rate of CSF formation and flow, since this regulates their concentration in the CNS. It has been shown that the concentration of substances in the brain can be influenced markedly by changing their concentration in CSF, either by modifying CSF secretion rate or by altering their active transport out of the CSF. Alterations of acid-base balance are also important, since they can change the membranes and thereby affect their anti-distribution of anticonvulsants across cell convulsive activity.

DRUG INTERACTIONS-DISTRIBUTION

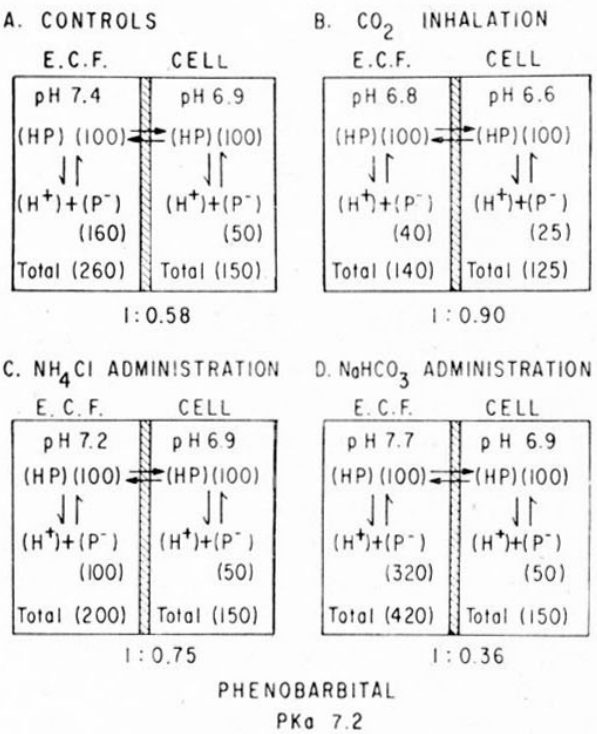


Fig. 1. — *Theoretical effect of pH changes on the distribution of phenobarbital (pKa 7.2) across cell membranes. The ratios were calculated from the extracellular and intracellular pH values and the pKa by means of the Henderson-Hasselbalch equation. See text for discussion.*

Figure 1 illustrates changes of intracellular and extra cellular concentrations of phenobarbital as calculated from the Henderson-Hasselbach equation. The normal ratio of concentrations of intracellular to extracellular phenobarbital is 0.58 as shown in A. If carbon dioxide is inhaled, the extracellular pH can be reduced to 6.8 and intracellular pH to 6.6, and the calculated distribution ratio becomes 0.9, as shown in B. If extracellular pH is reduced to 7.2, by administration of NH_4Cl without a change in intracellular pH, the distribution ratio becomes 0.75. On the other hand, if extracellular pH is increased to 7.4 by the administration of sodium bicarbonate, and again without alteration of the intracellular pH, the distribution ratio would be 0.36. In studies by Waddell and Butler [2], the distribution ratios for phenobarbital have been found to be as predicted on the basis of its pKa value and the pH conditions indicated.

Acid-base changes also influence the binding of drugs to plasma and tissue constituents. Thus, other agents which modify pH have an important effect on the distribution of antiepileptics, as well as upon their absorption, and through these mechanisms influence the degree of control exerted by these agents on epileptic patients.

Perhaps the most important and direct mechanism for modifying drug levels in patients with epilepsy involves the effect of one agent on the metabolism of another. The biotransformation of most antiepileptics is mediated by drug-metabolizing enzymes (mixed function oxidases) in the endoplasmic reticulum or microsomes of the liver. Various factors influence the activity of the microsomal enzymes and thus can modify the rate of drug biotransformation. Some drugs increase the activity of such enzymes (a process called induction) and others decrease their activity. Phenobarbital is a well known inducer of microsomal drug-metabolizing enzymes and thus acts to increase the rate of metabolism of other drugs. This results in a reduction of the plasma level of the other drug. This type of drug interaction is illustrated in Figure 2 between chronically administered DPH and phenobarbital. A reverse effect is shown with

DRUG INTERACTIONS-BIOTRANSFORMATION

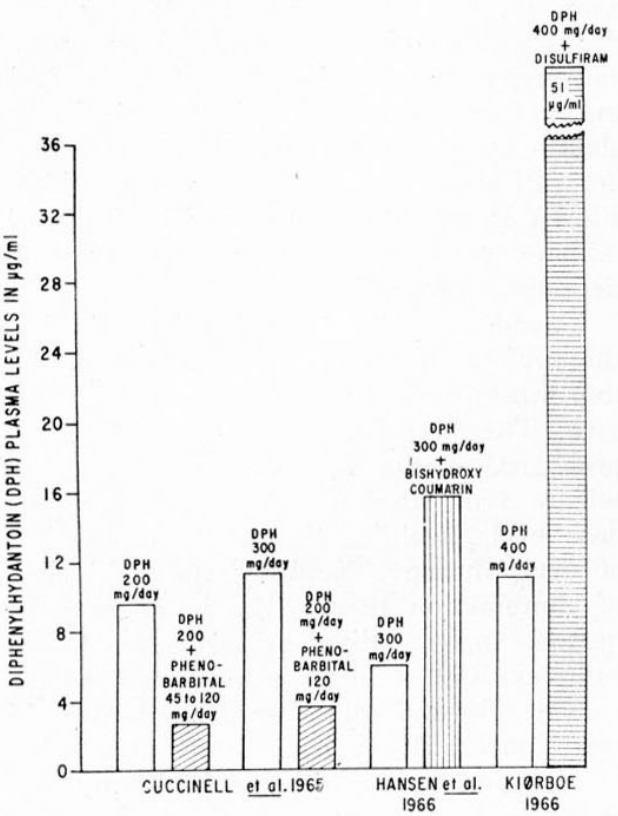


Fig. 2. — *The influence of various simultaneously administered drugs on the plasma levels of DPH in patients receiving it chronically for the treatment of epilepsy. The data are plotted from the results of the various authors listed along the abscissa* (*Cuccinell* et al., 1965; *Hansen* et al., 1966; *Kirboe,* 1966). *See text for discussion.*

bishydroxycoumarin and disulfiram. In these instances, the hepatic microsomal enzymes are inhibited and, as a result, the rate of DPH metabolism is reduced and the plasma levels of DPH consequently are higher.

Whereas phenobarbital lowers the plasma levels of DPH by enzyme induction as explained, it may also produce a reverse effect by competing with DPH for the same enzyme system. Drug competition, therefore, likewise may alter drug levels and constitutes another form of drug interaction. One drug may displace another from its binding sites on plasma proteins and, thus, in still another way may affect the plasma levels of the displaced agent.

Drugs that increase DPH plasma levels usually do so either by inhibiting its biotransformation, or by displacing its protein binding. This occurs with bishydroxycoumarin, phenyramidol, disulfiram, sulthiame, chloramphenical, methylphenidate, chlordiazepoxide or diazepan and isoniazid. Other agents that are less well documented are phenylbutazone, sulfaphenazole, chlorpromazine, estrogens, halothane and ethosuximide. DPH toxicity has been reported on this basis with bishydroxycoumarin, sulthiame and disulfiram. On the other hand, if the level of DPH is below its effective therapeutic range, such drugs may improve seizure control by elevating the DPH levels.

Drugs that lower DPH levels generally do so by inducing the drug-metabolizing enzymes in the liver, as already described. Phenobarbital is the most notable enzyme inducer, but this may also occur with carbamazepine, ethanol and folic acid. One study, for example, found that alcohol could reduce the plasma levels of DPH as much as 50 % (Kater, *et al.* [5]). The end result is a reduction in the antiepileptic effectiveness of DPH, in which case compensatory higher doses may be required.

Another aspect of this same problem is the effect of antiepileptic agents on other drugs. Thus, DPH has been shown to lower the plasma levels of digitoxin, bishydroxycoumarin, metyrapone and the insecticide DDT. The same has been shown for dexamethasone, cortisol and vitamin D_3. The latter may result in hypocalcemia and osteomalacia. DPH, phenobarbital and primidone have also been associated with reduced levels of folate, which in turn produces megaloblastic anemia. Folate is essential to several major metabolic processes in the brain, such as the synthesis of purines (DNA and RNA), proteins and methionine (necessary for all methylating processes) and also the hydroxylation of tyrosine and tryptophan (precursors of catecholamines and indoleamines). However, aside from megaloblastic anemia, the clinical effects of prolonged folate deficiency have been disputed, such as its antagonism to DPH as an antiepileptic and its neuropsychiatric complications (Aird and Woodbury [1]).

Similarly, phenobarbital, as a result of its ability to induce drug-metabolizing enzymes in the liver, increases the biotransformation of many drugs (Cuccinell [3]), as already mentioned. One of the most dangerous in-

teractions concerns phenobarbital and bishydroxycoumarin. The metabolism of this agent is increased by phenobarbital and thus higher doses are required to produce its anticoagulent effect. Serious bleeding may occur if phenobarbital is withdrawn. A concomitant adjustment of the anticoagulant is required to avoid this effect.

In summary, drug interactions that influence the effective, therapeutic plasma levels of drugs, regardless of whether produced by alterations of absorption, distribution, degradation or excretion, may be seen to be complex and must be checked directly by determinations of the plasma levels of the drugs involved. In the case of the antiepileptics, this is important when their usual oral doses fail to provide the expected degree of protection, or when a toxic reaction develops. Although other causes may account for unexpected responses, it still is important to be sure of the plasma levels. The most common cause of ineffective therapy is the failure of the patient to take the prescribed doses. However, other causes that must be considered are malabsorption syndromes and other abnormalities of the gastro intestinal tract. In addition, diffuse and intense epileptogenic mechanisms, such as infectious processes, may not respond to the usual doses and plasma levels of antiepileptics.

Toxic reactions to antiepileptics, on the other hand, may be due to hepatic and genito-urinary conditions as well as drug interactions, as already explained. Not uncommonly, however, the patient may be taking excessive doses, either as a result of mental confusion, forgetfullness or otherwise. Some toxic reactions, of course, are due to hypersensitivity or allergic reactions. Genetic and underlying metabolic mechanisms also may alter the plasma levels of drugs and produce unexpected results.

The therapeutic and toxic plasma levels of the more important antiepileptic drugs is shown in Table I. The situation is altered, however, if combination therapy is required, as is so often the case in epilepsy. This may be required, for example, in patients exhibiting more than one type of seizure, or again when the severity of the seizure disorder is such that it can not be controlled by any one antiepileptic alone. The situation is also complicated by such drugs as primidone, because of its partial conversion to phenobarbital. One is dealing in this instance with the principal metabolite of primidone, methylethylmalonamide (PEMA), as well as phenobarbital. PEMA is an antiepileptic and initially primidone, itself, has been shown to have antiepileptic properties.

Considering the complexities of drug therapy in epilepsy, it is not surprising that some patients receive less than optimal care. The physician is confronted by many problems, including accurate diagnosis of seizure type, the adjustment of adequate dose levels, avoiding the toxic complications of drug therapy, handling the difficulties of combination therapy, as is so often required, and avoiding or adjusting to the complexitities of drug interactions, as discussed. Beyond all these factors, the epileptic susceptibility of patients may be altered by many mechanisms, including such systemic factors as hydration, electrolyte and acid-base imbalances, conditions producing hypoxia or hypoglycemia, endocrine dysfunctions and toxic states, whether endogenous or exogenous in origin. In line with the drug interactions previously discussed, the effect of hyperventilation on acid-base balance as influenced by emotional, tension factors and also the possible excessive use of dietary stimulants and alcohol must be considered in patients who are refractory to antiepileptic measures. Directly or indirectly, all the factors mentioned can influence the underlying physicochemical mechanisms that determine seizure susceptibility and, therefore, the relationship between a given antiepileptic and seizure control is not a simple or direct one, even when controlled by blood plasms determinations. The problem of epilepsy involves many complex facets and a broader therapeutic approach is required in refractory, problem patients, which takes into consideration all factors contributing significantly to the underlying seizure susceptibility of each patient. The factors mentioned vary enormously from patient to patient and, when important in a given patient, should be regulated as part of the overall

ANTIEPILEPTIC DRUG THERAPY
THERAPEUTIC AND TOXIC PLASMA LEVELS, PLASMA HALF-LIFE AND PLASMA BINDING

DRUG	THERAPEUTIC LEVELS		TOXIC LEVEL	PLASMA HALF - LIFE	PLASMA BINDING
	MEAN (ug/ml)	RANGE (ug/ml)	(ug/ml)	(hr)	%
PHENOBARBITAL	25	15-40	> 40	96 ± 12 (53-140)	46
DIPHENYLHYDANTOIN (Dilantin, DPH)	12	8-20	15-20-Nystagmus 20-30-Ataxia, etc.	24 ± 12 (7-42)	89
PRIMIDONE (Mysoline)	8	5-10	10-Nystag., Sed. 15-Ataxia, etc.	6.5 ± 1 - Primid. 24-48 - PEMA 96 - Phenobarb.	- 0 - 0 + - 50 ± %
ETHOSUXIMIDE (Zarontin)	60	40-80	> 100	30 - Children 60 - Adults	0
TRIMETHADIONE (Tridione, TMO)	20.5 (as TMO) 765 (as DMO)	6-41 475 - 1200	——— ———	16	0
DIAZEPAM (Valium)	0.3	0.16 - 0.70	———	8-10 (fast phase) 2-8 days (slow)	?
CARBAMAZEPINE (Tegretol)	4	3-7	8-10 (50 %)	Ca 19 (12-30)	Ca 80

antiepileptic regimen. This would include an optimal adjustment of antiepileptic drugs which also would take into consideration the type and doses of other neurotropic agents that the patient may require.

SUMMARY

Advances in neuropharmacology have greatly increased our knowledge of neurotropic drugs, some of which may enhance and others lessen epileptic susceptibility. Because we live in a drug age, it is important that the clinician be fully aware of all drugs that his epileptic patients are taking, since in some instances these may increase their seizure susceptibility. For the same reason, the subject of drug interactions has become of major importance; some drugs may increase and others lower the levels of antiepileptic agents when taken concomitantly. Such interactions, thus, either may result in toxic effects, or at the other extreme may result in inadequate doses for the control of seizures. The pharmacological basis of these interactions will be discussed and their overall effect on the management of epilepsy will be presented in a broad perspective, which includes all mechanisms serving either to enhance or to lower epileptic seizure threshold.

A direct corollary of the above concerns the need of determining the plasma levels of antiepileptic agents. Drug interactions may modify the situation as already discussed. Recent studies, also, show that many patients do not systematically take the drugs prescribed and some may take more than prescribed. In other instances, the usual oral doses do not produce plasma levels in the therapeutic range of the antiepileptic agents being used, or again may result in toxic levels. Unexpected responses to antiepileptic therapy, whether inadequate or toxic, therefore, should be checked by plasma determinations. The clinical pharmacology involved in these aberrant conditions will be discussed, as well as the therapeutic and toxic plasma levels of the more commonly used antiepileptic drugs.

RESUMEN

Los avances en la neurofarmacología han aumentado en alto grado nuestro conocimiento de las drogas neurotrópicas, algunas de las cuales pueden acrecentar y otras disminuir la susceptibilidad epiléptica. Debido a que vivimos en la época de las drogas, es importante que el clínico conozca plenamente qué drogas ingieren sus pacientes epilépticos, desde que en algunos casos éstas pueden aumentar su susceptibilidad a la crisis. Por la misma razón, el tema de las interacciones de drogas ha llegado a ser de la mayor importancia; algunas drogas pueden aumentar y otras disminuir los niveles de los agentes antiepilépticos cuando se toman concomitantemente. Tales interacciones, por lo tanto, pueden resultar ya sea en efectos tóxicos, o por el contrario, pueden generar dosis inadecuadas para controlar los ataques. La base farmacológica de estas interacciones es discutida y su efecto sobre todo en el manejo de la epilepsia se presenta en una amplia perspectiva, que incluye todos los mecanismos sirviendo, ya sea para aumentar o disminuir el umbral del ataque epiléptico.

Un directo corolario de lo antedicho lo constituye la necesidad de determinar los niveles de plasma de los agentes antiepilépticos, las interacciones de las drogas pueden modificar la situación, tal como ha sido expresado. Asimismo, estudios recientes demuestran que muchos pacientes no toman las drogas prescriptas sistemáticamente, y algunos podrían tomar más de lo que se les ha indicado . En otras instancias, las usuales dosis orales no producen niveles de plasma en el nivel terapéutico que corresponde a los agentes antiepilépticos empleados; otras veces pueden dar lugar a niveles tóxicos. Respuestas inesperadas a la terapéutica antiepiléptica, ya fuere inadecuada o tóxi-

ca, por lo tanto, deben ser controladas por determinaciones de plasma. La farmacología clínica relacionada con estas condiciones aberrantes, es discutida, así como también los niveles de plasma terapéuticos y tóxicos de las drogas antiepilépticas, más comúnmente usadas.

RÉSUMÉ

Les progrès récénts en Neuropharmacologie ont élargit considerablement nôtre connaissance des agents neurotropes. Parce que nous vivons dans un monde orienté vers drogues et médicaments, il est important que le clinicien soit au courant de l'action des anticonvulsants qu'il préscrit a ses malades épileptiques. En effet ces médicaments peuvent élever la susceptibilité du patient aux états de mal. Pour la même raison, l'étude de l'interaction de ces médicaments est d'un intérêt majeur. Lorsque administrés simultanément certains peuvent augmenter et d'autres abaisser le taux sanguin des anticonvulsants préscrits. Ces interactions peuvent résulter ainsi soit en une action toxique, ou à l'opposer un taux serique d'anticonvulsants insuffisants pour un traitement efficace. La base pharmacologique de ces interactions sera discutée et leur effet global sur le traitement des états de mal sera presente dans une perspective elargie qui inclura tous les mécanismes connus provoquant soit la hausse ou la baisse du seuil épileptique.

Un collaire directe concerne la nécessité de déterminer les taux seriques des médicaments anticonvulsivants. Il est bien connu que les épileptiques qui ne suivent pas les régimes préscrits sont nombreux. Par ailleurs les régimes oraux peuvent résulter en des niveaux sanguins hors des limites therapeutiques ou encore atteindre le seuil toxique. Ainsi, les effets inattendus du traitement anticommital, soit insuffisants ou toxiques, doivent être contrôlés par le taux sanguin des agents employés. L'aspect pharmacologique de ces effets inattendus sera discuté ainsi que les limites therapeutiques et toxiques du taux sanguin des médicaments anticonvulsants courament employés.

ZUSAMMENFASSUNG

Fortschritte in der Neuropharmakologie haben unser Wissen bezüglich neurotropischer Präparate sehr gefördert, insoweit als diese oder jene unter ihnren die Neigung zu epileptischen Anfällen steigern oder harabsetzen. Da wir in einer arzneiorientierten Zeit leben, muss der Kliniker über alle Mittel, die ei nepileptischer Patient einnimmt, genauestens orientiert sein, umsomehr als jene die Anfallsneigung hier und da steigern können. Aus dem gleichen Grund hat das Problem der Wechselwirkung zwischen den Arzneimitteln grosses Interesse hervorgerufen. Es gibt Pharmaka, welche bei gleichzeitiger Einnahme die Wirkung der antiepileptischen Drogen verstärken, während andere sie abschwächen. Solche Wechselwirkungen können daher einerseits zu toxischen Erscheinungen führen, anderseits, in extremen Fällen, zu einer inadequaten Kontrolle der Anfälle. Sowohl die pharmakologische Grunlage dieser Wechselwirkungen soll hier besprochen werden als auch deren Gesamtwirkung auf die Behandlung der Epilepsie, wobei wir auf die weiter Perspektive abzielen, die all Mechanismen einschliesst, welche die Anfallsschwelle entweder zu erhöhen oder herabzusetzen vermögen.

Eine Parallole zu diesen Erwägungen stellt die Notwendigkeit dar, die Plasmakonzentration der Antiepileptika zu bestimmen. Auch hier können Wechselwirkungen zwischen den Mitteln die Verhälnisse beeinflussen. Kurzliche Untersuchungen haben bestätigt, dass viele Patienten ihre Mittel nicht vorschriftsmässig einnehmen. In anderen Fällen führen die gewöhnlich verschriebenen Dosen zu Plasmakonzentrationen, welche entweder unterhalb des therapeutischen

Niveaus liegen, oder dieses überschreitend toxisch wirken. Unerwartete Reaktionen in der Epilepsiebehandlung — Un wirksamkeit oder Intoxikation — müssen daher durch die Bestimmung der Plasmakonzentration kontrolliert werden. Sowohl die klinische Pharmakologie dieser Abweichungen ist der Gegenstand der folgenden Erörterungen als auch die Plasmakonzentration der üblichen antiepileptischen Mittel, welche eine therapeutische oder toxische Wirkung hervorrufen.

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The Paradoxical Effects of CNS Stimulants on Hyperkinetic Behavior

Relation of Response to Degree of Activity and Brain Damage

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NEUROLOGICAL MECHANISMS of hyperkinesia are not completely understood. Diffuse brain lesions are thought to be a major cause of a large percentage of clinical cases of hyperactive behavior [1]. In a recent study [2] on hyperkinesia in children, fifty-seven per cent of the patients had a history of brain injury or other cerebral damage, and all but one patient had neurological signs of minimal brain dysfunction. In certain cases where the diagnosis of brain damage may be uncertain, other etiological factors such as delayed maturation of the brain and psychogenic disorders have been invoked [3]. In many patients the hyperactivity may be controlled and learning disabilities benefited by various drugs [4], and central nervous system stimulants such as methylphenidate (Ritalin) and dextro-amphetamine (Dexedrine) are most effective. In contrast, phenobarbital has an excitant effect [5] and is contraindicated in the treatment of hyperactive behavior. The paradoxical calming effect of stimulants on hyperactive children has not been fully explained and the present clinical and laboratory studies were designed to investigate the relation of the degree of activity and brain damage to the drug response and also, to develop an experimental model for the development of new pharmacological therapies for hyperactivity.

Experimental neuroanatomical studies of hyperkinesia have been concerned with the effects of destruction of different cortical and subcortical structures on locomotor activity. Bilateral removal of the prefrontal and frontal areas in the monkey causes the greatest total increase in activity [6]. Lesions in Walker's area 13 of the orbital surface produce, for any single cortical area, the most extreme degree of hypermotility [7, 8]. Parietal lobe lesions in both the monkey [9] and rat [10] can result in hyperactivity, but this is not as marked as in frontal lobe lesions. Destruction of subcortical structures, such as the striatum [11], interpenduncular nucleus [12], and parts of the hypothalamus [13, 14] can induce hyperactivity. These experimental findings are of importance in understanding the clinical observation that diffuse brain damage is of significance in the etiology of hyperkinesis in children.

CLINICAL STUDIES

Twenty-eight children, 5 to 14 years of age, were evaluated because of hyperactive behavior and associated learning disabilities. Twenty-four patients were male and four were female. A history of brain injury or other cerebral damage was obtained in 17 (61 %) patients, and the electroencephalogram was abnormal in 14 (50 %). The neurological signs of minimal brain dysfunction and their frequency (shown in parentheses) were as follows: impairment of rapid alternating movements of forearms [13]; impaired finger tapping [11]; dyspraxic tandem gait [9]; cortical sensory loss, mainly

graphanesthesia [9]; impaired hopping [7]; finger-to-nose incoordination[6]; Babinski signs[6]; speech disorder [4]; involuntary movements, mainly choreiform, when arms held in outstretched posture [4].

The degree of motor restlessness and hypermotility was measured by an actometer, a method shown to be reliable in studies of drug effects on motor activity [15, 16]. The instrument consists of an automatically winding calendar wrist watch with the pendulum attached directly to the hands of the watch. The pendulum rotates in a plane parallel to the face, and movements with a component at right angles to this plane are recorded. The actometer was worn on the wrist of the nondominant arm during the 45-minute test periods and the activity was measured in units of hours and minutes. The effect of methylphenidate on motor activity was evaluated using double-blind technique and random allocation of patients to drug treatment or placebo groups. The tablets of methylphenidate and the placebo were indistinguishable. The subjects were divided into two groups, one received the placebo, the other methylphenidate according to a system of random permutations. After three weeks of the initial medication a cross-over design was employed and the alternate medication was given for another three-week period in the same dosage schedule as the first course of treatment. The initial daily dose of each medication was 0.5 mg/kg/body weight given in two equal divided amounts after breakfast and lunch; the dose was increased to 1 mg/kg/day after one week of treatment and a dose of 2 mg/kg/day was given during the third week. The degree of motor activity was measured before the trial of medication, at the end of the third week of the initial treatment, and on the last day of the alternate therapy. The maximum dose of methylphenidate at the time of testing ranged from 0.3 to 2.3 mg/kg/day with a mean dose of 1.5 mg/kg/day; the majority of the patients had received and tolerated the largest prescribed dose of 2 mg/kg/daily.

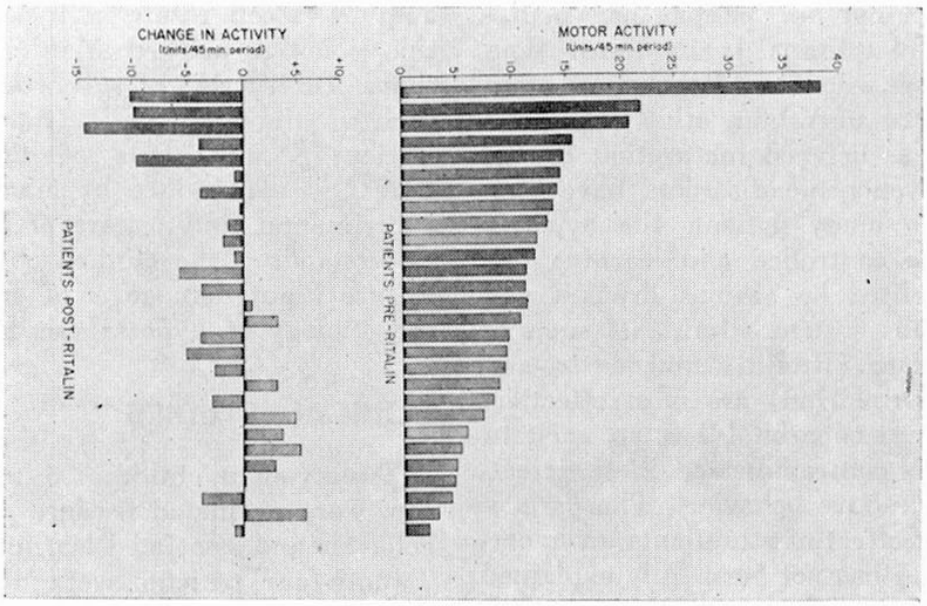


Fig. 1. — *Motor activity of 28 patients before treatment with mehylphenidate correlated with the change in activity after treatment.*

Clinical Results:

Fig. 1 shows the actometer units for the 28 patients arranged in the order of their level of motor activity before treatment and the subsequent change in activity following administration of methylphenidate. The activity before therapy varied from a maximum of 38 units in the most active to 2 units in the least active child. The effect of methylphenidate was related to the level of motor activity before treatment; a depressant effect was recorded in patients with the higher levels of activity whereas a

stimulant effect occurred in those with lower activity levels. Nineteen (68 %) patients were benefited by the drugs; 8 (28 %) showed an increase in activity and one was unchanged.

Fig. 2 shows the frequency of abnormal neurologic signs in patients arranged as in Fig. 1, according to the pre-treatment level of activity, in decreasing order from left to right; the degree of neurologic abnormal-

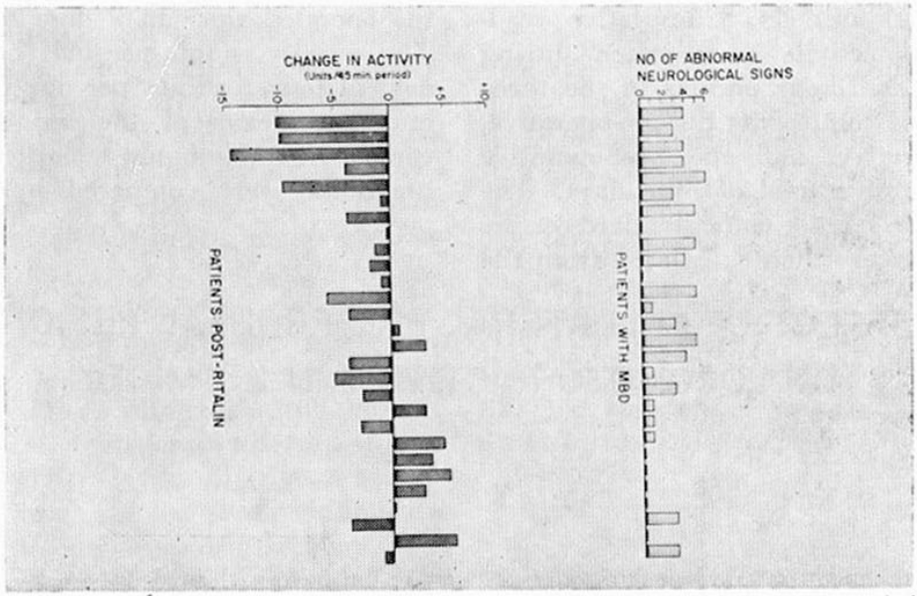


Fig. 2. — *Number of abnormal neurologic signs in patients arranged in order shown in Figure* 1, *and correlated with the change in activity after methylphenidate.*

ity is correlated with the methylphenidate-induced changes in motor activity. Patients with the highest incidence of abnormal neurologic signs tended to have the greatest degree of motor activity before therapy (r, + 0.38; $P < 0.05$), and they were most likely to benefit from methylphenidate by a reduction in activity levels (r, - 0.59; $P < 0.005$). In responsive patients the average number of neurologic abnormalities was 34 ± .42, whereas in the subjects made more active by the drug, the average number of abnormal signs was 1.0 ± .69 ($t = 3.15$; $P < 0.01$). The placebo appeared to cause a reduction in activity but the degree of change was significantly less than that following methylphenidate (t, 5.45; $P < .01$).

LABORATORY STUDIES

Male albino mice, weighing 20-38 gm and 10 to 20 weeks old, were used in this investigation. Thirty-one experimental animals were successfully operated on aseptically under intraperitoneal pentobarbital (60 mg/kg) or ether anesthesia. The prefrontal lesions were made by suction through a small cannula. At the conclusion of the experiments the animals were sacrificed by a lethal dose of pentobarbital; the brains were removed, fixed in formalin and preserved for macroscopic and microscopic study. The brains were sectioned and then stained with the Kluver-Barrera combination stain for fibers and cells of the nervous system. Unilateral prefrontal lesions were made in twenty-five mice, and bilateral lesions in a one stage operation in six mice. A second operation was carried out on four of the animals with unilateral lesions at which time the other prefrontal region was destroyed. Four mice in the unilateral group died after the pre-operative and post-operative activity levels were determined.

Locomotor activity was measured by means of six activity cages, the center having a cylinder that serves as the housing for the infrared generator which emits beams of light. As the animal moves about

the circular raceway these beams are broken, initiating electrical impulses which operate the counter automatically. A similar system of recording has been compared with other methods and has been found to give an accurate measure of locomotor activity of small animals. Cumulative readings of total activity were taken during each of four half-hour periods in the three successive days comprising the pre-operative, the post-operative, and the post-operative drug period, for a total of nine days. The mean activity counts and standard errors of the means were then calculated from the activity measurements on the animals at each half-hour period for the sum of three day experimental periods and these results were compared. Methylphenidate hydrochloride (Ritalin Bydrochloride) was administered by the intraperitoneal route to the operated mice in a dose of 25 mg/kg. The activity counts per half hour for three days at four readings per day were summed and the means of the animals benefited versus the animals not benefited by methylphenidate were compared by the Student test.

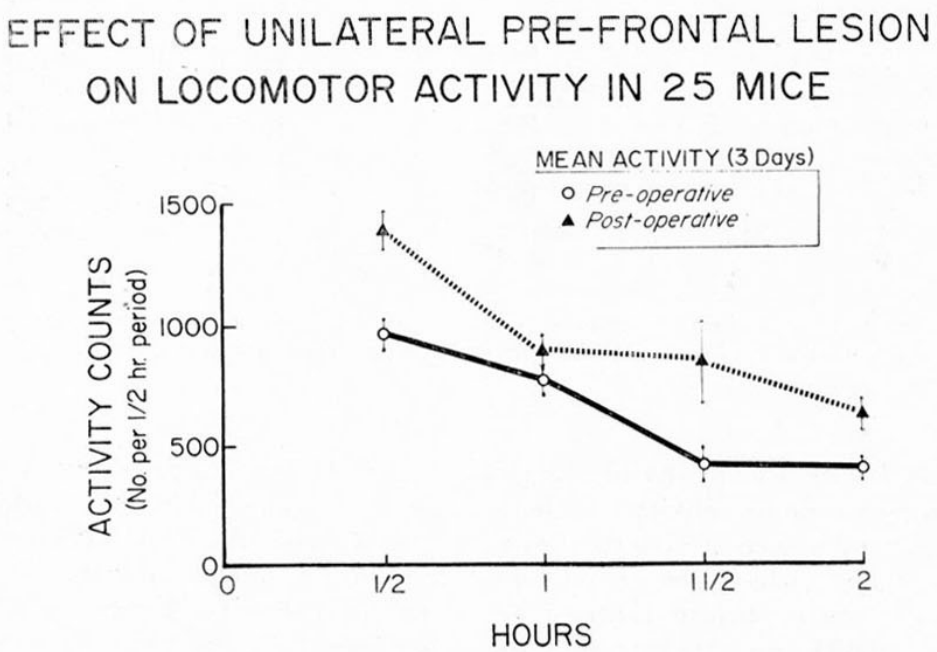


Fig. 3. (a) *Effect of unilateral prefrontal lesions on locomotor activity in* 25 *mice.*

Laboratory Results

Figures 3 (a) and 3 (b) show the effects of unilateral and bilateral prefrontal cortical lesions respectively, on the locomotor activity of mice. An increase in activity was observed following operation in all except six animals of the unilateral lesion group, and five of these showed a reduction in activity. Six mice with the highest levels of post-operative activity responded to methylphenidate with a reduction in locomotor activity, whereas twenty-five mice with lesser degrees of hyperactivity or hypoactivity following operation were stimulated by methylphenidate. A somewhat proportional relationship between the degree of

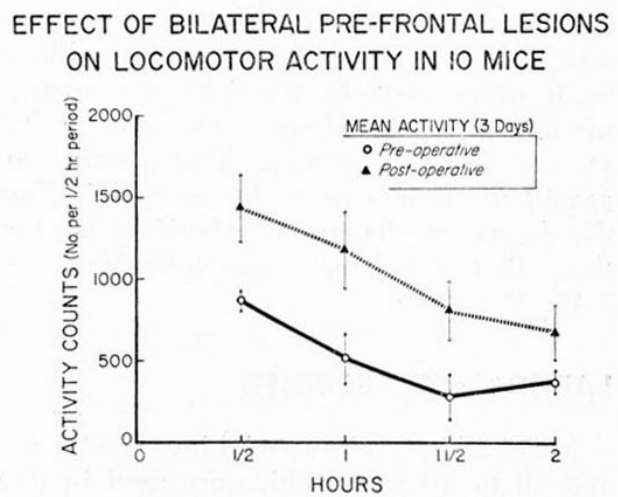


Fig. 3. (b) *Effect of bilateral prefrontal lesions on locomotor activity in* 10 *mice.*

post-operative activity and the effect of methylphenidate was observed. In animals with greater than 250 % increases in activity post-operatively, methylphenidate had a quietening effect, whereas those with activity changes of 75 % to 200 % and less than 50 % showed moderate and severe degrees of stimulation, respectively, following methylphenidate. Figure 4 (a) illustrates the reduction in activity following methylphenidate in the six mice with maximal post-operative activity levels. Figure 4 (b) shows the stimulant effect of methylphenidate on 25 mice with low to moderate post-operative activity levels. Table 1 compares and contrasts the means of the summed activity counts in pre-operative, post-operative, and post-operative drug treated animals, grouped according to drug response. There are significant differences between the activity levels of the two post-operative groups, and the changes following methylphenidate, whereas the activity levels of the two pre-operative groups of mice were not significantly different.

DISCUSSION

The central nervous system stimulants, methylphenidate and dextroamphetamine, are the most effective agents presently available for the treatment of children with hyperactivity and minimal brain dysfunction. The results of the present study show a close correlation between the clinical and laboratory evaluations of methylphenidate. The beneficial effect of methylphenidate on hyperactivity is related to the level of motor activity before treatment and the incidence of abnormal neurological signs. Patients with the greatest number of signs of minimal brain dysfunction tend to be the most active and are more likely to benefit from the drug whereas those with lower levels of activity and fewer signs may be unaffected or made worse. The laboratory observations also show that methylphenidate has a depressant effect on the hypermotility of those animals which are the most active following prefrontal brain lesions, and a stimulating action on those with lower activity following operation and in normal non-brain-damaged animals. Patients with a relatively high level of motor activity and a high incidence of minimal abnormalities on neurological examination should be selected for treatment with methylphenidate. Animals with prefrontal cerebral lesions are valuable experimental models for the testing of new drugs for potential clinical efficacy against hyperactive behavior.

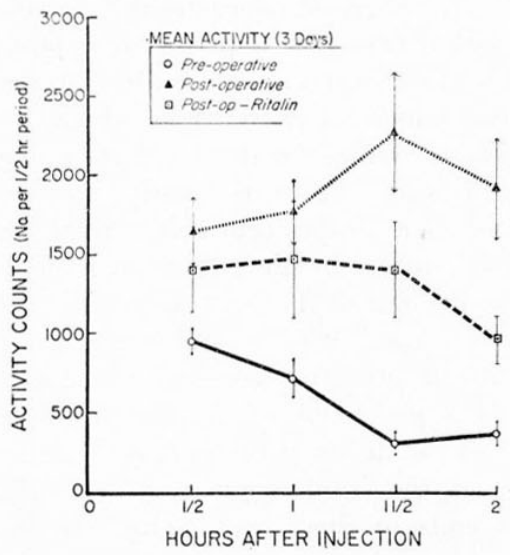


Fig. 4 (a) *Effect of methylphenidate in 6 brain-injured mice with maximal post-operative hyperactivity.*

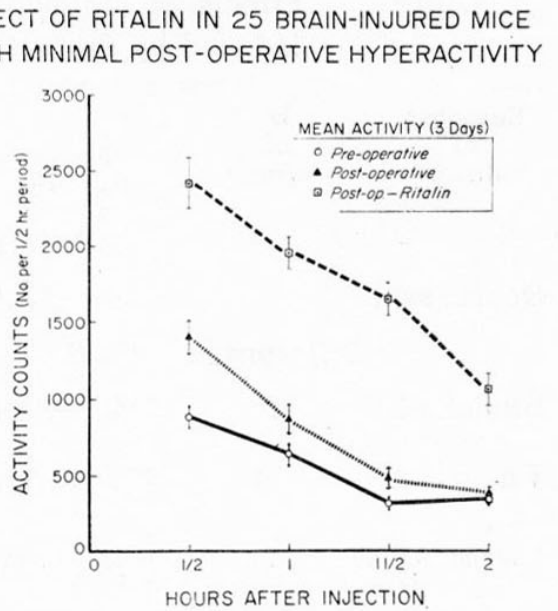


Fig. 4 (b) *Effect of methylphenidate in 25 brain-injured mice with minimal post-operative hyperactivity.*

TABLE 1. **Effects of Methylphenidate (Ritalin) on Hyperkinetic Behavior Induced by Prefrontal Lesions in Mice**

Response to Ritalin	N° of Animals	LOCOMOTOR ACTIVITY IN MICE *		
		Pre-operative	Post-operative	Postoperative —Ritalin
		Differences	**Differences**	
Depressant	6	592 ± 52 (P < .01)	1932 ± 45 (P < .01)	1334 ± 142
Differences:		(N. S.)	(P < .01)	(P < .05)
Stimulant	25	544 ± 29 (P < .01)	793 ± 49 (P < .01)	1769 ± 69
Total	31	599 ± 28 (P < .01)	958 ± 44 (P < .01)	1690 ± 61

* Mean activity counts ± standard errors per ½ hour period.

Drugs with optimum efficacy in the management of minimal brain dysfunction should control hyperactivity, but in addition, learning should be facilitated by effects on attention span, reduction of impulsiveness, and improvements in perception. Drug therapy should be used as an adjunct to remedial education. In a previous clinical study [2], methylphenidate was found to cause a significant improvement in the Draw-a-Man test of general intelligence and in the Frostig test of visual perception; auditory perception was not benefited by this central nervous system stimulant. In a subsequent investigation of the effects of medications on auditory perception, diphenylhydantoin sodium was found to increase the auditory perception for word memory and recall and this effect was related to the occurrence of paroxysmal seizure discharges in the electroencephalogram; in patients with normal electroencephalograms or only mild nonspecific dysrhythmias, auditory perception was unchanged [17]. In a preliminary uncontrolled study of pemoline (Cylert) auditory perception was improved, but the effect was unrelated to the presence of paroxysmal electroencephalographic changes [18]. The manifestations of minimal brain dysfunction are diverse and future studies should determine the specificity of action on visual and auditory perception, reading ability, coordination, conduct and personality, as well as the effect on hyperactivity.

There are a number of theories concerning the neural basis of hyperkinesia. Magoun [19] in discussing the subject of the inhibition of behavior states that persistent exploratory behavior and heightened distractibility are attributable to a release from frontal or temporal cortico-reticular inhibition of ascending systems. Mettler's [9] concept about hyperkinesia is that within the spectrum of hyperactivity two types can be distinguished and correlated with somewhat different types of structural brain damage. Frontal lobe injury results in overreactivity, i. e., hyperactivity directly related to the degree of external stimulation or distractibility. The other type of hyperkinesia, "essential overactivity", is subdivided into a transient deprivative hyperkinesia following parietal and occipital lesions and a disinhibitive hyperkinesia which he feels is due to lesions in the striatum and not to decortication. In this theory the striatum holds back proprioceptively driven activity by its outflow to the pallidum, which is the efferent limb of the route from the thalamus for proprioceptive - associated movement That the striatum receives a large system of fiber projections from the frontal cortex is now a definitive observation and since part of the fronto-striatal system originates and ends in those areas which if damaged cause hyperkinesia, it seems reasonable that both a structural and functional relationship exist.

One part of the limbic lobe, the orbital frontal region, projects on the hypothalamus and this system may also be implicated in the inhibition of behavior since hyperactivity results following its destruction [8, 13]. Primitive motor mechanisms of the visceral brain and olfactory system have been described, the exploratory or primitive search behavior being a function of olfaction used for the detection of food. The experimental work of Bailey [12] and others [9] placing lesions in the interpeduncular nucleus and habenulopeduncular tract resulting in obstinate progression indicates that the olfacto-habenulo-peduncular system is involved in motility. Physiological drives have been studied in relationship as influenced by stimulation by hormones, illumination, temperature and nutritional requirements and an internal activity drive quite apart from that reaction to any type of stimulation, may also be a neural basis for abnormal hyperactivity.

One might postulate that the site of action for methylphenidate is on the inhibitor systems such as the reticular formation, striatum, cortical regions, or limbic areas and its beneficial effect is produced by stimulation of such inhibitory mechanisms which in turn then suppress the hyperkinetic behavior. Further studies of experimentally-induced hyperactivity in animals should be of value both in the elucidation of the mechanism of action and in the development of potential new therapies for hyperactive behavior in children.

ACKNOWLEDGEMENTS

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SUMMARY

The beneficial effects of methylphenidate (Ritalin) in children with hyperkinetic behavior and certain perceptual disorders are well documented, but the specificity of response in relation to the etiology and degree of hyperactivity has not been fully elucidated. In the present study, the clinical impression has been confirmed that patients with brain damage are those most likely to respond to methylphenidate, and effectiveness has been related to the level of motor activity.

In initial laboratory evaluations, the locomotor activity of mice with prefrontal destructive lesions was measured by means of cages fitted with photoelectric cells; the mean activity counts on three successive days before operation were compared with measurements recorded for similar periods of time during the post-operative period and after treatment with methylphenidate. The activity expressed as mean activity counts per ½ hour period of observation was 568 ± 30 before operation. Post-operatively, the activity was increased in varying degrees up to four times the pre-operative measurements, the magnitude of the change being greater in animals with bilateral lesions than in those with unilateral prefrontal brain damage. In six animals with the most severe hyperkinesia, methylphenidate caused a significant suppression of activity (t, 9.4 - $P < .01$); the mean activity counts and standard errors per ½ hour in the pre-operative period, post-operatively, and after treatment with the drug post-operatively were 592 ± 52, 1932 ± 45, and 1334 ± 142, respectively. In 25 animals with lesser degrees of activity following operation, methylphenidate had a significant stimulant effect; a post-operative mean activity count of 793 ± 49 was elevated to 1769 ± 69 (t, 15.4: $P < .01$). A similar stimulant effect was observed in normal animals in previous studies in our laboratory.

In clinical evaluations, the motor activity of 30 school children with hyperkinesia and learning disabilities was measured by means of an actometer before and during treatment with methylphenidate or placebo in a double-blind controlled trial. Neurological signs of minimal brain dysfunction were elicited in all except one patient. A history of brain injury or other cerebral damage was obtained in 17 (57 %)

patients, and the electroencephalogram was abnormal in 15 (50 %). The level of activity before therapy varied from a maximum of 38 actometer units in the most active to 2 units in the least active child in the group. Suppression of activity by methylphenidate was observed in the patients with the higher levels of activity whereas a stimulant effect occurred in those with lower activity levels. Patients with the highest incidence of abnormal neurological signs tended to be most active and were most likely to benefit from methylphenidate. It is concluded that measurements of the degree of motor activity and examination for signs of neurological abnormalities may be used to predict responsiveness to methylphenidate in children with hyperkinetic behavior and minimal brain dysfunction.

RESUMEN

Los efectos beneficiosos de metilfenidato (Ritalin) en niños de conducta hiperquinética y ciertos desarreglos perceptuales están bien documentados, pero no ha sido plenamente definida la especificidad de la respuesta en relación con la etiología y el grado de hiperactividad. En el presente estudio, la impresión clínica ha sido confirmada, de que los enfermos con daño cerebral son los más propensos a responder al metilfenidato, y ha sido relacionada la efectividad con nivel de la actividad motora.

En las evaluaciones iniciales de laboratorio, se medía la actividad locomotora de los ratones con lesiones destructivas prefrontales por medio de jaulas equipadas con células fotoeléctricas; los recuentos de actividad media en tres días sucesivos antes de operar, fueron comparados con medidas registradas por espacios similares de tiempo durante el período post-operatorio y después de tratamiento con metilfenidato. La actividad expresada como recuentos de actividad media, por períodos de observación de ½ hora fue de 568 ± 30 antes de la operación. Post-operatoriamente, la actividad aumentó en grado variable hasta cuatro veces las medidas pre-operatorias, la magnitud del cambio siendo mayor en animales con lesiones bilaterales que en aquellos con daño cerebral prefrontal unilateral. En seis animales con la más severa hiperquinesia, el metilfenidato causó una supresión significativa de actividad (t, 9.4: $P < .01$): los recuentos de actividad media y errores standard por ½ hora en el período pre-operatorio post-operatoriamente, y después de tratamiento con la droga post-operatoriamente fueron 592 ± 52, 1932 ± 45, y 1334 ± 142, respectivamente. En 25 animales con menores grados de actividad después de la operación, el metilfenidato tuvo un efecto estimulante significativo: un recuento de actividad media post-operatoria de 793 ± 49 fue elevado a 1769 ± 69 (t, 15,4: $P < .01$). Un similar efecto estimulante fue observado en animales normales en estudios previos en nuestro laboratorio.

En las evaluaciones clínicas, la actividad motora de 30 niños escolares con hiperquinesia e incapacidad de aprendizaje fue medida por medio de un actómetro antes y durante el tratamiento con metilfenidato o un placebo en un estudio realizado al modo "doble ciego". Signos neurológicos de disfunción cerebral mínima fueron observados en todos excepto en un paciente.

Una historia de traumatismo cerebral u otro daño cerebral se comprobó en 17 (57 %) pacientes, y el electroencefalograma fue anormal en 15 (50 %). El nivel de actividad antes de la terapéutica variaba de un máximo de 38 unidades de actómetro en el más activo a 2 unidades en el niño menos activo en el grupo.

Se observó la supresión de actividad por metilfenidato en los pacientes con los más altos niveles de actividad, mientras que un efecto estimulante ocurrió en aquellos con niveles de actividad más bajos. Los pacientes con la más alta incidencia de signos neurológicos anormales tendían a ser más activos y eran los más propensos a beneficiarse del metilfenidato. Se concluye que las medidas del grado de actividad motora y el examen para signos de anormalidades neurológicas pueden usarse para pronosticar la sensibilidad al metilfenidato en niños con conducta hiperquinética y disfunción mínima del cerebro.

RÉSUMÉ

Les effets bienfaisants de la metilfenidate (Ritalin) chez les enfants de comportement hyperkinetique et certains dérangements de perception sont bien étudiés, mais il n'a pas été pleinement définie la spécificité de la réponse en relation avec l'étiologie et le degrée d'hyperactivité. Dans la présente étude, l'impression clinique a été confirmée, de ce que les malades avec dommage cérébral, sont les plus prédisposés à répondre à la metilfenidate et a été relationé l'effectivité avec niveau de l'activité motrice.

Dans les evaluations initiales de laboratoire, on mesuré l'activité motrice des souris avec lésions destructives préfrontales par le moyen de cages équipées de cellules photoelectriques; les vérifications d'activité moyenne sur 3 jours successifs avant d'opérer, furent comparées avec mesures enrégistrées par espaces de temps similaires pendant la période post-opératoire et après traîtement avec metilfenidate. L'activité exprimé comme verification d'activité moyenne pour périodes d'observation d'une ½ heure fut de 568 ± 30 avant l'opération. Post-opératoirement, l'activité a augmenté en degré jusqu'à 4 fois les mesures pré-opératoires, l'importance du changement fut supérieur chez les animaux avec lésions bilatérales que chez ceux que avait un dommâge cérébral unilatéral. Sur 6 animaux avec la plus importante hyperkinesie, le metilfenidate a causé une supression significative d'activité (t, 9.4: P <..01): les vérifications de l'activité moyenne et les erreurs standard par ½ heure en période de pré-opératoire et post-opératoire et après un traîtement avec la drogue post-opératoire furent de 592±52, 1932±45, et 1334±142, respectivement. Sur 25 animaux avec moins de degrés d'activité après l'opération, le metilfenidate a eu un effet stimulant significatif: une vérification d'activité moyenne post-opératoire de 793 ± 49 fut élevé jusqu'à 1769 ± 69 (t, 15,4: P <.01). Un effet stimulant similaire fut observé chez des animaux normaux en études préventives dans nôtre laboratoire.

Dans les evaluations cliniques, l'activité motrice de 30 enfants scolaires avec hyperkinesie et capacité d'apprentissage fut mesuré par moyen d'un actomètre avant et durant le traîtement avec metilfenidate ou un placebo dans une étude réalisée à la manière "Double Aveugle". Des signes neurologiques de dérangement cérébral minimum furent observés sur tous à l'exception d'un patient.

Une histoire de traumatisme cérébral ou autre dommage cérébral a été prouvé chez 17 patients (57 %) et l'électroencephalogramme fut anormal en 15 (50 %). Le nivel d'activité avant le traîtement variait d'un maximum de 38 unités d'actomètre chez le plus actif, à 2 unités chez l'enfant moins actif du groupe.

On a éprouvé la supression d'activité par metilfenidate chez les patients qui avaient les plus hauts niveaux d'activité, alors qu'un effet stimulant se produisait chez ceux dont le niveau d'activité était le plus bas. Les patients avec la plus haut incidence de signes neurologiques anormaux tendaient à être plus actifs et étaient les plus prédisposés à bénéficier du metilfenidate. On conclue que les mesures du degré d'activité motrice et l'examen par signes d'anormalité neurologiques peuvent s'utiliser pour pronostiquer la sensibilité au metilfenidate chez les enfants avec comportement hyperkinetique et dérangement minimum du cerveau.

ZUSAMMENFASSUNG

Die nützlichen Effekte von Methylphenidat (Ritalin) bei Kindern mit hyperkinetischer Leitung und gewissen wahrnehmbaren Unregelmässigkeiten sind gut dokumentiert, aber die Antwort in Bezug auf die Actiologie und den Grad der Hyperaktivität sind noch nicht völlig deffiniert worden. Bei der gegenwärtigen Studie ist die klinische Impression bestätigt worden, dass die Kranken mit Gehirnschäden die geeignetsten sind, um mit Methylphenidat zu reagieren, und konnte so die Relation des

Effektes in Bezug auf den Stand der motorischen Aktivität bestätigt werden.

Bei den Initialschätzungen im Laboratorium wurde die lokomotorische Aktivität der Mäuse mit präfrontalen destruktiven Schädigungen mit Hilfe von Käfigen mit photoelektrischen Zellen gemessen; die Nachzählung der mittleren Aktivität während drei Tage hintereinander vor der Operation wurde verglichen mit registrierten Massen entsprechend der eit während der der postoperativen Periode, und nach der Behandlung mit Methylphenidat. Die Aktivität, erhalten durch die Nachzählung der mit leren Aktivität während der Beobachtungs periode von ½ Stunde, war 568 ± 30 vor der Operation. Postoperativ erhöhte sich die Aktivität in variablem Grade bis zu viermal der präoperativen Masse, wobei die Stärke der Differenz grösser war bei Tieren mit bilateralen Schäden gegenüber denen mit präfrontalen unilateralen Gehirnschäden. Bei sechs Tieren mit stärkster Ryperkinese verusachte das Methylphenidat eine signifikante Supression der Aktivität (T, 9.4: $P < .01$): die Nachzählungen der medianen Aktivität und Standardirrungen für ½ Stunde bei der präoperativen Periode post-operativ, und nach der Behandlung mit der Droge postoperativ waren 592 ± 52 1932 ± 45, und 1334 ± 142 respektiv. Bei 25 Tieren mit gerirgeren Graden von Aktivität nach der Operation, hatte das Methylphenidat einen signifikativen stimulierenden Effekt; eine Nachzählung der mittleren postoperativen Aktivität von 793 ± 69 (t, 15,4: $P < .01$). Ein gleicher stimulierender effekt wurde bei normalen Tieren beobachtet während vorhergehender Studien in unserem Laboratorium.

Bei den klinischen Auswertungen wurde die motorische Aktivität bei 30 Cchulkindern mit Ryperkinese und Lernunfähigkeit mit Hilfe eines Aktometers vor und nach der Behandlung mit Methylphenidat oder mit einem Vergleichstier in einem Versuch nach Art des "doppelt blind" gemessen. Neurologische Zeichen einer Minimum Gehirndysfunktion wurden in allen Fällen mit Ausnahme von einem Patienten beobachtet.

Eine Historie von Gehirntrauma oder anderer Gehirnschädigung wurde bei 17 (57 %) Patienten beobachtet, und das Elektroenzephalogramm war anormal bei 15 (50 %). Das Niveau der Aktivität vor der Therapie schwankte zwischen einem Maximum von 38 Einheiten des Aktometers bei dem aktivsten und 2 Einheiten bei dem am wenigsten aktiven Kinde der Gruppe.

Die supression der Aktivität durch Methylphenidat wurde bei der Patienten mit den höchsten Stand der Aktivität beobachtet, währenddem ein stimulierender Effekt bei denen sich erwies mit einem niedrigeren Aktivitätsniveau. Die Patienten mit der höchsten Anzahl von anormalen neurologischen Zeichen zeigten sich aktiver und waren die geeignetsten für die Erfolgswirkung des Methylphenidat. Daraus wird geschlossen, dass die Masse der motorischen Aktivitätsgrade und das Examen der neurologischen Anormalitäten benutzt werden kann, um die Sensibilität gegenüber von Methylphenidat bei Kindern mit hyperkinetischem Kondukt und minimaler Gehirndysfunktion zu prognostizieren.

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Some Considerations and Implications of the Monoamine Theory of Sleep and Wakefulness.

Discussion of Prof. Jouvet's paper (page 141)

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Before I comment upon the mass of interrelated data and interpretations that are collectively the monoamine theory of sleep and wakefulness, I would like to remind the audience that, impressive though it may be, it is not the only contribution of the Lyon group. For example, they were the first to describe the EMG suppression associated with REM sleep and the fascinating PGO waves. These findings, together with the extensive neuroanatomical studies of the late 50's and early 60's, were really responsible for the conceptual quantum jump of the duality of sleep. They have pioneered in ontogenetic and phylogenetic studies. They have begun to study the inheritance of sleep characteristics. They have made important clinical contributions, both practically and conceptually. In short, if Jouvet's laboratory had never seen a drug or a test tube, it would still rank as one of the world's outstanding centers of sleep research.

A complete theory of sleep and wakefulness must account for behavioral and neurological facts of prodigious scope and complexity. The possibilities for controversy revolving around single points in the theoretical network are almost infinite. However, it is absolutely clear that the monoamine theory of sleep and wakefulness is by far the most ambitious and successful attempt to explain these states and how they operate, that anyone has yet propounded. Furthermore, while Dr. Jouvet has had the courage to be comprehensive in his scope, he has never been rigid. New data, usually from his own laboratory, has always been taken into account, leading to modification when appropriate, or, in other cases, the frank admission of uncertainty in interpretation.

In order to add perspective to this discussion, we should mention one or two little imperfections in Jouvet's approach to the problems of sleep and wakefulness. For example, his attitude toward stimulation may not seem perfectly logical. Those of you who have heard his discussion of the early locus coeruleus stimulations experiments will know what I mean. During this past year, we were trying to produce feline cataplexy with bilateral coeruleus stimulation and, knowing him well, I actually felt guilty! A second little imperfection is his attitude toward the thalamus. I became aware of this during a dramatic confrontation between Michel and Dr. Dominic Purpura at Maele in the summer of 1971. I mention this mainly for historical purposes, and the illustrations will offer a glimpse of certain original documents which have never before been released to the public.

Figure 1 shows an original drawing by Dr. Purpura to illustrate two views of Dr. Jouvet's theories. The house on the left is

Purpura's concept of a theory that does not take into account the synchronizing mechanisms of the thalamus, Purpura [21]. The house on the right, which does include these mechanisms, is where Purpura urged us all to live. "Where is the thalamus in your theory?" was his final challenge to Michel. Figure 2 is a photograph of a remarkable document. I believe it is the first time Michel Jouvet actually formulated his theory, blindfolded. At any rate the confrontation ended on a note of high excitement. "*There* is the place of the thalamus in my theory!" shouted Jouvet, as he pointed to the small circle above the hemispheres.

Figure 1

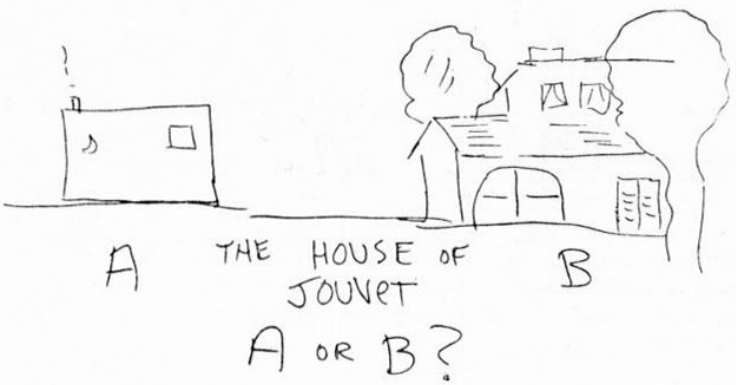


Fig. 1. — *A symbolic representation of the monoamine theory of sleep and wakefulness by Dominic Purpura. Note signature of the artist at lower left of drawing.*

Figure 2



Fig. 2. — *A quasi-symbolic representation of monoamine pathways and brain structures. The drawing is unsigned but hieroglyphic analysis has confirmed that the artist is Michel Jouvet. Th, thalamus; DA, dopamine; NA, noradrenaline; QS, NREM; AS, REM.*

The foregoing remarks obviously contain a touch of levity. However, if we give serious scrutiny to the "house of Jouvet" and, in particular, to the remarkable scope and complexity which I have already pointed out, we are forced to admit that it would be impossible to demolish this structure, or definitively affirm its existance with one or two well designed experiments. Jouvet [13] himself, has said: "The ideal experiment remains to be done. In fact, such an experiment is almost impossible at the present time." With regard to serotonin and slow wave (SWS or NRM) sleep, a first approximation would be a clearcut demonstration that the onset and maintenance of natural SWS was ineluctably associated with the release of serotonin at presynaptic sites or with transient elevation of its metabolytes. Sinho, *et al.* [25], have made an indirect attempt to show this by comparing regional brain levels of serotonin in cats sacrificed during wakefulness, after 10 minutes of SWS, or after 5 minutes of paradoxical sleep (PS or REMS). Cortical serotonin appears to be reduced after 10 minutes of SWS compared to wakefulness. This is illustrated in Figure 3.

We felt that this change could have been brought about by a massive release of cortical serotonin, most likely due to an increase in impulse traffic over serotonergic synapses during the specified time. How-

Figure 3

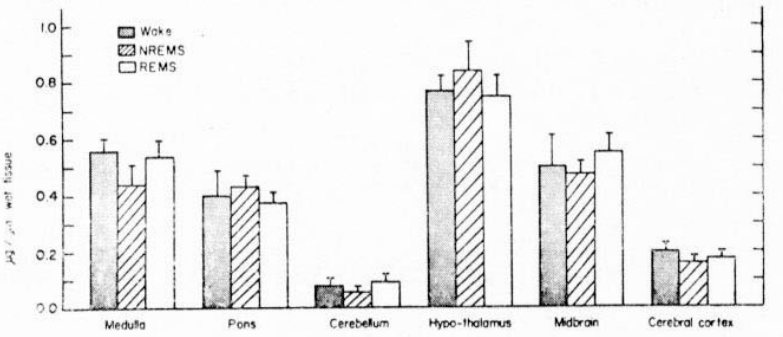


Fig. 3. — *5-HT contents (mean ± SE, μg/g) of different brain areas during wakefulness, after 10 minutes of NREM sleep, and after 5 minutes of REM sleep. Significance of difference between 2 groups was tested by Student t test. Asterisk marks a significant difference at level of* $p < .05$.

ever, since this was one of only two significant changes ($p < .05$) out of 36 (6 brain areas x 3 sleep-wakefulness states x 2 amines) by the Student/ "t" tests, the results should be viewed with considerable caution. We are now engaged in attempting to refine this crude approach by utilizing push-pull cannula techniques, although these, too, are not without their drawbacks.

Another approach has utilized frequent sampling of CSF during changes in sleep and wakefulness. In patients with low pressure hydrocephalus, Wyatt, *et al.* [30], obtained preliminary results showing that 5HIAA levels were higher during SWS than either wakefulness or PS. On the other hand, in the cat, Radulovacki [22] found no differences in 5HIAA levels during wakefulness, SWS, or PS utilizing samples obtained from chronically implanted cysterna magna cannulae. Stimulation of the dorsal raphe nucleus in the rat results in a prolonged increase of forebrain 5HIAA and a slight decrease of serotonin, Sheard and Aghajanian [24], Eccleston, *et al.* [4], and some investigators claim to have induced sleep in the rat by stimulating these areas, Kostowski and Giacalone [14], Gumulka, *et al.* [7]. Unfortunately, no one has been able to produce natural SWS in the cat by stimulating raphe nuclei to my knowledge. We have made many attempts ourselves. Parenthetically, we have compared the results of raphe dorsalis stimulation with stimulation at other sites in the cat, Jacobs, *et al.* [12], and have produced an effect that mimics a presumed function of serotonergic neurons, namely, gating of PGO waves. However, the complex nature of the phenomena under consideration means that in all these approaches, positive results are compelling, but negative results are inconclusive.

What about unit discharge? Here again, the results are interesting but difficult to interpret. Jouvet [13] has maintained that the anterior raphe neurons are mainly responsible for SWS. Our first naive prediction would surely be that units in the dorsal raphe would show increasing discharge rates coincident with the onset of SWS. On the contrary, McGinty, *et al.* [16], have shown in the cat that these units fire regularly during wakefulness and slow down slightly at the onset of SWS. In addition, during PS the units stop firing altogether. McGinty, *et al.* [16], suggest that dorsal raphe serotonergic neurons may act to constrain waking behaviors and/or events that interfere with sleep, in particular, they suggest that the firing patterns are compatible with the gating functions attributed to serotonergic neurons *vis a vis* PGO activity, Dement, *et al.* [3]. However, this interpretation is complicated by the fact that dorsal raphe neurons do not appear to project to the pontine areas that would be necessary to exert a re-

gulatory effect on putative phasic generators.

At this point, I would like to raise two issues which I regard as very important in the consideration of mechanisms of sleep and wakefulness. The first is simply that, when all is said and done, we really know very little about the nature of behavioral states and how transitions are accomplished. Falling asleep is easily the most dramatic and profound functional alteration in the mammalian repertoire. In an instant, the organism becomes blind, deaf, immobile, without volition, etc. We assume that a sudden, mysteriously initiated flood of serotonergic impulses just "turns off" the waking brain, overcomes the powerful waking influences, and so on. We look at that moment when slow waves and spindles appear in the EEG and search for meaningful biochemical, and neurophysiological correlations. However, for all we know, the "work" of a sleep system is accomplished during wakefulness, and the sleep system actually "eases off" when the transition is accomplished. In this case, the results of McGinty, *et al.* [16] would be just as predicted. Nobody is more aware of the deficiencies in our descriptive knowledge than Michel Jouvet and he consistently devotes a major share of his resources to this problem, ranging from obtaining greater precision in feline monoamine neuroanatomy, Maeda, *et al.* [15] to outlining the infinite neurophysiological nuances of the PGO waves and eye movement potentials, Gadea-Ciria and Jouvet [5]

The second important issue is the possibility of interactive reciprocity of the monoamine systems which Jouvet specifically proposes. In his most explicit statement, Jouvet [13], he maintains that it is possible to have two causes of insomnia and two causes of hypersomnia. Thus, insomnia may result from serotonergic deficiencies as after lesion of raphe neurons, or it may be induced by the activation of the ascending noradrenergic pontomesencephalic system. Contrariwise, hypersomnia would presumably follow activation of serotonergic systems, or destruction of ascending noradrenergic neurons. The most beautiful demonstration of the interactive principle was carried out by Petitjean and Jouvet (1970) who showed that destruction of the dorsal noradrenergic bundle at the level of the isthmus was followed by profound increase in both SWS and PS, and most interestingly, by an increase of both tryptophan and 5HIAA in forebrain. This interactive possibility migh help to resolve certain apparent controversies. For example, many investigators have tested the effects of parachlorophenylalanine (PCPA) on sleep. In man, PCPA administration has produced no change in SWS, Wyatt, *et al.* [29], Chernik, *et al.* [2]. In the rat, Rechtschaffen, *et al.* [23] have reported essentially no change in SWS with various schedules of PCPA treatment although Mouret, *et al.* [18] had previously reported considerable reduction in SWS. We have found that high doses of PCPA administered daily to the hamster elicit no changes whatsoever in sleep parameters. On the other hand, Weitzman, *et al.* [27] have reported substantial reduction in SWS with PCPA in the monkey, and Bert [1] has recently reported similar findings in the baboon . Finally, we found that chronic administration of PCPA in the cat was initially associated with marked insomnia but after a few days, both SWS and PS reappear despite the maintenance of a very low level of brain serotonin, Dement, *et al.* [3]. I do not feel that this is necessarily negative evidence, or that we must invoke a serotonin "micropool". Rather, the most promising interpretation is surely that SWS returns because of a change in activity of noradrenergic waking systems either induced by PCPA itself, Stolk, *et al.* [26] or arising as a natural response to the prolonged change in activity of antagonistic serotonergic neurons. If these changes occurred with sufficient rapidity, they could even explain the complete absence of an apparent response to PCPA.

The major foundation of the monoamine theory is the impressive threeway correlation between brainstem lesion, forebrain monoamine level, and total sleep time for both serotonin and noradrenaline, Jouvet [13]. This is work of heroic dimensions that is not likely to be replicated in its entirety in the near future. However, some confirmation has been forthcoming from Morgane's laboratory, Morgane and Stern [17]. Overall,

catecholamines and wakefulness may be the monoamine pillar that rests on the firmest ground. In addition to the lesion studies, pharmacological intervention has been least controversial. In our own laboratory, Henriksen and Dement [9], continuous intravenous administration of AMPT has produced a profound hypersomnia in cats.

The initiation and maintenance of PS continues to present the greatest puzzle and challenge in terms of a comprehensive and consistent theoretical formulation. This is fascinating story in and of itself. However, since we have recently discussed the monoamine theory with reference to PS at both Strasbourg and Sardinia, Henriksen, *et al.*[10, 11] and since we are running out of both space and time here[0] we will forgo further analysis of the data.

The important matter to emphasize in this discussion is that an incredibly complex collection of brain and behavioral functions has been encompassed under a single theoretical umbrella which will both stimulate and guide research. The monoamine theory of sleep and wakefulness is an unprecedented intellectual achievement. Investigators all over the world will continue to test various parts of the theory and it will either gain certainty and acceptance as it stands, undergo some modification, or out of the work will come a new theory.

It is also because of Jouvet's work that at last we have a theory complete enough to guide clinical research. An example of what we can expect in the future is the recent description of several types of hypersomnia by Mouret *et al.* [19] in which they attempt to correlate the clinical findings with biochemical studies of the CSF would be predicted by the monoamine theory. Of particular interest is their "non-wakefulness syndrome" associated with a failure of homovanilic acid accumulation in CSF after probenecid. We, Guilleminault and Dement [9] have confirmed this description in one patient.

Figure 4 is an American headline that will give some idea of the scope of the clinical problems. Most remedies for sleep disturbances have been developed on a trial and more than a few of these compounds have done more harm than good e. g. barbiturates and methoqualone. Furthermore, neither these nor any other commercially available hypnotics induce normal sleep. It is noteworthy that several attempts have been made to treat insomnia more rationally utilizing Jouvet's constructs, Hartmann, *et al.* [8], Wyatt [28]. Dextro-amphetamine is probably the most rational alerting drug since, in low doses, its primary effect of wakefulness enhancement almost certainly involves release of noradrenalin from terminals. This effect is completely blocked by pretreatment with alphamethylparatyrosine in the cat and the rat, Jouvet [13]. Unfortunately, with such a theoretically excellent compound and even with a natural precursor such as 5-hydroxytryptophan, exogenous administration is associated with side effects and the development of tolerance. Nonetheless, further understanding of the pathophysiology and pathobiochemistry of the sleep disorders and the development of effective treatments urgently needed by millions of human beings must be guided by basic knowledge about sleep and wakefulness and a coherent theory of their mechanisms. It is in this area that the work of Michel Jouvet may have its farthest reaching implications.

Figure 4

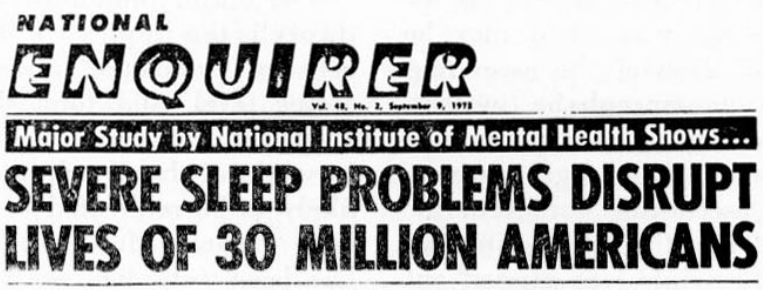

NATIONAL
ENQUIRER
Major Study by National Institute of Mental Health Shows...
SEVERE SLEEP PROBLEMS DISRUPT
LIVES OF 30 MILLION AMERICANS

Fig. 4. — *An American headline.*

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Disruption of Behavior in Cats by Chronic Amphetamine Intoxication

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Introduction

For almost 40 years now, since the introduction of amphetamine in the therapy of narcolepsy [24], the psychomotor effects of this and related compounds have been recognized as useful laboratory tools for the exploration of CNS mechanisms and widely utilized in neuropharmacology.

Measurements of amphetamine-induced locomotor activation and, in more recent years, of amphetamine-induced stereotyped movements in animals have yielded, when combined with pharmacological manipulation of the brain biogenic amines, valuable information on the functional nature and mechanisms of action of psychoactive compounds, as well as on the function of particular neurotransmitters [35]. In fact, these same aspects of the animal's motor output are currently employed for the evaluation of psychomotor stimulants [15] and in the screening of new agents with potential antipsychotic [16, 36] or antiparkinsonian activity [6].

The effects of amphetamine on the motor response rate in operant behavioral techniques have also been profitably used in pursuing an understanding of the behavioral mechanisms that underlie drug action [37]. However, although discrete, well-defined responses, such as the lever press, have proven sensitive to drug effects, they cannot reflect the variety of the evoked alterations and may allow misinterpretation of data if other dimensions of behavior are not considered simultaneously. Not only is the relationship of a single measure of motor activity to changes in patterning or to abnormal features in the animal's behavioral repertoire rarely simple, but the selectivity of the drug action (not to mention the influence of the environmental situation) adds to the complexity of the induced phenomena [3]. Fog [13] showed that the administration of amphetamine (1 mg/kg s.c.) or of morphine (1 mg/kg, s.c.) to rats provokes an increase in locomotor movements and rearing activity. The administration of amphetamine, however, inhibits social interactions and grooming, which are stimulated after the administration of morphine. Similarly, in the cat [23], oral treatment with amphetamine (2 mg/kg) or a like dose of H-610 (a morcamphane derivative with psychostimulant properties) produces an increase in locomotion. Whereas the latter compound also enhances hopping, climbing, and mewing, such

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responses are inhibited by amphetamine.

In a clinical context, while the relationship between singular phenomena produced in animals and observations in human pathologies are not readily apparent, the evaluation of drug-induced behavioral disorders at a molar level yields information of a more comparable order. Such a level of evaluation, however, confronts the researcher with both semantic and methodological problems.

From the semantic standpoint, the frequent, unqualified use of terms like "hyperkinesia", "chorea", "stereotypy", makes difficult the comparison of observations in different laboratories. Often the expression "extrapyramidal disorder", used as if it were a unity, is the magic phrase that opens the way to indiscriminate interpretations. If one hopes to draw parallels between experiments in animals and human pathologies, it is imperative to describe the morphological and qualitative characteristics of the alterations observed in such experiments, as well as the various combinations in which they appear.

From the methodological standpoint, devices usually employed in the quantitation of motor activity (jiggle cages, tread wheels, photocells, or the more sophisticated tuned oscillators) disregard significant qualitative information, as well as the very important postural component. These deficiencies can best be overcome by a direct observational technique that allows both qualitative assessment and the recording of phenomenological features. Such a technique was used in the experiments reviewed herein.

The current presentation is addressed to the development and evolution of motor abnormalities displayed by cats given amphetamine chronically. It attempts to delineate with clinical criteria the major components of the unfolding behavioral disruption. The stereotypic motor response to relatively large doses or to prolonged administration of amphetamine has been studied in a wide range of animals, including pigeons, guinea pigs, mice, rats, cats, and monkeys. Strong evidence has been obtained that the activation of dopamine is involved in eliciting this response [11, 25–27]. Less attention, however, has been given to associated motor disorders, including such dyskinetic manifestations as: retroflexion of the neck, sustained lifting and extension of a leg, and other abnormal postural phenomena in rats [10, 11]; bizarre dystonic postures and a dyssynchronous relationship of regional movements in cats [32, 12]; and myoclonic jerks, opisthotonic movements of the neck, head tremor, bruxism, and automatic movements of the orofacial region or of the extremities in monkeys [10, 11, 18, 19, 21].

Since it is likely that the motor effects of amphetamine reflect the dynamics underlying the intoxication process, all such alterations (including the stereotypic response) deserve further characterization. Assessment of their phenomenology may provide information germane to the behavioral states (schizophrenic-like psychosis, addiction) that the drug is known to produce in humans.

Methods

Phenomenological descriptions were obtained from a population of more than 60 female cats weighting between 2.5 and 3.5 kg that had been used (under similar experimental conditions) in the construction of a rating scale, the details of which are presented elsewhere [33]. Quantitative changes were formally evaluated, as described below, in a total of 12 animals stereotaxically implanted with electrodes in various subcortical nuclei. All animals were housed singly and fed *ad libitum* throughout the experiment. At least 2 weeks were allowed for recovery after surgery. Thereafter, each animal underwent a 5-day acclimation period during which it was left in the experimental setting for 2 hours each day. While in that setting, the animal received a daily intraperitoneal injection of saline (1 ml). Data collected on the fifth day (to be called Day 0) were used as control for changes elicited by handling during injection or by the injection itself. The experiments, conducted in a closed room, were monitored by means of a video camera focussed on the observational chamber - - a commercially available metal cage measuring 17.5 x 24 x 19.5 inches, to which a

wooden floor and a Plexiglas door and walls were attached.

After the 5-day acclimation period, the administration of methamphetamine hydrochloride was begun and continued for 11 days, the daily dosage being gradually increased from 15 to 35 mg/kg (as the free base). This amount was injected intraperitoneally in two equal doses at 8:00 A.M. and 4:00 P.M., so that the animals had 16 hours between days for recovery and sleep. No drug was given on the sixth and seventh days. This schedule is comparable to the "speed runs" noted in human addicts and carries less risk of mortality in cats than does continuous intoxication.

Each animal was placed in the observational chamber 20 minutes before the beginning of an experimental session. Phenomenological descriptions of the motor manifestations and simultaneous video tape and EEG recordings were made on Day 0, and on Days 1, 3, 8 and 11 of methamphetamine treatment. Data for each of these days were based on six 3-minute recording periods, one prior to the first injection of the day and the others at 20 seconds (immediate postinjection period or 00), 10, 20, 30, and 90 minutes after that injection. In order to evaluate the persistence of amphetamine effects after the cessation of dosage and to discriminate between conditioning to the experimental situation and conditioning to the injection itself, saline (1 ml) was injected intraperitoneally on Days 12 and 25. Recordings were taken before and immediately after the injection.

A time sampling procedure was applied to the rating of drug effects. Every 30 minute recording period was divided into eighteen 10-second observational intervals. Individual units of motor activity and function to be observed in each interval had been operationally defined and were scored, for postural features, on the basis of their duration. Both postural and kinetic motor components displayed were scored in relation to the animal's whole body and in relation to specific regions (head, trunk, legs, and tail). This approach allowed a very detailed appreciation of the drug effects. Finally, the scores for each individual item were transcribed onto data-processing cards to be organized and collated by computer.

Results

The compound nature of the motor alterations induced by chronic administration of amphetamine to the cat is illustrated in Table I, which shows the incidence of some of the rated motor items within the population of intervals for each of the given conditions in all animals. Individual consistent trends connected with the acute effects of the drug are apparent during any one day for most of the recorded items. Stereotyped movements and dystonia (camel-back phenomenon) appeared early and were the most conspicuous features throughout the intoxication cycle; ataxia and other hyperkinetic phenomena developed later. The cumulative effects of the drug differed from those in the naive animal in that features such as akathisia or shaking movements of the paws, not seen on Day 1, contributed to the total picture after repeated dosage. In addition, although stereotyped movements of the head decreased in frequency after successive days of treatment, the incidence of other motor manifestations (e.g., camel-back phenomenon, motor disjunction, ataxia) showed a progressive increase.

Initial Motor Effect and Its Evolution

About 5 minutes after drug administration on the first day of treatment, a reduction in spontaneous activity, along with increased arousal, muscular tension, and attentional focussing, was noticeable in most cats. Orienting movements of the head occurred rather frequently and usually had a hesitant quality. When physical approach to any point of interest was attempted at this time, its execution was slow and indecisive or it was arrested prior to completion.

In the early days of intoxication, it was often seen that the initial body posture displayed during the immediate postinjection period was sustained over some of the following periods. Several animals maintained either a crouched (all four legs flexed and

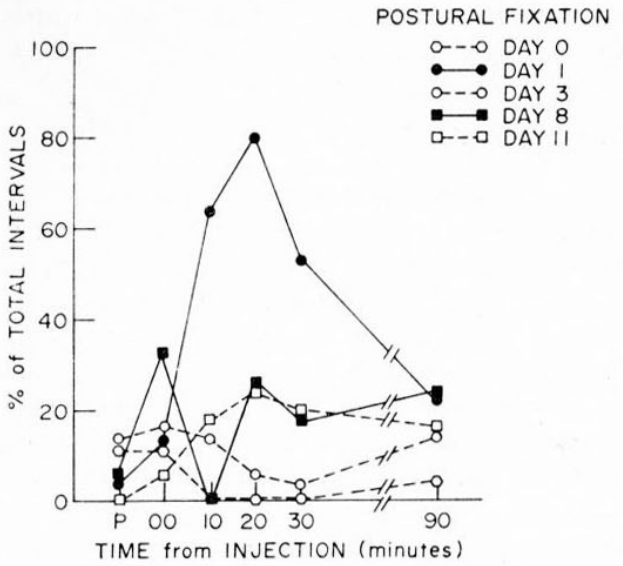


Fig. 1. — *Rate of occurrence of postural fixation given as a percentage of all intervals included under each condition. P = preinjection; 00 = immediately after injection.*

abdomen off the floor) or sphinxlike posture (abdomen on the floor) throughout an entire recording session. This decrease in motor initiative may be thought of as *inertia to execute movements or to change postures.* Figure 1 shows the mean occurrence of postural fixation (defined as the total absence of transient voluntary movements in the awake animal, with conservation of the body posture) in all subjects. The peak frequency was reached on Day 1, 20 minutes after injection. The decline in frequency beyond 20 minutes on Day 1 and the lower levels attained on subsequent days, correlate well with the progressive increase in transient activity and the development of hyperkinetic phenomena, to be described later. A relatively high incidence of postural fixation, however, was noted immediately after injection on Day 8, after two days in which no drug had been given. Inertia of the motor apparatus was also suggested by the occurrence of drooling in the presence of intact deglutitory mechanisms (usually in the early periods of each recording session) or by a "glazed" expression of the animal's face resulting from decrease of eye mobility, lack of blinking activity, and widened palpebral fissures.

After Day 1, reduction of postural adjustments could also be observed. For example, a cat standing with forelegs wide apart might not correct its progressive sliding on the floor until a loss of equilibrium was imminent — and even then, the postural adjustment would be only partially accomplished. Another animal might retain for too long a time an unusual sphinxlike posture, with one shoulder much higher than the other. When the animals walked, the paucity of automatic associated movements could be recognized by an almost fractionated propulsion or by a swaying and vacillating gait of ungraceful appearance.

In addition, motor disregard of segments of the body was noted. It appeared principally during the later stages of intoxication as a failure to place the hind paws properly, or as a tendency to "leave behind" the hindquarters, i.e., a series of stepping movements with the forelegs might be executed by an animal while the haunch retained a lying posture and was eventually dragged. Yet, neither muscular pain nor fatigue was responsible for this phenomenon, since active participation of the hindlegs in sporadic activities would follow.

The interaction of these features with concurrent dystonic phenomena, stereotyped or transient movements, increased spontaneous reflex activity, etc., contributed to a lack of proper relationship among postures or movements in two or more regions of the animal's body that we called "motor disjunction" (Table I).

Development of the Stereotyped Motor Response

The initial decrease in motor initiative, with a relative increase of orienting movements of the head induced by amphetamine, appeared to set the stage for the beginning of stereotyped motion at the head-neck region. Usually, a movement subserving shifts of attentional focus was slowly repeated in a back and forth sequence that acquired rhythmicity, the evolving pattern being related to the nature of the initial activity. Thus, an animal lying on its side might start a hindlimb grooming response but stop suddenly before the leg reached the mouth. This leg might then remain out-

SOME INDUCED MOTOR ALTERATIONS AFTER CHRONIC AMPHETAMINE TREATMENT IN THE CAT

MOTOR ALTERATION	C* N=876	DAY 1 N=1260				DAY 3 N=1169				DAYS 6 & 7	DAY 8 N=504				DAY 11 N=960				DAY 12* N=270		DAY 25* N=108	
		PRE	00	10-30	90	PRE	00	10-30	90		PRE	00	10-30	90	PRE	00	10-30	90	PRE	00	PRE	00
HYPERKINESIA																						
Head Stereotyped Mvts.																						
Minutia-Search Pattern	0.3	0.5	7.6	22.3	33.8	0.0	0.0	16.0	13.7		0.9	15.8	49.5	55.6	3.3	10.5	31.8	43.7	11.2	32.5	0.0	13.0
Up-and-Down Pattern	0.0	0.0	0.0	23.3	18.7	0.0	7.2	12.1	7.1	No	0.0	6.5	31.7	50.0	8.9	9.3	19.5	6.9	7.4	13.9	0.0	0.0
Side-to-Side Pattern	0.0	0.0	0.0	36.7	21.2	9.6	11.6	20.2	9.6		0.7	16.6	43.5	0.0	0.0	0.0	4.1	7.6	0.0	0.0	1.9	1.9
Balinese Pattern	0.0	0.0	0.0	0.0	9.1	0.0	0.0	7.4	0.0	Drug	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Others	0.0	0.0	0.0	8.3	9.1	0.0	0.0	0.0	0.0		0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Pivoting Mvts.	0.1	0.0	0.0	0.0	7.6	0.0	0.0	9.9	11.2	Administration	0.9	0.0	19.9	22.3	0.6	0.0	19.1	18.1	0.0	0.0	0.0	3.7
Paw-shaking Mvts.	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.0		0.0	0.0	0.0	0.0	0.6	0.6	1.5	4.2	0.0	0.0	0.0	0.0
Akathisia	0.0	0.0	0.0	0.0	0.0	0.0	0.0	25.1	25.9		0.0	0.0	23.6	0.0	23.5	20.4	43.4	50.2	4.9	33.3	0.0	0.0
DYSTONIA																						
Camel-Back Phenomenon	10.0	8.3	13.6	55.5	54.5	11.1	39.4	67.0	70.6		5.9	60.2	66.6	97.2	54.7	77.2	82.2	97.2	54.9	84.3	33.3	100.0
Hunching-Back Mvts.	0.0	0.0	0.0	2.6	38.9	0.0	0.0	12.9	8.6		0.0	0.0	25.9	30.6	4.5	0.0	4.6	9.0	0.0	0.0	0.0	0.0
Leg Extensor Posturing	0.1	0.0	3.0	2.8	0.0	0.0	1.1	1.1	1.0		0.9	0.0	0.0	0.0	1.2	0.0	0.4	2.1	0.0	2.8	0.0	0.0
MOTOR DISJUNCTION	0.0	0.0	0.0	16.0	45.5	0.0	4.4	27.8	24.9		3.7	4.6	41.7	36.1	12.8	14.8	1.7	12.5	0.0	27.8	0.0	0.0
ATAXIA	0.0	0.0	0.0	2.8	18.2	0.0	0.0	30.8	60.4		0.0	14.8	40.3	75.0	30.2	35.2	71.3	87.5	33.3	50.0	0.0	0.0

TABLE 1. — Some Amphetamine-Induced Motor Alterations

Entries in the table represent the rate of occurrence of the indicated items as percentage of all intervals included under the given condition. C (Control) = All conditions on day 0; PRE = preinjection condition; 00 = condition immediately after injection; 10-30 = all intervals in the 10—, 20—, and 30—minute postinjection conditions; 90 = the 90—minute postinjection condition.

stretched as in a cateleptic posture (leg-extensor posturing, Table I) for many minutes. A sniffing stereotypy might evolve out of this "abortive grooming response" by the locking-in of the initial head movement toward the outstretched limb.

Motor stereotypy appeared on Day 1 within 15 minutes after the amphetamine injection. It was invariably induced in all 12 subjects, although 3 of them failed to show it on Day 3 and 1 failed to on Day 8. These animals did, however, remain in postural fixation for most of that time. The mean occurrence of stereotyped movements across days and conditions in all animals is illustrated in Figure 2. Maximum levels were reached on Day 1 at 30 minutes and on Day 8 at 20 minutes after injection. The high levels seen on Day 8 might be explained by replenishment of the depleted dopamine stores during Days 6 and 7 (when no drug had been administered), plus a low norepinephrine/dopamine ratio (due to the slower synthesis of norepinephrine) that has been shown to be associated with stereotypy [14]. A variation in the time course of the stereotyped response across days is revealed by a fall-off after 30 minutes on Day 1 and after 20 minutes on Day 3 that might be attributable to decreased dopamine turnover, due to a negative feedback from the stimulated dopamine receptor, with consequent inability to maintain the amphetamine-induced stereotypy.

Stereotyped movements unrelated to the acute effects of the drug is noticeable in the preinjection and the immediate postinjection periods on days following Day 1. They reflect an "accidental conditioning" effect [9] triggered by the stimuli associated with the experimental setting. On Days 12 and 25 (saline injection), the predominance of the conditioned response to the injection itself is demonstrated. Similar phenomena were observed with respect to such autonomic responses as salivation and pupil dilation.

Characterization of the Stereotyped Motor Response

In our experimental setting, the amphetamine-induced stereotypy was predominantly a regional activity. *Stereotyped head movements* were usually repeated in a regular and rhythmic sequence, describing paths of displacement recognizable as kinetic configurations. These were neither many nor varied, so we were able to individualize and define them. The four most frequently observed (Figure 3) were named: (a)

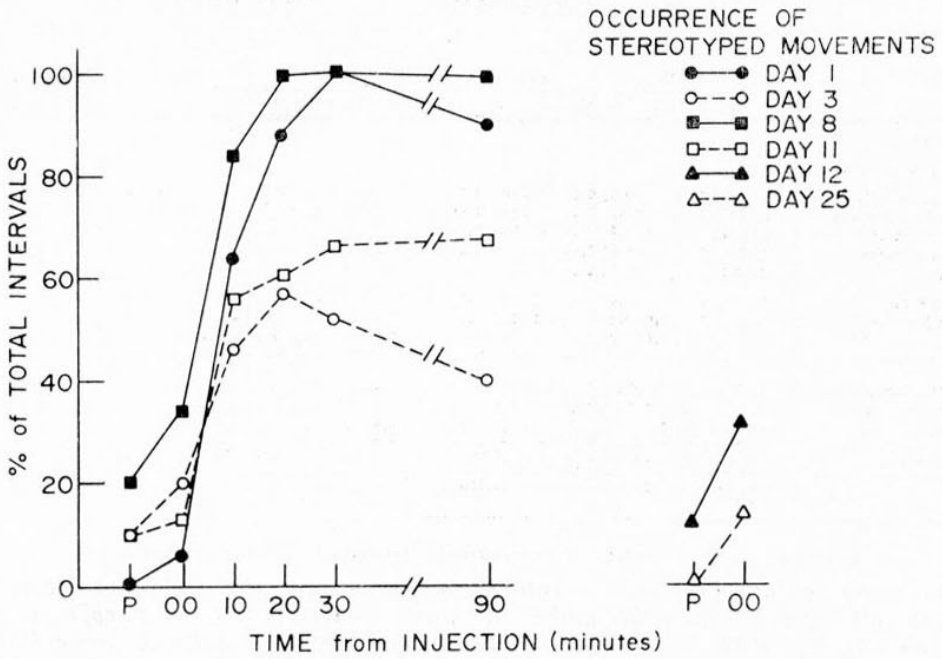


Fig. 2. — *Intervals in which any stereotyped movement was observed, given as a percentage of the total number of intervals rated under each experimental condition. P = preinjection; 00 = immediately after injection.*

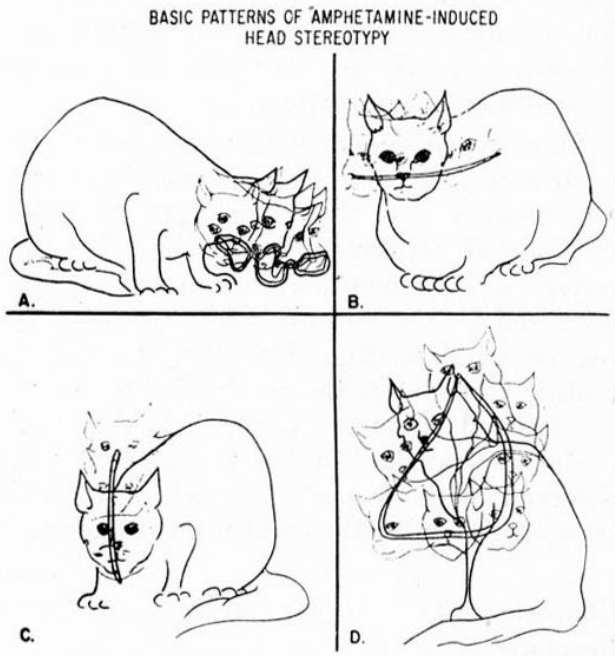


Fig. 3. — *Basic patterns of amphetamine-induced head stereotypies:* (A) *minutia-search;* (B) *side-to-side;* (C) *up-and-down;* (D) *Balinese.*

minutia-search pattern (pecking-like head movements executed as if the cat were sniffing out a tiny morsel of food); (b) side-to-side pattern; (c) up-and-down pattern; and (d) Balinese pattern (circumduction head-neck movement around the base of the neck, in which the tip of the animal's nose describes a more or less irregular ovoid or circular path). Side-to-side, Balinese, and up-and-down patterns are formed by head-neck movements that normally orient the snout to a position for sniffing activity. Alternatively, these movements can orient the head for visual regard. The spontaneous (unrelated to drug) occurrence of sniffing activity similar to the minutia-search pattern was recorded during control and Day 1, immediately after injection (Table I). Evaluation of the four basic patterns and of other head stereotypies showed a reduction in the number of patterns occurring toward the later stages of the intoxication cycle. On each recording session, the configuration termed minutia-search appears to be more sustained response than the other patterns and remains into the last recording period as the predominant one.

Stereotypies of the trunk and/or legs usually consisted of selected forms of locomotion such as: pivoting (oscillating movement of the trunk with the forelegs stepping to alternate sides of the relatively fixed hindlegs); circling; leg repositioning; backward and forward stepping pumping (up and down displacement of the trunk due to successive flexion and extension of all four

legs simultaneously without their being lifted from the floor); hunching, etc. Pivoting and pumping movements had a strong compulsive quality and were long lasting. The other stereotypies were usually of short duration and were frequently interrupted by the increasing motor reactiveness manifested in the later periods.

Figure 4 illustrates the distribution of stereotyped movements in the head, trunk, or leg regions across days. Head stereotypies were not only the most prominent, but were also the first to appear. Body stereotypies were seen in the later periods of Day 1, and in earlier periods on subsequent days. On Days 3 and 11, their incidence did not

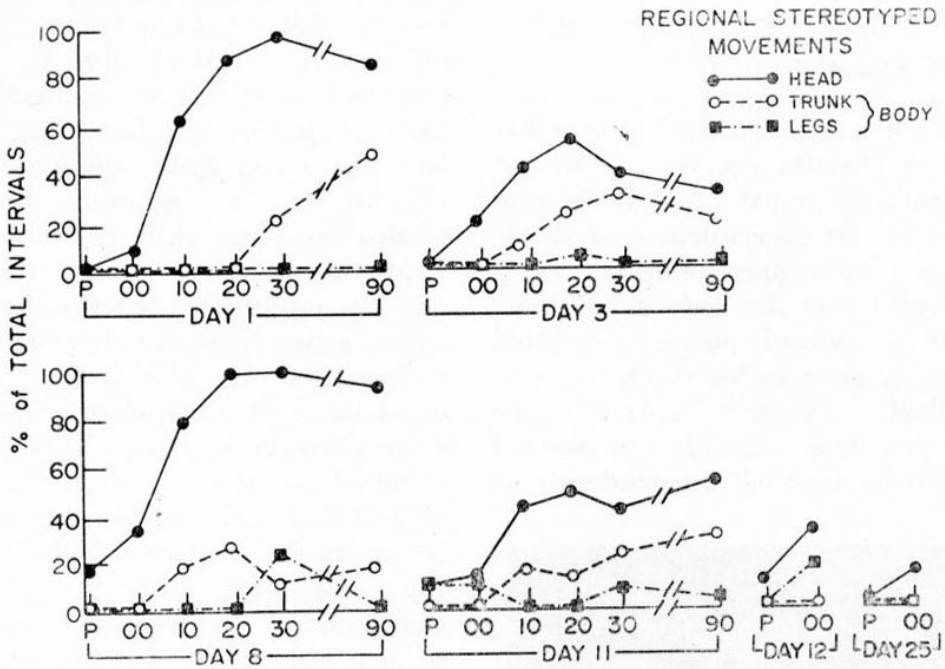


Fig. 4. — *Rate of occurrence of stereotyped movements in the head and body (trunk and leg regions), given as a percentage of the total number of intervals rated under each condition. P = preinjection; 00 = immediately after injection.*

decrease to the same extent as did that of head stereotypy, which suggests that different mechanisms may underlie the two types of stereotypies (*e.g.* differential catecholamine effect in the naive versus the depleted supersensitive animal). Interestingly, the development of the body stereotypies was observed to be related to reaching a certain level of arousal and reactivity.

Occasionally, *simultaneous regional stereotyped movements* develop. Thus, in a standing animal with an intense side-to-side head stereotypy, the lateral displacement of the head might increase progressively. In such case, stereotyped pivoting is started, but the head stereotypy persists for a while before dropping out. If the animal is not standing, complex stereotypy may develop with time from the increasing dystonia and the earlier mentioned deficiency in postural adjusting movements and motor disregard. For example, an up-and-backward looking movement of the head forcibly directed toward the posterior end of the body might be incorporated suddenly into an ongoing head stereotypy. Due to an increasingly shorter return phase, this looking component would, in time, induce a widebased stance of the forelegs and a progressive lateral curving of the trunk. If the animal was sitting, the hindquarters would fall on a side and lie motionless, with an outstretched hindlimb in a cateleptic posture. Pushing-up movements of the forequarter, along with sporadic repositioning of one foreleg, would then be included in the total picture. Finally, after several minutes of these forced activities, the increasing curvature of the trunk would cause the disregarded hindquarter to be dragged along. Such complex

stereotyped and disjunctive activity might persist for as long as 20 minutes, so that the animal's orientation in the cage would make several 360-degree turns. This progression illustrates the presence of a hypokinetic background and the high degree of paroxysmal compulsion attached to amphetamine intoxication.

Concomitant Dystonia, Spontaneous Reflex Activity, and Ataxia

The segmental autonomy of body parts observed in the simultaneous occurrence of regional stereotypies remained evident from the early days of the experiment as dystonic manifestations. These manifestations had a selectivity of effect on the body as a whole, and persistent awkward postures resulted from tightening of muscles in diverse regions of the body. An early feature was the legextensor posturing already mentioned (Table I), which occurred independently of posture or activity, and at times in more than one leg (Figure 5). Its appearance in a standing animal was usually followed by a change to either a sitting or lying position. With continued (dosage) slow periodic flexor or extensor responses superimposed on the outstretched limbs were observed and signaled an excess of reflex activity in antagonistic muscles. The normal synchronous coordination of locomotion was, at times, affected by localized dystonia. Thus, during circling movements along the outline of the cage, a hindleg, after being lifted, might be slow to flex again and might remain in the air for a few seconds in a backward-extended position, while the other extremities kept the locomotor progression. This sequence might be repeated on successive steps, with increasing dyssynchrony.

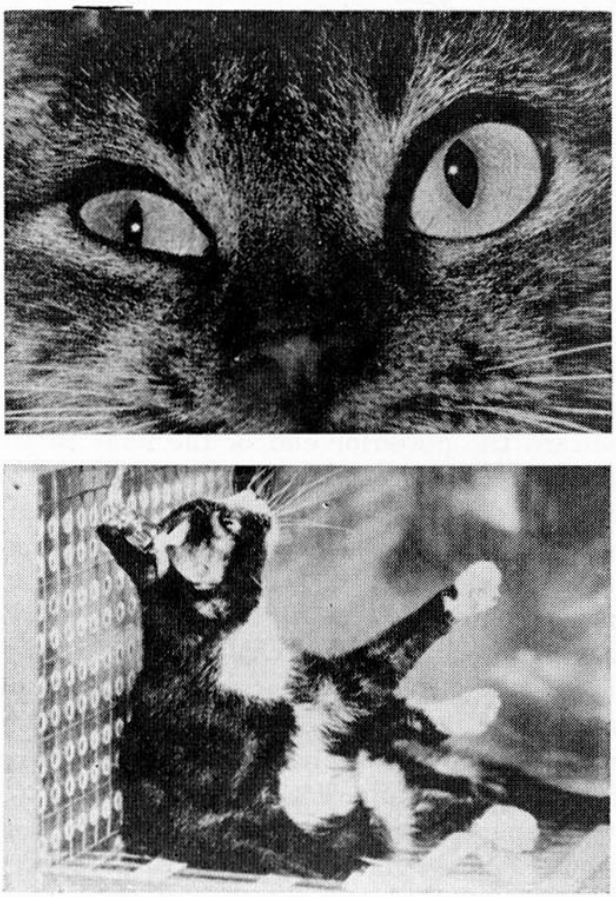


Fig. 5. — *Top: Ophthalmic dyskinesias (unilateral blepharospasm and mydriasis). Bottom: Regional dystonia (sustained leg-extensor posturing).*

Increased muscular tonus was most marked at the axial musculature and resulted in a dorsolumbar kyphosis. This hunched back (camel-back phenomenon, Table I) usually lasted for the entire recording session. Although its relatively high incidence during control may have been related to the dimensions of the cage, a high susceptibility of the animals to conditioning is demonstrated by its prominence on the days of saline administration (12 and 25). Transient hunching (hunching-back movements, Table I), at times overlapping the camel-back, appeared during the late periods of each recording session, either as a result of active forelegs backing up against fixed hypertonic hindlegs or as compensatory movements associated with the execution of a head stereotypy. Not infrenquently, cats in a crouched or a sitting posture would hold the tail in a horizontal extended position, parallel to the floor, but not touching it, similar to the Straub phenomenon observed in mice and rats given opiates. In a few animals, a moderate crucifixion-like posture developed by the locking of the proximal joints of the forelegs within an abnormal range.

During the late stages of hyperarousal and motor reactivity, the occurrence of regional dystonia was illustrated vividly by jumping with sudden retroflexive movements of the head (recoil-like movements), exaggerated arching of the back, and exten-

sion and curling of the tail. A typical propped-up posture with stiff appearance developed in most animals. This configuration, which we call the "camel posture", was characterized by wide-based hyperextended hindlegs, camel-back, and extended tail showing a waxy immobility with sporadic twitch-like movements. The increased reflex activity developed in conjunction with the camel posture in the form of sudden and uncontrolled jumps after a forepaw had come into contact with the animal's own saliva deposited on the floor. Both extension and flexion resulted from massive contraction of the affected muscles of the entire leg indicating the activation of proprioceptive and exteroceptive reflex mechanisms that participate in local postural reactions, such as the positive supporting reaction and the magnet reaction. Such manifestations were indicative of a dissociation between the underlying postural base and the superimposed movements.

Ataxia, considered here as an alteration of either the kinetic or the static configuration of the animal, was recognized by inadequate control of the range and precision of movements and/or by quivering of flexed and/or extended regions of the body. It appeared toward the last period of Day 1 and increased progressively on subsequent days (Table I). On some occasions, the motor incoordination demonstrated through staggering body movements while the cat was standing (astasia) or walking (abasia) seemed to be responsible for the adoption of a sitting or lying posture in an otherwise hyperaroused and over-reactive animal.

Late Hyperkinetic Phenomena and Non-Stereotyped Abnormal Movements

The most representative expression of a dissociation between the underlying postural base and the superimposed movements was the appearance of akathisia on Day 3 (Table I), manifested in both sitting and standing postures by continuous and non-patterned repositioning of the legs with a restless quality, as if the animal were attempting a change in location. Fig. 6 illustrates the occurrence of akathisia across days and conditions in all animals. The highest incidence in all recording periods occurred on Day 11. In the early periods of each day, akathisia was an increasing feature and, except on Day 8, it was sustained over the other periods. On that day,

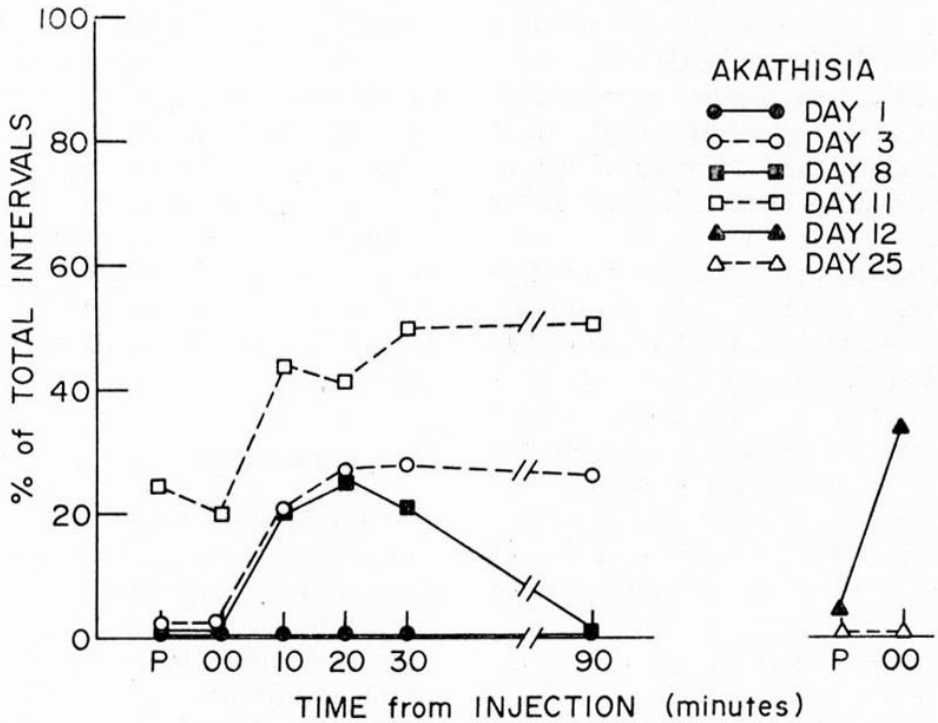


Fig. 6. — *Presence of akathisia within the indicated days of the amphetamine intoxication cycle and after interruption of drug administration. P = preinjection; 00 = immediately after injection. Mean of* 12 *cats.*

after two days in which no drug had been given, increased availability of catecholamines, especially dopamine, may account for the final decline. Initiation of akathisia was seen to occur consistently before the 10-minute recording period, and prior to any drug action. This finding, in addition to the prominence of akathisia on Day 12 (saline administration), reflects the participation of a conditioning effect that may be related to the compulsive component that underlies its appearance in human patients. Unlike other conditioned responses, akathisia did not appear on Day 25.

On the last day of amphetamine injection (Day 11), in highly aroused animals, akathisia was occasionally preceded or interrupted by bouts of alternating forward and backward stepping. Other psychomotor impulsions, although rarely seen, were fast spinning movements similar to the "tail-chasing" phenomenon and cursive locomotor hyperkinesia.

Localized dyskinetic movements, such as muscular twitches and myoclonic jerks of the trunk, as well as orofacial dyskinesias, were noticeable in some subjects by Day 8, and had become more prominent on Day 11. Within a recording session, the appearance, time course, and localization of such phenomena were quite irregular and different for individual animals. Sporadic twitches about the face, blepharospasm (Fig. 5) appearing after drug administration and persisting for more than 2 hours, and tongue movements were observed. The latter showed up frequently in association with chewing movements and, at times, were followed by strong head shakes. A sudden swing of the head with fast extrusion of the tongue (termed "fly-catching movement") was sometimes seen. On a few occasions, a slow lingual protrusion ended with the tip of the tongue remaining out of the mouth for several minutes. However, most distinctly, tongue movements consisted of bouts of fast in-and-out movements lasting for 1 or 2 minutes.

Peculiar abnormal movements of the extremities (Table I, pawshaking movements) occurred with no relation to other ongoing activity when the animals were walking or standing. Most commonly, a foreleg would be abruptly lifted from the floor and shaken rapidly and violently, with alternating flexion and extension of the paw, as if the cat were attempting to shake something off it. This movement might be repeated irregularly two or three times within a minute and then be followed by visual examination or initiation of a grooming response that vanished in a few seconds. In addition to the shaking movements, clonic dorsiflexions of the distal segment of a previously raised hindleg were occasionally seen. Such dyskinesias of the limbs were apparently similar to those induced temporarily in the cat by injection of dexamphetamine, dopa, dopamine, or 3-methoxythyramine unilaterally into the rostromedial part of the caudate nucleus [5] or, permanently, after unilateral lesion of the anteroventral region of the caudate nucleus [20]. These dyskinesias, however, lacked the athetoid quality reported in these cases.

Toward the last days of the intoxication cycle (Days 8 and 11), the manifestations of hyperkinesia prevailed and constituted the foreground of the behavioral picture. The breakdown of organized behavior was evidenced at that point by the occurrence of signs of hallucination, such as striking at non-existent objects in the air, sudden retreating movements or eluding jumps associated with a fixed staring gaze, all of which were very much suggestive of a human psychotic episode.

In summing up our observations, we offer a descriptive topographical classification of amphetamine-induced dyskinesias in the cat paralleling that proposed by Barbeau *et al* [2] for the abnormal movements produced in patients treated with L-Dopa (see Appendix).

Discussion

Overlapped and interacting in the complex polymorphism of induced alterations, three major symptomatological components (hypokinesia, dystonia and hyperkinesia) were discernible in the unfolding amphetamine syndrome.

The hypokinetic component, which appeared as the initial motor response at the beginning of the treatment, remained pro-

minent in the earlier periods and, in a few animals, lasted throughout entire recording sessions of later days. Most frequently, however, this component constituted a background on which the other alterations were superimposed. It is noteworthy that the mechanisms underlying hypokinesia might be connected with features known to occur in drug addicts, for example, catatonic forms of amphetamine psychosis with cataleptic manifestations [34] and the "overamping" effect of large intravenous dose of amphetamine. The latter often consists of a paralysis-like state that may last hours or days, during which the user is unable or unwilling to move [17]. Descriptions of overamping by abusers are highly suggestive of hypokinetic or akinetic phenomena. Typical is the statement made by a patient with a long-standing history of amphetamine abuse who was seen in the psychiatric ward of Duke Hospital: "Many times after a shot I was catatonic... I'd sit there completely still and fixed as a statue."

Manifestations of the dystonic component, which came to the fore after the early periods of the first day of treatment, showed clearly a relation-ship to the acute effects of the drug. On subsequent days, a more intense and earlier development occurred.

At all times, the stereotyped motor response appeared as the prelude of the rising hyperkinetic component and although composed of movements that were not abnormal by themselves, was abnormal because of its automatic quality and persistent sequential repetition. The development of hyperkinetic activity other than the stereotypic motor response paralleled the increased level of arousal and was demonstrative of a progressive breakdown of organized behavior also observed in humans developing amphetamine psychosis, a feature frequently indistinguishable clinically from some forms of endogenous schizophrenia. The data presented here point to the fact that recognition of dyskinetic signs in humans prior to the emergence of a psychotic episode may provide hints for a differential diagnosis. In fact, motor abnormalities similar to those we described for the cat have been reported in a few patients treated with small doses of dextroamphetamine sulfate [22] and in one case of amphetamine poisoning [31]. Only brief references to these phenomena may be found in reviews pertaining to the complications of chronic amphetamine abuse, although their frequent occurrence is noted. Ashkroft *et al.* [1] for example, pointed out that bruxism and continuous chewing movements with rubbing of the tongue along the inside of the lower lip (perhaps leading to the development of buccolingual ulcers) may be useful signs for recognizing amphetamine addicts. In addition to bruxism, various orofacial stereotyped movements and jerking of the arms were reported by a group of 10 advanced addicts [28].

Schiorring [30] observed grimacing and involuntary movements of the arms in phenmetrazine addicts as well. Most recently, Rylander [29] designated these "meaningless, unwilled, partially choreiform movements" observable in abusers of stimulant drugs as the "jerking syndrome" and emphasized its occurrence in the great majority of 20 such patients whom he interrogated.

Although voluntarily controllable tremors occur [17], it is common knowledge in the drug subculture that "meth heads" often have the fidgets and are unable to sit still [4].

Finally, insofar as analogy between motor manifestations in the cat and man is feasible, it is striking that most dyskinetic features listed in the Appendix can be compared with others reported to occur in patients treated with neuroleptic drugs [7, 8] or with L-Dopa [2]. This resemblance was emphasized particularly by the development of akathisia a manifestation most frequently accompanying tardive dyskinesia. Nevertheless the fact that all alterations receded soon after the interruption of drug administration, unlike the case of tardive dyskinesia, calls for caution in identifying the amphetamine syndrome with any clinicopathological entity.

SUMMARY

The development and evolution of motor abnormalities displayed by cats treated with methamphetamine hydrochloride, i.p. (dosage gradually increased from 15 mg/kg per day to 35 mg/kg per day) over a period of 11 days is delineated with a clinical criterion.

Data were gathered through phenomenological descriptions of a population of more than 60 animals, and through rating of units of motor activity and function from videotape recordings of the experimental sessions in a total of 12 cats. Saline injections prior to drug treatment provided control values for changes elicited by handling during injection or by the injection itself. The persistence of amphetamine effects after cessation of dosage and the conditioning to the experimental situation or to the injection itself were evaluated on days 12 and 25 (saline injection) of the intoxication cycle.

Three overlapping categories of symptoms (hypokinesia, dystonia, and hyperkinesia) are indicated as major components of the unfolding amphetamine syndrome. An initial reduction of spontaneous activity appeared to set the stage for the beginning of repetitious movements in one or more segments of the animal's body. Four basic patterns of head-neck stereotypy ("minutia-search", "side-to-side", "up-and-down", and "Balinese") were individualized and their relative frequencies of occurrence were assessed. The segmental autonomy of body parts was also apparent through regional dystonic manifestations ("leg-extensor posturing" "camel-back phenomenon", "camel posture", "hunching-back movements").

Hyperkinesia, a progressively earlier development on the successive days of drug administration, appeared as increased sensitivity toward the environment with motor reactivity and hyperreflexia, localized dyskinetic features (myoclonic jerks, oro-facial and leg dyskinesias), and akathisia. In the end stages, much of the motor reactiveness could be oriented towards "internal" cues (hallucinatory behavior) and was demonstrative of the final disruption of organized behavior.

Most dystonic-dyskinetic manifestations observed were comparable with those reported in patients after prolonged treatment with neuroleptics or L-Dopa.

RESUMEN

El desarrollo y la evolución de las anormalidades motoras demostradas por los gatos tratados con hidrocloruro de metamfetamina, i.p. (dosis aumentada gradualmente de 15 mg/kg por día a 35 mg/kg por día) durante un período de 11 días es delineado con un criterio clínico.

Se recogió información por descripciones fenomenológicas de una población de más de 60 animales, y considerando las unidades de actividad motora y función de registros video-tape de las sesiones experimentales en un total de 12 gatos. Inyecciones salinas previas al tratamiento de la droga proveyeron valores de control para cambios provocados por el manipuleo durante la inyección o por la inyección en sí. La persistencia de los efectos de la anfetamina luego que pasa la dosis y el condicionamiento a la situación experimental a la inyección misma fueron evaluados los días 12 y 25 (inyección salina) del ciclo de intoxicación.

Tres categorías sobrepuestas de síntomas (hipoquinesia, distonía e hiperquinesia) están indicados como los principales componentes del desarrollo del síndrome anfetamínico. Una reducción inicial de la actividad espontánea parecía preparar la situación para el comienzo de movimientos repetitivos en uno o más segmentos del cuerpo del animal. Cuatro cuadros básicos de estereotipia cabeza - cuello fueron individualizados (búsqueda minuciosa "de lado a lado" "Arriba y abajo" y "Balinese") y la relativa frecuencia en que aparecían, fueron comprobados. La autonomía segmentaria de partes del cuerpo también era visible a través de manifestaciones distonales regionales

(postura extensión de la pierna, fenómeno de lomo de camello, movimiento de arqueo del lomo).

La hiperquinesia, un desarrollo progresivamente más primario en los días sucesivos a la administración de la droga, aparecieron como una sensibilidad aumentada hacia el medio ambiente con reactividad motora e hiperreflexión, características disquinéticas localizadas (sacudones mioclónicos, disquinesias oro-faciales y de la pierna) y "acatisia". En las etapas finales, mucho de la reactividad motora podría ser orientada hacia sus vivencias internas (comportamiento halucinatorio) y demostraba perturbación final del comportamiento organizado.

La mayoría de las manifestaciones distónicas-disquinéticas observadas se comparaban a las que se señalaban en pacientes luego de un prolongado tratamiento con neurolépticos o con L-Dopa.

RÉSUMÉ

Le développement et l'évolution des anomalies motrices démontrées pour les chats traîrés avec l'hidrochlorure de metamfetamine, i.p. (doses augmentés graduellement de 15 mg/kg à 35 mg/ par jour) durant une période de 11 jours est souligné critérium clinique.

On a receuilli une information par descriptions fenomenologiques d'une population de plus de 60 animaux, et considérant les unités d'activité motrice et fonction des régistres video-tape des séances expérimentales en un total de 12 chats.

Des injections salées préalables au traîtement de la drogue, provoquèrent des valeurs de contrôle pour les changements provoqués par la manipulation durant l'injection en soi. La persistance des effets de la anfitamine après que cesse la dose et le conditionnement de la situation expérimentale ou de l'injection même furent évalués les 12 et 25 jours (injection salée) du cicle d'intoxication.

Trois catégories superposées de syntômes (Hypoquinesie, distonie ou hyperquinesie) sont indiqués comme les principaux composants du développement du syndrome anfetamine. Une réduction initiale de l'activité spontanée paraît préparer la situation pour le commencement des mouvements répétés en un ou plusieurs segments du corps de l'animal. Quatre cadres basiques de stéréotipie tête - cou furent individualisé (recherche minutieuse "de côté à côté" en haut et en bas et Balinese et la relative fréquence dans lesquelles apparaissent furent prouvés. L'autonomie segmentaire des parties du corps également était visible à travers les manifestations distonales régionales (position extension de la jambe, phénomène du dos de chameau, mouvements arqués du dos). La hyperquinesie, un développement progressif plus primaire dans les jours succesifs à l'administration de la drogue, apparurent comme une sensibilité augmentée jusqu'a une ambiance moyenne, avec activité motrice et hypereaction caractéristiques - disquinétiques localisées (secousses myoloniques, disquinesies oro-faciales, et de la jambe) et acatisi.

Dans les étapes finales, beaucoup de l'activité motrice pourrait être orienté jusqu'à son humour interne (comportement hallucinatoire) et démontrait une perturbation finale du comportement organisé.

La majorité des manifestations distoniques - disquinétiques observées, se comparent à celles signalées chez les patients après trâitement prolongé avec neuroleptique ou avec L-Dopa.

ZUSAMMENFASSUNG

Die Entwicklung und Evolution motorischer Abnormitäten, die sich in einem Zeitraum von 11 Tagen zeigen, wenn Katzen mit Metamphetamin Hydrochlorid i.p. (die Dosis allmählich von 15 mg/kg pro Tag auf 35 mg/kg pro Tag erhöht), behandelt werden, wird mit klinischem Kriterum beschrieben.

Die Informationen wurden durch phänomenologische Beschreibungen einer Anzahl von mehr als 60 Tieren gesammelt, und durch Abschätzen der Einheiten motorischer Aktivität und Funktionen von Videotape Registrierungen der Versuchssitzungen von total 12 Katzen. Salinische Einspritzungen vor der Behandlung mit der Droge lieferten Kontrollwerte für Veränderungen, die durch Behandlungen während der Injektion oder durch die Injektion selbst hervorgerufen wurden. Das Bestehenbleiben des Amphetamin-Effekts nach Beendigung der Dosierung und die Anpassung an die experimentelle Situation oder die Injektion selbst, wurden am 12 und 25. Tag (Salinische Einspritzung) des Zyklus der Intoxikation ausgewertet.

Besonders drei Kategorien von Symptomen (Hypokinesis, Distonie, und Hyperkinesis) treten als hauptsächlichste Komponenten der Entwicklung der Amphetamine Syndrome auf. Eine anfänglische Verringerung der spontanen Aktivität schien die Situation vorzubereiten für den Beginn von wiederholten Bewegungen in dem einen oder anderen Teil des Tierkörpers. Vier fundamentale Beispiele von Kopf-Hals Stereotopie ("unaufhörlisches Suchen, "von einer Seite auf die andere, von oben nach unten, und "Balinese") wurden individualisiert und ihre relative Häufigkeit des Vorkommens wurden festgestellt. Die segmentale Autonomie der einzelnen Körperteile wurde auch sichtbar durch regional dystonale Äusserungen ("Position des Beinausstreckens, Phänomen des Kamel-Rückens, Kamel-Haltung, Rückenkrümmen). Die Hyperkinese, eine allmählich frühere Entwicklung in den folgenden Tagen der Drogenzufuhr, trat als erhöhte Empfindlichkeit der Umgebung gegenüber auf mit motorischer Reaktivität und Hyperreflexion, lokalisierten dyskinetischen Merkmalen (myoklonische Zuckungen, Dyskynesie oro-facial und des Beines), sowie Akathisia. Im Endstadium konnte viel von der motorischen Reaktivität nach internen Aufgaben orientiert werden (halluzinatorisches Betragen) und zeigte das endgültige Aufhören jedes organisierten Benehmens.

Die meisten distonischen-dyskinetischen Aeusserungen, die beobachtet wurden, waren mit denen vergleichbar, die von Patienten berichtet wurden, die längere Zeit mit Neuroleptics oder L-Dopa behandelt worden waren.

APPENDIX

Dyskinetic Features Exhibited by Cats Under Chronic Amphetamine Intoxication *

CEPHALIC DYSKINESIAS

Ophthalmic:

—Pseudoexophthalmos (wide-eyed, "glazed" expression).
—Sudden blepharospasm, unilateral and persistent.
—Intermittent mydriasis.
—Unilateral persistent mydriasis.

Facial:

—Sporadic twitches.
—Hemifacial spasm.

Orolingual:

—Irregularly repeated chewing movements.
—Short-lasting bouts of fast protrusive movements of the tongue.
—Prolonged extrusion of the tip of the tongue in the midline.
—Single and rapid protrusion of the tongue with sudden swing of the head (fly-catching movement).
—Slow licking motions on the floor or the wall of the cage.

Cervical:

—Head staggering.
—Head tremor (rare).
—Head shakes and sudden retroflexion (recoil-like movements).

TRUNCAL DYSKINESIAS

Respiratory:

—Hyperventilation with panting.

* Observed more than once in a population of more than 60 animals.

Statokinetic:

—Dorsolumbar kyphosis (camel-back phenomenon).
—Lateral flexion of the spine (scoliosis) while sitting.
—Compensatory or spontaneous hunching-back movements.
—Staggering while standing or walking.
—Oscillations ("swaying in the breeze") while sitting or standing.
—Alternating lateral movement while standing, with stepping of the forelegs and fixed hindlegs.
—Restlessness (akathisia).
—Myoclonic jerks of intercostal or abdominal muscles.

FORELEG DYSKINESIAS

When lying down or sitting:

—Adduction and fixation of the entire foreleg, with or without flexion of the paw (foreleg-extensor posturing).
—Claw extension, with or without spreading of the toes (paw-fanning).

When standing or walking:

—Increased base with proximal hypotonia (manifested by a tendency for the legs to slide apart and the maintenance of a moderate crucifixion-like posture).
—Fast and jerky shaking-off movements, with alternating flexion and extension of the paw (paw-shaking movements).
—Slow reaching out or fast pawing movements.
—Restless repositioning or stepping movements (akathisia) that also occur while the animal is sitting.

When lying down or sitting:

—Extensor posturing movement, with or without internal rotation and with or without periodic superimposed flexion and extension motions (hindleg-extensor posturing).
—Extensor spasms (kicking - like movements).
—Claw extension, with or without spreading of the toes (paw-fanning).
—Restlessness (akathisia).

When standing or walking:

—Increased base and fixed hyperextension (in concurrence with camel-back phenomenon and plastic-like tail: camel posture).
—Distal segment in contact with the floor and supporting the body (rabbit hindleg).
—Increased permanence in the air, in a backward-extended position, while walking.
—Slow extension and abduction movement with paw-shaking.
—Raising followed by clonic contractions of the distal segment.
—More rapid, sudden propulsion of the whole hind limb.
—Restless repositioning and stepping movements (akathisia) that also occur while the animal is sitting.

CAUDAL DYSKINESIAS

—Straub-like phenomenon and plastic immobility (squirrel-like tail).
—Twitching-like movements of the tip of the tail.
—Violent gyrating movements when the cat is in a motor overreactive state.

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Parkinsonism, Levodopa, and Intelligence

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The role of catecholamines in mental function has been assessed repeatedly in man by correlation of abnormal behavior states with levels of various catecholamine metabolites. Parkinson's Disease, with its injury to dopaminergic neurons, provides an opportunity to examine behavior as a function of such injury and during replacement therapy with the catecholamine precursor, L-DOPA.

We chose to examine intellectual function with the Wechsler Adult Intelligence Scale (WAIS), a test which was developed and standardized in the New York area from which we draw our patients and which has norms which allow precise correction for the intellectual decline of natural aging [1].

The WAIS was administered to 41 men and 22 women with idiopathic Parkinson's Disease prior to L-DOPA treatment. These patients were part of a therapeutic trial of DOPA [2] and were selected solely on the basis of simultaneous availability of examiner and patient. Nine other patients were selected but not tested because of refusal to cooperate [4], inability to comprehend [3], or inability to use their hands [2]. The 63 patients examined ranged in age from 38 to 82, with a mean of 64.4 years. Their average length of illness was 7.2 years (1-36) and 9 had undergone a thalamotomy or pallidotomy. All but 7 were being treated with anticholinergic medication. The mean educational level was 13.3 years.

The results of WAIS tests are shown in Table 1. IQ score for individual intellectual functions varied widely. Though the mean Full Scale IQ score was normal (107.2), the Mean Verbal score (115.6) exceeded the Mean Performance score (95.3) by 20.3 points. Factor scores ranged from 115.8 for Verbal Comprehension (Information, Comprehension, Similarities, Vocabulary) through 106.8 for Memory- attention (Arithmetic, Digit Span) to 91.5 for Perceptual Organization (Block Design, Object Assembly).

The difference between Verbal and Performance IQ's is often used as an index of toxic or organic disruption of intellectual functions. A 20 point superiority of Verbal over Performance IQ is seen in only 2 % of normals, but was found in 57.1 % of our patients.

Can these alterations in WAIS scores by Parkinsonian patients be explained by extraneous factors rather than a primary effect of Parkinson's Disease on intellectual ability? We have considered the effects of depression, impaired motility, aging, medication, and prior brain surgery. Comparison of 27 age and education matched Parkinsonian and hospitalized depressed patients showed that Verbal-Performance differences of 20 points or more were 3 times more frequent and those of 25 points or more 9 times more frequent in Parkinsonism than in depression.

All the performance subtests of the WAIS except picture completion require manual maneuvers and so one might explain poor performance by poor motility. However, even the picture completion score was 15.6 points lower in Parkinsonian than in de-

pressed patients. Timing of subtests works against the bradykinetic patient, but if patients were allowed all the time they wanted, they still did poorly in Block Design, Object Assembly, and Picture Arrangement.

Aging is corrected for by the WAIS test itself. Comparison of scores from untreated patients, those taking anticholinergics, and those post surgery showed no statistical differences.

We therefore conclude that intellectual impairment is associated with Parkinson's Disease itself [3]. It follows that replacement of the presumed transmitter lacking in Parkinsonism might alter the intellectual as well as motor component of the illness.

To examine this possibility, we have retested patients from our original series twice. Forty patients were tested 5-13 months after onset of treatment with L-DOPA [4]. They were 29 men and 11 women ranging in age from 39 to 82 with a mean of 63.6 years. Their DOPA dose ranged from 4-8 grams/day.

Table 2 shows pre treatment and 8 months WAIS scores along with t test comparison of the differences of the means. Verbal IQ increased 7.0 points, Performance IQ 10.4 points, and Full Scale 9.0 points, all significant at 0.001 level. Forty-five percent of the patients improved at least 10 points in Full Scale IQ, as did 27.5 % of the patients in Verbal IQ, and 47.5 % in Performance IQ. Factor scores for Verbal Comprehension, Memory attention, and Perceptual Organization also improved significantly to a p value < 0.001.

Pearson product-moment correlation coefficients between pretreatment scores and changes in scores after treatment showed a barely significant relationship (0.05) for Performance IQ and significant correlation (0.01) for all 3 factor scores. This demonstrates that patients with lower pretreatment scores improved more than those who were intellectually intact to begin with.

Twenty-four patients were examined again after 19-44 months of L-DOPA therapy [5]. Their average L-DOPA dose was 4.5 grams/day. WAIS scores reverted to a level not significantly different from those prior to treatment. Only a single patient maintained an improvement of 10 points in Performance IQ. Thirty-eight percent of the group declined 10 points or more in Performance IQ between 8 and 30 months of treatment. Change in Full Scale IQ between 8 and 30 months correlated significantly with ratings of physical symptoms($p<0.05$) and functional disability ($p<0.001$). Changes in Full Scale IQ scores in individual patients at 8 months correlated with changes in the same patients between 8 and 30 months at a level $p < .05$, indicating a true return to baseline status by previously improved patients.

Why did the intellectual performance of Parkinsonians improve from abnormally low levels and then decline again?

In a separate approach to this problem, we have examined 10 patients who became severely demented during therapy with L-DOPA. Their age, duration of disease, and severity of motor impairment were not different from the larger group of patients. Cessation of L-DOPA therapy for at least 7 days in each case eliminated agitation and hallucinations in 2 instances, but was associated with them in one other. Intellectual performance did not improve in any case. Metabolic studies and brain scan were normal. Pneumoencephalograms in 6 patients showed mild to marked ventricular enlargement. A ventricular atrial shunt in one patient had no effect. In short, no specific abnormality was found.

Artifacts such as practice effect and normal aging cannot account for the magnitude of the changes in WAIS scores which were observed [6–8], A placebo effect is conceivable, but difficult to document in view of the obvious clinical benefit from L-DOPA.

Replenishing dopamine in the brain could improve intellectual performance by altering sub cortical input or by influencing noradrenergic modulation of cortical functions. Decline of such improvement might represent loss of enough dopaminergic or adrenergic terminals, temporarily enriched by L-DOPA treatment. On the other hand, non-specific activation by L-DOPA coupled with inexorable cortical atrophy associated with Parkinson's Disease [9] could equally well account for our results.

TABLE I — Means and Standard Deviations of WAIS IQ Scores for a Group of 63 Parkinsonians

Score	M	SD	Score	M	SD
Perceptual organization	91.5	17.0	Verbal	115.6	13.4
Verbal comprehension	115.8	12.0	Performance	95.3	14.9
Memory - attention	106.8	14.0	Full scale	107.2	13.5

TABLE II — WAIS Verbal, Performance, and Full Scale IQ Scores Before and After Levodopa Treatment

	VERBAL IQ Scale			PERFORMANCE IQ Scale			FULL SCALE IQ Scale	
	Mean	SD		Mean	SD		Mean	SD
Pre	116.5	13.8	Pre	95.4	13.1	Pre	107.8	12.8
Post	123.5	12.7	Post	105.8	13.0	Post	116.8	12.3
Diff	7.0	5.1	Diff	10.4	7.3	Diff	9.0	5.2
t	8.5		t	9.0		t	10.8	
p	< 0.001		p	< 0.001		p	< 0.001	

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Intellectual Deficits in Parkinsonism

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Discussion

Dr. Sweet and his collaborators have pioneered in assessing the intellectual deficits in parkinsonism and their responsiveness to the use of L-Dopa. The results of their study raises the question as to whether the observed transient increases in the WAIS score seen in the early phases of levodopa therapy are a direct effect of the drug on intellectual function or merely reflect the improvement in motor difficulties which are well documented in the disorder. From our data, we have felt that the improvement seen on the WAIS, specially on the performance part of the test is to a considerable extent explained by an improvement in sensorimotor integration and reaction time. This is based on the fact that many of the sub-tests of the WAIS depend upon speed of sensorimotor responses.

In our own studies, we have found that concomitant with the improvement in the mai or parkinson symptoms, patients on levodopa therapy show greater ability to perform sensorimotor tasks; repetitive tapping under unimanual and bimanual conditions as well as tracking a light moving at random on a screen. This improvement occurs four weeks after initiation of levodopa therapy and is still present after one year. These results are in agreement with those of other investigators who also reported improvement in relatively simple motor tasks such as ballistic tapping, placement of pegs in a pegboard, finger dexterity, as well as in more complex tasks such as rotary pursuit, maze tracking and decreased error correction time in marking a target with a jovstick. They may explain the discrepancy between the Performance IQ and Verbal IQ on the Wechsler which Dr. Sweet has pointed out. Although speed of response as he indicated is not a factor in the Picture Completion task, there may be other modes of sensorimotor integration which are operative. It is, of course, obvious that overall IQ's are determined from subtests in which a number of factors are at play. In an effort to dissect these out, we have screened patients using specially designed test situations. We have mentioned two related to reaction time, "vigilance" and speed of sensorimotor performance. We have now begun to look at memory mechanism since reports in the literature and complaints of parkinson patients on or off levodopa suggest interference in this sphere. Parkinson patients were divided into groups as follows based on the duration of treatment with levodopa, 1) patients who had not received levodopa ($N=18$), 2) patients on levodopa for 12-34 months ($N=17$), 3) patients on levodopa for 24-35 months ($N=27$), and 4) patients on levodopa for 36-47 months ($N=24$). In addition, 22 normal controls were tested who were equated on the basis of age (F age 0.8360 non-significant) and Wechsler Verbal IQ (FIQ 0.0425 non-significant). The average Verbal IQ of these five groups was 110 and the average age was 63 years. All five groups ere administered the Wechsler Memory Test. An analysis of variance was performed on the Memory Quotients of the groups demonstrating a significant difference between them ($F=3.23$ $p<.05$). Further statistical analyses showed that the Memory Quotients of all the parkinson patients were significantly lower than the Memory Quotients of all normal persons tested. However, there was not a significant difference between the memory quotients of any of the parkinson groups when the patient groups were compared with each other — in other words, either before or up to four years of levodopa treatment no change was produced in the memory quotients in pa-

tients that had been matched on the basis of the Verbal IQ — they all remained inferior to the normal controls.

A subsequent analysis of the subtests of the Wechsler Memory Test, indicated that in three of the subtests the parkinson patients were significantly inferior to the normal controls, both before and during levodopa: 1) Logical Memory assessed by the number of concepts remembered from paragraphs read to the subjects, 2) Visual Reproduction which entailed seeing a figure for 10 seconds and then reproducing the design in its absence, and 3) Paired Associates-learning task, involving new and old learning where the subject has to recall the response associated with the stimulus word presented. On the other subtests Information and Orientation — dealing with common information; Mental Control — counting backwards as rapidly as possible, reciting the alphabet and adding in serial threes; as well as Digit Span (forwards and backwards), parkinson patients were not significantly different from normals.

In general, these findings indicate that parkinson patients are deficient in this area prior or during levodopa treatment. In fact we have increasing evidence on additional tests of memory, sorting and categorizing tests (cognitive tests) that patients are impaired as compared with matched controls.

In summary, it is our impression that intellectual function does not improve concomitant with the improvement observed in neurologic symptoms during treatment with levodopa. It would appear that reported increases in IQ scores are based on more general factors such as improvement in reaction time, attention span and increases in simple motor performance.

In fact, studies now in progress indicate that when parkinson patients prior and during levodopa therapy are compared with matched controls, they are impaired in cognitive tests which involve memory, concept formation and perceptual motor integration.

The Effect of Psychotropyc Drugs on Learning Ability

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(An Experimental Study)

The increasing use of tranquillizers —justifiable or not— has, admittedly, posed a great number of questions, part of which the Pharmacological Laboratory is called upon to answer. A great number of them, however, especially their effect on the behaviour and the various mental functions, must be answered by psychological experiment or observation. ....

The present experimental study aims at investigating whether a single dose of a tranquillizer (antipsychotic or anti-anxiety) has, or not, a favorable or unfavorable effect on the learning ability of a healthy adult.

Of course, it would be much more interesting to find out whether the long-term use of these drugs affects the learning ability or not. However, as only patients make such use, the effect on the learning ability would be, in this case, equivalent to the therapeutic effect of the drugs.

On the other hand, a great number of healthy people — especially students — makes occasional use of such drugs (especially against anxiety) in the hope that by alleviating the mental stress, of which they suffer mainly during the period of mental hard work, or their slight free-floating anxiety, they would achieve an increase of their mental performance. The present experimental study has tried to answer this question.

We studied the effect of six drugs which are most widely used in our country. Two minor tranquillizers: Meprobamate, at a dosage of 200 mgms, and Chlordiazepoxide, at a dosage of 5 mgms, two major tranquillizers of the group of Phenothiazines: Chlorpromazine, at a dosage of 25 mgms, and Fluphenazine, at a dosage of one mgm, one drug of the group of Butyrophenone: Haloperidol, at a dosage of 0,5 mgms, and finally Phenobarbitone (as this one has an entirely different kind of effect) which was given at a dosage of 60 mgms.

Material - Preparation: 53 healthy volunteers, 16 female and 27 male, took part in this study. The majority of them were students (42 in all, of which 32 were from the Medical School, 6 from the Polytechnic and 4 from the School of Physics and Mathematics), whereas the remaining 11 were young post-graduates, all of them from the University of Thessaloniki (6 doctors of Medicine, 2 architects, 2 political engineers and 1 mathematician).

Their ages varied from 19 to 30 years, with an average age of 22,4 years.

Their I. Q. varied between 112 and 128 (average 118) which means that the subjects belonged to the group of higher intelligence.

Usually, a few days before the start of the successive tests, the candidates were briefed

in small groups (5 to 6 subjects) on the conditions of the experiment, the tests to be used were explained to them, some preliminary tests were carried out and the initial files were completed.

Those of the volunteers who had used in the past any of the above drugs, either occasionally or as a regular treatment, and had, therefore, personal experience of their effect, were excluded from this experiment.

Tests: During the experiment, a group of five learning Tests, which had been used successfully in previous studies in the field of learning ability, was used. These Tests were as follows:

Test Nº 1): Learning by heart of a verse from a classic Greek poet, which had to be unknown to the subject and every line of which consisted of 7-9 syllables.

Test Nº 2): Learning by heart of 3 series of figures, the numbers of which were linked by a logical pattern, so that it was only necessary for the subject to learn and remember only the first number and the key, these two being always single figures (e. g. series 3, 7, 11, 14, 18, 22 — first number 3, key + 4).

Test Nº 3): Looking at 8 photographs of landscapes and then recalling and recognizing them from amongst 20 such photographs.

Test Nº 4: Learning of 6 nonsensical syllables (e. g. pat, cet, noc, mix, tsak, pouf — all of these having no meaning whatsoever in the Greek language).

These 4 Tests were written on separate sheets of paper and were distributed to the subjects who were allowed to keep them for 10 min. Following that, Test Nº 5 was read twice to the subjects. This consisted of a short story which contained 6 characteristic elements, all of them in twos (localities, names, time of the day, colours, etc.

After a period of 5 minutes, during which an irrelevant conversation took place, there followed a check of what the subjects could remember from the Tests, in any sequence that each subject preferred.

Sequence of sessions: Each subject took part in a series of 8 couples of sessions.

The first couple of sessions took place without the use of any drug and formed the basis of evaluation (sessions AI, AII).

For these sessions we always chose the time of maximum mental performance of the subjects. Thus, 31 of the volunteers took part in the experiment in the morning hours, after breakfast, 19 of them in the afternoon hours and the remaining 3 in the evening hours, after dinner. The period of maximum mental performance was specified by the subjects themselves, according to how they were used to work.

The time sequence of the sessions was as follows: one hour after breakfast (and following the administration of the drug) the first session took part (AI) and lasted 25 to 30 min. Following this, the subjects were free for one hour, to use their time in any way they wanted, and afterwards the second session took part (AII). In the sessions which took part after the administration of the drug, this was given always after a full meal (so as to correspond to the usual way in which drugs are taken).

Between two successive couples of sessions there intervened always a period of one week or longer (according to the wish of the subjects themselves) so as to diminish, as much as possible, the experience which the subjects had had from the previous sessions.

The experiment was a double-blind one, the drug being administered always in the form of a white starch capsule. The Tests were coded by the letters A, B, C, D, E, F, G, H and the Latin numbers I and II. Only at the end of the whole experiment were we informed of the sequence in which the drugs had been administered to each of the subjects. In one of the sessions a PLACEBO had been administered instead of the drug.

All the subjects were forbidden the use of even the smallest amount of alcohol, both on the day before and during the day of the sessions. The meal, which preceded the administration of the drug, was completely devoid of any amount of either caffeine or theophylline.

In order to avoid any possible effect resulting from the change of environment and the conditions of experiment, we chose to carry out all the sessions in the familiar

place of work of each subject (home, office, study or library) where the person in charge of the experiment met the subject on the pre-arranged days.

On the evening following each couple of sessions or the next day, the subjects were asked to prepare a brief report on their own subjective reaction towards the experiment, their mental mood before and during the experiment, their mental performance both during the time before and after the experiment.

Also, after the end of the whole series of sessions, the subjects were asked about their subjective experience of, and reaction to, the whole experiment. Each individual file was completed by various other questions (general condition of health, habits of everyday life, the use of tobacco or alcohol by the subjects, etc.) with a view of using this material for further investigation of other parameters in the field of learning ability.

Evaluation: As has already been stated, the initial sessions AI and AII, that is the ones where no drug was administered, were used as the basis for marking the results of the whole experiment. Each individual Test, if fully successful, received 20 points so that the maximum score was 100 points. The Tests following the administration of the drug were marked in a similar way so that we could achieve a direct comparison of the results, both of the individual Tests and of the whole performance.

Results: As has already been reported in a previous paper of ours, the Tests which were used, and the time allotted for learning each one of them, were apparently fairly easy, at least where our subjects were concerned. A great number of subjects (15) scored 100 points in sessions AI and AII.

A comparison of the scoring of sessions AI and AII in the group of the remaining 38 subjects shows a significant improvement in the performance in session AII. As in this investigation no external factors were allowed to infuence the performance (such as were reported in a previous study of ours) one could say that the improvement noticed in the second session was mainly due to the experience gained from the first session, so that the subjects could make a better use of their allotted time for learning. This was also the subjective impression of the subjects themselves: Thus, from the whole group of the 38 subjects, 8 of them scored during session AII 100 points, 13 more improved their performance considerably and only 4 of them scored less than in session AI.

These findings limit, of course, considerably the number of subjects who could show an improvement of their performance after the administration of drugs. This was taken into consideration during the statistical evaluation of the results.

The same finding has a special validity during the evaluation following the administration of drugs, especially in those cases where, instead of an improvement, there was an impairment of the learning ability in session AII, which coincided in time with the period of maximum concentration in the blood of the drugs used.

As was expected, there was no relation between learning ability and I. Q. (according to the HAWIE Tests).

We shall now report on the effect of the drugs on learning ability.

During the sessions where a PLACEBO was used, no considerable difference was noticed in the performance compared with the initial sessions AI and AII.

Whereas 8 subjects showed an impairment of learning ability during the first session (one —10 points, four —6,6 points and three —3,0 points) and 5 subjects showed an impairment during the second session (four —6,6 points and one —3,3 points) this impairment is counter-balanced by increased performances during the same sessions by other subjects, so that the total results showed an improvement of +1,2 %, a fact which confirms again that experience was the main factor in the successive sessions.

The same can be said as regards the experiments following the administration of Chlordiazepoxide at a dosage of 5 mgms. Here, too, the impairment of learning ability (7 subjects in the first session, 4 in the second session) was counter-balanced by the increased performance of other subjects (6 in the first session and 6 in the second

session) so that, again, the total results showed an improvement, even though negligible, amounting to + 0,6 %.

Aproximately the same level of performance was achieved by the subjects following the administration of Haloperidol (at a dosage of 0,5 mgms) and Fluphenazine (9 at a dosage of 1 mgm). Here, again, the impairment of learning ability of certain subjects was counter-balanced by the increased performance of other subjects. Thus, when Haloperidol was administered, a total impairment of performance of only —0,3 % was observed, whereas following the administration of Fluphenazine a negligible improvement of + 0,2 % was noticed. Again, during the experiments with these two drugs, the second session showed improvement of performance as compared with the first session, so that again the factor of experience must have been decisive. The effect of the drugs as such should be almost excluded as, if this had played an important part, this should have been observed already during the first session and should have increased during the second session.

The subjective experience of the subjects as regards the improvement or impairment of their performance during the experiments with the three above-mentioned drugs, contains the basic fact that most of the subjects could not explain the reason for these changes in their performance. Especially where the performance was increased, none of the subjects could attribute it to any specific cause. On the contrary, where an impairment of performance was noticed, 7 of the subjects attributed it to a feeling of a considerable, and unpleasant, physical weakness (3 subjects who had received Haloperidol, 2 subjects following the administration of Fluphenazine and 2 subjects following both Haloperidol and Fluphenazine).

Very interesting results were observed after the administration of Meprobamate, which is considered a very mild drug. Even though the total results showed a negligible impairment of learning ability of only —0,2 %, there were considerable differences of performance between the first and second sessions. Thus, whereas in the first session there was an improvement of performance which amounted to a total increase of + 4 % (far more than any produced by the previously mentioned ones), this improvement gave place to a considerable impairment during the second session, so that the final result was negative and as low —3,3 %. These results are similar, on first appearance, with those obtained following the use of Phenobarbitone (as is reported later on) though there are some important differences.

The total result following the use of Meprobamate is characterized, as has been mentioned, by greatly increased performances on the part of some subjects. For example, 6 subjects produced an impairment of 13.3 %, one of 12.5 % and one of 10 %. Amongst these subjects, there are four who had shown excellent performances in the other sessions (scoring 100 points in sessions AI and AII and the sessions following the administration of Chlordiazepoxide, Haloperidol, Fluphenazine and the first session after the administration of Meprobamate) four more of these subjects had shown satisfactory performances both after the various other sessions and during the first session following the use of Meprobamate.

The subjective experience of the subjects themselves as regards this impairment of their performance, contains these main characteristic elements: a feeling of physical weakness and an indifference toward the result, as well as a slight dizziness and a marked tendency to sleep.

The fact should also be mentioned that the majority of these subjects was amongst the young ones (between 19 and 23 years of age). There were 7 female and 7 male (in other words, the ratio was here 1:1. while the total ratio of the subjects's sex was approximately 2 male : 1 female).

In the sessions following the use of Phenobarbitone, we observed an impairment of learning ability which in the first session was slight but which became much more evident in the second session. Thus, the total impairment of the first session was —1.3 %, while that of the second session was —4.6 %. The characteristic element here (as in the sessions following the administration of Chlorpromazine) was that

the subjects who showed an impairment in the first session did as badly, or even more so, as in the second session. This fact is in complete contrast to the initial observation, where no drug had been used and where, as has already been mentioned, there was an improvement of performance in the second session, which had been attributed to the experience the subjects had gained, especially as regards the correct use of the allotted time.

The subjective impression of the subjects concerning their performance was typical. They attributed their impairment to their increasing sleepiness and only to that.

As regards the final results, we had similar findings in the sessions following the use of Chlorpromazine, where, however, we observed a peculiarity which did not agree with our pharmacological research findings, according to which, the greatest concentration of the drug in the blood is to be found 2 - 4 hours after each administration. In our experiment, the greatest impairment was observed during the first session (—4.8 %), whereas in the second session the impairment was less (—3.2 %).

Here, too, the subjects attributed the impairment to their marked tendency to sleep, which, however, they could temporarily overcome, though it was increased during the second session. During the first series, this sleepiness was slight and the subjects did not have to try hard to overcome it. A great number of the subjects also blamed their indifference towards the results for the impairment of their performance.

As regards the general mental performance of the subjects the evening following the morning session or the day after an evening session, we found out that the subjects, who had taken the Tests in the evening, felt that their mental performance the next day was their usual one. On the other hand, a great number of those subjects who had taken the Tests in the morning hours, felt that their performance in the evening was impaired. In fact, 8 of the subjects were of the opinion that following the administration of Fluphenazine, they were "in no mood for work" and that, in spite of their efforts, their performance was below otherage. Similary, 10 subjects felt that they could not perform satisfactorily in the evening, following the administration of Haloperidol in the morning, two of them having, in fact, to abandon every effort, as they felt that it was "useless". In the experiments where Chlordiazepoxide had been administered in the morning, the subjects on the whole reported satisfactory performance in the evening. When Meprobamate had been given in the morning, 6 of the subjects (4 female and 2 male) reported impaired performance. These subjects were amongst the ones who had also shown an impairment during the morning session. Ten subjects also complained of impaired performance in the evening, following the administration of Chlorpromazine in the morning. Finally, after the morning use of Phenobarbitone, 14 subjects reported impaired performance in the evening.

There is a similarity with the above in the performance of the subjects who had received psychotropic drugs in the morning. Thus, 5 subjects reported reduced evening performances following the use of Haloperidol, Fluphenazine, Phenobarbitone and Chlorpromazine 3 following the use of Haloperidol, Phenobarbitone, Chlorpromazine and Meprobamate and 2 following the use of Fluphenazine, Phenobarbitone and Chlorpromazine.

It should be noted that the subjects who reported impairment in their evening performance were not necessarily the ones who had shown such an impairment during the morning experiments, except those who had shown impairment after the administration of Meprobamate and who did badly both during the morning sessions and in the evening hours.

Discussion

Right from the beginning, the fact should be emphasized that none of the drugs under study could produce an improvement of learning ability, unless this ability had been already disturbed by pathological causes.

On the contrary, when these drugs are used occasionally, especially in the morning hours, they may lead to an impairment of performance either immediately after being

taken or during the time of their greatest concentration in the blood. They may also cause a prolonged disturbance of performance during the rest of the day. This disturbance was reported subjectively by a great number of the subjects, though it was not investigated experimentally during the present study.

The sole exception between the six drugs was Chlordiazepoxide, which did not affect the performance, either for better or for worse. This drug, however, had been given at the small dosage of only 5 mgms.

The results following the use of Meprobamate pose a great number of questions and must be discussed at greater length. The first question is, whether the improvement of performance which was observed in the first session might simply be a coincidence. Such coincidence, however, was not observed with any of the other drugs or with the PLACEBO. One could perhaps say that it was due to the experience gained by the subjects. Such an explanation would not agree with the conditions of the experiment, as, of the subjects who showed an improvement of performance, two had received Meprobamate during the first couple of session, one during the second, three during the third and the remaining nine in any other order. One should therefore, look for other causes in order to explain this improvement. The subjective evaluation of the subjects themselves cannot help us in this direction (six of them could not attribute it to any cause, three believed that they were, anyway, "in better shape", already, from the morning of that day, while the remaining six felt that the improvement was due to the drug).

If the improvement was actually due to Meprobamate, and taking into consideration the period of greatest concentration of the drug in the blood, one should expect that small doses of the drug (50-100 mgms) would result in an improvement of learning ability for a longer period after the administration of the drug. So as to confirm this experimentally, we asked seven of the subjects, who had reported improvement, to take part in a further experiment following the administration of 100 mgms of Meprobamate. The sessions of this experiment took place again one and two hours after the administration of the drug. In the first session, that is one hour after the administration of 100 mgms of Meprobamate, no significant change of learning ability was observed as compared with experiment AI, while in the second session, an improvement was observed, which, however, did not exceed that of experiment AII (in which no drug had been used). One has, therefore, to attribute this improvement of performance to a chance coincidence after all.

This fact proves —once more— how difficult it is to evaluate the results of psychopharmacological experiments when there is no similarity in the findings.

The remarkable impairment of learning ability, which was observed in some of the subjects during the second session, must, in our opinion, be attributed to a specific sensitivity of some people towards psychotropic drugs, a fact which is well-known to every clinician who uses such drugs. Why this "specific sensitivity" was observed, in our experiments, mainly after the use of Meprobamate, why was it more prevalent amongst the female subjects, why was it not accompanied by any observable sensitivity to any of the other drugs —all these are questions to which we are not able to give a concrete answer.

The definite conclusion of the whole experiment, however, is that the use of even mild tranquillizers must be avoided, as they affect learning ability adversely, unless there are concrete psychopathological indications pointing to the need of a specific therapeutic treatment with such drugs.



S. OKINAKA

Teaching of Neurology in Japan



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Development of Neurology in Japan

It seems certain that neurology in Japan has become well-established recently, although it was considered to be some years delay from the western countries. Since the first neurological society has been established 15 years ago in Fukuoka, the neurological sciences has been developing tremendously, reaching the level of international standard.

Western neurology was introduced in Japan by late Prof. K. Miura (1864-1950), who studied neurology from Profs. Erb and Charcot. However, in spite of various endeavor, neurology had been situated in the deep valley between internal medicine, neuropsychiatry and surgery without any independent status. After the end of World War II, there occurred vigorous move to establish the independent neurology in Japan by the group of younger internal medical people interested in neurology. About that time neurology was taught to students by internists and neuropsychiatrists without integral programs. The only related society was the Japanese Society of Psychiatry and Neurology, most of the members were psychiatrists.

With the collabortative efforts by Drs. S. Katsunuma (internal medicine, President of Nagoya University, died in 1963), Okinaka, Katsuki, and encouraged by Drs. H. H. Reese, L. T. Kurland, D. McAlpine and van Bogaert, the first independent neurological society, "Japanese Society of Clinical Neurology" was established in 1963 presided by Prof. Katsuki in Fukuoka.

This name was revised as "Japanese Society of Neurology" in the next year. The Society has about 700 starting members and now the membership exceeds more than 2000. The 15th Anniversary (Annual Congress) was held this year. Each year about 150 or more papers are reported at the annual meetings.

This Society has seven regional societies throughout Japan, which have periodical local academic meetings. It could be said that the neurological teaching and researches have been greatly accelerated by this active society.

Establishment of Neurological Department at University

Until 16 years ago, there was no independent chair for neurology in Japan as the departmental status. In 1963, the first independent Department of Neurology was established at Kyushu University named as Neurological Institute, Kyushu University and one of the authors (Y. K.) has been apointed as the full professor and chairman. Succeeding to this, Departments of Neurology have been established to University of Tokyo (Prof. Toyokura), Niigata (Prof. Tsubaki), Tohoku (Prof. Itahara), and others. Juntendo University (Prof. Narabayashi) and Tottori University (Prof. Shimoda) also have specified department.

Besides these institute, division of Neurology in the department of internal medicine have been developed in Toho (Tokyo), Kawasaki (Okayama), Hiroshima, Shinshu (Matsumoto City) Medical Schools or Uni-

versities with full professors. Thus relatively rapid increase in numbers of departments or divisions of neurology in Japan strengthen the neurological teaching and research very much.

Principle of Teaching of Neurology in Japan

The general trends in the teaching of neurology in Japan could be as follows:

1. Neurology must stand on the base of internal medicine in order to give general scope of the neurological medicine. Internal medicine is required in most of the departments before starting the specialty teaching.
2. Contact with basic sciences, such as anatomy, pathology, physiology, chemistry, immunology, virology, epidemiology, etc., is encouraged during the clinical training.
3. To encourage the international or global exchange of knowledge in order to introduce the various excellent ideas to our country is essential.
4. Undergraduate neurological teaching is important in order to give ability to every student to evaluate various neurological problems in various medical fields.
5. Postgraduate teachings should be reinforced.
6. Neurological teaching for the practioners also important in order to give recent advances or trends of neurological problems.

Neurological Teaching in Japan, Undergraduate

I (Y. K.) would like to describe the outline of the neurological teaching at the Neurological Institute, Kyushu University. Neurology has been taught to the students as an integral part of the internal medicine, although the teaching staffs are neurologists. Also close relationship with neurosurgery, a partner of the Neurological Institute, has been kept. Undergraduate teaching consists of two functions: lectures and clinical clerkship. Lectures start from the latter semester of the second year to the fourth year (medical school is of four-year-course). At the second year, general concepts of neurology (introduction to neurology) with physical diagnostic methods, are taught and the total hours are about 30.

Lectures for the senior medical students, 3rd and 4th year, clinical grand lectures with patients and slides are given totaling about 20 times for one student. These lectures are more detailed in the neurological problems with some research advance.

Stress is also laid on the clinical clerkship training as the required course to all students. At the 3rd year, two weeks outpatient clerkship for neurology and neurosurgery is required. During the two weeks students are asked to perform the history taking, physical diagnosis, and discussion with professors in the morning hours. The continuous two weeks out-patient clerkship for neurology (neurosurgery inclusive) might be effective to get some ideas on the physical diagnosis and introduction to neurology.

At the fourth year students also two week inpatient clerkship for neurology and neurosurgery are required, and neurology and neurosurgery cooperate in teaching.

During this hospital clerkship, the students are trained with superviser, in history taking, neurological examinations, interpretation of the laboratory examinations, such as EEG, angiography, EMG, biochemical studies, etc.

During these periods subjects of clinical teachings include neuropathies, myopathies, degenerative disease, demyelinating, toxic metabolic, vascular, traumatic, neoplastic diseases and other medical neurological problems. Examinations to students are performed three times; at the end of the introductory lectures in the 2nd year semester, at the end of hospital clerkship and at the graduation. Failure to any of these or absence of any clerkship inhibit the graduation from the medical school.

Postgraduate Neurological Teaching

Number of postgraduate trainees are accepted to our Institute. The first year residents are sent to medical wards to get

training in internal medicine and medical diagnostic procedures. The trainees will get the concept of neurology in the wide areas of medicine as well as the need for specialty training. All the residents enjoy these experiences. From the second year residents, specific trainings are given at the neurology wards. The trainings include clinical patient care, diagnosis, EEG, EMG, nerve conduction studies, angiographic procedures, and rehabilitation. As the elective procedures muscle biopsy, histochemical studies, nerve biopsy studies, enzymatic examinations are trained, which is continuous to the clinical research. The training period is usually four years.

Encouragement of Clinical Research

Residents are encouraged to perform the clinical research during the training period, such as case (autopsy) reports, clinical physiology (evoked potential studies in various neurological disorders, etc.), biopsy studies for muscles and nerves to study the neuropathies and myopathies, biochemical studies for metabolic diseases, etc. All the residents are encouraged to attend various neurological academic meetings to stimulate their scientific ambitions and to report their studies. Each year more than 50 printed papers are reported from our department.

Textbooks and Journals

In Japan increasing numbers of journals for neurology and textbooks written by Japanese are being published. The Japanese Journals are "Brain and Nerve", "Clinical Neurology" (Official journal of the Japanese Society of Neurology), "Neurological Medicine" (just recently started), "Advances of Neurological Sciences", etc. Journals for the related fields, clinical neurophysiology and others are important. As the textbook of neurology, "Clinical Neurology" (Tsubaki et al.), "Neurological Symptomatology" (Hirayama), several books of neurological diagnostic procedures are published. As a part of the Handbook of Internal Medicine, large volume of neurological sections are published. Summarizing these, in Japan, teaching of neurology by their own textbook written by mother tongue are being widely used.

Of course, students and residents are well aquainted with the famous western textbooks such as Merritt, Brain, Mayo Clinic's diagnostics, etc. Also western neurological journals are almost all provided at the departmental library.

Future Aspects

Specialty training should have the Specialty Board System. The Japanese Society of Neurology has a committee for the Board (chairman, Y.K.) and will start to have board examination in the near future. The level of the board examination should be in a high level. If these will be successful, it is hoped that our neurological teaching and practice will have the final goal and the societies will get the merit.

Neurology is generally very highly appreciated in Japan. Various important social diseases such as Minamata disease, Niigata Minamata disease, SMON (clioquinol neuromyelopathy) and other toxic neurological problems, are being solved by the neurologists. Also the Japanese Government, Department of Welfare, has started the national projects for various serious diseases, such as multiple sclerosis, progressive muscular dystrophies, SMON, myasthenia gravis, amyotrophic lateral sclerosis, and for most of these national projects, neurologists are playing important roles. Such situation facilitates the public recognition of the importance of neurological teaching and sciences.

However, we have to face that many medical schools are still not properly organized for neurological teaching. The standardization of the neurological teaching for undergraduate as well as for postgraduate training will be the next important goal for us.

SUMMARY

Neurology has been exceedingly developed in Japan for the last 15 years, after the establishment of the independent neurological society "Japanese Society of Neurology" and many departments of neurology or divisions of neurology in various medical schools. The fundamental of neurological teaching in Japan is widely based on the internal medicine, and active teaching in the undergraduate as well as postgraduate steps are being done. There are many Japanese neurology textbooks and journals. Specialty Board Examination for Neurology is now being prepared. There are many active and capable leaders in neurology in Japan, and we hope that the Neurological Teaching in Japan will be very promising in the future.

Personality

Prof. THEOPHILE ALAJOUANINE

Prof Alajouanine was recently homaged as one of the leader figures of the french and world Neurology.
We reproduce here a personality profil published in the "International Journal of Neurology" in the issue of Brain Vascular Diseases.



Halfway along the route from Bourges to Montluçon, there is a column that indicates that this is the center of France.

This geographical center of France has all the sentimental aspect which is attributed to the heart which has been considered for ages whence the emotions emanate.

This region sweet, gay, and gentle permeates human nature with the influence of its charm. There stands the ancient feudal castle of the Bourbon l'Archambault surrounded by an historical atmosphere.

From that place there came to Paris many years ago a young "Bourbonnais" whose ideal was to become a philosopher and a writer, and due to his thirst for a deeper knowledge of human nature, was attracted toward Medicine. And from there it was a logical step to the two branches that are nearer to the supreme mysteries of life, Neurology and Psychiatry.

Who was he? This young fellow, bohemian sensitive and energetic was going to be one of the glories of contemporary French Medicine, the Professor of Neurology at the Salpêtrière, Prof. Théophile Alajouanine.

"Every human life", says Alexis Carrel, "is a story that writes itself".

Many of these lives pass by ignored by the rest of the world, and others are carefully studied to uncover the secrets of their fruitful existence.

The action of the environment upon human personality and the reaction thus aroused in it molds man's future.

As a young student Alajouanine had his first contact with Surgery under the talented surgeon Tuffier. He was dazzled by the deft skill of the latter and so full of awe that he considered such activity a little too supercharged for his contemplative spirit; so he decided to become a clinician.

Every successful life is a living testimony of the beneficial influence that various persons have exercised upon its formation.

The ancient pre school "College Moulinois", which lighted the torch of idealism in several generations under its care, mold-

ed the spirit of the sensitive Alajouanine in the love of Science, Humanism, and definitively shaped his moral life.

Thus his mind was ready to attract every particle of knowledge, every spark of wisdom like a magnet.

The first years in Medical School were held in an unusual hospital constructed over Bastion 29. His first experiences as a medical student were with a very extraordinary individual even unusual for those days, Dr. Jules Auclair.

He was also a Bourbonnais, and a clinician who, surrounded by a mysterious atmosphere, spent many hours a day in the laboratory mashing Koch's baciles, seeking a way to isolate its chemical structure, study its biology and the therapeutics of tuberculosis.

Even though his research didn't make any impact on the history of Medicine he remains for Alajouanine an example of the honest and unselfish work of a doctor passionately in love with science, even though his efforts ended as Shakespeare says, "embracing a dream's shadow".

Never in later years did Alajouanine remember having the same mystical feeling like the one he experienced with Auclair in Bastion 29. This place seemed to him to be a sacred building that stood flanking some Parnasus where only the initiated could cross its threshold.

More typical experiences like those in every student's life followed those early ones.

Many renowned French leaders of Medicine poured into his mind the results of their fruitful lives.

The shadows of the First World War were upon his beloved France, and Alajouanine interrupted his internship "pour faire la Guerre" from 14-18. After serving many years in war time France, his career as an army doctor ended in sojourn in the Orient where everlasting friendships were made with Britishers, and there the enthusiastic defender of liberty, gladly surrended his own to the charm of an English lady, that became the faithful companion of his life.

France found in Dr. Alajouanine a faithful soldier, a loyal guardian of its liberty. His services as an army doctor in 1914-1918, and as a member of the Committee of Medical Resistance (President Pasteur Vallery-Radot) were rewarded with military distinctions of: Croix de Guerre 1914-18 (2 citations regiment-division), Chevalier de la Légion d'Honneur 1940, Officier de la Légion d'Honneur 1950.

Alajouanine earned the intern's gold medal (happy memories are the ones concerning the time he spent as an intern).

The golden years of his youth spent between the Bicêtre and Salpêtrière Hospital were regarded by Alajouanine as the most exciting and profitable ones of his life.

How suitable for peripatetic talks was the Versailles-like atmosphere that surrounded the Salpêtrière. There in the open air of the courts and with the severe silhouettes of the ancient building in the background the young students exchanged ideas. Many times they interrupted their inspired discourses to read with attention and emotion the souvenir that the unfaithful Manon left on the edge of an old well.

Every mystery encountered in treating the patients was a challenge to the dynamic interns' enthusiasm. Even the presente of the aged and the infirmed aroused in them zest of conquest of the enigma of life and death.

Neuropsychiatry was the key and Ariadna's thread to guide their logical thought through the labyrinthic road lead to the most puzzling problems of human existence and beyond to psychological and metaphysical speculations.

Why, if Alajouanine spent most of his internship among psychiatrists and loved so much to deal with psychological problems, did he decide to become a neurologist?

Psychiatry seemed to him in that time an exploration of the mind without much scientific evidence such as is found in Neurology. He felt he needed to base his studies on more concrete subjects, with a definite terminology.

Neurology offered him a science based on anatomy and physiology, enriched with findings every time more precise, with accurate controls, and a neuropathology where the cause of illness could be established.

So he decided to become a Neurologist, and fate led him to a person who played a key role in fulfilling this wish.

Like the sound of a cord sets in vibra-

tion another through sympathy, a great personality arouses resonances in another akin to it.

Friendships born of this sort of affinity survive time and death.

Thus Pasteur and Biot, Schumann and Brahms, Foix and Alajounanine.

To describe one is to list the virtues of the other, no better mirror can be chosen than the one of the spirit of a true friend.

As the old French proverbs goes "Qui s'ensemble se ressemble".

Where and when did Alajouanine meet Foix?

One memorable day in February 1914, on duty at the Salpêtrière as a young interne Alajouanine found a "fossil".

In the picturesque vocabulary of French medical student a "fossil" means an old intern.

That fossil had a peculiar and a striking personality. He was one of those people who radiate authority mixed with cordiality. The younger student was immediately won over by his superior competence. Intuitively he knew that a real teacher was hidden in this fellow whose dark brown eyes had a luminous shine, and whose sonorous voice had a warm and friendly inflection.

Foix was the one that had the most influence in Alajouanine's decision to become a Neurologist.

A real bond of friendship was interwoven in those lives so alike in their intellectual vivacity, their scientific curiosity, enhanced by an imagination that soars high and perceives far into the speculative horizon of the inner world.

Foix was for Alajouanine like an elder brother, whose judgement he could trust. Foix was the prototype of French mentality at its best. He became one of the greatest neurologists of France.

With clear certitude he faced the most puzzling problems of neurology at his time, and nowadays many researches and discoveries are based on facts established by his inquiring and logical thinking.

Thus, he introduced new views over the old concepts about the pathology of brain vascular diseases. His magnificent way of studying and interpreting every detail was accompanied by his ability to perform a synthesis that embraced the whole problem.

Divers kinds of brain softening have been classified by Foix. His contributions clarifying the pathogenical problems of vascular disease are regarded nowadays as classical ones on this subject.

We were deprived of other brilliant contributions to our Sciences when Death with its icy breath withered this life that was flourishing in all its many virtues, and at the peak of its intellectual powers.

The loss of Foix when he was only 45 years old, was a great shock for Alajouanine. He had shared so many things with him. The older intern had guided him into the intricacies of neurology. He had been his comrade during the torrid campaign in Macedonia in 1918. He had worked with him under Professor Pierre Marie. All this together made of Foix one of the most tender remembrances of his life, and whose name is always surrounded with the sorrow of his early demise.

The neurological bibliography is enriched with definitive conquest made by the team of these French inquisitive minds and the Late Cerebellar Atrophy with cortical predominance, is usually referred to as Cerebellar Atrophy of Marie, Foix and Alajouanine Type, and the Necrotic Subacute Myelitis as Foix and Alajouanine Disease. Along with Dr. Petit Dutaillis from 1927 to 1930, Dr. Alajouanine began the studies on intervertebral disc and thus he opened this important chapter of our speciality publishing the first papers on sciatica of discal origin.

But the long journey toward perfection wasn't void of many great leaders and Alajouanine was lucky to have had as his teacher, giants in the History of French Neurology like Pierre Marie, under whose direction he worked with Foix, Souques, and with Guillain and each of them has exercised his influence and shares the honour of having his former student in the Chair of Neurology at the Salpêtrière.

During the time Dr. Alajouanine worked with Pierre Marie, he met one of his best American friends Prof. Percival Bayley. From those far away days, an everlasting bond of friendship can be looked upon as a symbol that through science the world can be more strongly unified than by other means.

The University of Illinois has honored



AU TEMPS DU GRAND ROI ET DE LENCLOS
"Your reflexes are in good shape
Oh Joy Nini!"

From "Le Rictus", 1031 (humorous Medical Journal ad noum medicorum) we reproduce this drawing in which the fine French "sprit" fetes one of the most outstanding doctors making, a pun of his surname (A LA JOIE NINE! sounds in French like Alajouanine).

Prof. Alajouanine with the high distinction of Doctor Honoris Causa.

I had known for a long while the professional personality of Prof. Alajouanine through his writings, when I met him for the first time here in Montevideo.

He was visiting our country in 1938 and one day entering the Neurological Institute of the old Maciel Hospital, I was introduced to Prof. Alajouanine of Paris.

I found myself shaking hands with a short stout man, with a frank and cordial smile.

The feature that impressed me most was his eyes.

There is something that is found especially in the gaze of the people from the country, something that is lacking in most of the people that come from big cities. That is a mischievousness mixed with a tender glitter such as the one Will Rogers had.

It seems to be that nature nurtures the soul of those that are in contact with it from early years with an especial simplicity, tenderness, love and wisdom.

Good humour and friendliness, was felt at once in the presence of Prof. Alajouanine, and that was followed by respect and admiration when we saw the way he studied the neurological patients.

In those far off days of our training as a young neurologist, it was a custom in this country (now things are changed) that the history of the patient was read, then the next day after a carefully elaborated diagnosis the results were expounded before an audience.

To see this French neurologist, calmly hearing the history of the patient, and immediately telling afterwards the correct diagnosis and prognosis, it was for us something like a neurological Oracle of Delphian.

AS PROFESSOR OF NEUROLOGY

The History of the Chair of Neurology at the Salpêtrière, constitutes a long golden chain that links the glorious names of Charcot, Raymond, Dejerine, Pierre Marie, Guillain and nowdays it is brilliantly held by Professor Alajouanine.

On the occasion of the inaugural lecture of the Chair of Neurology in 1947, Alajouanine not only paid homage to the inheritance of the past, but looked to the future with an inquisitive mind. I can't resist the temptation to refer here to some of the very interesting concepts expounded upon clinical neurology and the so called scientific neurology in this initial class.

He was preoccupied about the relationship of these two different approaches to neurology. He remarked that the aim of Medicine was to understand, cure, and prevent illness. A patient is a spontaneous experiment that nature performs in human beings.

Everything is needed to help him, all scientific and technical knowledge must serve as a source of information for diagnostic and therapeutic purposes.

He resented the current view that clinical studies were regarded as obsolete, and not as the very back-bone, of medical practice.

This did not mean that every new technique was not useful, but that they must remain as an auxiliary tool of clinical information.

Another aspect of Neurology that worried Alajouanine was the multiplicity of branches everyone of which seems to be followed as a separate science, a division that tends to destroy the unity that must be found in every human attempt to conquer illness.

Lecomte Du Nouy says: "Pour comprendre, dans un sens assez restreint, un mécanisme il faut le démonter". That is true, and because of that Neurology is a speciality divided in many subspecialities.

But we share with Prof. Alajouanine his concept that it is necessary that the clinician can put together all the pieces again and understand the whole mechanism.

Thus, he states in his lectures that Neurology is constantly and dangerously broadening its field and that new specialists must face the dilemma of coping with so vast a field of knowledge such as Normal and Comparative Anatomy of the Nervous System, Embriology and Organogenesis, Physiology, Psychology, Physical, Chemical and Humoral Biology of nervous system; with its connected techniques of ocular, vestibular, electrical, and electroencephalographic investigation.

And adding to all this the long time that is needed to have a proper knowledge of anatomo-clinic studies. Many specialists are led to devote their lives to learn more and more of less and less.

But, as Alajouanine insists, it is necessary that some persons unify and give meaning to all these bits of knowledge in order that they really work in the sense of usefulness in the final control of disease.

Many years have passed since Professor Alajouanine has fully demonstrated himself to be the capable leader of much research both of a clinical and of an experimental nature.

His outstanding achievements in the field of clinical and scientific neurology, won for him the PRIX BREANT 1959. (Prize of the Academy of Sciences.)

This work demonstrated his ability to carry out his project of unifying the clinical and the experimental work.

To mention only some of the many achievements of Prof. Alajouanine in his chair we will refer to the creation of a "Center of Speech Studies" at the Salpêtrière, from which important papers have been written in connection with speech disturbances, embracing the whole aspect of this important neurological problem.

Patients are studied from the psychological point of view, with personally devised techniques created to register the speech and important aspects of reeducation.

These studies originated many monographs, and Prof. Alajouanine was invited, to London and Montreal, to deliver lectures about his important contributions to speech pathology, especially those related to aphasia.

Every year under the sponsorship of the Claude Bernard Association Neurophysiological Week is held at the Salpêtrière.

There is expounded the research done at the Centre of Neurophysiclogical Studies created also by Prof. Alajouanine and which is devoted to answering the most important questions concerning the organization of the nervous system. From this research conclusions are extracted in order to help explain the principal disturbances of nervous activity.

Among the most important ones, are studies performed on the activity of the temporal lobe, on the occipital lobe, on the rhinencephalon, as well as studies on the pain problem, epilepsy, tetanus, and sensorial integration.

It would take many pages of this Journal to detail here the numerous papers on very important subjects of Neurology which we owe to Prof. Alajouanine.

Such gratifying lives as that of Prof. Alajouanine must surely be due to his very gifted nature.

He has been defined as a person who is above all of that smallness of nature that drowns many talents.

Many scholastic generations of young neurologists have found in him an example of intelligence that spreads knowledge not as cold light of reason, but as warmed by the radiance of the immense kindness of his heart.

THEOPHILE ALAJOUANINE, WRITER

The bohemian youngster, whose imaginative and inquisitive mind was in love with writing, was held back in Alajouanine's subconscious mind, while Medicine invaded his whole personality with its imperious demands upon his time.

Once this tyranny felt by every medical

student was released, the writer surviving in him, was strong enough to resist the suffocating lock-out in the mind's attic. So, reinforced by knowledge, seasoned by experience, his literary gift flourished in many substantial articles published by "La Nouvelle Revue Française", "Cahier de la Pléiade le Divan", "Cahiers Bourbonnais", "Cahiers Charles Louis Philippe". Several studies about the lives and works of famous people were written by him, there are such lives as those of Bauville et Sainte-Beuve, Charles Louis Philippe, Valery Larbaud, etc.

Occasionally it happens that I have had in my hand a very witty preface written recently by Prof. Alajouanine as a preface of the book's catalogue of Librarie Gallimard. In it he describes several kinds of Bibliophiles, his remark on the differences established between Bibliophile and Bibliomania is interesting and also his conclusion about the special physiology and psychology of people affected by the most extended of our cultural diseases.

As you can see, Medicine is already taking revenge on the writer, influencing this literary mind by the ruling word of his kingdom.

VICTOR SORIANO

• News

THE AMERICAN NEUROLOGICAL ASSOCIATION

Joseph M. Foley, President

From:
Peritz Scheinberg, Secly.
U. of Miami School of Medicine
Dept. of Neurology
P. O. Box 520875 Biscayne Annex
Miami, Florida 33152

CALL FOR PAPERS

The Centennial Meeting will be held at the New York Hilton, New York City, June 2, 3, 4, 1975. Our present plans call for the First Session to begin at 9:00 A.M. on June 2, adjourning at noon on the 4th.

Those applying for a place on the program should submit two abstracts to the Secretary as early as possible, but no later than Wednesday, JANUARY 15, 1975 as follows:

1. On the form enclosed for the program an abstract not exceeding 200 words, double spaced. No illustrations or tables are to be included. Additional forms may be requested of the Secretary. Please give all information requested on the form. Failure to do so will result in its return for completion. No carbons are needed, and all copies should be returned.
2. A second abstract, in duplicate, for publication in the Transactions, not exceeding 1000 words, typewritten, double spaced on 8½" x 11" white bond paper giving name and city of the author(s). No illustrations or tables will be published in the Transactions.
3. Those submitting abstracts should enclose two (2) self-addressed *stamped* postcards for notification of receipt of abstracts and action of the Program Committee. Presentation from the platform will be limited to 10 minutes.
4. *Discussions:* For purposes of this meeting names of discussants are not being requested at this time. If accepted such may be requested of the author by the Program Committee, or the committee may request discussants of its choice. Time will be allowed for spontaneous discussion and all members are urged to participate.

Publication of Papers: By vote of the membership, the Archives of Neurology has been designated as the official journal of the American Neurological Association. All papers presented at the Annual Meeting must be submitted to the Chief Editor, Dr. Fred Plum, New York Hospital, 525 E. 68th St., New York, New York 10021, for acceptance or rejection by the Editorial Board of the Archives. Members not wishing to have their papers considered by the Archives must obtain a release in writing from the Chief Editor before submitting them for publication elsewhere. Abstracts must report work not presented or published prior to the meeting.

THE AMERICAN NEUROLOGICAL ASSOCIATION NEWSLETTER

The purpose of this newsletter is to keep the membership informed of the discussions and actions of the Council, and to encourage thereby active input and participation in the affairs of the ANA by all members.

It was reported that we have a small operating deficit which eventually will require reconsideration of the dues structure. The Council postponed any definite action until the June meeting.

Future meetings:

1. 1975 - June 2nd, 3rd, & 4th, New York Hilton Hotel. This, of course, will be the Centennial Meeting and registration is expected to be high. For that reason we urge that you send your request for room reservations as promptly as possible. Reservation cards are enclosed. There will be a Gala Cocktail Party at the Metropolitan Museum, arrangements being made by the local arrangements committee.

2. 1976 - June 14th, 15th, & 16th, Mark Hopkins Hotel, San Francisco.

3. 1977 - June 13th, 14th, 15th, Palmer House, Chicago.

All the above meetings will be immediately preceded by the Meeting of the American Association of Neuropathologists.

The President instructed the long range planning committee to consider the advisability of a change in the time of the meetings for subsequent years. It has been suggested that the June meeting too closely follows the Academy meeting and that we might benefit by changing our meeting time to the Fall. One suggestion was to consider meeting in October in conjunction with the Neurosciences Society. Membership reaction to these proposals would be appreciated.

Archives of Neurology - In view of recent unilateral decisions by the AMA Board of Trustees in regards publications, Editor Fred Plum was requested to explore alternatives in the publication of the Archives of Neurology, in the event that it was felt appropriate by the ANA Council and membership to publish this Journal without AMA sponsorship. Dr. Plum has already actively investigated other possibilities. In this regard the Council again discussed the question as to whether the Transactions of the ANA should continue to be published since it is a moneylosing venture. It was generally felt that if the AMA assumed complete responsibility for the Archives that immediate reconsideration of the need for the Transactions would be undertaken.

The Program Committee recommended that our membership be more active in soliciting high quality presentations for the annual scientific program.

As of November 30, 1974 there were 272 active members, a number of Senior and Associate members having elected Active membership status. The Council reviewed the recommendations of the Membership Advisory Committee in detail and reviewed the membership proposals. First proposers have been informed of the action of the Council in each instance.

A new application form is being printed to provide additional and more exclusive information for the Membership Advisory Committee at its future meetings.

The Council discussed, informally and formally, the developments at the recent meeting of the Association of the American Medical Colleges and specifically the Council of Academic Societies. The impacts of the proposed new Health Manpower Legislation on Neurology were discussed, with specific reference to the possible restrictions on specialty training, capitation fund restrictions for medical students, restriction of training opportunities for foreign medical graduates, etc. President Foley proposed one of the sessions of the June meeting be devoted to additional information about these highly pertinent problems. The Council would welcome comments and further information from members, particularly suggestions in regards the ways in which the ANA can effectively influence future legislation.

In this regard Dr. Paul Bucy reviewed the activities of the National Committee for Research in Neurological Diseases, indicating that he was resigning as Chairman. A new Chairman has not been appointed. The American Neurologic Association along with many other neurologic and special sensory organizations provides support, although inadequately, for this important organization which originally was formed to provide authoritative and helpful informational sources for Congress. Dr. Donald Tower has called a meeting of various key neurological and special sensory organizations, for informational and advisory purposes, to be held at NIH sometime in January and the AMA will be represented at that meeting.

All members are urged to send to Council to this office suggestions, comments, complaints, etc., provided that they are designed to improve the ANA.

Best wishes for the New Year.

Peritz Scheinberg, M. D.
Secretary

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The American Electroencephalography Society has formed a Committee for International Collaboration in Teaching and Research. The goals of the committee are:

1. To establish contacts for Latin American scientists and students with USA scientists and teachers interested in collaborative work.
2. To establish a roster of USA scientists and teachers willing to donate leave or sabbatical time to work in institutions requesting such visits.
3. To establish a registry of surplus labo-

ratory equipment, books and journals for transfer to those in need.

If interested in further information, please contact:

Professor John M. Rhodes
Department of Neurology
School of Medicine
University of New Mexico
Albuquerque, New Mexico 87131
U.S.A.

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DR. BURNS TO HEAD RENAL SECTION AT ST. VINCENT'S

Dr. Godfrey C. Burns has been appointed Chief of the Renal Service at St. Vincent's Hospital and Medical Center of New York, Department of Medicine Director Dr. William J. Grace announced today.

Dr. Burns' new duties include management of the Hospital's dialysis and hypertension programs as well as coordination of the teaching and research activities of the Department.

Prior to this appointment Dr. Burns was Associate Chief of the Renal Service at St. Vincent's and Head of the Renal-Hypertensive Section at the Boston, Massachusetts Naval Hospital.

An instructor in Clinical Medicine at the New York University School of Medicine, Dr. Burns is a graduate of the Howard University College of Medicine. He completed his internship, residency and renal-disease fellowship at St. Vincent's in 1970.

Dr. Burns is certified by the American board of Internal Medicine and is a member of the New York County Medical Society, the New York Society of Nephrology, and the National Medical Association.

St. Vincent's is an 802 bed acute care hospital serving 500,000 people on Manhattan's lower west side.

Contact: Edward C. Haggerty
(212) 620 - 1418
or
Peter Rosenthal
(212) 620 - 1418

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TENTATIVE PROGRAM TORSION DYSTONIA CONFERENCE 1975

Friday, May 30 and Saturday, May 31, New York City

Friday, May 30

EVENING

AT HOTEL
DINNER - 7:00 PM
HISTORY - 8:00 - 9:30 PM

W. ZEMAN
Dystonia, a review

R. ELDRIDGE
The views of Flatau and Sterling on dystonia in 1911

Saturday, May 31

MORNING

THE NEUROLOGIC INSTITUTE
8:30 - 10:00 AM

GENERAL LECTURES

D. PURPURA
Anatomy of the Basal Ganglia

S. FAHN
Chemistry of the Basal Ganglia

I. H. SCHEINBURG
Pathophysiology of dystonia in Wilson's disease

Break 10:00 - 10:15 AM

10:15 - 11:15 AM

GENETIC STUDIES

S. BUNDEY
Genetic studies of 60 English families with dystonia

V. MARKOWA
Evidence for two hereditary forms of dystonia in Russia

R. GOODMAN
Dystonia in three Israeli populations

11:15 - 12:00 PM

CLINICAL VARIANTS

C. MARSDEN
Idiopathic, late onset torsion dystonia

N. SCRIBANU
X = linked torsion dystonia

R. HASLAM
Psychological aspects of torsion dystonia

N. ALLEN
Juvenile parkinsonism or torsion dystonia

12:00 - 12:30 PM

CLINIC
STAFF OF THE NEUROLOGIC INSTITUTE AND OTHERS
Presentation of patients

AFTERNOON

THE NEUROLOGIC INSTITUTE
LUNCH - 12:30 - 2:00 PM

2.00 - 2:30 PM

EPIDEMIOLOGY

G. GOLDEN
Dystonia in the black American

S. GIMENEZ - ROLDAN
Dystonia in the Spanish Gypsy

H. NARABAYASHI
Hereditary and acquired dystonia in Japan

2:30 - 3:45 PM

BIOCHEMISTRY AND EXPERIMENTAL MODELS

I. COOPER
Results of cryocerebellar biopsy in dystonia

F. WOOTEN, W. KANTER and .R ELDRIDGE
Evidence for elevated dopamine-beta-hydroxylase with autosomal dominant torsion dystonia - Experience in 100 patients

M. COLEMAN
Catecholamine and glutamine metabolism in torsion dystonia

A. BARBEAU
Trace metals, experimental dystonia and torsion dystonia

M. GOLDSTEIN
Experimental torticollis in the monkey
Break - 3:45 - 4:00 PM

4:00 - 5:30 PM

MANAGEMENT

M. SEGAWA
Treatment of dystonia and dystonia variants with L-DOPA in Japan

M. GELLER, N. CHRISTOFF and M. YAHR
Carbamazepine in dystonia; success in 10 patients

W. HORTON, W. STUART and R. ELDRIDGE
Dantrolene Sodium in dystonia; results in 7 patients treated in a double blind study

I. H. SCHEINBURG
Lioresal in dystonia; a pilot study with 5 patients

I. COOPER and M. RIKLAN
Long term results of thalamic surgery in 150 patients with dystonia

J. VAN BUREN
Equivocal results of thalamic surgery in dystonia

EVENING

DINNER - 7:00 PM

8:30 PM

MARJORIE GUTHRIE
The Role of Patient Organizations in Neurologic Research

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• Book Reviews

EPILEPTIC SEIZURES

by HENRI GASTAUT, MD and ROGER BROUGHTON, MD.

286 pp. CHARLES C. THOMAS - Publisher. Springfield. Illinois.

This excellent book was performed with studies made with accurate and detailed clinical observations of every type of epileptic crisis with Electroencephalographic and poligraphic studies referred to Electrocardiogram, Pneumogram, Electrodermogram, Plethysmogram, Barogram (Pressure recording, intragastric pressure, intrabladder pressure, intra-arterial catheterization), micturation recorder, electromyogram, oculogram, actogram (for converting movement into current). Other techniques are mentioned for documentation such as filming, etc. Activating and differentiating techniques are described; hyperventilation nitrous oxide breathing, oculo-cardiac and other reflexes, carotid artery compression, photic stimulation, auditory, tactile and other stimuli, sleep activation, use of convulsant drugs. Everything is explained in detail.

After epileptic seizures are studied; clinical features and Pathophysiology.

A) GENERALIZED EPILEPTIC SEIZURES.

1) Tonic clonic seizures (Grand Mal Seizures). 2) Tonic Seizures. 3) Clonic Seizures. 4) Infantile Spasms. 5) Bilateral Myoclonus. 6) Absences. 7) Atonic Seizures. 8) Akinetic Seizures.

A thorough clinical description of each one of these types of epileptic crises is made with the respective records, and after the Pathophysiology of each one of the mentioned types of epileptic seizures is studied.

B) UNILATERAL EPILEPTIC SEIZURES.

1) Unilateral Tonic-Clonic Seizures (Hemitonic-clonic Seizures). 2) Unilateral Tonic Seizures (Hemitonic Seizures). 3) Unilateral Clonic Seizures (Hemiclonic Seizures). 4) Unilateral Infantile Spasms. 5) Unilateral Massive Myoclonus. 6) Other Seizure Types - Pathophysiology of Unilateral Epileptic Seizures.

C) PARTIAL EPILEPTIC SEIZURES.

1) With simple symptomatology. 2) With complex symptomatology. 3) Partial Seizures with Secondary Generalization. Pathophysiology of Partial Epileptic Seizures.

COMBINATIONS OF EPILEPTIC SEIZURES (including the Epilepsies).

A) Forms of Epilepsy according to the temporal distribution and precipitation of the seizures: 1. Isolated seizures. 2. Repeated Seizures: The Epilepsies. 3. Prolonged and Frequently Repeated Seizures: Status Epilepticus.

B) Forms of Epilepsy according to the Clinical Features and Pathophysiology of the constituent seizures: 1. Generalized Epilepsies. 2. Unilateral Epilepsies. 3. Partial Epilepsies.

C) Forms of Epilepsy according to the age of the patient: 1. Epilepsies of the newborn. 2. Epilepsies of Infancy. 3. Epilepsies of Childhood. 4. Epilepsies of Adolescence, Adulthood and old age.

D) Forms of Epilepsy according to the Etiology of the Seizures: 1. Non-organic Epilepsies (Functional Epilepsies). 2. Organic Epilepsies.

E) A possible unitary classification of the epilepsies.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS.

A) Positive Diagnosis: 1. Clinical Approach. 2. Electroencephalographic Approach. 3. Radiological Approach. 4. Biological Laboratory Approach. 5. Psychological Approach.

B) Differential Diagnosis: 1. Anoxic Seizures (Hypoxic Seizures). 2. Toxic Seizures. 3. Psychic Seizures. 4. Hypnic Seizures. 5. Miscellaneous Disorders.

TREATMENT

As an appendix: Clinical and Electroencephalographical classification of Epileptic Seizures.

From what we said it is possible to infer the wealth of information that may be gathered from this book that collects observations and studies performed in one of the

most important institutes of the world in this specialty.

Víctor Soriano

★★★

EPILEPSY ITS PHENOMENA IN MAN

Edited by **MARY A. B., Brazier**
UCLA FORUM in Medical Sciences.
Number 17. 391 pages.

ACADEMIC PRESS - New York and London - 1973.

Different subjects that constitute partial approaches to fundamental matters in the knowledge of epilepsy are treated in this book edited by Mary A. B. Brazier with chapters written by very distinguished authors.

Mary A. B. Brazier makes a Historical Introduction, emphasizing on the contributions of Kaufman about the mechanisms of the abnormal discharges in epilepsy.

O. D. Creutzfeldt treats the synaptic organization of the cerebral cortex and its role in epilepsy.

The lack of synaptic inhibition is not the only reason of epileptic activity in the cortex, but it is a very important factor to facilitate the seizure.

The abnormal nerve cell depolarization of neurons of the brain are the immediate cause of self sustained seizure. The cortex is unique in its aptitudes to have recurrent excitation. Recurrent inhibition is a feature that exists in practically all sub-systems of the Central Nervous System. Dis-inhibition plays an important role in the unmasking of basic epileptic excitatory disturbances.

Daniel A. Pollen writes on Focal Epilepsy and the neurological impairment hypothesis. There is much anatomical, surgical and physiological evidence in favour of this hypothesis, but still it is not proved.

Robert Naquet refers to the Contribution of Experimental Epilepsy to understanding some particular forms in man. It is useful to investigate the respective roles played by certain nuclei in the brainstem on the one hand and by the cerebral cortex on the other in the pattern and the release of paroxysmal frontorolandic EEG discharges evoked by intermitent light stimulation.

Depth recordings in man in temporal lobe epilepsy by P. Buser, J. Baucaud and J. Talairach. They consider time relationships between interictal spontaneous discharges and besides intent to establish with their technique regional connections in the lymbic system. Connection between ipsilateral structures of the Basal Rhinencephalon - Transrhinencephalic connections. Connections between Rhinencephalon and Cingulate Girus.

Richard D. Walter treats tactical considerations leading to surgical treatment of limbic epilepsy. Localization of focus is obtained from ictal recordings that can be technically facilitated using telemetry techniques.

H. Petsche and P. Rappelaberger study the problem of synchronization in the spread of Epileptic Discharges leading to seizures in man. In cerebral cortex the deepest layer seems to play the most significant role in the propagation of the seizure patterns. An inverse relationship seems to exist between wave duration and speed of propagation.

Electrical seizure discharges within the human brain: The problem of spread is treated by Mary A. B. Brazier. The spread follows not only anatomical connections, but also electrophysiologically identified pathways.

Behavioral correlates of generalized spike wave discharge in the electroencephalogram, by J. Kiffin Penry. He emphasizes the importance to prove the efficacy of antiepileptic drugs in the treatment of patients with epilepsy.

Janice R. Stevens writes on Psychomotor Epilepsy and Schizophrenia. A common Anatomy? Both diseases are related to disorders of different biochemical and anatomical systems. One is primarily cortical and thus more influenced by brain stem norepinephrine-serotonine modulation. The other is predominantly limbic striatal and in receipt of Dopamine and serotonine terminals from brain stem fluorescent nuclei. Clinical and experimental studies indicate important interactions between these systems.

David D. Daly: Circadian Cycles and Seizures. Seizures on a wakening seem associated with those epilepsies variously termed centro-encephalic, reticulo - cortical or common generalized.

C. Ajmone Marsan and L. Goldhammer: Clinical ictal patterns and electrographic data in cases of partial seizures of frontal-central-parietal origin. Epileptogenic processes localized in certain cortical regions tend to manifest themselves with (or without) certain seizure patterns.

Gian Franco Rossi treats the problems of analysis and interpretation of electrocerebral signals in human epilepsy, a neurosurgeon's view. The electrophysiological criteria helpful in locating the epileptogenic zone through stereotaxically implanted electrodes is studied, mainly in temporal lobe patients.

P. H. Grandall: Developments in Direct recordings from epileptogenic regions in the surgical treatment of partial epilepsies.

M. E. Scheibel and A. B. Scheibel: Hippocampal Pathology in Temporal Lobe Epilepsy. A. Golgi survey. The study of hippocampal tissue from patients with temporal lobe epilepsy has served to emphasize the frequency with which minimal changes can be found in isolated neurons and even in portions of the dendrite system of single nerve cells. The authors suggest that these findings can be putatively assigned to some type of progressive pathological process possibly of genetic enzymatic or slow virus nature.

Structural substrates of Seizure Foci in the human temporal lobe —W. John Brown— 65 % Hippocampal sclerosis was demonstrated —Hamartimata were found in 18 %— one malignant neoplasm revealed and no lesion was evident in 14 %.

This brilliant book must be read by all the specialists in neurosciences, who will find many very interesting things related with the problem of Epilepsy.

Víctor Soriano

Lab. CELSIUS

LUVAX — 5 MEDAZEPAN

LUVAX — 10 "

ANSIOLITICO SIN EFECTO HIPNOTICO

REPRESENTACION ARMOUR

ACTH - AR ..... 40 u. i.

ACTH - AR gel ..... 40 u. i.

CHYMAR 1 cc. ..... 5000 u. i. Quimotripsina

ARMOUR SIGNIFICA PROTECCION