International Journal of Neurology

ISSUE DEDICATED TO:

TOXIC DISEASES OF THE NERVOUS SYSTEM

VOLUME 11 NUMBER 4

INTERNATIONAL JOURNAL OF NEUROLOGY

CONTENTS OF VOL. 11 — NUMBER 4

Editorial

Certain kind of toxic substances are prone to settle on the brain, other on the spinal cord and some of them on the peripheral nerves.

There are some toxics than can damage different sectors of the nervous system producing in this way more than one clinical picture.

The toxic manifestations are studied in its clinical, histological and chemical aspects. We are going to refer to those toxics that can damage the nervous system.

We will also mention some clinical pictures that can be produced for different toxics.

MANGANESE

The miners that extract manganese and inhale much ore dust, may be affected by psychiatric and neurological ailments. The inhaled dust produces cough, then is swallowed and can be in this way absorbed through the gastrointestinal tract. In chronic intoxication by manganese, the frequent clinical picture is a parkinsonian Syndrome. In few instances a muscular dystonie may be observed.

Cirrhosis of the liver and degenerative changes in the neurons of the basal ganglia and cerbral cortex can be detected.

The Parkinsonian syndrome has similar clinical characterists to that observed in humans for some unknown cause.

It is considered that manganese affect the melanine of the brain.

In squirrel monkeys experiments have been made treating them with manganese dioxide which produced rigidity, dystonia and tremor. It was observed disturbed brain amine matabolism with appreciable lower caudate nucleus DA and 5 HT concentrations.

These changes of the brain amines are specific for basal ganglia.

We must point out that parkinsonism produced by chronic intoxication with manganese must be treated with the same medication than similar extrapyramidal pictures of different etiology. Thus they improve with L Dopa.

Chronic lead intoxication damages almost all the organs of the body.

Concerning the nervous system, this toxic may produce a chronic polyneuropathy or an acute encephalopathy.

Lead polineuritis is a motor neuritis that damages especially the extensor muscles of the fingers and wrist. It happens almost exclusively in adults.

It is frequently seen in those workers who handle substances that contain lead, pottery glaziers, painters; also it could occur as an accidental intoxication.

The polineuritis generally begins by damaging the extremities of the fingers and wrist, usually in a bilateral way, but sometimes one arm is affected before the other. It is akin to a radial nerve palsy with the difference that the brachioradialis muscle is spared.

Rarely are the lower extremitis involved· Laboratory findings may show traces of lead in the cerebro spinal fluid, urine, feces.

The proteim content of the cerebro spinal fluid may be increased.

Lead encephalopathy occurs almost exclusively in children that carry things to their mouth containing lead material, lead containing paint on crib, toys and walls. Now is less frequent because paint with lead is not more used.

The encephalopathy shows an important cerebral edema and damage to the capillaries that may become necrotic.

There are degenerative changes in the nerve cells and myelin sheaths accompanied by proliferation of the glial cells.

Frequenthy these begin with convulsive seizures of a generalized or focal nature with coma or lethargy.

After seizures there may appear in the clinical picture, hemiplegia, cerebellar ataxia and other neurological symptoms, oculomotor, or facial paralysis.

It can be observed choked optic dises or optic atrophy.

The cerebro spinal fluid demostrates an increasing of the protein level with normal or augmented cell count.

The analysis of urine shows albumin and frequently coproporphirin and glucose.

The epiphyseal ends of the bones show on x ray opaque lines.

It is not possible to find in the literature accurate information about the pathomecanism of this intoxication. It is unknown as to the correlation between the symptoms of lead intoxication such as anemia and renal lesion and the onset of the neuropathie. It seems to be that the finding of lead is much highar in the liver than in any part of the nervous system.

This poses the question whether the lead acts directly on the nervous system.

Damage in the peripheral nerves occur primarily on the Schwaun cells.

The sector of myelin that is in relationship with the degenerated Schwan cells shows splitting of the major and minor dense lines and membranous blebs formation .The way of acting of the lead to provoke these disturbances is unknown.

It is believed that perhaps lead blocks the action of groups of enzimes producing insufficient fatty acid synthesis or elongation, and thereby destabilization of myclin.

THALLIUM

The intoxication may be accidental by ingestion of rat poisons, depilatory creams and other substances containing thallium.

If the amount of toxis taken is great, death happens in a short time.

The clinical manifestatacions of the intoxication related to the nervous system are convulsions· delirium, blindmess, cranial nerve palsies, and weakness of the extremities. These symptoms are preceded by gastrointestinal symptoms: epigastric pain, vomiting and diarrhea.

In the chronic form of intoxication producced by small amounts of the toxic absorbed from the skin, polineuritis, optica neuritis and alopecia may be observed. This chronic intoxication, generally has good prognosis for life.

MERCURY

Acute intoxication damage to the kidney and the patient can be afected by delirium, coma and convulsions.

Chronic intoxication occasionally produces neurological complications,these are tremor that start in arms and spread to lower limbs and cephalic region, paresthesias of mouth, tongue and extremities, cerebellar incoordination, weakness, dysartria, constriction of visual field· blindness.

Sometimes the following psychic changes are also observed, mental deterioration, irritability and apathy. In addition pyramidal signs and muscular atrophy have been observed.

The Minamata Disease in Japan is produced by eating animals that are impregnated with mercurial compounds that were received with water or foods.

Chronic mercury intoxication may be consequence from the administration of mercurial drugs or exposure in industry.

ARSENIC

The intoxication may be accidental, by insecticides, rat poison, etc. In the nervous system produces polineuritis, optic neuritis.

When intravenous are injected organic arsenical compounds with therapentic purposes, may appear as a toxic complication, acute hemorragic encephalopathy.

Ingestion of large amount of aresenic by mouth may produce convulsive seisures and death. If the patient recover, after several weeks may develop a polineuritis.

COPPER-Wilson's Disease.

Copper under abnormal conditions or in exces can be toxic.

Intoxication originated by copper sulphate has been observed when this substance is used for the treatment for burns or by accidental ingestion.

In experiments performed on pidgeons minimal dosis of the toxic reaching the subarachnoid space, produced convulsions and death.

Toxic effect happens as a consequence of the inhibition of the membrane AT Pase Copper inhibit several of enzyme systenas.

In human beings copper biochemistry is linked to Wilson's disease which is an hereditary disease, caracterised by disturbances in movemants, by subacute on chronic liver disease, renal disorder copper's deposit in the corner, and the Kayser Fleischer rings.

Copper has a primordial role as an intracellular oxidase as the final carrier in the electrontransfer chair of the ultimate source at the cellular level.

Still it is not determined what its role is in the brain, but it is thought that perhaps in subcortical nuclei is present in enczims entailed to oxidation of Dopamine. In respect to Wilson's Disease it must be noted, that Copper's transport and storage are disturbed. This provokes a positive copper's equilibrium with the accumulation in the body of a great exces of Copper, in particular in the liver, brain and kidneys. Another significant fact is that copper is toxic for some enczimes systems, particularly for those that are mediated through a SH group at the active catalytic centre. Some patients show apparent tremor or spontanious movement, some with dystonia, others with choreiform movements some are akinetic.

Occasionally one observes transient conciousness obnubilation, also epileptic seizure. Some patients suffer severe psychiatric disturbances.

In the parkinsonian syndrome it the degeneration of the pigmented nuclei of the brain, is observed which those have the highest copper content.

Many patients with Wilson's disease show parkinsonian symptoms.

May be in Wilson's Disease the excess of copper's produces a disturbance of the metabolism of the Dopamine transmissor system.

In the early states, copper may potentiate synthesis, conducting to abnormal movements, later when copper's concentration surpass an initial level, synthesis is inhibited and a more tipical Parkinsonian Syndrome appears that leads to akinesia.

CYANIDE - Demyelination

Cyanide intoxication is a demyelinating disease with particular suceptibility of the corpus callosum.

The oligodendrocytes are also affected and shows swelling of the endoplastic reticulum in the perikarion.

In damaged areas a diminution of cerebrosides and DNA is observed.

Also it has been verified that axons lose calcium which is an essential element for their stability.

CARBON MONOXIDE

Poisoning by CO produces extensive demyelination in the Central Nervous System with gliosis, but preservation of the U fibers.

Leucoencephalopathy following acute CO poisoning has been reported. The alterations of the white matter in man are caused by destructive changes of venules and capillaries that affect the Blood Brain Barrier.

Biochemical studies made in humans after intoxication with carbon monoxide made evident a reduction of phospholipids, cerebrosides and colesterol.

Biochemical changes in grey substances are not observed.

Poisoning in severe cases results in coma and death.

If the patient recovers from an important intoxication, symptoms of brain damage, aphasia, apraxia, hemiplegia, cortical blindnes, dyskinesias or typical signs of Parkinsonism may be observed.

If the intoxication is not severe the patient shows headache, drowsiness, mental confusion.

ETHYL ALCOHOL

Alcoholic polineuritis

Alcoholic polineuritis originated by chronic intoxication with alcohol has been associated with a defficiency in thiamine originated by insufficient consumption in the diet of chronic alcoholic together with the chronic gastritis and the disturbances of the gastrointestinal function that they frequently present.

In some cases low levels of nicotinic acid, pyridoxine, folic acid, patothenic acid, biotin and riboflavin have been observed.

Augmentation of the level of blood piruvate in patients with alcoholic polineuropathy have been mentioned.

In any case the role played by vitaminic deficiency is still not well studied.

We will mention without refering to their characteristics, other diseases that can be produced by chronic alcohol intoxications. Wer-

nicke's polioencephalitis, Korsakoff's psychosis· delirium tremens, acute auditory hallucinosis, alcoholic convulsive seizures, mental-deterioration and parenchymatous cerebellar degeneration.

Alcohol also in an exagerated dose produces an acute intoxication. This condition is evident when the blood level of alcohol reachs the figure of 150 mg per cent.

If it is of 250 mg. a coma state is produced. When the level is higher than 400 — 500 mg. per cent, then death occurs.

METHYL ALCOHOL

Methyl alcohol produces acidosis, cerebral edema.

Poisoning by this substance takes place by accident in industry or by ingestion and may be fatal. Symptoms of the intoxication are headache, blurring of vision, drowsiness, cianosis, dyspnea, abdominal pain, vomiting.

If the patient recovers from the intoxication it is very probable that he will be blind.

BELLADONA

When this substance is excesivelly ingested it can produce a clinical stateof hallucinations, delusions and acute psychotic states. Generally this evolution is not fatal. If a patient has special susceptibility, a therapeutic doseproduces dilatation of the pupils, dryness of the mouth, and difficulty in the convergence of the eyes.

BARBITURATES

These are utilized as hypnotics and in the treatment of convulsive disorders. As happens with other hypnotics they creat a form of addiction.

Sometimes they are taken purpose by in great dose to commit suicide.

When they are taken in excess they can produce slowness of mental processes, drowsines· thickness of the speech, headache, psychotic state, ataxia of the gait, and nistagmus.

When the drug is slowly with drawed to avoid convulsions, generally the mentioned symptoms disappear.

Acute intoxication with high dose of barbiturates produces deep coma, loss of deep reflexes, cyanosis, slowness of respiration.

On some occasions, the process can end in death. Nevertheless with proper treatment, the patient generally recovers without sequel.

HYDANTOINS

Dilantin the diphenyl derivative of hydantoin is the most used of the hydantoins.

In the nervous system it may produce toxic side effects, acute cerebellar ataxia and nystagmus, mild polyneuritis, and psychotic manifestations.

Cerebellar manifestations are the most frequent of these complications and in most cases disappear if Dilantin is changed by another antiepileptic drug.

If in a few days after ataxia improve, the patient receives again Dilantin the disturbance do not reappear. This subject is very well studied in this issue by Ziegler.

DYSKINESIAS PRODUCED BY DRUGS

Disturbances of movements provoked by drugs, are evident with the use of modern psychotropic drugs. We will mention Phenothiazines, Butyrophenones and Reserpine.

They produce improvement in paychiatric disorders but as side effects may provoke Diskinetic disturbances, Experiments made in rats with reserpine produce in the animals, tremor, rigidity and akinesia, this seems to be related with the brain amine depleting effect or reserpine which may be reversed by intravenous injection of L-dopa and L5HTP.

Also it motor disturbances with Phenothiazines and Butyrophenones can be observed. In experimental studies, it has been observed that with these drugs brain amine levels are little affected. Its action is oriented toward blocking of the amine receptors.

In parkinsonian patients treatment with L-dopa may produce involuntary movements, which can be caused by a local excessive DA-ergic activity/5HF ergic activity.

POLYNEUROPATHY DUE TO ORGANO PHOSPHORUS COMPOUNDS

In the United States in year 1930 there appeared a motor neuritis which was demonstrated to be provoked by ingestion of a drink that contained as adulterant triorthocresylphosphate (TOCP). In following years it has been verified that many cases of polyneuropathy have been provoked by this substance.

Cases resembling polyneuropathy have been observed as consequence of intoxications produced by organo-phosphorus anticholinesterase compounds with potential insecticidal activity.

Compounds that provoke this polyneuropathy are all esters of phosphorus containing acids and they are inhibitors of esterases.

Evidently inhibition of cholinesterase activity is a cause of intoxication. Studies made in experimental animals prove that these intoxications degenerate both axis cylinders and myelin sheaths in the central nervous system and the peripheral nerves.

Johson has shown that the nervous system contains an enxyme which he has been called the neurotoxic esterase. He thinks that this neurotoxicity is related to its phosphorilation and the "neurotoxic effect is a result of phosphorilation as such and not a consequence of prolonged deficiency of the esterase activity.

We wish to express our gratefulness to the excellent group of authors, who contributed to this issue with deep knowledge and broad experiencie on one of the most complex neurological subjects. Their bright concepts will be very useful to our readers engaged in the solution, understanding and managements of one of the most complicated patients to be confronted.

Prof. Dr. Víctor Soriano.

n-Hexane Polineuropathy

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Recently, an intoxication of organic solvents to the human nervous system has been emphasized in the neurological field all over the world. n-Hexane had long been believed an organic solvent with extremely low toxicity and widely used in the fields of printing, extraction of vegitable oil or cleaning process. However, its neurotoxic property had gradually become apparent and in Japan Yamada (14) (1964) first reported on 5 cases of polyneuropathy due to n-hexane in the printing plants, which were clinically and carefully examined by two groups of the investigators[10,13]) (1964 and 1965). Since this report an attention had arisen in the industrial fields and more 12 cases had been reported from several areas of Japan. And in 1967 a large outbreak of n-hexane polyneuropathy occurred among workers of manufacturing sandals and slippers. Since that time the clinical and hygienic investigations have been carried out and the neurotoxic property of n-hexane has been widely educated and after 4 years there are no patient nor new occurrence among the workers. In this paper, a large outbreak of n-hexane polyneuropathy will be described and discussed in detail.

Outline of Outbreak

In summer, 1967, two patients complaining of severe quadriplegia visited to the out-patient clinic of the Department of Internal Medicine, Nagoya University Hospital, who were residents in Fukaya District of Kuwana City, Mie Prefecture. Inquiry for their occupation and environment disclosed that a certain kind of organic solvent they had dealt with during their works of manufacturing sandals and slippers, and furthermore, and outbreak of the occurrence of many patients with similar disorders among the workers. To clarify the situation of Fukaya District on both disorder and environment, the epidemiological and clinical investigations had been carried out from September, 1967 to May, 1968. Fukaya District of Kuwana City, 30 killometers south apart from Nagoya City, has a population of 3,500. Moot of the inhabitants in this area have been

engaged in making sandals and slippers as their conventional means of livelihood.

Of 1662 workers checked by the questionaire, the suspicious 296 subjects were picked up and medical, especially neurological examinations were performed on them By these procedures 93 cases of polyneuropathy were found. The polyneuropathy patients were, without exception, those who had been engaged in the pasting processes. They had been working more than 8 hours a day in the narrow poorly ventilated dwelling where vapor of the volatile solvent filled in the room. Samples of the paste were gas-chromatographically analyzed and it was proven that the organic solvent consisted of mainly n-hexane (more than 70 percent)and a small amout of toluene Also, gas concentration in the working rooms tested on n-hexane ranged 500 to 2,500 p.p.m. which was 5 to 25 times as much as Maximal Allowable Concentration in Japan.

Nutritional deficiency and infectious or toxic agents other than n-hexane were ruled out as its etiology in each case. These disorders were diagnosed probably as an intoxication polyneuropathy due to n-hexane.

TABLE 1

The Frequency of Initial Symptoms

	Nº of Cases	Per Cent of Total, 93 Cases
Sensory disturbance	82	88.2
Numbness	64	68.8
Dysesthesia	10	10.8
Pain or tenderness	8	8.6
Muscle weakness of fatigability of the limbs	13	14.0
Blurredness of vision	12	12.9
Cold feeling of the limbs	12	12.9
Headache	8	8.6
Loss of body weight	8	8.6
Lassitude	3	3.2
Skin eruptions	2	2.2
Anorexia	2	2.2
Dizziness	1	1.1
Others	4	4.3

Clinical Features

The age of the patients ranged from 10 to 75 with an average of 40.6 years. The ratio of male to female was 1:3.5. Higher incidence in women was attributed to the working condition that women had been actually engaged in the pasting process in the small rooms.

The mode of onset was insidious in 83 cases (39.2%), but in the remainder it was subacute or acute in the patients severely affected.

The initial symptoms of the disorders are shown in the Table 1; numbness at the distal portion of the extremities in 82 cases (88.2%) and muscule fatigability in 13 cases (14.0%). In addition, some patients had cold feeling of the extremities, blurred vision, headache, easy fatigability, and anorexia or weight loss around the onset of polyneuropathy. These symptoms had progressed slowly or subacutely during the period of several months of the exposures

The symptoms and signs, which 93 cases revealed on the time of our examination, are summarized in Table 2. The chief manifestation among them was sensory and motor disorders of the extramities, which was symmetrical and distally dominant in glove and stocking distribution. Sensory disturbance, including all modalities of the sensation,

TABLE 2

Symptoms and Signs

	Nº of Cases	Per Cent of Total, 93 Cases
Cranial nerve involvement		
Anosmia	5	5.4
Blurring of vision	13	14.0
Constriction of visual field	7	7.5
Optic nerve atrophy	2	2.2
Retrobulbar neuritis	1	1.1
Numbness over the face	5	5.4
Weakness of facial muscles	2	2.2
Sensory disturbance		
Numbness	93	100.0
Dysesthesia	21	22.6
Pain or tenderness	5	5.4
Muscle weakness	40	43.0
Muscle atrophy	8	8.6
Reflexes		
Hypoactive	36	38.7
Hyperactive	10	10.8
Pathological reflexes	0	0
Micturition disturbance	1	1.1
Skin changes		
Coldness, Reddishness, Roughness	55	59.2
Emaciation	14	15.1
Anemia	3	3.3

was observed in all cases, while dysesthesia, neuralgic pain or tenderness were found in relatively small number of the cases only in earlier stages Forty patients had muscle weakness of the extremities, among which 36 had diminished tendon reflexs. Pyramidal tract signs were not detected in any case. Muscle atrophy was observed in severely ill 8 patients (8.6%). Only one case had urinary disturbance. As for the cranial nerves 5 had numbness on the face. Of 39 cases ophthalmologically examined, 8 cases had shown a few objective findings such as the restriction of visual field, optic nerve atrophy and axial optic neuritis. However, these findings were mild and there was no clear correlation between severity of the peripheral neuropathy and involvement of the optic nerve. About one-third of 93 cases had complained of one or a few of headache, flush, irritability, insomnia and dizziness during the exposure to n-hexane, but neither organic mental symptoms nor epileptic disorders were detected. In 55 cases (59.1%) the skin of the distal portion of the extrimities were rough, cold and reddishly discoloured. There were no evidence suggestive of damage in the respiratory, alimentary system, kidney, and liver.

According to the grade of severity 93 cases could be classified into three groups (Table 3); Group I-sensory polyneuropathy (53 cases), Group II-sensorimotor polyneuropathy (32 cases), and Group III-sensorimotor polyneuropathy with amyotrophy (8 cases). The grade or severity of the neurologic manifestations depends on hygienic condition.

TABLE 3

Classification based on the mode of involvement and clinical course of polyneuropathy

	III	II	I	R	Missing	Death
Spring, 1968	8(8.6)	32(34.4)	53(57.0)			
Summer, 1970 ...	0	5(5.5)	34(37.8)	51(56.7)	3	
Spring, 1972	0	0	7(7.9)	82(92.1)		1*

Group I Sensory Polyneuropathy
Group II Sensorimotor Polyneuropathy
Group III Sensorimotor Polyneuropathy with Amyotrophy
R: Completely recovered case
* died of gastric cancer

The clinical course of n-hexane polyneuropathy showed some characteristics. Eight cases of Group III revealed a continuous aggravation of the symptoms even after the patients were isolated away from n-hehane and treatment was instituted. The disorder reached its maximal intensity withi nthe course of 1 to 4 months after detachment from the work and then gradually subsided. The administration of prednisolone and large doses of vitamine B complex seemed to be considerably effective to delay the progression of the polyneuropathy The prognosis of the disease was, however, favourable as far as the patients were able to be secluded from a noxious environment in the earlier stage of the disorder, without any fatality.

Thus, all the patients could expect good prognosis in a few years after improvement of the environmental situation, but its detail will be mentioned afterwards in this report.

Laboratory Examinations

Several items of laboratory examinations had been performed as follows The urinalysis revealed positive urobilinogen reaction in 15 cases in which Group III showed the higher incidence and coproporphyrin in 4 cases. And only one case had anemia with less than 3:500.000/mm^3 of the red blood cell (RBC), and leukopenia less than 4.000/mm^3 was seen in one case. Six cases had more than 10.000/mm^3 of leukocytes (WBC). In blood chemistry total protein level of the serum showed to be normal with one exception. Thymol turbidity test was positive in two cases, and cephaline cholesterol flocculation test (CCF) was positive in 9 cases. No cases had increased level of SGOT or SGPT, but in 17 cases slight to moderate increasing level of serum lactic dehydrogenase (LDH) activity was encountered. Serologic test for syphilis proved negative in the all examined. Cerebrospinal fluid examined in 7 cases gave no significant results with normal pressure, cell count and protein content.

Furthermore, plethysmography was carried out in 11 patients, and revealed weak vasomotor response to the stimuli in 2 cases. Electromyography and measurement of conduction velocity of the peripheral nerves were performed in 44 cases; 11 of Group I, 25 of Group II and 8 of Group III. Electromyogram recorded from 176 muscles of 44 patients, which usually selected from each patient 4 muscles, flexor pollicis brevis, abductor digiti quinti, anterior tibial and gastrocnemius muscles, revealed that the most striking feature was an appearance of fibrillation potential and positive sharp wave (sign of denervation) in 15.3% and 19.9% of the examined muscles, respectively (Table 4). Interference pattern was reduced in 31.8%. Also, low amplitude potential were obtained in only 5.7% and high amplitude potential, and polyphasic potential were observed respectively in 18.2% and 44.3%. Those data show considerably low toxicity and early occurrence of recovery of the peripheral nerves in n-hexane polyneuropathy. As seen in Table 4,

TABLE 4
Number of muscles with abnormal findings in electromyography

Muscles	Upper extremity: Flexor poll. b rev. Abductor dig it. V	Lower extremity: Tibialis anter. Gastrocnemius	Total
Number of Muscles examined	88	88	176
Fibrillation potentials	18(20.5)	9(10.2)	27(15.3)
Positive sharp wave	16(18.2)	19(21.6)	35(19.9)
Fasciculation potentials	5(5.7)	1(1.1)	6(3.4)
Reduced interference pattern ..	19(21.6)	38(43.3)	56(31.9)
Low amplitude potentials	3(3.4)	7(8.0)	10(5.7)
High amplitude potentials	23(26.1)	9(10.2)	32(18.2)
Polyphasic potentials	49(55.7)	29(33.0	78(44.3)

( ): %

the small muscles of the upper extremities were affected more severely than of the lower extremities which may be due to n-hexane exposure around the manual work, and the former revealed more rapid improvement. Conduction velocity (Table 5) was measured in the distal portion of the ulnar, median, peroneal and tibial nerves below the elbow and knee joints. In the ulnar and median nerves, pathologic reduction of the motor nerve conduction velocity (MCV) below 45 meter per second was observed in 16 and 22 cases, respectively. In the peroneal and tibial nerves the reduction of MCV below 40 meter per second were in 21 and 31 cases, respectively, in which the former include 5 cases of no response indicating an advanced pathology. Evoked potentials (EP), which is, too, called a compound nerve conduction velocity and measured with the antidromic stimulation at the distal portion of the extremities, revealed the pathologic reduction below 40 meters per second in 7 cases of the ulnar nerve, 7 cases of median, 10 cases of peroneal and 15 cases of tibial. On sensory nerve conduction velocity (SCV) of the ulnar and median nerves 21 and 24 cases respectively, showed the reduction below 30 meters per second.

The incidence of abnormal findings in the electromyogram as well as in the conduction velocity was more remarkable in order of Group I, II and III. And as for the conduction velocity, the relationship between abnormal findings and severity of the disorder is clear in the measurement of MCV and SCV but Ep has no remarkable correlation.

Muscle biopsies of the anterior tibial muscle on 3 cases showed fatty degeneration, diminution in size of muscle fibers and association with a slight proliferation of sarcolemmal nuclei. Basophilic fibers and vesicular nuclei with prominent nucleoli were also observed. Biopsies of the sural nerve in 4 cases and of the superficial peroneal nerve in 2 cases were carried out, which showed demyelination, axonal destruction, and proliferation of Schwann cells (Table 6, Fig. 1). Lymphatic cell infiltration was found in one of total cases. Outstanding decrease of the nerve fibers especially with large diameters was observed in 3 cases.

TABLE 5

Number of cases of n-hexane polyneuropathy with reduced conduction velocity

	Number of Cases	MCV				EP				SCV	
		U	M	P	T	U	M	P	T	U	M
Group I	11	3	2	5	7	1	1	8	5	5	5
Group II	25	9	13	14	16	5	5	20	14	12	13
Group III	8	4	7	7	8	1	1	8	6	5	6
Total	44	16	22	21	31	7	7	10	15	21	24
(%)		(36.4)	(50.0)	(47.7)	(70.5)	(15.9)	(15.9)	(22.7)	(34.1)	(47.8)	(54.5)

MCV: motor nerve conduction velocity. EP: evoked potentials.
SCV: sensory nerve conduction velocity.
U: ulnar nerve. M: median nerve. P: Peroneal nerve. T: tibial nerve.

TABLE 6

Neuropathologic changes of the biopsied nerves

		age	sex	grade of sensory disorder	demyelination	axonal changes	proliferation of schwann cell	round cell infiltration
1.	O.T.	38	F	++	+	+—++	+	—
2.	O.Y.	27	F	++	+	++	+	—
3.	S.Y.	30	F	+	+	++	++	—
4.	K.K.	51	F	+	±	+—++	++	—
5.	M.K.	22	F	+++	++	++	++	+++
6.	I.K.	24	F	++—+++	+	+—++	+	—

biopsied nerves: case 1 - 4, Sural nerve
case 5, 6, Superficial peroneal nerve

Follow-up Study of Clinical Course

Since the occurrence of outbreak of the disease, hygienic and enviromental condition had been improved under the direction of the Health Center of Kuwana City and simultaneously clinical course of 93 cases were followed up from spring, 1968 to spring, 1972. In 1968 severe cases, including 8 cases of Group III, were admitted to several hospitals and the others were treated by two practioner with close communication to our group. About one-fifth of the cases recovered completely or nearly completely in the course of 3 to 18 months since the onset. In examination of summer, 1970 as seen in table 3, Group III was not detected, 51 cases (56.7%) were completerly recovered and there remained only Group II in 5 cases (5.5%)

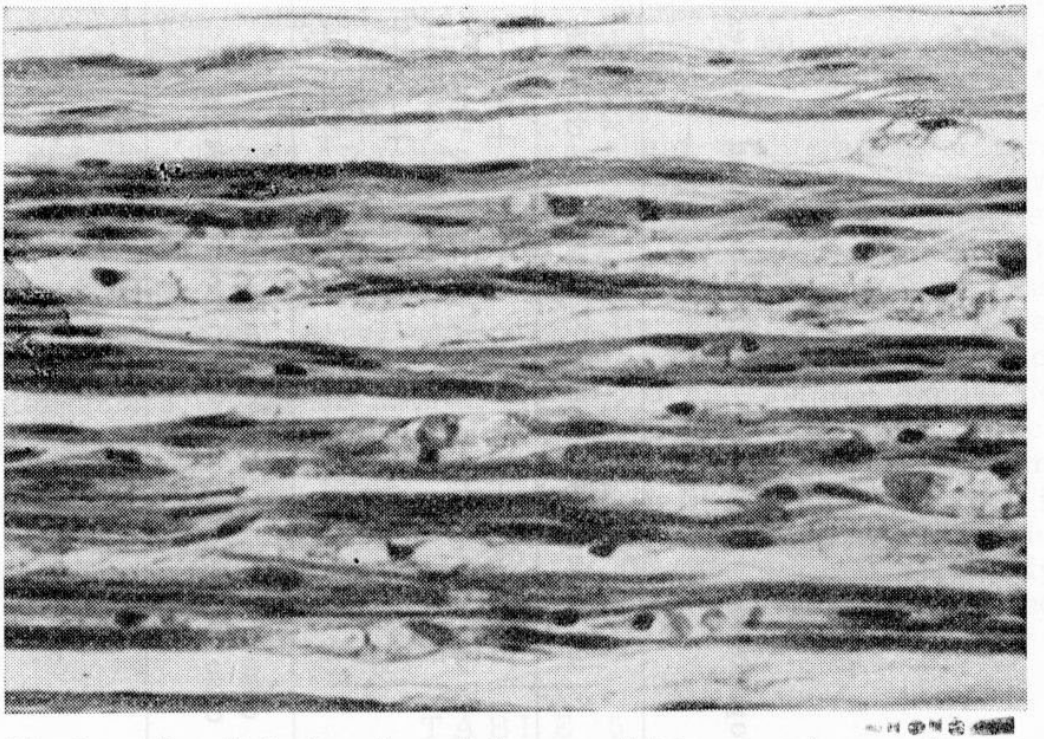

Fig. 1. — Longituinal section of the superficial peroneal nerve in case I. K. age 26, showing demyelination and axonal changes Masson-trichrome 450 X.

and Group I in 34 cases (37.8%), including 3 missing cases. Two years later, in spring, 1972, 82 cases (92.1%) were completely recovered and only 7 cases (7.9%) belonged to Group I, including one case of death. Twenty four (26.7%) of 90 cases except for missing 3 cases, during about 2 years from spring, 1968 to summer, 1970 and 17 of 38, excluding one died case in about next 2 years from summer, 1970 to spring, 1972, changed their works. Among the sandal makers, who have continued the same works after the onset of outbreak of n-hexane polyneuropathy, about 90% of them have had the equipment of powerful ventilator. Thus, the environmental improvement and the isolation from the work had directed to the recovery of the most cases in a few years and no occurrence of any new case of polyneuropathy.

DISCUSSION

Transient dizziness, headache and unconsciousness have been described as symptoms in an acute intoxication due to n-hexane. [4, 12, 29] As for a chronic n-hexane intoxication, glove and stocking type polyneuropathy has been reported by Oishi et al [10] (1964), Wada et al [13] (1965), Sobue et al [11, 12] (1968), Yamamura [15] (1969) in Japan. The polyneuropathy introduced by these authors developed from the workers exposed for a long term to the organic solvents including n-hexane. A large outbreak of polyneuropathy due to n-hexane intoxication reported by Sobue et al and Yamamura is the most important literature in this field. Recently Herskavitz et al [5] (1971) has mentioned a few cases of n-hexane polyneuropathy occurred as a result of industrial exposure.

Analyzing hygienic backgrounds on the chronic intoxication in Japan, Yamada [14] (1967) emphasized that the polyneuropathy developed under the rather unusual conditions: (1) the organic solvents including n-hexane were handled carelessly in a working room with very poorly ventilating system: (2) the workers were exposed to high concentration of n-hexane vapor (500 to 2,500 p.p.m.) for a long period over several hours. In relation to the clinical observations, Miyagaki [9] (1967) has demonstrated experimentally that muscular weakness and atrophy of the hind limbs of rats developed, following the exposure to n-hexane for one year.

The cardinal clinical manifestations are the distally dominant sensorimotor disturbances with symmetric distribution in glove and stocking type. Wada et al [13] pointed out that marked amyotrophy on the limbs was a characteristic feature in this intoxication, but of 93 cases in the author's series only 8 cases revealed the amyotrophy. It has been clarified that there is a wide spectrum in clinical manifestations of chronic n-hexane intoxication from the investigation of the outbreak in Fukaya district by the authors. Therefore this disorder is classified into three groups, namely sensory polyneuropathy, sensorimotor polyneuropathy and sensorimotor polyneuropathy with amyotrophy, and the muscular atrophy is not always a rule. The possibilty of the spinal cord involvement was presumed by Wada et al [13] from informing of transverse myelopathy at about 10th or 11th thoracic cord in his series. However, in our series there were no cases with pyramidal tract sign or sensory pattern suggesting the spinal cord lesion. As for the cranial nerve involvements, visual disorders, numbness over the face and so forth were observed in the present series, which have not been pointed out in the literature. In the chronic intoxication, there were found no mental disorders.

In intoxication due to the organic solvents, the liver damage occur fairly frequently, but from the results of this series and others it seems that the disturbances of liver function in the chronic n-hexane intoxication are mild and of little significance if present. Furthermore, the patients of n-hexane polyneuropathy did not show any significant disorders of the kidney and hematopoietic organs.

Kurita [7] (1967) has recently reported morphological changes in the peripheral nerve and muscle of rat induced by n-hexane. Miyagaki [9] (1967) has also recognized electromyographic findings suggesting denervation and reinnervation processes of the peripheral nerves in the experimental rat. In biopsied materials in present series diminution of muscle fiber size associated with slight increase of the sarcolenmal nuclei was noted. Demeyelination

and axonal changes were observed in the biopsied nerves. These pathological findings indicate that n-hexane has toxic effects upon the peripheral nerves. Commonly, pathologic changes in toxic polyneuropathy can be classified into major types: (1) Wallerian degeneration and (2) segmental demyelination. Selectivity in the substance of the nerve fibers and localization of the lesion in the nerve are variable according to the agent involving in an individual case. The pathology of the nerve in n-hexane polyneuropathy is a mixture of demyelination and axonal degeneration, severity of which is variable according to the case. The more detailed pathological study should be required to determine whether the demyelination in this lisease is due to a disorder of the Schwann cell or merely secondry to the axonal degeneration. Electromyographically abnormal findings in considerably high frequency of the cases corresponded to the degree of severity. But the findings are not specific to n-hexane polyneuropathy. The electromyography was more available in follow-up study that the nerve conduction velocity which had remained without any recovery over one year.

In the chronic n-hexane intoxication there are a few characteristics on the clinical course. Progression of the sympotoms for a while even after detachment from the exposure was noteworthy. The neurologic manifestations in 8 cases of sensorimotor polyneuropathy with amyotrophy reached their maximum within 2 months after hospitalization. This delay in development of the full clinical picture is recongnized, also, in thalidomide polyneuropathy [1] and T.O.C.P. intoxication. [2, 4] Similar phenomenon has been reported in patients with trichlorethylene poisoning by Buxton & Hayward [3] (1967). Some suggestions have been given to the explanation of these facts but mechanism remains unknown. The another outstanding feature during the clinical course of n-hexane polyneuropathy is seen in favourable prognosis. On the previous several reports it was uneasy that the severe cases with amyotrophy due to the exposure for a long period did not cure of the neurologic disorder even 2 or 3 years after its occurrence and permanent damage might have remained even if the patient has left his work and received an adequate treatment. [5, 13,] However, according to follow-up study of clinical course in our series, approximately 4 years after the outbreak only 7 cases (7.9%) remained with mild sensory impairment on the distal portion of the extremities and there was not seen the amyotrophic change. The rest of the patients except for 7 cases had recovered completely (92.1%) and went back to their employments.

Along through studies on a large outbreak of n-hexane polyneuropathy, it became clear that the toxicity of n-hexane was much greater than commonly supposed, although the affected polyneuropathy showed the fortunate prognosis. Before this outbreak the regulation governing the use of n-hexane was 500 p.p.m. but after that it was changed to a new standard of 100 p.p.m. as the Maximal Allowable Atmospheric Concentration, in Japan. In U.S.A. the regulation is still 500 p.p.m., but it is emphasized that a re-evaluttion of the present allowable limit value of n-hexane be undertaken as n-hexane polyneuropathy has been reported recently in U.S.A.

Recently, not only in industrial use but also glue-sniffing a few cases of toxic polyneuropathy has been reported in Japan. [8] The glue, which is an adhesive agent "Bond" in trade name and contains the same amount of n-hexane and toluene (in 25% each), is addicted to in-

hale the volatile gas of Bond and after about half year flaccid quadriplegia with amyotrophy was noted, for which n-hexane is considered to be chiefly responsible.

SUMMARY

A large outbreak of n-hexane polyneuropathy at Fukaya District, Mie Prefecture in Japan was investigated and clinical studies were made.

1. Ninety-three patients with n-hexane polyneuropathy were found from 1662 workers exposed to the organic solvents, which were proved to consist mainly of n-hexane and a small amount of toluene.
2. Clinical features of the cases were the neuropathies with distribution of glove and stocking type which were classified into three groups: sensory polyneuropathy (Group I) 53, cases, sensorimotor polyneuropathy (Group II) 32 cases, and sensorimotor polyneuropathy with amyotrophy (Group III) 8 cases. Cranial nerve involvements such as visual disorders and numbness over the face were observed. There were no cases with the symptoms and signs suggesting the spinal cord and brain lesions. In severe cases the clinical manifestations progressed for about 2 months even after detachment from the noxious environment. Approximately 4 years after the onset of outbreak only 7 cases remain with mild sensory impairments, providing a favourable prognosis.
3. Laboratory examinations including urinalysis, complete blood count, liver function tests, serologic test for syphilis and cerebrospinal fluid studies, revealed no significant abnormalities. Electromyography and measurement of conduction velocity of the peripheral nerves were performed in 44 cases, about 50% of which showed abnormal findings with denervation and reinnervation of the nerves. Biopsy studies of the peripheral nerves and muscles disclosed demyelination and axonal degeneration in the nerves and neurogenic atrophy in the muscles.

RESUMEN

Una gran erupción de n-hexane polineuropatía en el Distrito Fukaya, Prefectura de Mis en el Japón, ha sido investigada y se han realizado estudios clínicos.

1. Noventa y tres pacientes con n-hexane polineuropatía fueron hallados entre 1662 trabajadores expuestos a los disolventes orgánicos, los cuales se demostró estaban compuestos principalmente de n-hexane y de una pequeña cantidad de tolueno.
2. Los cuadros clínicos de estas observaciones han sido las neuropatías con distribución de tipo guante y calceta, las cuales

fueron clasificadas en tres grupos: polineuropatía sensitiva (grupo 1) 53 casos, polineuropatía sensitivo motriz (grupo 2) 32 casos y polineuropatía sensitivo motriz con amiotrofia (grupo 3) 8 casos. Han sido observados, trastornos en los nervios craneales, tales como perturbaciones visuales y adormecimiento de la cara. No se observó ningún caso con síntomas y signos que pudieran sugerir lesiones de la médula y del cerebro.

En los casos severos las manifestaciones clínicas progresaron en alrededor de 2 meses aún después de separarlos del ambiente nocivo. Aproximadamente 4 años después del comienzo del disturbio solamente 7 casos quedan con leves trastornos sensitivos, brindando un pronóstico favorable.

3. Exámenes de laboratorio, incluyendo análisis de orina, numeración completa de glóbulos sanguíneos pruebas funcionales de hígado, reacciones serológicas de la sífilis y estudios del líquido cefalorraquídeo no revelaron anormalidades significativas. Electromiografía y medida de velocidad de conducción de los nervios periféricos fueron realizados en 44 casos, alrededor del 50% de los cuales mostraron hallazgos anormales con denervación y reinervación de los nervios. Biopsia de los nervios periféricos y de los músculos descubrió desmielinización y degeneración axonal en los nervios y atrofia neurogénica en los músculos.

RÉSUMÉ

Une grande émission de n-hexane neuropathie dans le District Fukaya, Préfecture de Mie au Japon a été recherchée et études cliniques ont été effectuées.

1. Quatre-vingt-trois malades avec n-hexane neuropathie ont été trouvés chez 1662 travaileurs exposés aux dissolvants organiques, qui on été prouvés de se composer principlement de n-hexane et d'une petite quantité de toluène.
2. Tableaux cliniques de ces observations on été des neuropathies avec distribution de type de gant et de bas, qui ont été classifiées en trois groupes: polyneuropathie sensitive (Group I) 53 cas, polyneuropathie sensitivo - motrice (Group II) 32 cas, et polyneuropathie sensitivo motrice aver amyotrophie (Group III) 8 cas. Perturbations des nerfs craniens comme troubles visueles et engrourdissement sur la face ont été observées. Il n'y a eu aucun cas avec symptômes et signes qui suggérent lesions spinales et cérébrales. Approximativement 4 ans après le début d'émission seulement 7 cas restent avec troubles sensitifs faibles pourvoyant un pronostic favorable.
3. Examens biologiques, y compris analyses de l'unine, numérations complètes du sang, tests de fonctions hépatiques, réactions sérologiques de la syphilis et explorations du liquide céphalo - rachidien n'ont révélé aucune anomalie significative. Electromyographie et mesure de vitesse de conduction du nerf

péripherique ont été accomplies chez 44 cas, dont l'environ 50% ont montré résultats anormaux avec dénervation et réinnervation des nerfs. Biopsie des nerfs périphériques et des muscles ont découvert démyélinisations et dégénérations axonales des nerfs et atrophies neurogènes des muscles.

ZUSAMMENFASSUNG

Ein grober Ausbruch von n-Hexan Polyneuropathie im Fukaya - Distrikt der Mie Präfektur in Japan wurde untersucht und klinische Nachforschungen wurden angestellt.

1. Von 1662 Arbeitern, die organischen Lösungsmitteln, welche erwiesenermaben in der Hauptsache aus n-Hexan und einer kleinen Menge Toluen bestanden, ausgesetzt waren, wurden 93 Patienten mit n-Hexan Polyneuropathie ermittelt.
2. Die klinischen Merkmale der Fälle waren die Neuropathien mit Verbreitung des Handschuh und Strumpf-Typs, die in drei Gruppen unterteilt wurden: Sensorische Polyneuropathie (Gruppe I) 53 Fälle, sensorimotorische Polyneuropathie (Gruppe II) 32 Fälle und sensorimotrische Polyneuropathie mit Amyotrophie (Gruppe III) 8 Fälle. Beeinträchtigungen des Gehirnnervs wie Sehstörungen und Hypesthesie im Gesicht wurden beobachtet. Es gab keine Fälle, bei denen Symptome und Anzeichen, die auf Rückenmark- und Gehirnverletzungen hinweisen, vorhanden waren. In schweren Fällen schritten die Krankheitserscheinungen sogar nach Entfernung aus der schädlichen Umgebung für weitere zwei Monate fort. Ungefähr vier Jahre nach Beginn des Ausbruches verbleiben lediglich sieben Fälle mit leichten sensorischen Störungen, wodurch eine günstige Prognose gegeben ist.
3. Laboruntersuchungen einschlie-Blich Urinanalyse, vollständiger Blutzählung, Leberfunktionstests, serologischer Tests auf Syphilis und Studien der Cerebrospinalflüssigkeit ergaben keine wesentlichen Abnormitäten. Elektromyograpie und Messung der Leitungsgeschwindigkeit der peripherer Nerven wurden in 44 Fällen durchgeführt, wobei sich bei ca. 50% abnormale Befunde mit Denervation und Reinnervation der Nerven ergaben. Biopsie-Untersuchungen der peripheren Nerven und Muskeln ergaben Demyelination und axonale Degenerierung in den Nerven und neurogenische Atrophie in den Muskeln.

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Experimental Neuropathology and Clinical Neurology of Chloroquine Side Effects

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Therapeutic Indications of Chloroquine

Chloroquine (Resochin(R), Résoquine(R), Sanoquin(R), Reumachlor(R)) was first synthesized in 1939[4] and introduced into practical medicine in 1947. The main indications of the drug were at that time the prophylaxis and therapy of malaria as well as the therapy of several other protozoan diseases such as the tissue phase of amebic hepatitis and lambliasis. When chloroquine-resistent falciparum malaria first appeared in tropical Latin-America and in Southeast-Asia, the drug had already been proven a very successful anti-inflammatory substance. The new indications, especially the treatment of several rheumatic diseases, however, required much higher doses of chloroquine for months or years. In consequence of this long-term use a number of undesirable side effects, predominantly in the nervous and muscular systems, have been observed. Since this time chloroquine has been of special neurological and neuropathological interest.

Principles of Therapeutic Actions of Chloroquine

The metabolic pathways of chloroquine have been investigated extensively, especially with regard to the therapeutic effect of the substance.[19, 31,45] Some of these intermediary processes are of essential significance in thes etiology of the neurological side effects and neuropathological changes due to the drug, while others are rather negligible in this concern.[24] The metabolic aspects of the neurotoxicology of chloroquine will be discussed in context with the experimental pathology of the different side effects.

Chloroquine forms molecular complexes with DNAs, and inhibits DNA-dependent nucleic acid polymerase reactions in vivo.[8] The intercalating binding of the drug to plasmodial DNA and inhibition of DNA synthesis in malaria schizonts are considered to have a share in the anti-malarial action of the substance.[27, 28]

— In addition a reversible binding of chloroquine to several physiological pigments such as mela-

nin[c] and hemoglobin[30] has been disclosed. The binding to human hemoglobin is responsible for the fact that the drug is present in red blood cells in a concentration which is approximately twice that in plasma. This is another factor in the effectiveness of chloroquine against malaria schizonts.

— The drug has a dose-dependent membrane-stabilizing[12] and membrane - labilizing effect[20] especially demonstated in erythrocytes[2, 3] and lysosomes[39, 42] in many pharmacological experiments. The concentration of the drug in lysosomes and in the lysosome-like autophagic vesicle of malaria parasites[2, 3, 27, 28, 38] is most probably the main factor of the thereapeutic action of the drug as an anti-inflammatory and as an anti-malarial substance.

Chloroquine proved a very effective inhibitor of the lysosomal enzyme cathepsin B_1[43] and inhibits lysosomal degradation of mucopolysaccharides[25] and low-density lipoprotein[15] in tissue cultures.

— The impairment by chloroquine of many digestive processes normally going on within lysosomes is the main factor in neurotoxicity of the drug. especially in neuronal storagedystrophy.

Side Effects of Chloroquine Therapy

The principal side effects are the neurological disturbances, primarily the myoneuropathy, [5, 9, 13, 21, 29, 44] irreversible retinopathy,[17] and nerve deafness.[34] Psychoses,[16] epileptic seizures[36] and acute extrapyramidal motor movements[37] due to the drug have also been reported. The retinopathy may be complicated by a keratopathy. As chloroquine passes through the placental barrier, cochlear damage was also noted in children of mothers who took the drug during the first trimester of pregnancy. The cardiomyopathy corresponds to the myopathy. In addition blue-black pigmentations and depigmentations involving skin and mucous membranes and hair bleaching have been observed.

Retinopathy

In incipient cases of chloroquine retinopathy the only clinical sign may be a macular ring scotoma. In advanced cases produced by long-term administration of the drug the depressed or even absent electroretinogram indicates lesions of the rods and cones. Frequently a perimacular oval patch of depigmentation can be observed, and sometimes a complete disappearance of macula pigment. Histopathological examination in man revealed segmental disappearance of rods and cones.[6, 17]

Myoneuropathy

A myoneuropathy (this term is less misleading than "neuromyopathy" since the muscle changes are not neurogenic) has been described frequently.[5, 9, 13, 21, 29, 44] The clinical pattern is unusual and consistent: the muscular weakness begins in the proximal muscles of the lower limbs and may progress slowly to the trunk, neck and proximal muscles of the upper limbs. Sometimes facial and respiratory muscles and outer and inner eye muscles may also be affected. The myotatic reflexes are sluggish or absent and there is no interference with the sensory modalities or the pyramidal tracts. Electromyography revealed in the same muscles simultaneously, both myopathic and neuropathic features. There may be widespread fibrillation and very little reduction of the number of motor units. Many of these units are highly polyphasic.

The conduction velocity of single nerves may be distinctly reduced. Muscle biopsy material showed marked vacuolar and granulovacuolar changes in many muscle fibres.[5, 29, 44] Some of the stored material was digestible by diastase indicating that these granules were glycogen. Electronmicroscopic investigations of biopsy material likewise disclosed comparatively many small membrane surrounded glycogen accumulations, mainly, however, accumulations of concentrically layered membranous bodies. There have been demonstrated accumulations of membranous cytoplasmic bodies also in axons found within bioptically obtained muscle tissue.[13, 11]

Experimental Neuropathology

Retinopathy

The complete pattern of the retinopathy has been elucidated experimentally.[1] Electronmicroscopically were seen amassements of concentrically layered membranous cytoplasmic bodies in every neuron type of the retina in rats. The process was most pronounced in the inner ganglion cell layer and very similar to the retinal changes seen in Tay-Sachs disease. Furthermore, our experimental investigations in rats disclosed considerable granular balloonings of axons in the optic nerves (Fig. 2) and balloonings of axon terminals in the anterior colliculi, indicating the neuronal nature of the process.

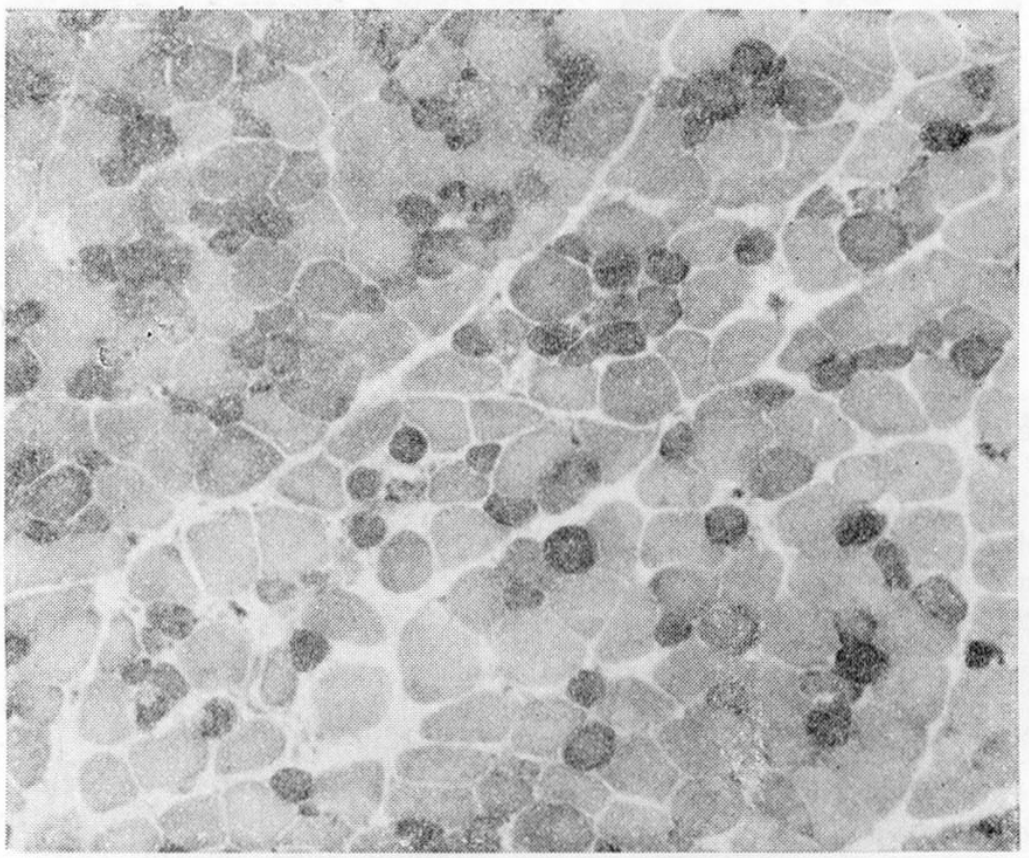

Fig. 1: Rat Ex. 4626; 8 days of chloroquine (250 mg/kg/day by stomach tube); m. tib. ant.; lactate dehydrogenase reaction (by MTT; with NAD); x 110; degeneration of the small calibrated type I muscle fiebres exclusively which are rich in oxidative enzyme.

Myoneuropathy

The typical pattern of the muscular lesions due to chloroquine had not been disclosed before experimental investigations. These showed the selective or predominant affection of the scattered, slow contracting, red (type I) muscles fibres within the mixed (so called white) muscles[35] (Fig. 1). In species with pure red muscles (such as the mm. semitendinosus and longissimus dorsi in rabbits and guinea pigs) these might be completely changed in contrast to the prevailing intact neighbouring muscles with different fibre types.[23] The fibre changes were of degenerative nature with some histiocytic and fibroblastic reaction. After formalin fixation many of the affected fibres showed extensive central vacuolation over long portions. The acid hematein test (Baker), however, revealed enormous accumulations of phospholipid granules within these vacuoles corresponding to the electronmicrospical finding of accumulations of myelin bodies.[22]

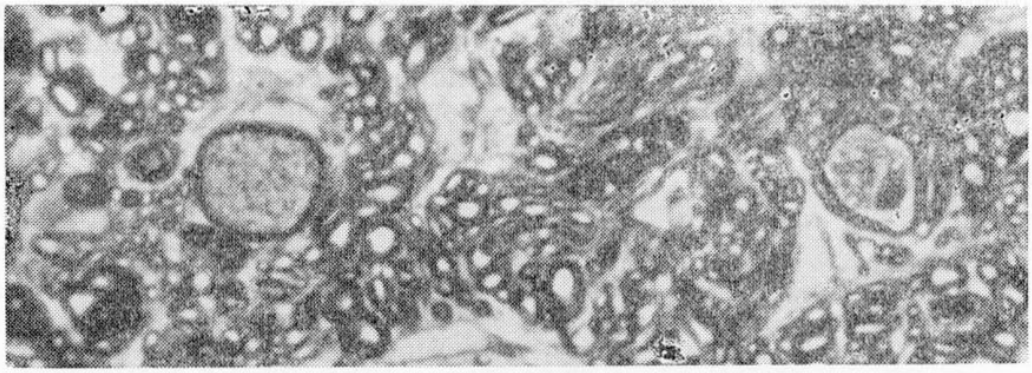

Fig. 2: Rat Ex. 6296; 169 days of chloroquine (2,0 g/kg food) within a period of 225 days; n. opticus, Epon, 2 μm section, p-phenylene diamine, x 1250. Two axon balloonings contain amassements of storage granules.

Some of these were membrane bound indicating their lysosomal origin. In addition, th estaining method of Best demonstrated the same degenerating fibre type equally studded with innumerable glycogen granule scomparable to the same finding in all fibre types in type II glycogenosis (Pompe).[22]

The experimentally and bioptically demonstrated glycogen accumulations were often seen within autophagic vacuoles.[10] These muscular lesions exceeded by far the experimental changes in peripheral motor nerve fibres. There was never seen a neurogenic pattern of the muscle fibre changes.

The accumulation of chloroquine in the muscular system is unlimited [18] and most probably due to a reversible binding of the drug to hemoglobin and melanin. A reversible binding of the structurally related quinacrine (Atebrin(R)) to myoglobinhas already been proven.[33] This factor and the inhibition of protein biosynthesis by chloroquine may be the cause of the predominant lesion of the type I muscle fibres.[23] The myoglobin contents and protein metabolism of this type are the highest of all muscle fibre types.

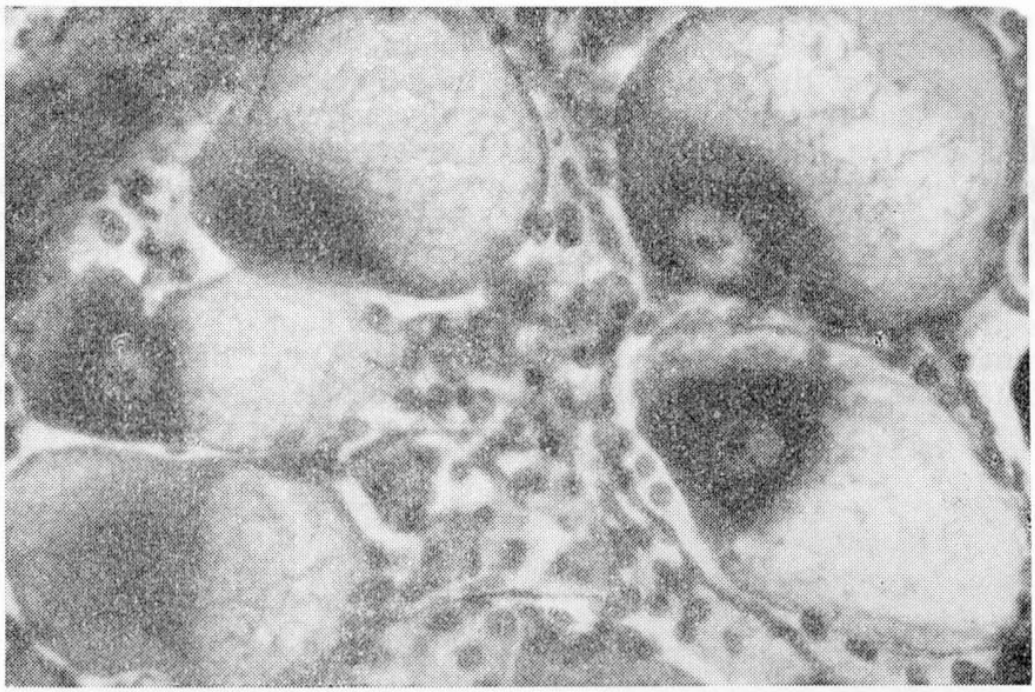

Fig. 3: Rabbit Ex. 4498; 126 days of chloroquine (100 mg/kg by stomach tube) within 153 days; lumbar posterior root ganglion; Bodian impregnation, x 480. Ballooned nerve cell perikarya, foamy structure of the storage regions.

Neuronal Storage Dystrophy

Accumulatoins of membranous cytoplasmic bodies caused by chronic chloroquine intoxication first were described in nerve cells in posterior root ganglia in swine.[14] This experimental change may imitate completely the morphological characteristics of the neuronal storage dystrophy well known in morbus Tay-Sachs. In Bodian impregnations the

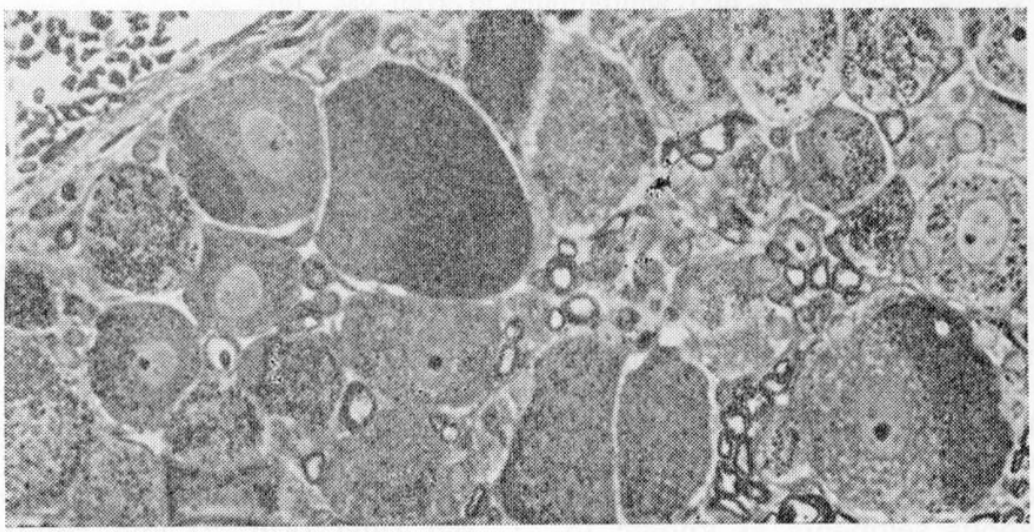

Fig. 4: Rabbit 4497; 134 days of chloroquine (100 mg/kg by stomach tube) within 252 days. Lumbar posterior root ganglion, Epon, 2 µm section, p-phenylene diamine, x 400. Granular storage material in all nerve cell bodies, several perigarya show balloonings.

perikarya were enormously enlarged and showed a foamy structure and a dislocation of the nucleus and Nissl bodies to the periphery of the cell body (Fig. 3 and 4). These granules were membranous cytoplasmic bodies, which, as a rule, were best preserved in posterior root ganglion cells in the perikarya. In rats these residual bodies were predominantly of the concentrically layered type (Fig. 5), in rabbits of the plan-parallel layered type (Fig. 6). In the nucleo-proximal balloonings these storage granules generally were smaller and not so well preserved and contained often fine granular or dusty material. Another remarkable, although, by far less frequently seen type of storage bodies were small to very large accumulations of glycogen granules or particles very often surrounded by one or several membranes. In nerve

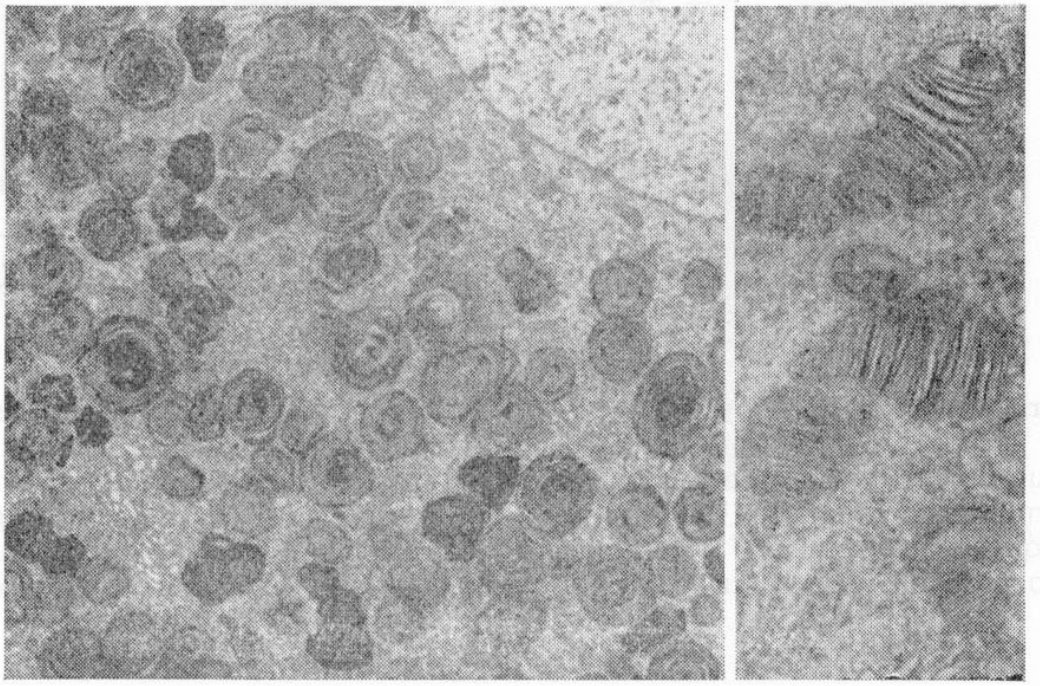

Fig. 5: Rat Ex. 5393; 145 days of chloroquine (2,0 g/kg food); trigeminal ganglion, Epon, x 7400. Perikaryon of a ganglion cell stuffed with many membranous cytoplasmic bodies of the concentric type and several amorphous granules.

Fig. 6: Experimental animal and ganglion of fig. 4. Epon, x 30.000. Perikaryon of a ganglion cell with membranous cytoplasmic bodies of the plan-parallel layered type.

cell perikarya of trigeminal ganglia in rats was now and then established the occurence of a type of storage bodies with extensive curvilinear and small parallel layered membranous segments as known in neuronal ceroid-lipofuscinosis in man.[22] Another local accentuation of ballooning amassements of granular material was seen in axonal endings in the gracile and cuneate nuclei. The innumerable residual bodies established here in rats were mostly of the concentrically layered type (Fig. 7) and smaller and not as well preserved as in the pericarya of these cells. Investigations in muscle spindles in the same spe-

cies revealed considerable axon balloonings of the same kind of the primary sensory endings[32]. Moreover our investigations in mini-pigs ascertained preterminal and terminal axonal balloonings in motor endplates[7]. The high selectivity of the neuronal storage process in the CNS[24] as well in this species is still an object of investigation. One of the most spectacular findings was the strong participation of the allocortex in the storage process in contrast to the abortive changes in the isocortex Another remarkable aspect was the pronounced storage

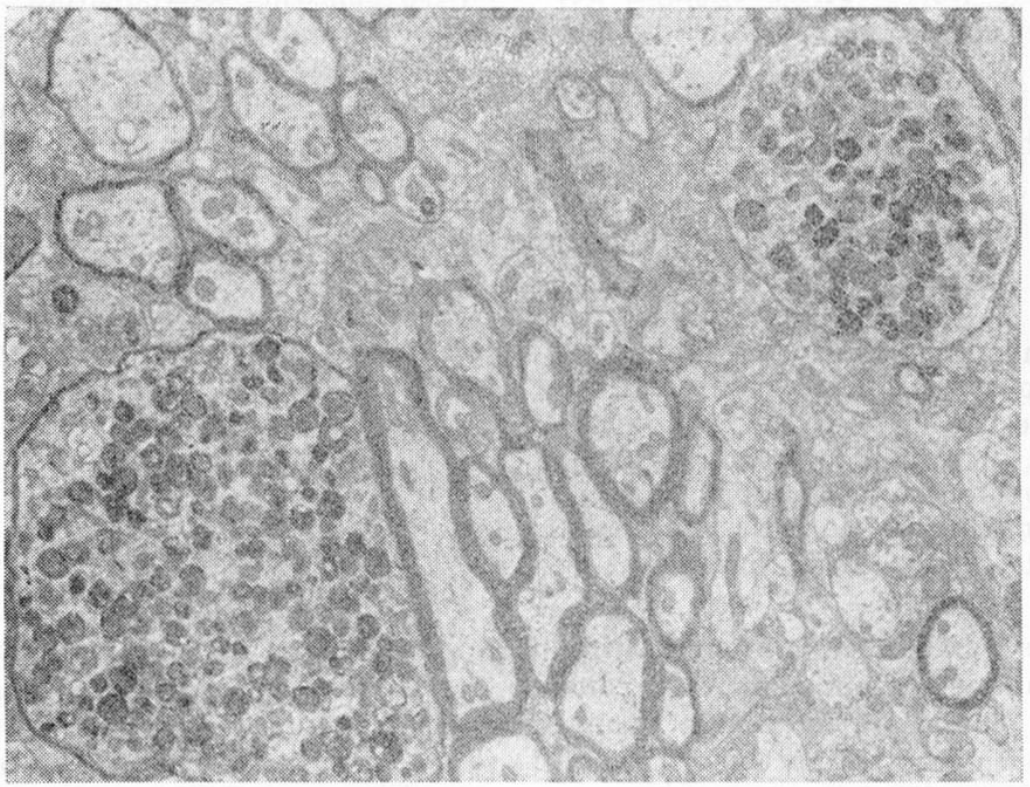

Fig. 7: Rat Ex. 6461; 220 days of chloroquine (2(0 g/kg food); nucleus gracilis, Epon, x 6600. Two terminal axon balloonings show amassements of residual bodies of the concentrically arranged membranous type, mostly, hoyever, containing amorphous or dusty material.

dystrophy of inhibitory ganglion cell types, especially of the basket cells in the Ammon's horn and in the cerebellar cortex. Some other centers of pronounced neuronal storage dystrophy in this species were the paraventricular and supraoptic nuclei and the substantia nigra. One of the most customary clinical side effects of long-term chloroquine intoxication in mini-pigs. may be mentioned in the latter context: continuous smack-and-chew movements comparable to oral dyskinesia caused by phenothiazine therapy in man.

SUMMARY

Experimental neuropathology has contributed a great deal to the understanding of neurological side effects of chloroquine therapy. The inusual clinical type of the myopathy in man depends primarily on the predominant lesion of the type I muscle fibres. These changes are not neurogenic though the myopathy is combined with considerable axonal manifestations of ganglion cell changes in peripheral nerves too. The type of nerve cell lesion caused by chloroquine was most successfully investigated in posterior root ganglion cells and has provided an excellent model of neuronal storage dystrophy. Several central nervous side effects of chloroquine are most probably due to the very selective participation of central nervous ganglion cell systems and ganglion cell types in the storage process most spectacular established up to now in pigs.

RESUMEN

La neuropatología experimental ha contribuido en forma apreciable a la comprensión de los efectos colaterales de la terapia con cloroquina. El tipo clínico poco usual de la miopatía en el hombre depende en primer lugar de la lesión predominante de las fibras musculares de tipo I.

Estos cambios no son neurogénicos aunque la miopatía está combinada con manifestaciones axonales considerables por cambios en células gangliónicas en nervios periféricos. El tipo de la lesión causada por cloroquina fue muy exitosamente investigada en células de ganglio de raíz posterior y ha brindado un excelente modelo de distrofia neuronal almacenada. Varios efectos colaterales nerviosos centrales de cloroquina son más probablemente debidos a la participación muy selectiva del sistema celular de ganglios nerviosos centrales y tipos de células ganglionares en el proceso de almacenaje más espectacular establecido hasta ahora en cerdos.

RÉSUMÉ

La neuropathologie expérimentale a contribué de façon appréciable à la comprebension des effects collatéraux de la thérapie à base de Clorequine.

Le type clinique de la myopathie chez l'homme dépend un premier lieu de la lésion prédominante des fibres musculaires de type I.

Ces modifications ne sont pas neurogéniques bien que la myopathie soit combiné eavec des manifestations axonales considérables a cause de changements dans des cellules ganglionnaires de nerfs périphériques. Le genre de lésion causé par la chloroquine a été étudiée avec succes dans des cellules de ganglions de racines postérieures et a montré un excellent exemple de distrophie neuronale accumulée. Divers effets collatéraux nerveux de la chloroquine sont probablement dus à la participation tres sélective du système cellulaire de ganglions nerveux centraux et de cellules ganglionnaires dans le processus d'accumulation le plus spectaculaire établi jusqu'a presente chez le porc.

ZUSAMMENFASSUNG

Di experimentelle Neuropathilogie hat viel zum Verständnis der neurologischen Nebenwirkungen der Therapie mit Chlorochin beigetragen. Der ungewöhnliche klinische Typ der Myopathie beim Menschen beruht in erster Linie auf der bevorzugten Schädigung der Typ I —Muskelfasern. Diese Veränderungen sind nicht neurogen ,obgleich die Myopathie mit erheblichen axonalen Manifestationen von Ganglienzellveränderungen auch in den peripheren Nerven einhergeht. Der Typ der Nervenzellschädigung durch Chlorochin wurde am erfolgreichsten an Spinalganglienzellen untersucht und ergab ein ausgezeichnetes Modell für die neuronale Speicherdystrophie. Verschiedene zentralnervöse Nebenwirkungen des Chlorochins beruhen sehr wahrscheinlich auf der sehr selektiven Beteiligung zentralnervöser Ganglienzellsysteme und Ganglienzelltypen am Speicherprocess, die bisher am eindrucksvollsten bei Schweinen festgestellt werden konnte.

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Respiratory Reanimation in Extremely Severe course of Botulism

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The severe course of botulism is accompanied by respiratory insufficiency. Its pathogenesis has been studied sufficiently well. It was proved (L. M. Popova, 1964) that botulism causes the disorder of the function of the lower group of the cranial nerves innervating the muscles of the throat, larynx and tongue, as well as the function of the spinal cord nuclei responsible for the innervation of the diaphragm and intercostal muscles. Thus, respiratory insufficiency in botulism is accounted for by the peripheral disorders in which bulbar disturbances are associated with paralyses of the respiratory muscles. Patients develop obstruction of the respiratory tract, weakening or cessation of respiratory movements and disorder of the cough reflex mechanism.

The above-mentioned symptom complex is the main cause of lethal outcomes The total mortality rate in botulism is in the range of 25.9 to 28 % (K. I. Matveyev; A. M. Koritsky, 1937). However, these figures are not accurate since they are related to lethal outcomes both in severe and mild forms of botulism. The analysis of lethal outcomes during the outbreak of botulism made on the basis of the materials of A. M. Koritsky showed that the severe course with a favourable outcome had been in 52 of 270 patients; 124 patients had suffered from mild and latent forms of the disease, and all 94 patients with extremely severe course of the process had died. Thus, if the total mortality rate approached 30% the mortality rate among the patients with severe and extremely severe forms accounted for 64 %. According to Dolman (1961), the mortality rate in severe forms of botulism is up to 76.7 %.

A high mortality rate, sufficiently studied pathogenesis of respiratory insufficiency in botulism make it necessary to develop and widely introduce into practice the most effective methods of treating respirotary paralysis in botulism.

Material and Method

1. Sixteen patients with extremely severe forms of botulism were admitted to the Reanimation Department of the Institute of Neu-

rology of the USSR Academy of Medical Sciences.

2. Neurological examination was performed by standard methods. General symptomatology of botulic toxicoinfection has been sufficiently described in the literature (A. M. Koritsky, N. A. Govseyev et al.). The state of bulbar and respiratory functions was specially analyzed. The study was made of the restoration of breathing, functions of the soft palate, throat, larynx, and tongue during respiratory reanimation.

The evaluation of the functions was made in scores:

5 — normal;
4 — complete range of movements, force is diminished;
3 — range of movements is preserved, force is absent;
2 — limitation of movements, force is absent;
1 — weak movements;
0 — absence of movements.

3. Measurements of pulmonary ventilation (minute volume of ventilation (MVV) , tidal volume - TV, vital capacity of the lungs - VC) were made by means of the RPP - I ventilometer (error is ± 5 %).

4. Respiratory reanimation in botulism was performed according to the technique developed for acute poliomyelitis and other nervous diseases accompanied by respiratory insufficiency. Prolonged artificial ventilation of the lungs was carried out by using the Engström respirator (Sweden).

Results

Incubation period in all patients (Table I) was short (from 3 to 48 hours) This is typical of extremely severe course of the disease. The diagnosis of botulic toxicoinfection was made on an average on the fourth day and at the same time antibotulism serum was administered Poisoning was caused in most patients by home-made canned vegetables (mushrooms) and fish. Poisoning with toxin A predominated. The signs of respiratory insufficiency appeared on an average on the third day In three patients they appeared suddenly and all of them underwent immediate intubation and thereafter tracheostomy. Clinical picture of botulic toxicoinfection has been described in detail (N. V. Mirtovsky, N. A. Govseyev). Therefore the present paper deals with the state of the functions of vital importance the disturbances of which can result in lethal outcome.

The state of bulbar functions. Under normal conditions the muscles of the soft palate throat, larynx and tongue provide a free passage of the air into the respiratory tract and by means of associated movements defend them from inhalation of the content of the throat and digestive tract.

In botulism disengagement of the function of the above-mentioned muscles leads to obstruction of the respiratory tract. Let us consider the function of these muscles during respiratory reanimation.

The muscles of the soft palate. In all patients its mobility became limited since the second day of the illness and in the subsequent 6-12 days the cessation of the movements and fading of the movements of the soft palate and throat occurred. The restoration of the function began since the 14th-20th day of the illness and by the 26th-32nd day a complete range of movements was attained. Only in two patients (M. and E.) snuffling voice and limited functions of the soft palate in combination with fatigue when making repeated movements were observed up to the 40th day of the illness.

The function of swallowing appeared to most affected in all patients. On the second day of the illness dysphagia developed and by

TABLE I

GENERAL INFORMATION ABOUT PATIENTS UNDER PROLONGED RESPIRATORY REANIMATION

№	Patient's	Sex and age	Epidemiological analysis and type of toxin	Incubation period in hours	Respir. reanim.				On what day vital functions were restored		On what day cannulation was made	On what day of the disease patients were discharged	Outcome	Note
					On what day serum was administered	Day of appearance of first signs of respiratory insufficiency	Day when tracheostomy was made	Total duration of artificial ventilation in days	Type of respirator	swallowing (removal of tube)	respiration (switching off apparatus)			
1.	N.	32/m	home-made canned vegetables (type A)	13	3	3	4	44	DP-I 3 days Engström 41 days	42	48	55	74	recovery	paresis of accommodation 23 oD
2.	Sin.	39/m	fried fish (type B)	24	3	2x)	3	44	Engström	42	46	57	75	—"—	paresis of accommodation +4 oD
3.	B.	25/m	fish (group poisoning)	43	7	3	8	26	—"—	36	33	55	106	—"—	paresis of accommodation for 2 years +4 oD
4.	Sad.	28/m	home-made mushrooms	12	5	4	5	30	—"—	24	35	38	50	—"—	paresis of accommodation +4 oD
5.	M.	31/f	parenteral contamination (type A)	24	3	4x)	4	43	—"—	18	47	50	56	—"—	paresis of accommodation +2 oD
6.	Ya.	51/m	home-made canned vegetables (type A)	12	3	3	3	37	—"—	24	40	43	65	—"—	paresis of accommodation +4.5 D
7.	Ch.	26/m	—"— (group poisoning)	24	7	4	7	22	—"—	26	29	33	56	—"—	paresis of accommodation
8.	Pod.	10/f	—"— (type A)	48	2	2	2	24	Engström	37	26	42	50	—"—	paresis of accommodation +1.5 D
9.	E.	12/f	sausage (type A)	24	2	2	2	34	22 days Gullberg 2 days Engström	34	36	40	59	—"—	paresis of accommodation +1.5 D
10.	Push.	7/f	home-made fish (group poisoning)	48	5	5	5	15	Engström 13 days Gullberg 2 days	15	18	20	29	—"—	paresis of accommodation
11.	K.	19/f	laboratory poisoning with toxin of type A	6	3	3x)	4	28	Engström 26 days DP-8 2 days	25	31	33	47	—"—	paresis of accommodation +3.0 D
12.	G.	28/m	home-made fish type A	6	1	1	1	1	DP-2	—	2	8	18	—"—	normal
13.	B.	38/m	canned meat type A	12	4	4	7	9	Engström	15	16	17	37	—"—	paresis of accommodation +3.0 D
14.	T.	9/m	home-made vegetables type B	12	8	4	8	252	Engström 125 days Gullberg 127 days	—	—	—	—	death	syndrome of decortication
15.	N.	22/m	home-made mushrooms	18	2	3	4	25	Engström	20	25	28	45	recovery	paresis of accommodation +3 D
16.	N.	52/f	—"—	3	3	3	3	11	Engström	8	11	15	21	recovery	normal

Note: x) Patients Sin., M., K. were intubated before tracheostomy.

the sixth day aphagia occurred. The restoration of swallowing began since the 15th-26th day and went on gradually up to the 34th-42nd day of the illness (figures 1,2). Of some interest is a peculiar myasthenia-like character of the restoration of swallowing. The patients ate 50-100 ml of semiliquid food and then rapidly fatigued, the food leaked through into the nasopharynx. Therefore removal of the tube in order to prevent aspiration was performed only on a complete restoration of swallowing.

The functions of the laryngeal muscles. The voice became husky in 9 patients by the 2nd-3rd day of the illness and six patients had aphonia by this time. The examination of the larynx in the first days was difficult owing to paralysis of the epiglottis which was lowered, immobile during phonation and closed

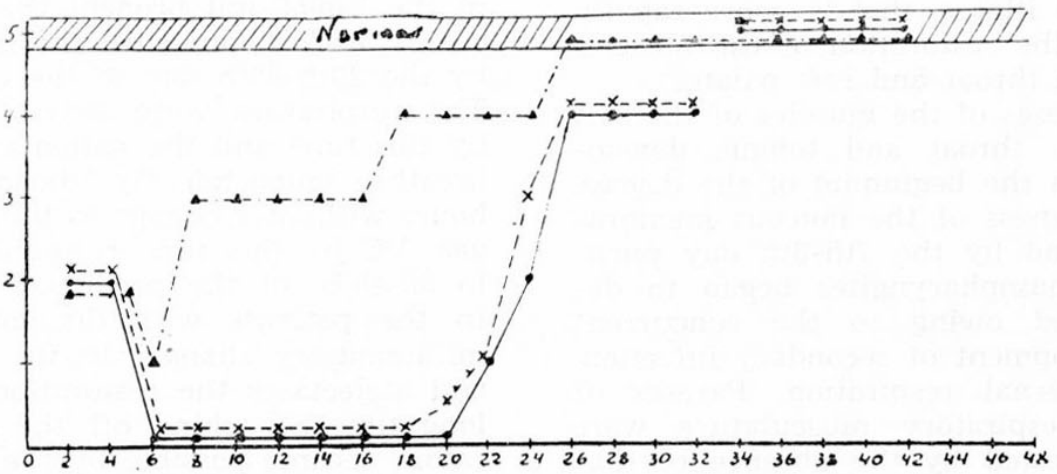

Fig. 1. Patient N.
The state of bulbar functions
———— swallowing
— . — . — tongue
— — — — soft palate
On the axis of ordinates - evaluation of the function in scores
On the abscissa axis - days of illness

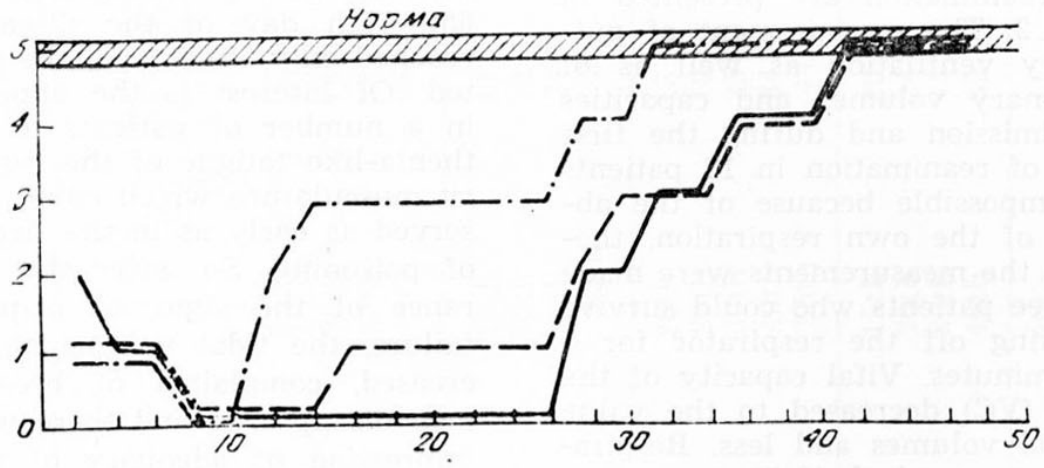

Fig. 2. Patient K.
———— swallowing
X — X soft palate
A — . — A tongue
On the axis of ordinates - evaluation of the function in scores
On the abscissa axis - days of illness

the entry into the larynx. The restoration of the function of the laryngeal muscles began since the 10th-15th day of the disease. The recovery occurred by the end of the third week.

The functions of the muscles of the tongue. Dysarthria appeared since the second day of the illness and developed into anarthria by the 8th day. The functional restoration took place even in the most severe cases from the 14th through the 24th day of the illness, that is, more rapidly than the restoration of the muscles of the throat and soft palate.

Pareses of the muscles of the soft palate, throat and tongue developed in the beginning of the disease in dryness of the mucous membranes and by the 7th-8th day purulent nasopharyngites began to developed owing to the concurrent development of secondary infection.

External respiration. Pareses of the respiratory musculature were manifested by the absence of diaphragmatic respiration a sharp diminution of mobility of the intercostal muscles, the disappearance of the cough reflex.

The most typical parameters of external respiration during respiratory reanimation are presented in Table 2. The measurement of pulmonary ventilation as well as of pulmonary volumes and capacities on admission and during the first week of reanimation in 12 patients was impossible because of the absence of the own respiration, therefore the measurements were made in three patients who could survive switching off the respirator for 5 to 8 minutes. Vital capacity of the lungs (VC) decreased to the value of tidal volumes and less. Respiratory rate reached 40-52 per minute. Minute volume of ventilation (MVV) decreased to 40-50 % of the predicted value.

A systematic measurement of the indices of MVV and VC were initiated during the third week of the illness. By this time switching off the respirator became possible. In the great majority of patients respiratory rate was in the range of 20-28 per minute, tidal volumes increased to 250-300 ml, VC growed to 13-24 % of the predicted value. A further restoration of pulmonary volumes and ventilation depended on the dissemination of inflammatory process in the lungs. In rapid involution of inflammatory processes in the lungs and bronchi the indices of MVV approached the normal by the 29th-30th day of the disease The respirators were switched off by this time and the patients could breathe independently during 24 hours without a change in the blood gas. VC by this time restored only to 30-40 % of the predicted value. In the patients with disseminated inflammatory changes in the lungs and atelectases the restoration took long time Switching off the respirators became possible by the 30th-35th day of the illness but in this case saturation (SaO_2) significantly decreased. The own breathing in these patients and complete switching off the artificial ventilation apparatus took place on the 36th-48th day of the illness. Even on the 65th-75th day of the disease VC reached only 59-80 % of the predicted. Of interest is the appearance in a number of patients of myasthenia-like fatigue of the respiratory musculature which could be observed as early as in the first days of poisoning. So, after the appearance of the signs of respiratory failure, the tidal volume again increased, complaints of breathlessness disappeared and there was the impression of adequacy of pulmonary ventilation. However, the attacks of breathlessness occurred again.

The following observation provides an example of such myasthenia-

THE INDICES OF EXTERNAL RESPIRATION IN BOTULISM PATIENTS DURING RESPIRATORY REANIMATION

TABLE 2

Patient's name	Day of the disease	VC (in % in relation to predicted)	Respiratory rate (per minute)	Tidal volume (ml)	MVV (in % in relation to predicted	For what term switching off respirators is possible
K.	5th	—	40	150		About 5 min
	10th	—	24	200	51.4	" 5 "
	15th	12	28	250	86	" 5 "
	20th	15	19	150-300	69	11 min
	30th	34	21	250	64	4 hours
	40th	64	19	300		24 hours a day
Ch.	10th	11.4	23	160	42.9	About 5 min
	15th	13	26	250	75	" 5 "
	30th	24	22	370		24 hours a day
	55th	88	18			
M.	20th	13	20	190	54.3	About 5 min
	25th	19	22	300		" 5 "
	30th	25	21			Up to 1 hour
	40th	34.5	24	370		24 hours a day
	55th	44.9	22			
Soz.	15th	20	23	310	78	About 5 min
	20th	24	18	344	80	" 5 "
	30th	44	20	460		About 1 hour
	40th	69	16			24 hours a day
Sin.	30th	11.9	24	250	45.3	About 5 min
	35th	24	22	260	50.0	Up to 2 hours
	55th	59.6	20	450		24 hours a day

like character of the respiratory movements.

Patient M., aged 31. On 11 November 1967, the defect of the tibial bone was replaced by joint homotransplant. During the operation 250 ml of fibrinolytic blood was transfused. On 3 November pains in the throat and difficulty with swallowing appeared. These symptoms were considered to be the sequelae of endotracheal anesthesia. On the second day vision diminution, aphagia, aphonia and ptosis occurred. Botulism contamination with donor fibrinolytic blood was suspected.(*) Antibotulism serum was administered. On 5 November breathlessness appeared, on the next day there occurred respiratory failure and cardiac disorder. Intubation with subsequent artificial ventilation was performed. Several hours later the own respiration became possible, the intubator was removed; the attack of breathlessness again took place in a short lapse of time. Repeated intubation was made, it was followed by tracheostomy and for 42 days controlled ventilation by the Engström respirator. Subsequently the patient recovered, paresis of accomodation was +2.0 D.

Respiratory reanimation in botulism was carried out according to the standard technique which had been developed for acute poliomyelitis and other nervous diseases associated with respiratory insufficiency. Two principles were adhered to during treatment:

1) elimination of the respiratory tract obstruction;
2) provision of adequate pulmonary ventilation by means of respirators.

Elimination of the respiratory tract obstruction was attained through carrying out tracheostomy with cuffed tube. The indications for tracheostomy and endotracheal artificial ventilation in botulism are pareses of the muscles of the throat, larynx and tongue with complaints of respiratory distress; pareses of the respiratory muscles with a decrease in VC to 25-30% of the predicted; decreased cough reflex; reduction of SaO_2 to 91 % in adults and 93 % in children; atelectases and inflammatory processes in the lungs.

Some difficulties were presented by removal of atelectases. In atelectases there are successfully used lavage of the tracheobronchial tree with physiological solution and antibiotics in combination with compression of the thorax and artificial ventilation under positive pressure. In the first hours following the development of atelectasis this method permits to provide patent bronchi and elimination of atelectases. In patients with severe botulism who suffer from paralyses of the respiratory muscles and in whom the cough reflex is absent, the lavage of the bronchi is accompanied by cyanosis and tachycardia therefore the lavage was made by using small amounts of physiological solution in combination with the chest compression lasting for not more than 20-30 sec.

Artificial ventilation (AV) was conducted by means of the Engström respirator. The duration of AV was determined by the degree of restoration of the own breathing and bulbar functions, the indices of MVV, VC, tv, the blood gas composition, the state of acid-alkali balance and also pulmonary pathology.

Bilateral bronchopneumonias and atelectases were noted during clinica land radiological examination in two patients before tracheostomy was performed. Purulent tracheobronchitis was in all patients: inmediately after tracheostomy, purulent secretion was sucked from the trachea and bronchi, sometimes with putrescent pungent smell. In the

subsequent days during respiratory reanimation in six patients there were observed disseminated bronchopneumonias and in three patients atelectases of the lobes and separate segments of the lungs.

SaO_2 during respiratory reanimation in four patients approached the normal value (SaO_2 94-96%), in nine patients it was decreased to 90-93% that was accounted for by inflammatory processes in the lungs and bronchi. Acid-alkali balance in three patients was normal, in 10 patients there were observed compensated gas alkalosis (pCO_2 24-28 mm Hg) and a decrease in the level of actual bicarbonate (15-17 mEq/1) and buffer excess (up to-5-7.5 mEq/1). Only in one patient H. on the 7th day of the disease metabolic acidosis was observed (pH 7.26; pCO_2 35.2 MM HG, standard bicarbonate 16.5 mEq/1, actual bicarbonate 15.7 mEq/1, base excess-10 mEq/1, total CO_2 16.7 mEq/1 which could be explained by renal pathology and acute hypoxemia that developed during transportation of the patient. The restoration of normal indices of acid-alkali balance took place in different time intervals as the own breathing restored.

The experience of employment of respiratory reanimation in many diseases of the nervous system has shown that in botulism, as distinct from other diseases of the nervous system, the damage of viscera was particulary pronounced.

Renal function disorder was in 11 patients. In six patients of them it was marked during the first 8-14 days of the disease. In five patients the signs of severe renal pathology were observed: a decrease in diuresis, specific gravity of the urine, the appearance of protein (to 0.6-1%). In the sediment hyaline granular cylinders an dred blood cells were found. The level of residual nitrogen reached 82-149 mg%. There was noted a pronounced cyclic character of the course of renal syndrome: oliguria for the first two weeks of the illness and an increase in the residual nitrogen level until the end of the third week of the illness. With the restoration of diuresis (the 3rd-4th week of the illness) the residual nitrogen content fell and pathologic elements in the urine gradually disappeared.

The most typical disorder of the renal function was observed in patient N, aged 32. He fell ill on 21 November 1965 when dizziness and diplopia appeared. On the second day vomiting, unstable gait, ptosis of the lids developed. On the third day there were disturbance of respiration and swallowing. On the fourth day tracheostomy was made and AV was commenced by using a respirator controlled by pressure. The patient was admitted on the 7th day of the disease. Twenty minutes before arrival to the centre he lost consciousness.

Profound sopor, twitching of the extremities, chill-like tremor of the muscles. Rigidity of the neck muscles, the Kernig's sign on two sides. Reaction of the pupils to light is absent. Purulent ulcer of the cornea, left-side iridocyclitis. Ophthalmoplegia. Drop of the lower jaw. Immobility of the soft palate and tongue. Absence of active movements in the extremities. Marked tendon reflexes. No abdominal reflexes. No response to pain stimulation. Right-side pulmonary pneumonia. Heart sounds are dull. Arterial pressure 85/60-50/0 mm. Pulse rate 120-160 per minute, weak. Rectal temperature 41.6°. Abdomen is retracted, soft. Daily diuresis 250 ml. Residual nitrogen 140-171 mg%, urea 62 mg%. Urinalysis on the 8th-12th day of the disease: specific gravity 1020-1010, protein 0.9-1.8, hyaline granular cylinders 2-1 in the visual field, red cells 4-6 in the visual field, blood detrite, cylindroids 1-2 in the visual field. Blood

test: Hb 15.3 g% (92 U.), red cells 4710000 ,leucocytes 21300, protein 7.5%, neutrophiles 84.5%, lymphocytes 4.5, monocytes 3.5, ESR 58 mm per hour.

The improvement of the neurological status began since the 12 th day of the disease: consciousness, the movements of the lower jaw and tongue increased, there appeared the movements of the arms and legs. Diuresis increased up to 800 ml and by the 14th day of the disease it became normal. Temperature fell to 38-37.8°. Arterial pressure 175/70 mm Hg, pulse rate 120-106 per minute. The improvement of the bulbar functions occurred gradually. Residual nitrogen level decreased to normal on the 23rd day of the disease. Intravenous drip administration of isotonic solutions and sigmamycon was continued until the 20th day of the disease. Artificial ventilation was necessary until the 48th day of the disease and tube feeding until the 42nd day. Subsequently the patient recovered. He was discharged on the 74th day. Paresis of accommodation up to +3.0 D was noted.

The state of cardiovascular system. During respiratory reanimation pulse rate and arterial pressure were recorded every three hours. The analysis of these data showed that in the patients tachycardia and periodical fall of arterial pressure to 80/40 mm were noted until the 8th-14th day of the disease. In nine patients tachycardia was observed in the presence of stable values of arterial pressure which were similar to normal. The heart borders were enlarged in four patients. In 8 patients dull character of the heart sounds was noted. In 4 patients there were slowering of atrioventricular conduction and myocardial circulatory insufficiency in the ECG. There was evidence of trophic changes of the myocardium of local character. Patient N. on the 14th day of the disease exhibited sinoauricular blockade, toxic myocarditis.

By the 50th-60th day of the illness the indices of the cardiovascular activity did not diflected from normal.

The gastrointestinal tract. During reanimation a satisfactory function of the stomach was found. A good evacuation of the food was noted on feeding with nutritive mixtures through a tube at 3-4 hour intervals. Intestinal paresis was observed until the 7th day of reanimation in 7 patients, until the 14th day in 2, until the 20th day in 3; intestinal function was normal only in one patient.

The morphological changes of the blood were of one type in all patients. Extreme fluctuations of leucocytosis were from 9800 to 21300.

The number of segmentonuclear elements increased from 60 to 73%. Left-side shift was moderate: extreme fluctuationts of the rod-nuclear leucocytes were from 11.5 to 27%. Lymphopenia was revealed regularly and it reached sometimes 7.5%. Aneosinophylia was in six patients and persisted until the 15th-16th day of the disease. Shift to juvenile forms was revealed only in two patients until the 10th day of the illness. Erythrocyte sedimentation rate was considerably increased: in ten patients it attained 37-63 mm per hour and persisted until the 30th-33rd day of the disease. A decrease in the red blood cells to 2460000 and a fall in hemoglobin level to 7 g% was found only in the patients suffering from repeated bleedings from the ulcers at tracheostomy site.

The changes of carbohydrate and protein metabolism were of similar type. Since the first week of the disease transient hyperglicemia was noted: blood sugar level increased to 178-250 mg%. There were observed reversible shifts of protein fractions, a decrease in A/G coeffi-

cient ,a significant rise in the level of α and α_2 globulines.

Moderately pronounced hypopotassemia was observed constantly (17.4-10.8 mg%).

Discussion

Botulic infection in extremely severe course of the disease is accompanied by a selective damage of the bulbar and respiratory functions. The pathogenesis of these disorders is accounted for by presynaptic blockade of excitation of the myoneural synapses and acetylcholine release disturbance (Gutman et al., 1976). The occurrence of paralyses is also explained by pathogenetic action of botulism toxin on motor neurons of the spinal cord (Mikhailova S.D.). In the literature there is a few of communications on the use of prolonged artificial ventilation in botulism (Rosen, 1938; Bofenkamp, 1949; Popova L. M., 1964).

The present paper shows that timely replacement of temporarily lost bulbar and respiratory functions is accompanied by a complete restoration. The effect of treating severe forms of botulism is high: 15 out of 16 patients completely recovered. In 13 patients paresis of accommodation from +2.0 to +4.0 was noted within 2-4 years after the disease. As seen from Table I, only one patient died on the 252nd day of the disease in the signs of decerebration resulting from a long-term decrease of arterial pressure and a fall of the cerebral blood flow. Histological study of the central nervous system (Popova L. M., 1970) showed extensive necroses of the cerebral cortex, the basal ganglia and the diencephalon. In fact the cause of death was not botulism but the sequelae of the decrease in the cerebral blood flow and arterial hypoxemia. Persistent hypotension was produced by allergic shock which developed during intravenous administration of antibotulism serum. The restoration of vital capacity of the lungs occurred in most patients by the end of the 2nd-3rd month of the illness (Table 2).

In botulism, as distinct from other diseases of the nervous system, various lesions of viscera were observed during respiratory reanimation.

Purulent and inflammatory processes in the bronchi and lungs have not been described in the clinical picture of botulism (Korutsky A. M.). This is probably accounted for by the fact that most patients died on the 6th-8th day after poisoning and pulmonary pathology clinically was not always determined definitely. At the same time pathologically in botulism (I. Zilbert, 1937) there were constantly found pneumonias sometimes with extensive areas of purulent interstitial infiltration, that indicated the development of purulent pneumonia since the very beginning of the disease. In the pathogenesis of purulent bronchopneumonia, of importance is a concomitant secondary infection developing in the presence of severe intoxication, as well as aspiration of mucus and food into the respiratory tract as a result of bulbar paralysis. Non-specific character of inflammatory bronchopulmonary processes is confirmed by bacteriological studies as cultures of pus from the tracheobronchial tree since the first days of respiratory reanimation (approximately on the 4th-5th day of the disease) showed various flora as a rule being resistant to most antibiotics.

S. Ya. Shteinberg noted that the changes of the cardiovascular system in botulism were not greatly pronounced. Even in lethal outcome of the disease the cardiac activity stops after respiratory failure to which attention was drawn by Berkovsky in as early as 1957 (cit. K. I. Matveyev).

However, in extremely severe course of the disease, myocardial circulatory disorders caused by hypoxemia develop along with toxicoinfectious process. This corresponds to morphological changes in the heart. R. M. Fishman found in the myocardium circulatory disorder in form of hyperemia, hemorrhages, sometimes in combination with fragmentation of the myocardial fibres, homogeneously wax-like degeneration resembling Zenker's degeneration.

Disorders of renal function in botulism has not yet been described. In contrast, D. N. Kutsygin et al. considered that toxin of botulism did not cause significant damage of the kidneys, although morphological study always showed acute nephrosis.

According to the data of R. M. Fishman, in the renal parenchyma, along with blood circulation disorder, there are observed necrosis of convoluted tubules and glomerular infiltration.

In conformity with the classification by E. M. Tareyev, disorders of renal function in botulism are classified as toxico-infectious lesions with the signs of renal insufficiency. In our observations the relationship between the renal syndrome and general severity of the disease, the presence of hypoxemia and circulatory disorders was also determined.

The effectiveness of respiratory reanimation in botulism is very high. Lethal outcomes in this disease are a non-justified medical loss as all patients recover and return to work. In severe course of botulism of primary importance is timely use of the complex of respiratory reanimation.

SUMMARY

Mortality in severe and extremely severe cases of botulism reaches 60 %. Its main cause is respiratory paralysis. The paper reports on reanimation of 16 patients with extremely severe form of the disease. According to literature data this is the largest group studied. The paper furnishes data on external respiration, blood gas changes, acid-base balance, manner of restoration of vital functions and pathology of the internal organs during respiratory reanimation.

Indications for respiratory reanimation were: 1) pareses of the muscles of pharynx, glottis and tongue and complaints of difficult breathing, 2) pareses of respiratory muscles with decrease of the vital volume to 25-30% of normal, 3) decrease of the cough reflex, 4) drop of blood oxygenation to 91% in adults and to 93% in children, 5) atelectases and inflammatory processes in the lungs and bronchi. Artificial ventilation was achieved with the aid of volume respirators with independent respiratory cycle rate (Engstrom). Aspiration of secretions from airways was carried out with electric aspirator (vacuum 8-9 m water).

Respiratory resuscitation proved highly effective. Out of 16 patients only one 9 year old child died, who was admitted with syndrome of decerebration. Artificial respiration lasted for 252 days with child comatose. Death was not due to botulism but the sequelae of the decrease in the cerebral blood flow and arterial hypoxemia. Persistent

hypotension was produced by aller- intravenous administration of anti-botulism serum. Autopsy showed extensive necroses of the brain cortex. To-day with modern respiratory resuscitation methods death in severe forms of botulism is inexcusable. Treatment in special respiratory centres is mandatory.
gic shock which developed during

RESUMEN

La mortalidad en casos severos y extremadamente severos de botulismo alcanza el 60%. Su causa principal es la parálisis respiratoria. Este trabajo menciona acerca de la reanimación de 16 pacientes con forma extremadamente severa de la enfermedad. De acuerdo con los datos de la literatura este es el grupo más grande estudiado. El trabajo suministra datos acerca de respiración externa, cambios de gases de la sangre, equilibrio ácido básico, modo de restaurar funciones vitales y patología de los órganos internos durante la reanimación respiratoria.

Las indicaciones para la reanimación respiratoria fueron:

1) paresia de los músculos de la faringe, glotis y lengua, y quejas de dificultad respiratoria, 2) paresia de músculos respiratorios con decrecimiento del volumen vital a 25-30% de lo normal, 3) disminución del reflejo de la tos, 4) descenso de la oxigenación sanguínea al 91% en adultos y a 93% en niños, 5) atelectasias y procesos inflamatorios en los pulmones y bronquios. Ventilación artificial fue realizada con la ayuda de respiradores de volumen con ritmo independiente de ciclo respiratorio (Engstrom). La aspiración de secreciones de las vías aéreas fue conducida con aspirador eléctrico (vacío 8-9 m agua).

La resucitación respiratoria probó ser altamente efectiva. De los 16 pacientes sólo falleció un niño de 9 años de edad, quien fue admitido con un síndrome de decerebración. La respiración artificial se prolongó 252 días con niño comatoso. La muerte no fue producida por botulismo, si no que fue secuela del descenso del flujo sanguíneo cerebral e hipoxemia arterial. La hipotensión persistente fue producida por shock alérgico el cual se desarrolló durante la administración intravenosa de suero antibotulismo. La autopsia mostró una extensa necrosis de la corteza cerebral. Hoy con los métodos modernos de resucitación respiratoria, la muerte en las formas severas de botulismo, es inexcusable. El tratamiento en centros respiratorios especiales es obligatorio.

RÈSUMÉ

La mortalité dans les cas sévères et extrememement sévères de botulisme atteint 60%. La cause principale en est la paralysie respiratoire. Ce travail traite de la réanimation de 16 patients présentant une forme extrêmement sévère de la maladie. D'Après les renseignements fournis par la littérature médicale, c'est la le groupe les plus nombreux qui ait été étudié. Le travail donne des précisions concernante la respiration externe, les échanges gazeuz du sang, l'équilibre acide - base, la façan de restaurer les fonctions vitales et la pathologie des organes internes au cours de la réanimation respiratoire.

Les indicacions au sujet de la réanimation respiratoire on été les suivantes:

1) Parésie des muscles de pharynx, de la glotte et de la langue et plaintes de difficulté respiratoire. 2) Parésie de muscles respiratoires avec décroissance du volume vital jusqu'a 25-30% de la normale. 3) Disminition du réflexe de la toux. 4) Diminution de l'oxygene sanguin a 91% chez les adults et 93% chez les enfants. 5) Atelectase et processus inflammatoires dans les poumons et les bronches. 6) La ventilation artificille a été réalisée avec l'aide de respirateurs de volume à rythme indépendant dy cycle respiratoire (Engstrom). L'aspiration des secretions des voies aériennes a été conduite avec un aspirateur électrique (vide 8-9 m d'eau).

La sresucitation respiratoire s'est mostrée tres effective, des 16 patients, seul un enfant de 9 ans est décédé, qui avait été admis avec un syndrome de décérébration. La respiration artificiele a été prolongée pendant 252 yours pour des enfants dans le coma. La morte n'a pas été due au botulisme mais a été une séquelle de la diminition du flux sanguin cérébral et de l'hypoxémie artérielle. L'hypotension persisttante a été produite par le choc allergique du a l'administration intraveineuse de sérum antibotulique. L'autopsie a montré une intense nécrose de l'écorce cerebrale. De nos jours, avec les méthodes modernes de résucitation respiratoire, la morte dans des cas sévères de botulisme est inexcusable. Le traitement dans des centres respiratoires spécialisés est obligatoire.

ZUSAMMENFASSUNG

Die Sterblichkeit bei ernsten und besonders ernsten Fällen von Botulismus beträgt 60%. Ihre Raupturs ache ist die Atmungslähmung. Diese Arbeit erwähnt die Wiederbelebung von 16 Patienten bei einer besonders ernsten Form der Krankheit. Entsprechend den Daten der Literatur ist dies die grösste Gruppe,, die studiert wurde. Die Arbeit bringt Daten über die externe Atmung, Gaswechsel des Blutes, Gleichgewicht der Säurebasis, Art der Wiederherstellung von vitalen Funktionen und Pathologie der internen Organe während der Wiederherstellung der Atmung.

Die Indikationen für die Atemwiederherstellung waren:

1) Paresie der Pharynxmuskeln, Glotis und Zunge, und Klage über Atmungsschwierigkeiten; 2) Parese der Atmungsmuskeln mit Abnahme des Vitalvolumens von 25-30% des normalen; 3) Minderung des Rustenreflexes; 4) Abnahme der Oxidation des Blutes von 91% bei Erwachsenen und 93% bei Kindern; 5) Atelectase und Entzündungsprozesse in den Lungen und Bronchien.

Künstliche Ventilation wurde mit Hilfe von Respiradoren von Volumen und unabhängigen Rythmus des Atmungszyclus (Engstrom). Die Aspiration von Sekreten der Luftwege mit einem elektrischen Aspirador (Vacuum 8-9 m Wasser).

Die respiratorische Neubelebung erwies sich höchst effektiv, von den 16 Patienten starb nur ein Kind von 9 Jahren, das mit einem Syndrom

von Decerebration eingeliefert wurde. Die künstliche Atmung verlängerte sich auf 252 Tage bei dem komatösen Kimd. Der Tod wurde nicht produziert durch Botulismus, auch nicht als Folge der Abnahme des Blutzufuhr zum Gehirn oder der arteriellen Hypoxemie. Der bestehende Unterdruck wurde hervorgerufen durch allergischen Schock, der sich während der intravenösen Zufuhr von Antibotulismusserum entwickelte. Die Autopsie zeig te eine ausgedehnte Nekrose der Hirnrinde. Heute mit den modernen Methoden der Atmungswiederbelebung, ist der Tod bei den schweren Formen von Botulismus unentschuldbar. Die Behandlung in speziellen Atmungszentren ist obligatorisch.

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Toxic States Delirium and Epilepsy as Expressions of Disturbance of Inhibitory Mechanisms

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In 1935, Wolff and Curran (9) detailed the behavior of 106 patients exhibiting symptoms in the category called "delirium". Their intent was to correlate the content of these toxic states with: 1) "The specific type of noxious agent," and with 2) "The individual equipment and experience of the subject." Similar disorders of mental function were found to result from 28 causes. They noted that the qualities of delirium bear a striking resemblance to epileptic seizures. They include: restlessness, tremor, defective sphincter control, sleeplessness, fever, sweating, pallor and flushing, tachycardia and nausea, constipation and diarrhea. They also include disturbances of thought processes such as a poorly sustained attention, difficult concentration, impaired recent memory, poor calculatory ability, increased suggestability, lability of mood ranging from dreamy dazed states to periods of excitability and apprehension, misinterpretations and illusions categorized as auditory and visual pervesions, distortion of spatial proportions, tactile hallucination, olfactory, and gustatory sensations and equilibratory dreams. The authors drew attention to the similarity between their documentation of delirium and the roster of aura in epilepsy arranged by Lennox and Cobb (5) who catalogued the seizure experiences reported by 750 patients.

Seizure manifestations can be subdivided to reflect both functional anatomic and physiologic pathways. These include: disorder of mental state, consciousness and mood, visceral disturbance, gastrointestinal sensations as well as feelings related

to temperature and circulation, breathing and activity of salivary glands, pain, distortion of feeling on body surface, a loss of feeling, disturbances of vision, hearing, smell and taste, finally, abnormal motor activity or paresis. A detailed description of symptoms in each of these categories recapitulates characteristics of delirium.

The similarities between delirium and seizures presents the possibility of relating one to the other. It is reasonable to suggest that the manifestations of delirium reflect disturbed function of particular neuronal systems and that the causal factor is not specific but acts only as a trigger. Further, the inference can be made that the pathways mediating symptoms are shared by seizure disorders. The two states can occur concurrently. The incidence of seizures during delirium is not uncommon and instances of post-convulsive delirium are cited. (9) What should be the clinical and/or neurophysiologic basis for differentiating states of abnormal function of similar neuronal systems? What are the similarities in their production and mechanism?

Wolff and Curran were concerned with the correlation between the content of delirium and the individual equipment and experience of the subject. They stated, "The distinction between a delusional belief and the metaphorical statement 'As if'... would be a matter of individual interpretation." The delusional and hallucinatory experiences reflected distinctive personal characteristics derived from the memories, drives and attitudes which were a part of each of the patient's everyday life. These qualities of mental functioning as well as perversions of space and time relationships which are the hallmarks of delirium can now be considered from the viewpoint of biochemistry, immunology, genetics, anatomy and electrophysiology. Each of these basic disciplines has been applied to the development of recent knowledge of brain mechanisms. (1) As a base for devising a model of brain mechanisms involved in normal function, we have focused on abnormal clinical and EEG data.

In light of Von Bekesy's [8] investigations of perception, a discussion of neuronal mechanisms subserving hearing, taste, smell, vision and various forms of sensation on body surfaces must highlight the importance of sensory inhhibition. He has described the way in which sensory inhibition is a determinant in the discrimination of quantity and quality of various sensory stimuli. This is accomplished by directing an afferent impulse to a precise cortical area. It is a focusing mechanism which conducts sensory input to appropriate neuronal elements and selects the number and type of cortical units which are activated by a sensory stimulus. The discharge of this activated cortex in turn excites additional neurons which are necessary for the interpretation of, and the reaction to, a sensory stimulus. It is tempting to speculate that such a focusing device is a general mechanism of the central nervous system for defining the characteristics of responding units. The constellation of neuronal elements which are essential for appropriate response to any given sensory stimulus would be pre-determined by prior learning and experience. Responses to basic sensory stimuli such as sound, flavor, odor light and touch could be integrated with the individual patterns of motor and emotional behavior.

It would be reasonable to envisage toxic disorders as a disturbance of this brain mechanism. The common means by which diverse noxious agents may cause similar clinical disorders can be thought of as a depletion of inhibition. In the absence of inhibition the perception of

the stimulus would become distorted because cortex not appropriately reactive to a sensory stimulus would also become responsive. In turn, pathways mediating the behavioral and motor responses derived from discharge of cortex which had received sensory stimulation in error would be augmented and inappropriate, resulting in abnormal response patterns in the form of delirium or seizures. Thus toxic states in which there is distortion of sensory perception can be used to demonstrate the integration of different sensory modalities into systems of motor, behavioral and emotional activity. It is therefore suggested that movement, behavior and emotion are derived from sensory stimulation and that inhibition is an important means by which this is accomplished.

The observations which serve as a basis for our theoretical model are the abnormal electrographic responses in patients demonstrating photic myoclonus, prothic induced seizures, and spontaneous seizures. These results illustrate a relationship which can be thought of in terms of an inhibition, excitation balance.

METHODS

Light stimulation has been routine in all EEG examinations during the past 9 years at the West Haven Veterans Hospital. A Grass model 3-B stimulator was used. The light source was placed 3 to 6 inches directly before the patient's eyes. Unless specifically modified, eyes remained closed during the flicker period. The room light was dimmed but not darkened. Stimulation was begun at a flash frequency of 2 per second with the graded in increments of 2 per second up to a frequency of 16 per second. Flicker stimulation was maintained at each frequency for 15-30 seconds and the flash rate increased without interruption of the flicker. The total period of stimulation lasted 3-5 minutes .This routine has been altered in a random manner whenever unusual EEG or clinical effects were observed. The duration, sequence and order of the flicker pattern was not identical for each patient, nor was the background illumination of ligth intensity. No attempt was made to eliminate sounds in the room. The characteristics of stihulation were not uniform and there was variation in the number and location of retinal units stimulated. The duration and intensity of the light at each retinal point and the sequence of retinal areas involved was not reproductible. In addition, a low volume click was generated by the lamp. In spite of these stimulus variables a pattern of reproducible responses has been observed.

RESULTS

The recodrs of thirty patients in whom myoclonus or seizures were induced, showed patterns of response to light which were similar to the records of patients in waom only photic following was observed. The only distinguishing feature between these two groups was the presence of photic myoclonus or seizures. The peak driving frequency was 12 flashes per second and the second highest incidence 6 per second, but responses were present at all flash frequencies befween 2 and 16 per second. Light responses were as frequent on the right as on the left side. However, responses occurred independently on either side as well as simultaneously on both sides. They were localized to the parietal and occipital electrodes. Rarely were responses present in the anterior electrode placements. There were 77 parietal responses, 55 occipital and 17 frontal. Fast or slow harmonics were counted in 44 of 61 records, but in only one record were both present. Twelve patients sustained photic myoclonus alone,

Fourteen patients convulsed without preceding myoclonus. In two patients, myoclonus and convulsions occurred in sequence during a single examination.

Selected cases illustrate points of similarity in the clinical and EEG characteristics ohtoxic states due to a variety of causes. Sensory stimulation in the form of flickered light resulted in activation of neural systems which are inappropriate to the stimulus, thus inducing seizures and/or photic myoclonus. Another group of case histories and EEG patterns highlights the similarities between toxic states and epilepsy.

CASE HISTORIES

CASE I — A 48 year old man drank heavily for 15 years. His admission to the hospital was precipitated by weakness and unsteadiness as well as episodes of loss of consciousness. Physical examination revealed a wide-based gait, there was ataxia of all limbs and his liver was enlarged. The EEG on the day of admission demonstrated photic myoclonus (Fig. 1). Daily records during the next 6 days repeated the original responses. The photic myoclonic response was abolished when he opened his eyes. He left the hospital at the end of the 6-day period with all neurologic abnormality cleared. He returned 1 week later for repeat electroencephal-ographic study which failed to induce photic myoclonus.

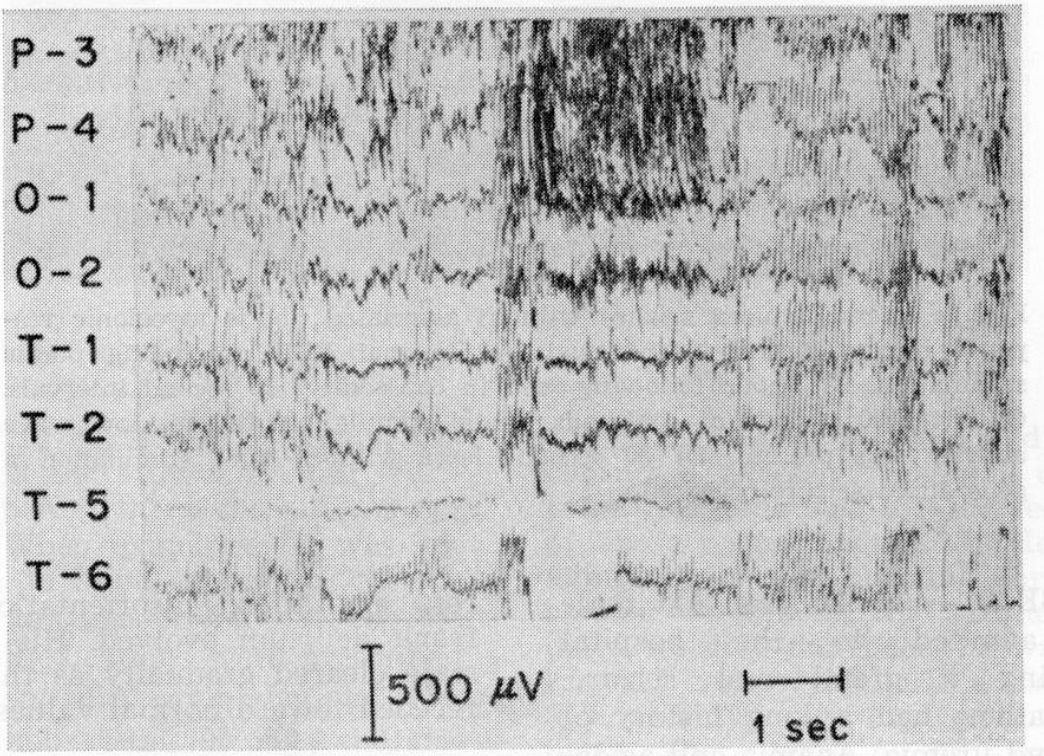

Fig. 1: Photic myoclonus during alcohol withdrawal period. Myoclonic response wasnot present when eyes are open (center portion of tracing).

CASE 2 — A 36 year old male alcoholic was admitted to the hospital for evaluation of episodes of dizziness, sweating and loss of consciousness which had begun 3 months earlier. Examination found him to be tremulous, disoriented in time and place, with poor memory and concentration. An EEG was done during the period of delirium. Photic myoclonus did not occur but a convulsive seizure was induced. When the delirium han cleared thirteen days later, repeat photic stimulation failed to induce abnormal responses.

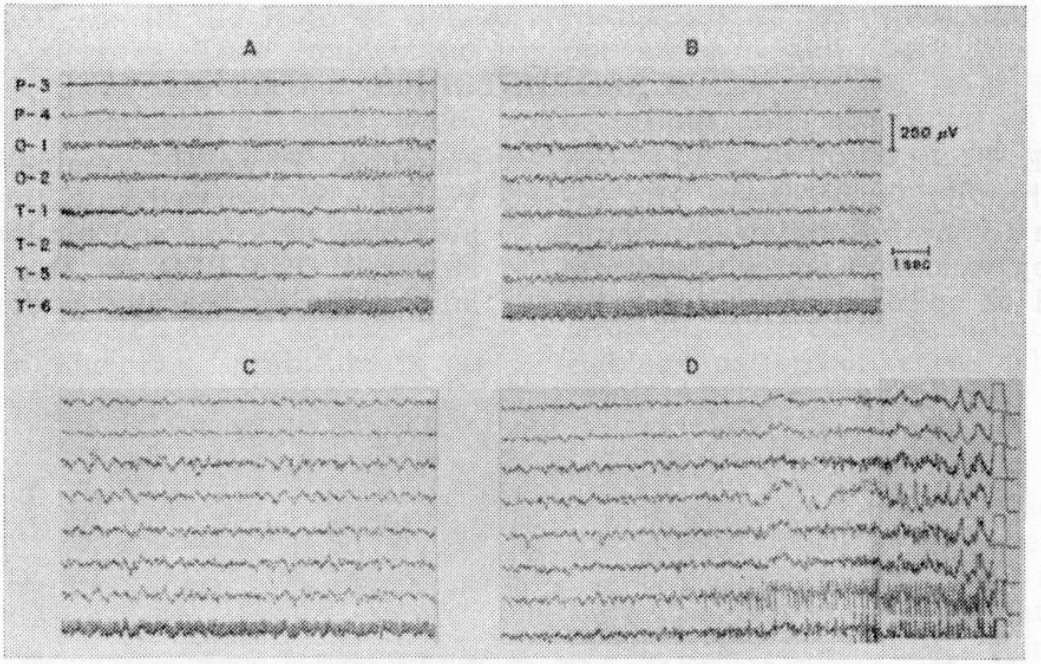

Fig. 2: Photic induced seizure without associated photic myoclonic response during alcohol withdrawal. A) Normal EEG preceeding photic stimulation. B) Photic following seen in consecutive 10 second intervals. C) After 80 seionds of contiuous photic stimulation diffuse slow wave activity was present. D) 30 seconds later without light stimulation a generalized seizure occurred.

CASE 3 — A 44 year old male was admited to the hospital following a grand mal seizure. The patient had a long history of gout and uremia. Anemia and acidosis were frequent clinical problems. Examination showed him to be lethargic but coherent and responsive. The BUN was 204 mg%, serum calcium 5.8 mg%, serum phosphorous 10.5 mg % and CO_2 18 mg%. On the day of admission photic stimulation induced a convulsion. During the first hospital week additional seizures, aggitation, disorientation and frank delirium evolved. His mental state cleared gradually as the BUN receded toward normal values.

CASE 4 — A 36 year old male chronic alcoholic has been admitted to the hospital on many occasions because of acute intoxication and seizures. He is known to have cirrhosis of the liver. As a consequence of treatment with paraldehyde he substituted paraldehyde for alcohol and consumed 20 cc per day regularly. Two days prior to hospital ad-

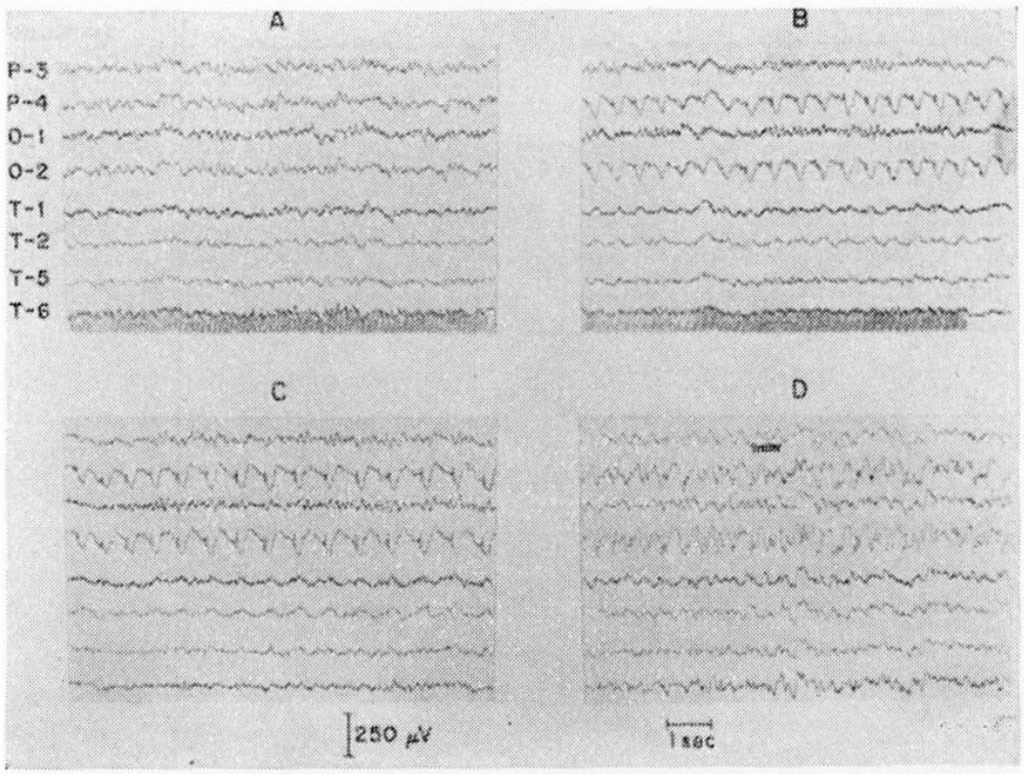

Fig. 3: Generalized seizure during uremic encephalopathy. A) Photic stimulation without EEG response. B) During the next 50 seconds focal seizure activity developed on right side. C) Seizure activity persinsting after termination of photc stimulation. D) 2 minutes later seizure has become generalized and associated with clinical convulsion.

mission his paraldehyde supply was exhausted and after a 48 hour withdrawal period three convulsions occurred. When examined he was not oriented in time, appeared chronicalli ill and was tremulous. The following medications were prescribed and given: diphenylhydantoin, 300 mg. phenobarbital, 90 mg., thorazine, 75 mg. and secobarbital, 50 mg. He slept through the night, the following morning abnormal responses to photic stimulation were observed. 48 hours later delirium tremens developed. It subsided in 4 - 5 days. Two weeks after the initial EEG a repeat study did not show abnormal response to photic stimulation.

CASE 5 — A 46 year old man consumed excessive amounts of alcohol and sedatives to ease feelings of anxiety and depression. He was admitted to the hospital for psychiatric treatment. In addition to daily whiskey and beer, he was taking 25 mg. of Mellaril 4 times a day and 100 mg. of Nembutal at nigth. There were no physical abnormalities and mentation was intact. The EEG demonstrated photic induced myoclonic response. Focal cortical seizures developed sequentially in the two hemispheres subsequent to stimulation. These were associated with states of mental confusion, in which he spoke spontaneously as though responding to vitual and aditory hallucinations.

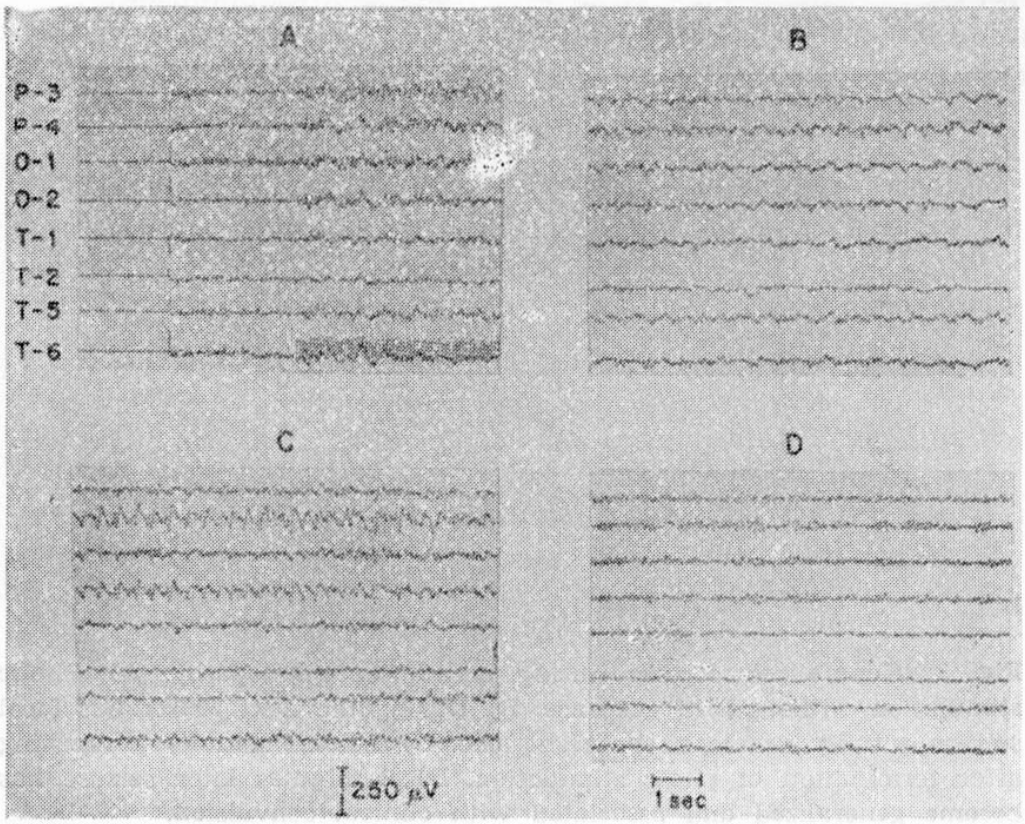

Fig. 4: Focal cortical seizure activity without clinic alseizure during paraldehyde withdrawal and preceeding the onset of delirium tremens. A) Normal resting EEG and onset of photic stimulation. B) 100 seconds later after termination of light stimulation spike and slow wave activity developed on right side. C) Peak of seizure activity reached 70 seconds later. D) 40 seconds later normal pattern has returned without clinical evidence of seizure.

CASE 6 — A 49 year truck driver was admitted to the hospital for examination 4 months after an initial generalize seizure. He had been an amateur boxer and also suffered many other incidents of head injury throughout childhood and adult life. General physical and neurological examinations were normal as were routine laboratory studies. The resting EEG and pneumonencephalogram were normal. Photic stimulation induced a convlusion.

CASE 7 — A 49 year old epileptic male complained of slowness and inaccuracy in his thinking. As foreman of an engineering crew, he was called upon for frequent decisions but found difficulty concentrating on problems and formulating answers. He tried to continue at work but recognized his deficiency. The symptoms had evolved intermittently over a period of several weeks. Grand mal seizures had recurred infrequently during a ten year in-

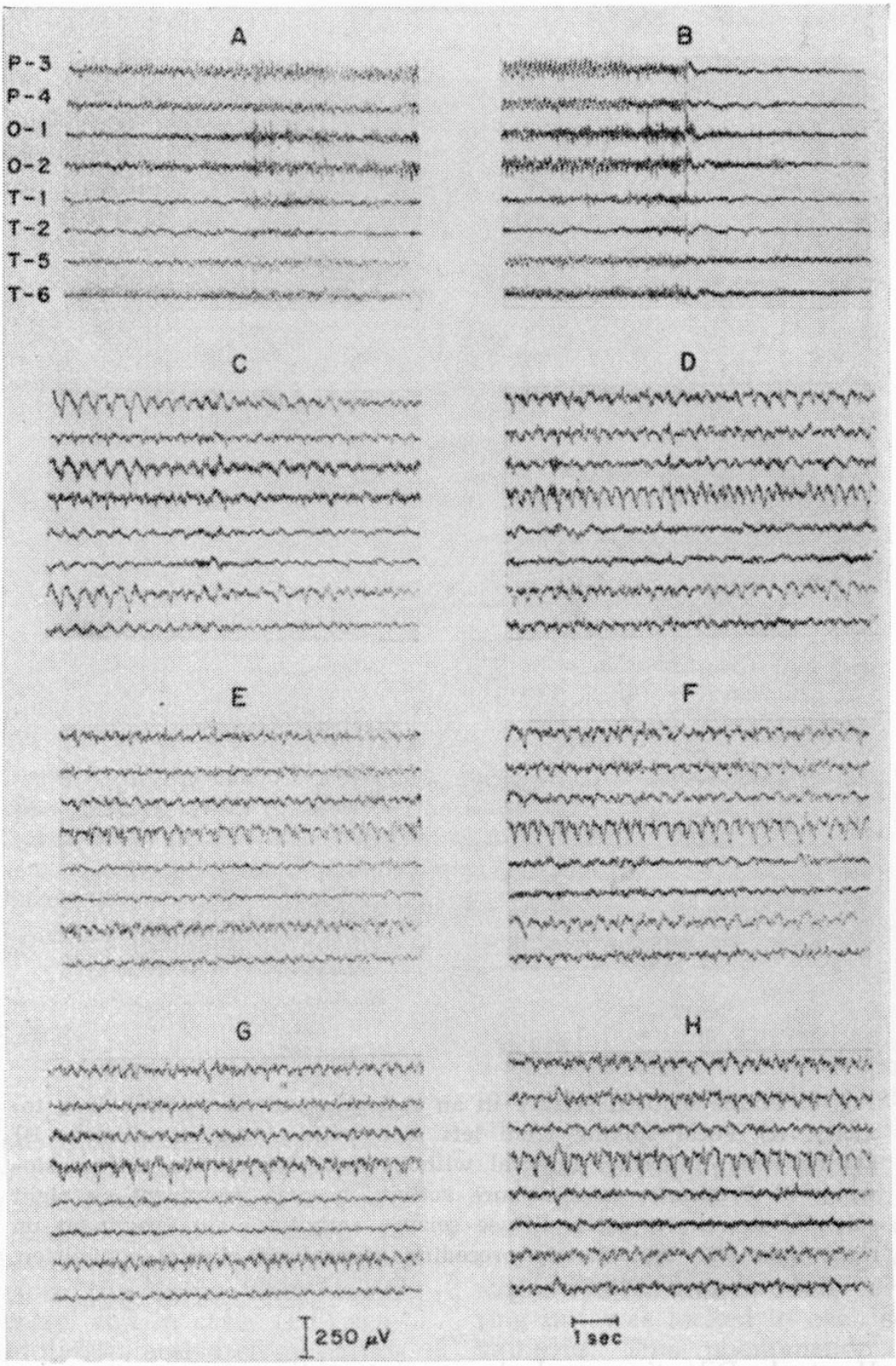

Fig. 5: Multlple focal cortical seizure with hallucinations developing dnring acute drug intoxication and alcohol withdrawal. A. and B) Continuous 10 second intervals showing photic induced myoclonic response that stops when stimulus is turned off. C) 3 minutes later without light stimulus seizure discharges appear on left side. D) 90 seconds later left sided discharges are diminishing while seizure activity develops independently on right side. E) In the next 10 second interval patient is actively hallucinating. F) $1^1/_2$ minutes later seizure discharges are prominent on right side. G and H) Consecutive 10 second intervals during which patient becomes rational in spite of continued focal seizure activity.

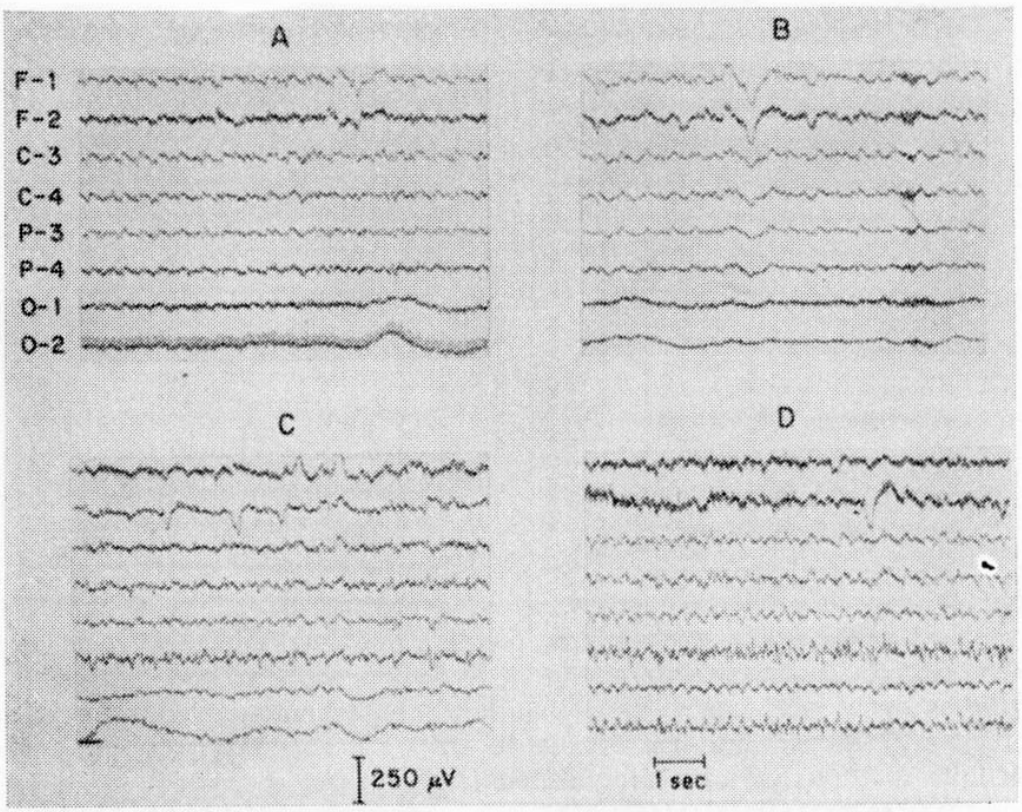

Fig. 6: Photic induced seizure in an epileptic patient without drug toxicity. A) Focal spiking from left side with photic stimulation. B) During next 10 second interval without light stimulation diffuse slowing. C) 2 minutes later seizure activity become prominent on right side. D) 9 minutes later diffuse seizure activity, more prominent on right than left, immediately preceding generalized clinical convulsion.

terval. He took Dilantin regularly and had no generalized attacks for a 5 year interval prior to onset of these symptoms. As he discussed symptoms there were interruptions in his flow of speech recurrent at intervals of seconds to minutes. Each break lasted less than a minute. No automatic movements, changes of muscle tone or vasomotor phenomena were noted. An EEG displayed a pattern of recurrent generalized seizure activity which was present again on the following day. (Fig. 7).

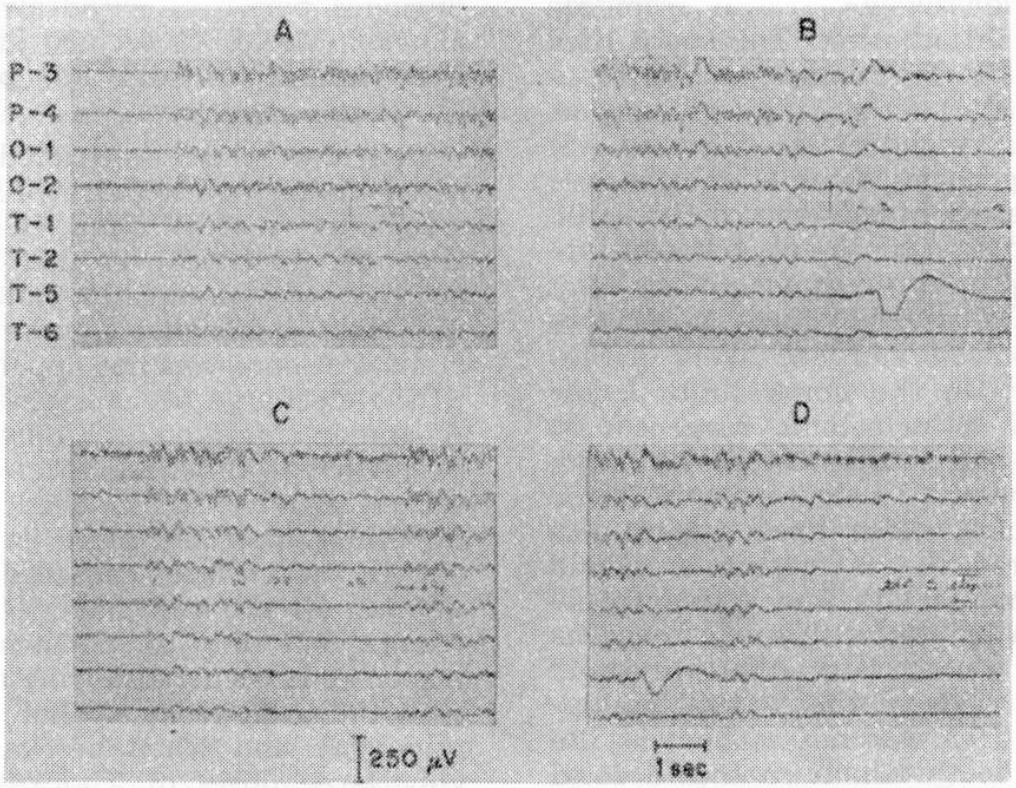

Fig. 7: Altered state of awareness during spontaneous seizure in an epileptic patient. A) Spontaneous onset of generalized seizure activity. During this interval patient was asked to count. B) In next 10 seconds seizure activity stops and patient begins to count. C) In spite of further seizure activity 20 seconds later and 40 seconds later. D) counting continues without interruption.

DISCUSSION

The cases presented are examples to demonstrate a relationship between toxic states with delerium and primary seizure disorders. There are clinical characteristics common to both which suggest that they share pathways in the brain. They occur concurrently, and in cases (1-6) sensory stimulation activated a pathologic response. We have postulated that these responses to photic stimulation represent spread of excitation from visual to motor and other patways because of a breakdown in inhibition. The lapse in inhibitory mechanisms is a temporary state which can be brought about by a variety of causes. The period of produced inhibition can be responsible for clinical manifestations of delirium or seizures.

Photic myoclonus occurred in case 1 while seizures did not. Each flash of light was associated with a muscle twitch. The activity of the motor system was not self-perpetuating but was locked to each sensory stimulus. This phenomenon occurs only when the eyes are closed. During approximately one week of withdrawal from alcohol, the susceptibility to photic myoclonus diminished and disappeared. Our formulation would suggest a temporary reduction of inhibition which permitted spread of light stimulus into

motor pathways. We have observed photic myoclonus frequently during the period of withdrawal from alcoholic intoxication. This may precede delirium tremens and seizures or it may be the only evidence of alcoholic withdrawal. Gastaut (2) studying photic stimulation after administration of metrazol defined the myoclonic response as a burst of large amplitude rhythmic spikes of a frequency equal to flash, bilaterally synchronized and appearing predominantly in the upper limb. A succession of myoclonic responses at shorter and shorter intervals would, in his view, develop into the tonic phase of a generalized seizure. He considered the myoclonic threshold synonomous with convulsive threshold. In patient with seizures secondary to a cortical scar the threshold for discharge of the cortical epileptogenic area was not as high as the myoclonic threshold so that a focal seizure could be produced before the myoclonic response was obtained and before a generalized seizure would result. When the myoclonic threshold was sufficiently low, metrazol was not essential to the production of electrical and clinical events indistinguishable from those obtained after metrazol administration. Thus, metrazol was not an essential component of the responses described. In the framework of our hypothesis, we consider the myoclonic response to be an example of inappropriate response to visual stimulus due to a partial breakdown of inhibitory mechanisms. A further reduction in inhibition could permit spread of response to other neural systems causing interference with autonomic functions, other sensory reception, higher integrative functions and consciousnes. In this way the myoclonic response need not progress to a tonic clonic seizure and the two thresnicclonic seizureand the two thresholds would not be synonomous. Case 2 illustrates the separation of myoclonus and seizures. A convulsion was induced by photic stimulation during a period of withdrawal from alcohol. The EEG seizure discharge was generalized and not preceded by photic myoclonus.

Delirium is not restricted to alcohol toxicity or withdrawal. It was associated with uremia in case 3 (Fig. 3). Electrical cortical seizure activity was photically induced in the right hemisphere, however the clinical seizure was not apparent until the discharge became generalized. A similar condition was observed in case 4 (Fig. 4) where focal cortical seizure activity was induced by photic stimulation during a period of toxicity which later caused delirium. Patient (4) did not have a clinical seizure, but only an abnormal EEG response. It occurred during a period of withdrawal from alcohol and paraldehyde and when he was receiving large doses of Thorazine. The EEG returned to normal in the ensuing two week interval when these conditions terminated. We would suggest that sustained focal cortical seizure discharge in the EEG in both cases, during a period of toxic delirium, was the result of inadequate inhibitory mechanisms. A further reduction of inhibition in case 3 permitted generalization of the seizure discharge and a clinical grand mal seizure resulted. In case 4 the response was contained in a localized cortical area and there was no evident clinical seizure. The important observation (6) that experimentally initiated paroxysmal discharging foci are surrounded by areas of enhanced inhibitory potential is pertinent to these observations. If inhibition serves to contain the paroxysmal discharge, then other neural systems are free to function normally.

All of the separate responses illustrated in the previous four cases are seen together in one patient, Case 5, Fig. 5. During acute withdrawal from alcohol and sedatives, while

not clinically delirious, photic stimulation produced photic myoclonus which terminated when the light was off. This was followed by a spontaneous seizure discharge from a left cortical and then a right cortical focus. Mental confusion and hallucinations accompanied the focal cortical discharges. The myoclonic response did not progress to a sustained paroxysmal discharge but terminated well before the seizure developed. This again illustrates a separate mechanism for photic myoclonus and photic induced seizures. It is also important to note that two distinct and separate electrical cortical seizure discharges were sustained independently. The occurrence of a delirium like state as the clinical counterpart of the focal seizure discharge seen in the EEG, is of interest because it supports the proposition that delirium and some seizures may be expressed through the same neural pathway.

The sixth case illustrates photically induced focal cortical seizure activity in a non-toxic subject. A toxic state then is not the sole predisposing factor in photically induced seizure activity. These responses may be seen as well in epilepsy. In this subject a seizure potential existed. Without photic stimulation the brain was able to contain the paroxysmal tendency.

The final case gives some insight into the properties and effects of hypersynchronous paraxysmal brain activity whether it is induced or spontaneously occurs. In this case, auditory communication during a seizure was received and retained but the response was blocked until the seizure subsided. If the seizure occurred during a period when the patient was responding to an auditory instruction, the response continued in spite of the seizure activity. Therefore the seizure activity interfered only with one aspect of The brains's ability to process and respond to an auditory signal. One way of viewing this is to postulate a system that acts to isolate the abnormal discharge from the remainder of the functioning CNS. When this isolating mechaism breaks down, the seizure becomes generalized and interferes with additional aspects of CNS funtion. Partial disturbances of inhibition limit the seizure activity and there is interference with some brain functions while leaving others intact. In a similar way reduced inhibition impairs the ability of the brain to focus and to limit the sensory input to appropriate CNS receptor areas. As a result of the activation of neuronal systems inappropriately, the interpretation of the input is distorted and there are aberrant associations with prior memory traces. The clinical expression of this may take the form of toxic delirium. Sensory inhibition by acting as a focusing and filtering mechanism helps elaborate sensory stimuli into precise perceptions and also plays a role in integrating responses. This interpretation of sensory inhibition provides a means of understanding how inhibition subserves normal motor, as well as behavioral function. Once can also view a sustained state of sensory deprivation as an example of the effect of reduced sensory inhibition. A clinical condition similar to toxic delirium may be brought about by withdrawal of sensory stimulation in the awake state, and there are many similarities between sleep dreams and delirium. We cite these as examples of the dependence of the brain on sensory stimulation in order to maintain normal function.

It is pertinent to the present hypothesis that the content of delirium and seizures often reflects previous experience of the patient.
In addition to the descriptions of Lennox and Cobb [5], Wolff and Curran [9], this relationship was docu-

mented by Sisler et al [7] in descriptions of an entity termed **epilepsia cursiva,** a form of psychomotor epilepsy. Several other studies in the literature also appear to be consistent with the present hypothesis.

Goff et al [3] in studying the effects of convulsive doses of 11-dimethylhydrazine on somatosensory evoked responses demonstrated an increase in the primary negative evoked response prior to the occurrence of a clinical seizure. They relate this to increased cortical excitability rather than increased afferent stimulation. Assuming that this compound, like other hydrazines, interferes with the production of gamma-amino butyric acid and that this is related to an interference with inhibitory mechanisms in the brain an imbalance between excitatory and inhibitory influences, at least in the cortex, results. The observation that this increased excitation related to decreased inhibition always precedes seizure is important for the present hypothesis. Hishikawa et al [4] studies visual evoked responses in photosensitive epileptic patients. They found components of the visual evoked response to be enhanced in the epileptic patients in comparison to controls. This is similar to the experimentally induced alterations in inhibitory mechanisms in that a response to sensory stimulation is exaggerated. In this context, toxic states may be considered to act in a similar manner to drug induced alterations in inhibition such as the hydrazines or to the unexplained alterations in sensory response found in photosensitive epileptics. The consequence is an abnormal response to stimulation which reflects the function of the neural systems so activated, resulting in photic myoclonus, seizures, photic myoclonus delirium or a combination of all of these.

SUMARY

The clinical expressions of encecephalopathies may resemble the manifestations of some seizures. This similarity between the content of seizures and delirium, which has also been noted by Wolff, Curran, Cobb and Lennox, suggests that they share pathways in the central nervous system. We have formulated a single mechanism responsible for the distortion of perception which takes the form of a delirium or in other instances may cause seizures.

The studies of Von Bekesy and others indicate the important role of inhibition in sensory perception. Photic stimulation produced seizures or photic myoclonus in a group of patients in whom drug or metabolic encephalopathy and/or a seizure disorder was present. These abnormal responses to sensory stimulation have been interpreted to indicate a breakdown of inhibition. The state of reduced inhibition permits overflow of sensory response to activate neuronal systems responsible for the sensory distortions of the delirium, and for production of the seizures.

The content of thought disordes and behavior due to intoxication is derived from the experiences of the individual so affected and can be thought of as representing a distortion of the perceptions which are a basis of the normal thought and behavioral activity of that individual. It is suggested that states of reduced sensory inhibition can be responsible for disturbances of mental function. Conversely, inhibition subserves normal mental activity.

RESUMEN

Las expresiones clínicas de las encefalopatías pueden parecerse a las manifestaciones de algunas crisis epilépticas. Esta similitud entre el contenido de las crisis y el delirio que ya ha sido señalada por Wolff, Curran, Cobb y Lennox, sugiere que comparten vías comunes en el sistema nervioso central. Hemos formulado un mecanismo simple responsable de la distorsión de la percepción que en ocasiones toma la forma de un delirio y en otras oportunidades puede dar lugar a crisis epilépticas.

Los estudios de Von Bekesy y otros indican la importancia de la inhibición en la percepción sensitiva. La estimulación fótica dio lugar a crisis epilépticas o a myoclonus fótico en un grupo de pacientes que presentaban encefalopatía por drogas o metabólica y/o trastornos epilépticos. Estas respuestas anormales a la estimulación han sido interpretadas como indicadores del abatimiento de la inhibición. El estado de inhibición reducida permite el exceso de respuesta sensorial para activar los sistemas neuronales responsables de las distorsiones sensoriales del delirio y de la producción de las crisis epilépticas.

El contenido de la perturbación del pensamiento y el comportamiento debidos a la intoxicación derivan de las experiencias del individuo así afectado y pueden ser consideradas como representando una distorsión de las percepciones que son la base del pensamiento normal y de la actividad del comportamiento del mismo.

Se sugiere que los estados de inhibición sensorial reducida pueden ser responsables de las perturbaciones de la función mental. Inversamente la inhibición facilita la actividad mental normal.

RÉSUMÈ

Les expressions cliniques des encéphalopathies peuvent ressembler aux manifestations de quelques crises épileptiques. Cette similitude entre le contenu des crises et le délire qui a déjà été observée par Wolff, Curran, Cobb et Lennox, suggère qu'ils partagent des voies communes au système nerveux central. Nous avons formulé un mécanisme simple responsable du dérèglement de la perception qui parfois prend la forme d'un délire ou bien peut provoquer des crises épileptiques.

Les études de Von Bekesy et d'autres indiquent l'importance de l'inhibition dans la perception sensorielle La stimulation photique a provoqué des crises épileptiques ou un myoclonus photique chez un groupe de patients qui présentaient une encéphalopathie par drogues ou métabolique et/ou des dérèglements épileptiques. Ces réponses anormales à la stimulation ont été interprétées comme des indicateurs du (breakdown) l'abatiment de l'inhibition. L'etat d'inhibition reduite permet l'excès de la réponse sensorielle pour activer les systèmes neuronaux responsables des dérèglements sensoriaux du délire et de la production de crises épileptiques.

Le contenu de la perturbation de la pensée et du comportement dùs à l'intoxication dérivent des expériences de l'individu ainsi affecté et peuvent être considérées comme représentant un dérèglement des perception qui sont à la base de la pensée normale et del'activité du comportement de la même. On suggère que les états d'inhibition sensorielle réduite peuvent être responsables des derèglements de la fonction mentale. Inversement l'inhibition facilite l'activité mentale normale.

ZUSAMMENFASSUNG

Die kliniscen Asusserungen der Encephalopathien koennen denen gewisser epileptischer Krisen aehnlich sein. Diese Aohnlichkeit zwischen dem Eharacter gewisser epileptischer Anfarlles and dem Delirium, die schon von Wolff, Curran, Cobb, und Lennox festgesttellt worden ist, fuehrt zu der Annahme, dass diese gleiche Wege im zentralen Nervensystem gehen, Wir haben einen einfachen Mechanismus formuliert, der fuer die Distorsion der Wahrenejmung verantwortlich ist, der gelegentlich Form eines Delirium annimt und bei anderen Gelegenheiten. Anlass zu epileptischen Anfaellen geben kann. Die Studien von Von Bekesy und anderen betonen die Bedeutung, die die Hemmung der sensitiven Wahrnehmung hat.

Die photische Reizume hat bei einer Gruppe von Patienten, die durch Drogen oder Storungen des Stoff wechselts und oder epileptische Storungen hervorgerulene Encephalopattien litten, zu Myoclonus gefuhrt.

Diese anormalen Reaktionen auf die Stimulierung sindals Angeichen fuer die Schawachung der Hemmung ausgelegt worden. Der Zustand der reduzierten Hemmung ermoglicht ein Uebermass an sensorielle Reaktion, un die Neuronensyteme anzuregen, die fuer die sensoriellen Distorsionen des Delirium und die epileptischen Krisen verantwortlich sind. Der Inhalt der Stoerungen des Denkvermoegens und das Betragen auf durch Intoxzikation beruhen auf den Erfahrungen des so affozierten Individuums und koennen als Vorstellungen der Wahrnehmungen angesehen werden, die die Basis des normalen Denkens un der Verhaltenstaetigkeit desselben sind. Man nimmt an, dass der Zustand der beschrenkten sensoriellen Hemmung Ursache fuer die Stoerung der geistigen Funktionen sein kann Umgekehrt, ermoeglicht die Hemmung die normale geistige Taetigkeit.

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Manifestation Neurologiques Toxiques au Cours des Traitements Antiangoreux.

(Maleate de Perhexiline et Clorhydrate d'Amiotadone)

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Parmi les médicaments utilisés ces dernières années avec beaucoup d'efficacité d'ailleurs dans le traitement de l'angor coronarien, certains témoignent d'effets secondaires nocifs pour le système nerveux tels les neuropathies périphériques ou les mouvements anormaux induits par le maleate de perhexiline ou le chlorhydrate d'amiodarone. Il parait interessant de rappeler les caractéristiques de ces atteintes afin de pouvoir soit les prévenir soit les traiter dans de brefs délais.

LE MALEATE DE PERHEXILINE, ** dérivé de la pipéridine intervient au niveau cardiaque par action vasodilatatrice coronarienne directe et en modifiant le métabolisme du myocarde avec meilleure utilisation des lactates et de l'oxygène. Mais il interfère également avec les grandes voies métaboliques générales comme en témoignent les effets secondaires signalés: perte de poids (1) (11), troubles du métabolisme glucidique (10) (24) et lipidique (8), atteinte hépatique (14) (20).

Cités initialement comme de simples phénomènes d'intolérance peu gênants (parenthesies, sensations ébrieuses, vertiges, lassitude) **les manifestations neurologiques** peuvent réaliser des tableaux cliniques beaucoup plus graves. Outre les syndromes extrapyramidaux retrouvés dans deux cas (5) (23), ce sont surtout des **neuropathies périphériques**.

Isolées pour la première fois en 1975 par l'un de nous (5), c'est à BOUSSER et coll (6) que l'on doit d'avoir précisé leur aspect polyradiculonévritique habituel. Depuis d'autres cas comportant des tableux cliniques identiques ont été rapportés (4) (7) (16) (19) (20) et la nature des altérations anatomopathologiques précisée par FARDEAU et ESCOUROLLE dans deux de ces publications.

Dans les 23 cas également répartis dans les deux sexes que nous avons retrouvé dans la littérature, l'atteinte neurologique se manifeste

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habituellement chez des sujets traités de manière prolongée entre 4 et 36 mois, les signes apparaissant d'autant plus précoces que la dose utilisée est plus forte, entre 4 et 6 mois (pour 400 mg. quotidiens) avec même des paresthésies dès la fin du premier mois dans un cas (5) et entre 15 mois à deux ans et demi avec des posologies plus minimes (200 mg/jour).

CLINIQUEMENT, le tableau neurologique précédé dans trois quart des cas par un amaigrissement qui peut être massif (entre 4 et 36 kg.) début habituellement par des **paresthésies** qui frappent par leur intensité et leur caractère désagréable, impressions de piqûres d'épingles ou de brulûres urticantes aux mains et aux pieds mais aussi sur le thorax, l'abdomen et parfois la région péribuccale et la langue. Rapidement les malades signalent des impressions de callosités, de coussinets métalliques brulants ou glaçés au niveau de la plante des pieds gênant la perception tactile et l'appui sur le sol avec troubles de la marche qui est déséquilibrée instable, ataxique. Dans quelques cas, des douleurs articulaires et musculaires spontanées ou provoquées viennent compléter ce tableau sensitif subjectif, tandis qu'apparaissent les **troubles moteurs,** parfois premies symptôme. Faiblesse prédominant initialement aux ceintures, signe du tabouret, démarche et attitude pseudomuyopathique, puis extension distale plus ou moins importante avec steppege au premier plan de la scène clinique dans trois cas et difficultés motrices des mains. L'amyotrophie, souvent difficile à apprécier derrière l'amaigrissement est notée quatre fois, des fasciculations parfois signalées.

A l'examen, la forçe segmentaire est modérement diminuée mais quatre malades au moins ne pouvaient plus se tenir debout. Les réflexes ostéotendineux sont en régle abolis de manière plus ou moins diffuse mais leur conservation au moins initiale ne change rien au diagnostic (4) (22). La sensibilité objective est plus ou moins altérée. Les troubles de la sensibilité profonde sont presque constants avec signe de Romberg et abolition de la pallesthésie aux membres inférieurs, alors que les perturbations des .sensibilités tactiles, thermiques et douloureuses réalisent des hypoesthésies voire de véritables anesthésies en chaussette ou en gant. Le signe de Lasègue n'a jamais été noté. Atteinte respiratoire ou paralysies des paires craniennes n'ont pas été recontrées jusqu'alors, par contre l'association à un oedème papillaire a été signalée cinq fois (4) (6) (7), oedème régressant après arrêt de la thérapeutique sans baisse de l'acuité visuelle dans son sillage. Enfin, s'il est courant d'entendre les malades se plaindre de sensations ébrieuses et vertigineuses et présenter une atteinte des voies vestibulaires dont la réalité est plus ou moins discutée, d'autres symptômes neurologiques peuvent enrichir la scéne notamment un tremblement de type cérebelleux ou extrapyramidal signalés par certains auteurs.

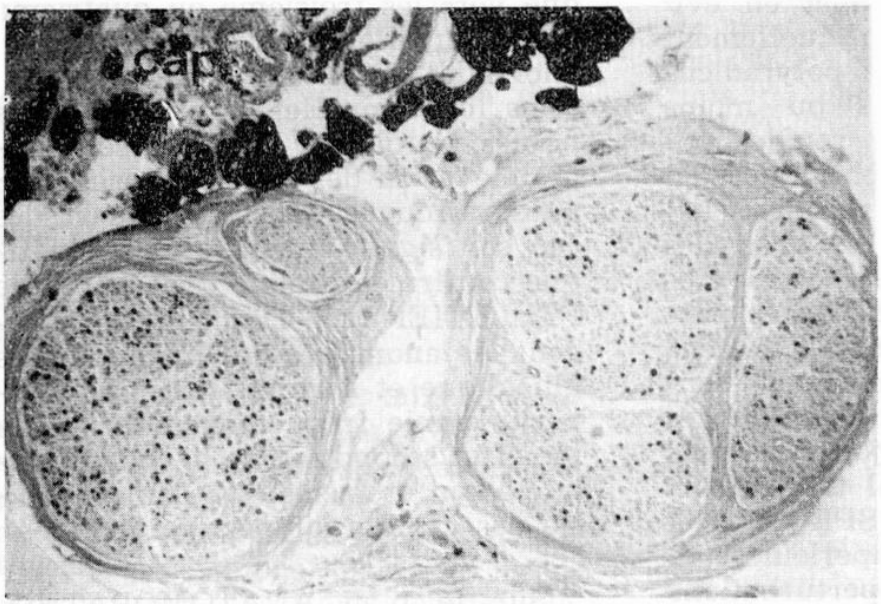
Cette sémiologie neurologique s'accompagne d'**anomalies paracliniques. Le liquide cephalo-rachidien** est habituellement le siège d'une dissociation albuminocytologique retrouvée quinze fois sur les dix neuf rachicentèses pratiquées L'abuminorachie va de 0,50 g/l jusqu'à plus de 4 g/l ,sans anomalies des globulines et avec un profil électrophorètique de type transudatif. L'évolution rapidement régressive de la protéinorachie après sevrage thérapeutique a été suivie dans un cas (4) avec passage de 3,34 g/l à 1,85 g/l en huit jours et 1,22 g/l en un mois. A une exception près (6), il n'est pas noté d'hypercytose.

L'électromyogramme met en évidence les anomalies habituellement recontrées au cours des polyradiculonévrites. Tracés plus ou moins appauvris à fréquence rapide, potentiels souvents polyphasiques de longue durée ce que retrouve l'étude en stimuladétection avec des potentiels évoqués musculaires étalés, desynchronisés d'une durée parfois supérieure à 24 ms. Les conductions nerveuses motrices sont plus ou moins ralenties selon les nerfs avec dans la majorité des cas un coup de frein distal très important (26 ms pour un SPE et 10 à 12 ms aux membres supérieurs) (4). On note également des perturbations de la conduction sensitive dans les quatre cas où elle a été explorée.

Le tableu clinique, biologique et électromyoraphique est donc habituellement celui d'une POLYRADICULONEVRITE SUBAIGUE voire même CHRONIQUE. Cependant dans les deux premiers cas décrits le tableau a été plutôt celui d'une POLYNEVRITE avec un déficit clinique moteur et sensitif à prédominance distale, un examen cytochimique du liquide cephalorachidien normal et des tracés électromyographiques très pauvres comportant des potentiels évoqués d'amplitude très réduite, sans coup de frein distal évident derrière un ralentissemente global de conduction.

De toutes façons, l'EVOLUTION apparait toujours favorable après arrêt de la thérapeutique à condition que l'état cardiaque permette un sevrage total et définitif. Les délais de régression des symptômes sont variables souvent assez rapides: un mois en ce qui concerne les paresthésies, les anomalies du fond d'oeil et la dissociation albuminocytologique; plus lentes en ce qui concerne le déficit moteur, l'aréflexie ostéotendineuse et les signes électriques qui ne commencent à régresser que vers les troisième ou quatrième mois. Parrallélement s'améliorent les anomalies reflètant les perturbations fonctionnelles d'autres organes nobles; le foie par exemple, soit simple élévation des transaminases sériques retrouvée dans trois quart des cas, soit signes d'insuffisance hépatique confirmée comme dans le cas de PELLETIER (20). De même se corrigent les anomalies des métabolismes glucidique et surtout lipidique, l'hyperlipidémie fréquement notée comme effet secondaire de la thérapeutique ayant été retrouvée dans la moitié des cas de polyneuropathie.

Sur le plan ANATOMOPATHOLOGIQUE, les études ont porté uniquement sur des prélèvements biopsiques, musculaires isolés dans trois cas, neuro-musculaires dans quatre autres et exclusivament nerveux dans deux cas. Les fragments biopsés ont tous été examinés en microscopie optique, en coupes semi-fines, et dans certains cas en microscopie électronique. Les lésions constatées confirment le caractère myélinique de l'atteinte déjà évoqué sur les données cliniques et les constatations électromyographiques. **En optique,** le muscle présente des signes d'atrophie de dénervation souvent minimes, en ilôts, avec des fibres anguleuses et une augmentation des noyaux, l'atrophie prédominant sur les fibres de type II. Le nerf est le siège d'une atteinte mylenique avec segmentation, diminution du nombre des fibres myélinisées avec un prolifération schwanienne qui peut réaliser des aspects en bulbe d'oignon. **Les études ultrastructurales** (7) (16) confirment la coexistence d'aspects de démyelinisation et de remyélinisation et surtout révèlent l'existence d'inclusions dans les cellules de Schwann, d'aspect plus ou moins hétérogène, qui paraissent lipidiques, dont on connait encore mal la signification mais qui ressemblent par certains aspect à celles que l'on re-



Figgure 1: MO: Rameau de nerf sural. Importante raréfaction des gaines de myéline qui sont colorées en noire. On note l'épaississement de la paroi du capillaire (cap) Préparation osmique; inclusion en paraffine. *

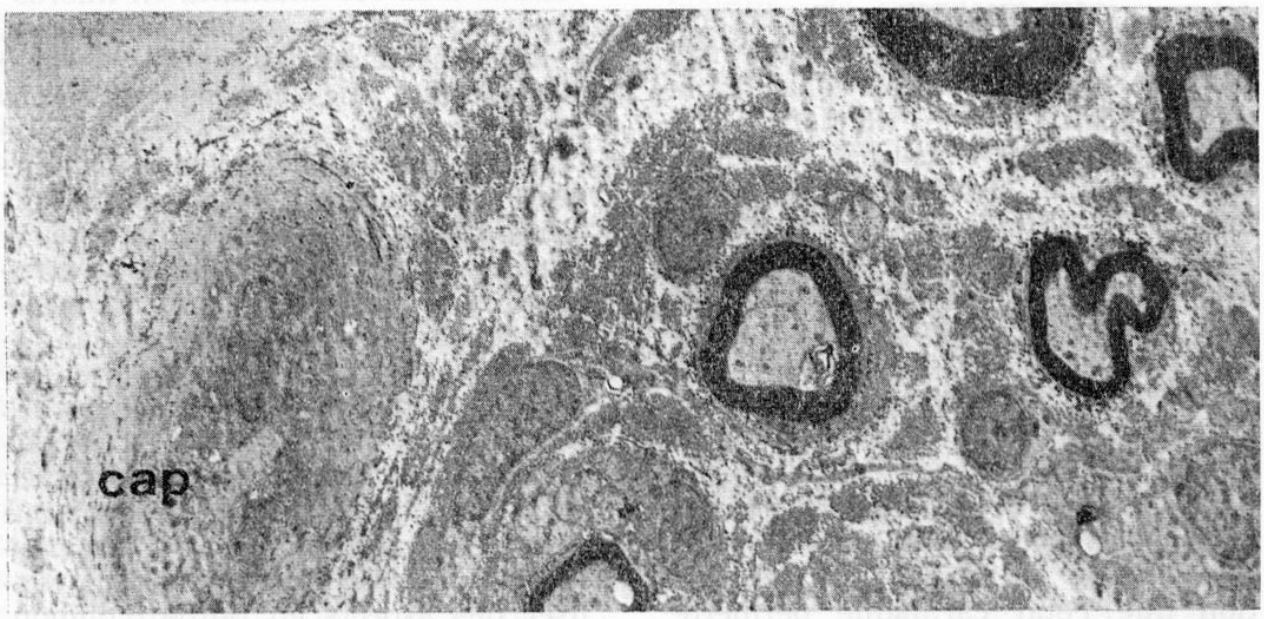


Figure 2: ME: Les rares gaines de myeline ont un aspect normal; leur mésaxone également. La fibrose est relativement importante. Le capillaire endoneural, visible à gauche (cap) présente une tuméfaction de ses cellules endothéliales et une hypertrophie de sal basale. Contraste acétate d'uramyl et citrate de plomb. Grossissement 3150.

* Les figures suivantes corresponden a biopsies de deux malades personnels, observation E.M.G. 22 737, et 25 867.

contre dans d'autres neuromyopathies toxiques (chloroquine, hypocholéstérolémiants) et ont également, d'après notre expérience, des analogies avec les accumulations lipidiques au sein des cellules de Schwann des neuropathies diabétiques (chez des malades non diabétiques). Ces mêmes inclusions sont encore reconnues dans les fibres amyéliniques, dans le muscle, la peau et les capillaires sous-cutanés. Les axones sont inconstamment touchés, mais deux fois sont signalées des altérations axonales avec aussi des inclusions, ce qui est un caractère tout à fait inhabituel parmi les neuropathies toxiques qui ordinairement lèsent préférentiellement les structures axonales. L'examen du nerf en immunofluorescence réalisé une fois n'a pas retrouvé de dépôts gammaglobuliniques. Le caractère particulier de cette atteinte neurale avec démyélinisation et remyelinisation réside en fait dans la présence de ces inclusions sur lesquelles des études complémentaires sont en cours.

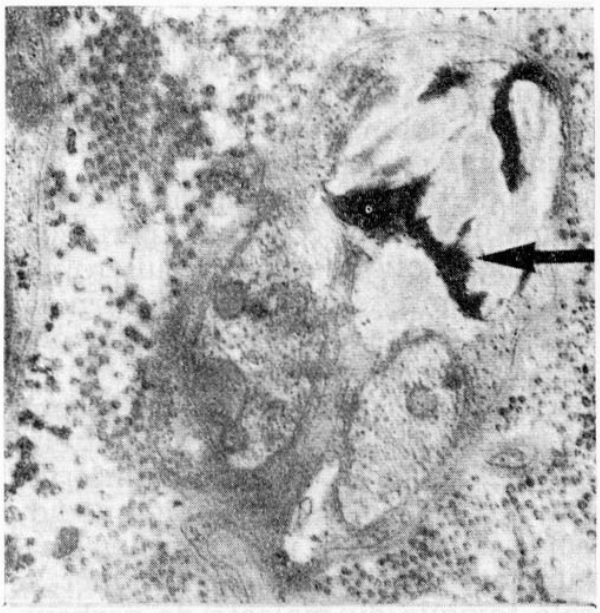


Figure 3: ME: Inclusion cptoplasmique **d'une cellule de Schwann de neurite amye**linique. On note l'aspect finement fibrillaire (flèche) d'une partie de l'inclusion, qu'aucune membrane ne limite. Grossissement 12300.

Le MECANISME PHYSIOPATHOLOGIQUE du déclenchement de ces polyneuropathies par le maleate de perhexiline reste encore hypothétique. Si un mécanisme immunoallergique a pu être retenu dans la génèse des rares polyradiculonévrites iatrogènes connues, notamment celles des sels d'or, il ne parait pas en aller de même pour le Pexid, encore q'une fois (20) les tesis de transformation lymphoblastique et d'inhibition de la migration des macrophages soient positifs en présence du médicament. Bien plutôt, la survenue très tardive des complications neurologiques suggèrent un phénomène toxique avec accumulation du produit dans l'organisme à des taux bien sepérieurs (7) à ceux attendus normalement sur les bases théoriques d'une demi-vie de trois à douze jours. Cette action

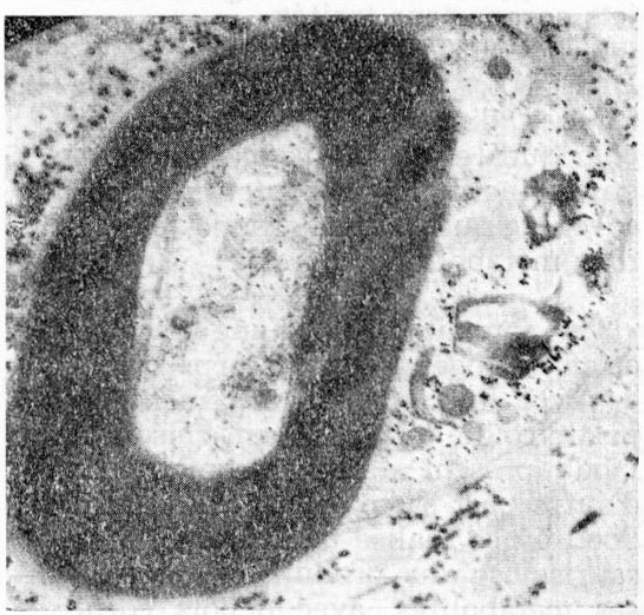


Figure 4: ME: Deux inclusions sont visibles dans le cytoplasme d'une cellule de Schwaann de neurite mpelinisé. Grossissement 12300.

toxique sur le système nerveux parait admise actuellement, mais la discussion entreprise par différents auteurs, notamment MUSSINI (22), d'une toxicité cellulaire directe sur les appareils mitochondrial ou lysosomial, ou indirecte par perturbation métabolique en particulier lipidique, demeure ouverte. En dernière analyse, la présence des inclusions, très probablement lipidiques, les hyperlipidémies régressives après arrêt de la thérapeutique, comme l'atteinte préférentielle de la myéline, véritable compartiment lipidique du nerf, constituent un faisceau d'arguments concourant à expliquer le rôle toxique du maleate de perhexiline par l'intermédiaire d'un trouble du métabolisme phospho-lipidique, Ce trouble peut, soit préexister, soit être provoqué par le médicament lui-même qui s'accumulerait dans l'organisme à la faveur de perturbation de son catabolisme hépatique ou de son élimination rénale. Ainsi, la conjonction nécessaire de plusieurs facteurs expliquerait la relative rareté des complications neurologiques par rapport au nombre de sujets coronariens traités.

LE CHLORHYDRATE D'AMIODARONE,*** derivé iodé des benzofuranes, diminue les résistances périphériques et la fréquence cardiaque en freinant les récepteurs α et 6 adrénergiques. Il n'a donc pas un rôle métabolique direct.

On cannait bien, d'une part ses effets iatrogènes sur le corps thyroïde avec hypo et plus rarement hyperthyroïdie (12 (13) en raison de l'iode présent dans sa composition; d'autre part sa toxicité au niveau de l'oeil oú se réalise une véritable thésaurismose du produit ou d'un de ses métabolites, avec dépôts cornéens signalés dans 90% des cas. Leur intensité est proportionnelle à la dose journalière et à la durée du traitement, débutant parfois au quinzième jour d'une thérapeutique par 600 mg quotidiens, disparaissant les progressivement après l'arrêt ou la forte réduction de la prescription. (2) (25). Habituellement il n'y a pas, ou peu, de répercussions fonctionnelles; un certain degré d'irritation oculaire, de photophobie et la perception de halos colorés autour des lumières peuvent être signalés par les malades, et une baisse de l'acuité visuelle modérée est retrouvée dans 10% des cas. Ces dépôts, que certains ont rapprochés du cercle vert cornéen de la maladie de Wilson, sont en fait bien différents, tant par leur situation, que par leur nature ou leur nature ou leur mécanisme de formation. Ils se localisent dans l'espace interpalpébral, au dessous de l'aire pupillaire et se condensent au début en une ligne horizontale ou légèrement oblique "ligne de force cornéenne". Leur aspect est celui de stries en "moustache de chat". Ils ont été étudiés sur le plan chimique et histologique à partir de rares biopsies (25). Ce sont des granulations intra-cytoplasmiques de nature en partie lipofuschinique, en partie mélanique, mais aussi avec une subtance probablement métabolite du médicament. Leur situation, précisée par étude ultrastructurale, est extrémement superficielle, dans la partie toute antérieure du stroma cornéen. Ils peuvent franchir la membrane de Bowman, mais il n'y en a jamais au niveau des structures endothéliodesmétiques ce qui les oppose aux dépots cupriques qui se font à partir de la chambre antérieure de l'oeil. L'imprégnation de la cornée par l'amiodarone se fait par voie externe, comme en témoignent la situation dans la fente palpébrale et la disposition en fonction de la structure du film lacrymal. L'étude du transit de Cordarone marquée à l'iode 131 confirme bien

*** CORDARONE - LABAZ

que le produit, probablement métabolite de la drogue, transite par les larmes et vient sédimenter dans l'aire palpébrale. A l'opposé de la chloroquine qui a un trapisme pour le tissu pigmenté, l'amiodarone n'entraine jamais de lésions chorrio-rétiniennes et finalement la thésaurismose cornéenne très fréquemment découverte ne constitue qu'un petit inconvénient, signal —symptome d'un surdosage.

Par contre, extrémement rares sont les **complications neurologiques.** Nous en avons retrouvé de deux types: Mouvementse anormaux sous forme de tremblement dans 4 cas, et neuropathie périphérique signalée une fois.

—Des activités tremblés d'intensité minime sont citées comme effets secondaires chez 14 % des patients examinés par les premiers expérimentateurs (9). C'est habituellement à partir d'une posologie totale de 12 à 15 g, que peuvent se manifester ces troubles qui diminuent rapidement après réduction des doses et disparaissent totalement à l'arrêt de la thérapeutique. Mais, parfois, le TREMBLEMENT peut être très intense, gêner considérablement les gestes de la vie quotidienne et conduirele malade chez le neurologue.

Ainsi, les deux cas décritis par LHUILLIER et coll. (17), chez lesquels s'est développé après cinq à six mois de traitement, un grand tremblement d'attitude et d'action totalement nettoyé dans le mois qui a suivi le sevrage de la drogue; et un cas personnel, concernant une femme de 67 ans, diabétique, présentant des crises de tachycardie paroxystique supra-ventriculaire, pour lesquelles furent prescrits en association Quinidurule et Cordarone, 800 mg/j depuis six mois. A partir d'une dose totale d'environ 120 g, se développeun syndrome dyskinétique où s'associent un petit tremblement de repos, une grande dyskinésie volitionelle d'attitude sur un fond d'hypotonie cerebelleuse, entrecoupée de quelques secousses myocloniques que l'on retrouve aussi au niveau de la langue. L'atteinte prédomine aux membres supérieurs, rendant impossible l'écriture, mais n'épargne pas les membres inférieurs. Il n'y a pas de perturbations thyroïdiennes, pas d'anomalies lipidiques. Dix huit jours après l'arrêt de la thérapeutique, l'activité anormale a presque totalement disparu et le malade peut a nouveau écrire et dessiner, tandis que persistent les dépôts cornéens notés à l'examen à la lampe à fente.

Dans le cas cité par LUSTMAN (18), on retrouve également un tremblement des deux mains, mais associé à une ataxie sensorielle avec paresthésies des membres inférieurs et troubles du sens positionnel des orteils et des doigts, apparus moins de un mois après la mise en route d'un traitement par 400 mg quotidiens. Malgré l'absence d'hyporéflexie ostéo-tendineuse et la normalité de l'électromyogramme, il n'est pas interdit de penser que ces troubles sensitifs qui comme le tremblement ont disparu après sevrage étaient les stigmates initiaux d'une neuropathie débutante.

—En effet une observation de NEUROPATHIE PERIPHERIQUE authentique, comparable à celles rencontrées avec le premier médicament, a été décrite par KAESER (15). Elle concerne une malade traitée depuis deux ans par de très grosses doses de Chlorhydrate d'Amiodarone, 1800 mg/j., qui présente un tableau de déficit moteur des membres inférieurs prédominant à la ceinture avec aréflexie ostéotendineuse et déficit distal des membres supérieurs. Sur le plan sensitif, perturbations du sens positionnel aux

mains et hypoesthésie à tous les modes aux jambes. Dans le liquide cephalorachidien, dissociation albumino-cytologique, et à l'électromyogramme ralentissement des conductions nerveuses motrices. A ce tableau de polyradiculopathie sensitivo-motrice subaigüe, s'assoçient, outre la classique atteinte cornéenne, une pigmentation cutanée bleuâtre du visage, altération dermatologique qui précédée d'une lucite, se retrouve dans 1 à 3% des cas en cours de traitement par l'amiodarone. Trois mois après l'arrêt de la thérapeutique, amélioration simultanée de la scène neurologique et des signes cutanés.

Comme pour le maleste de perhexiline, cette observation étaye sur le plan PHYSIOPATHOLOGIQUE l'hypothèse d'une neurotoxicité de l'amiodarone, intervenant par le biais d'un trouble métabolique lipidique, ceçi d'autant plus qu'il y a association aux anomalies cutanées. L'etude ultrastructurale des pigmentations cutanées (21), permet en effet de confirmer la nature lipochromatique des pigments intracellulaires, très certainement intramitochondriaux, et conduit les auteurs à éliminer l'hypothèse de la thésaurismose, au profit de celle de troubles métaboliques provoqués par le médicament ou l'un de ses métabolites, et aboutissant à l'acoumulation d'une substance pigmentée de type lipofuschinique.

En ce qui concerne les mouvements anormaux, leur PATHOGENIE reste encore imprécise. La rapidité de leur régréssion évoque un trouble métabolique transitoire peut-être par dysfonctionnement enzymatique hépatique, à moins qu'il ne s'agisse içi d'une conséquence de l'action α et β antagoniste du médicament sur les neurotransmetteurs adrénergiques dont il diminue la sécrétion (3).

RÉSUMÉ

Les manifestations neurologiques toxiques des médications antiangineuses sont rares, mais perfois sévrès. Les auteurs font une revue générale de 23 cas de neuropathies périphériques survenant au cours de traitements prolongés par le maleate de perhexiline. Il s'agit d'un tableau de polyradiculonevrite subaigüe ou chronique, parfois associé à un oédéme au fond d'oeil et accompagné sur le plan géneral d'un amaigrissement et dans la moitié des cas d'une hyperlipidémie.

Les symptômes régressent progressivement après l'arrêt de la thérapeutique. Les atteintes histologiques sont des altérations myéliniques avec des aspects de démyelinisation et de remyélinisation, et surtout présence en microscopie ultrastructurale d'inclusions hétérogènes, lipidiques peut-être lisozomiales, que l'on trouve au niveau du nerf, mais aussi dans le muscle et la peau. Ces altérations suggèrent un mécanisme physiopathologique toxique avec perturbation métabolique phospholipidique. En ce qui concerne le chlorhydrate d'amiodarone les complications sont extrèmement raes, avant tout tremblement composite, retrouvé 4 fois, et une polyradiculopathie sensitivo-motrice. Elles surviennent avec des posologies élevées, s'accompagnent toujours d'une thésaurismose cornéenne du produit ou d'un de ses métabolites et parfois d'une pigmentation cutanée. Le tremblement disparait rapidement après l'arrêt du traitement. La physiopathologie de ces mouvements anormaux est encore incertaine; perturbation métabolique enzymatique

rapidement réversible, ou bien intervention grâce au rôle et sur la sécrétion des neurotransmetteurs adrénrgiques?

L'existence de ces complications doit inciter à une certaine prudence dans les indications et la prescription de ces thérapeutiques, et surtout à une surveillance très attentive desmala des.

Il n'est point question de faire le procès de médications efficaces et utiles, dont les ennuis neurologiques restent rares en égard à l'importance des indications. Il demeure cependant que le médecin doit en être averti, tout à la fois pour en nuancer la prescription et en surveiller la posologie et la prise, la moindre alerte devant les faire interrompre.

Par ailleurs, d'un point de vue physiopathologique général, il est possible que semblables observations, particulièrement celles étudiées en micoscopie électronique, puissent fournir des modèles quasi-expérimentaux à l'analyse de certains processus pathologiques de "Surcharge" par viçiation métabolique au niveau du système nerveux périphérique ou central.

RESUMEN

Las manifestaciones neurológicas tóxicas de las medicaciones antianginosas son raras, pero a veces severas. Los autores hacen una revisión general de 23 casos de neuropatías periféricas sobrevenidas en el curso de tratamientos prolongados con malcato de perhexilina. Se trata de un cuadro de polivadiculoneuritis subaguda o crónica, a veces asociada a un edema de fondo de ojo y acompañada en el estado general de un enflaquecimiento y en la mitad de los casos de una hiperlipidemia.

Los síntomas retroceden progresivamente después de la detención de la terapéutica. Los cambios histológicos son alteraciones miclínicas con aspectos de demiclinización y de remiclinización y sobretodo prevencia en microscopia ultraestructural de miclusiones heterogéneas, lipídicas quizá lisozomiales, que se encuentra a nivel del nervio, pero también en músculo y la piel. Las alteraciones sugieren un mecanismo fisiopatológico tóxico con perturbación metabólica fosfolipídica. En lo que concierne al clorhidrato de amiodarona las complicaciones son extremadamente raras, ante todo temblor compuesto encontrado 4 veces y una poliradiculopatía sensitivo motriz. Ellas sobrevienen con posologías elevadas, se acompañan siempre de una tesaurismosis corneana del producto o de una de sus metabolitos y a veces de una pigmentación cutánea. El temblor desaparece rápidamente, después de la detención del tratamiento. La fisiopatología de estos movimientos anormales es aún incierta; perturbación metabólica enzimática rapidamente reversible, o bien intervención sobre la secresión de los neurotransmisores adrenergicos?

La existencia de estas complicaciones debe incitar a una cierta prudencia en las indicaciones y la prescripción de estas terapéuticas, y sobre todo a una vigilancia muy atenta de los enfermos.

SUMMARY

Toxic neurological manifestations due to antianginous drugs are rare but sometimes really severe.

The authors have thorougly studied 23 cases of patients suffering from peripheral neuropathies that appeared during prolonged treatment will with perhexiline maleate.

The clinical picture is that of a subacute or chronie polyradiculoneuritis sometimes associated with retinal edema and slenderness and in a half of the cases with hyperlipemia. The sympotomatology recedes progressively after the therapeutic is stopped.

The hystological changes that can be observed are myelinic alterations with demeyelinization and remyelinization aspects and above all it can be noticed in ultrastructural microscopy the presence of heterogeneous lipid inclusions, perhaps lysosomes that can be observed at the nerve level and also in the muscle and the skin.

The alterations suggest a toxic physiopathological mechanism with phospholipid metabolica disturbance. Concernig the amyodarome chlorydrate, its complications are very rare, which are compound tremor in four patients and sensitive motor polyradiculopathy in one patient. They are originated by elevated posology and they are always accompanied with corneal thesaurosis due to the drug or one of its metabolites and sometimes with a cutaneous pigmentation. The tremor disappear rapidly after the treatment is stopped. The physiopathology of these abnormal movements it is incertain up to now; it may be originated by enzymatic metabolic disturbance rapidly reversible or due to action the adrenergie neurotransmitters secretion. The presence of these complications must generate an attitude of prudence in the prescription of these kind of drugs and above all a close control of these pattients.

ZUSAMMENFASSUNG

Die neurologischen toxischen Manifestationen der antianginösen Medikamente sind selten. Die Autoren machen cine Revisation von 23 Fällen von peripheren Neuropatien, die im Laufe von längerer Behandlung mit Malato von Perhexilin vorgekommen sind. Es handelt sich um ein Bild von Polyrediculoneuritis, subakut und Chronisch, manches Mal assoziiert mit einem Oedem im Augenhintergrund und begleitet mit cinem allgemeicinen Zustand einer Gewichtsabnahme und bei dar Hälfte der Fälle einer Hyperlipidemie.

Die Symptome gehen progressiv zurück nach Aufhören der Medikamention. Die histologischen Änderungen sind myoclinische Alterationen mit der Erscheinung von Demiclination und Remiclination, und speziell von Anwesenheit im Ultrastrukturmikroskop von heterogenenlipischen Einschlüssen, vielleicht lysozomolen, die sich im Niveau des Nerven finden, aber auch im Muskel und der Haut. Die Alerationen suggerieren einen physiopathologischen Mechanismus der Phospholipoiden. Was das Chlorhydrat von Amiodaron betrifft, sind Komplikationen äusserst selten, vor allem Temblor zusammengesetzt 4 Mal festgestellt, und einer sensitiven motorischen Polyradiculopathie. Diese kommen von einer erhöhten Posologie, sind immer begleitet von einer Tesaurismus der Cornea von dem Produkt oder eines seiner Me-

tabolen, und manches Mal von einer Hautpigmentation. Der Temblor verschwindet schnell, nach der Aufhören der Behandlung. Die Physiopathologie dieser anormalen Erscheinungen ist noch un gewiss; Reversible metabolische enzymatiche reversible Perturtion, oder Intervention über die adrenoernergischen Neurotransmissorischen Sekretionen?

Die Existenz fieser Komplikationen sollte zu einer gewissen Vorsicht bei den Indikationen und der Verschreibung dieser Therapie anraten, und besonders zu einer sehr genauen Uberwachung der Erkrankten.

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Toxicity to the Nervous Sistem of Diphenylhydantoin: a Review

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Since its introduction 30 years ago by Merritt and Putram, diphenylhydantoin(DPH) has achieved general acceptance as the anticonvulsant of choice for various forms of seizure. More recently it has been introduced as a successful treatment for cardiac arrhythmias and has also been used in trigeminal neuralgia and other painful conditions. Large amounts of the drug are prescribed and consumed annually; at a recent symposium Goodman pointed out that DPH probably accounted for close to two-thirds of the total annual United States sales of approximately 15 million dollars for antiepileptic drugs.[26] It is, therefore, apparent that knowledge of all forms of acute and chronic toxicity of this drug in man should be widely disseminated. In the following pages the relationship of DPH toxicity to central nervous system and peripheral nervous system function will be discussed under four general headings: (1) The presumptive direct effect of the drug on various portions of the nervous system, (2) indirect effects on the nervous system mediated, for example, by anemia or adverse cardiovascular effects, (3) effects of diphenylhydantoin on certain laboratory tests and (4) the relationship between drug dosage and toxicity of the nervous system and the significance of DPH levels in the blood.

I. Direct Toxic Effects of Diphenylhydantoin on the Nervous System.

1. Cerebellar disturbances

The most striking and universal toxic effect of DPH is on cerebellar function. All reports of massive overdosage with this drug have described the gross ataxia and incoordination of both trunk and limbs. Patients develop a lurching gait and the characteristic coarse tremor of extremities on voluntary movement. Incoordination frequently progresses to the point that the patients cannot walk and frequently cannot stand. The gait disturbances are frequently quite bizarre, and when accompanied by the hyperactivity and disturbances in consciousness often caused by DPH toxicity, are not infrequently mistaken for other neurological disease or hysteria.[58] All signs of cerebellar dysfunction are frequently found prominent rebound phenome-

na, impaired check phenomena, hypotonia, and disorganization of succession movements. [3,33,69] Usually impairment of cerebellar function is transient, subsiding as the drug is metabolized and excreted.

Equally universal as a toxic sign, and also probably of cerebellar origin, is nystagmus. The latter is frequently the first manifestation of CNS toxicity. In mild cases it is seen only on extreme lateral gaze, but in more severe intoxication, is seen with the eyes in the neutral position [54] and is coarse and swinging in type.

In the intoxication from routine oral use of the drug, cerebellar dysfunction usually appears when DPH blood levels exceed 30 ug/ml. Some details of dosagetoxicity relationship will be discussed later. Nystagmus is the first sign and is followed by ataxia of gait and then incoordination of extremities. Intoxication experiments on rats and cats[50] and pigs[18] have shown that the brain and cerebellum contain high concentrations of DPH as compared to the rest of the central nervous system. The signs of cerebellar dysfunction usually disappear fairly promptly as blood and tissue levels of DPH drop upon reduction of dosage, but cases have been described of persistent ataxia following severe DPH intoxication.[32,41,50,61,83]

Pathological studies on experimental animals subjected to long-term DPH medication have shown atrophy of the Purkinje cells. [18, 47, 100] With quite large doses of the drug there was also described diffuse destruction of the granular cells and cystic gliosis in the cerebellar cortex and in the medullae of the folia. There apparently are no changes in the cerebella of animals dying from acute DPH intoxication, and survival must last two or more weeks for these pathological changes to be present. [50] Pathological studies in man with reference to DPH intoxication are few in number. Utterback reported a case of a patient dying in status epilepticus who showed changes in the Purkinje cells of the cerebellum [100] and Hoffmann [41] also reports a case of a young mann treated with large amounts of Dilantin for an acute seizure problem in whom the cerebellum showed disappearance of Purkinje cells. Haberland described 3 cases with Purkinje cell disappearance which he ascribed to long-term administration of DPH. [33]

Aside from the cellular changes notednoted above, nothing is known of the structural or functional changes underlying the cerebellar function of DPH intoxication. Recent studies on the ultrastructure of cerebellar tissue in rats intoxicated with high doses of DPH have shown lamellar concentric bodies similar to those seen in lipidoses in cells of all three layers of cerebellar cortex and preferentially along Purkinje cell dentrites. [19]

2. Coma and alterations in behavior and consciousness Characteristically the patients who are suffering acute intoxication from large doses of DPH are described as confused, disoriented, frequently hyperactive, or manic in behavior. [31, 39, 69, 72] Stupor or coma have been reported in man, although rarely. Respiratory depression from the drug is even more of a rarity but does occur, apparently usually in the clinical setting of restless coma, opisthotonic spells, and episodic apnea. Progressive shallowness of respiration leading to apnea in a flaccid immobile patient (as seen in barbiturate intoxication) does not occur.

Experimental studies of the drug toxicity in animals have revealed in

several species that animals go through a period of central nervous system stimulation. Gruber et al in testing large intravenous and intraperitoneal doses of DPH in mice, rats, rabbits and dogs produced depression of the central nervous system and death only after very large doses. [32] The respiratory depression which occurred may have been on a basis of primary depression to the central nervous system, although most of these animals had gone through episodes of repeated seizures. It is possible that in both man and animals a cause of dangerous central nervous system depression in acute intoxication is a post-ictal state, as animals and man usually first show prominent signs of CNS excitation and even production of seizures, a matter which will be discussed later in detail.

The drug, in summary, is strikingly ineffective as a central nervous system depressant (and incidentally as a suicidal agent) as witnessed by the fact that only 4 fatal cases of DPH intoxication from oral use of the drug had been reported to October. [52, 57, 90, 96] One case resulted from ingestion of 2 grams of DPH by a $4^1/_2$ year old child who lapsed into semicoma after going through a period of hyperactivity and ataxia; the authors felt that the child probably expired from brain changes secondary to hypoxia since cerebral edema and cerebellar tonsillar herniation was found at autopsy. [57] In another case a contributory cause of death may have been excessive use of stimulants; cardiac arrhythmia occurred, and the authors comment on the possible adverse effects of stimulants in acute DPH toxicity. [96] It appears that analeptics and stimulants are contraindicate probably because of the summation of their effect with direct effect of DPH in cardiac muscle.

Several cases of death from intravenous use of DPH have been reported but most of these deaths were fairly clearly attributable to adverse cardiovascular effects, to be described later. [101] In one case, however, a patient receiving intravenous DPH as therapy for atrial tachycardia and heart block developed rather abruptly opisthotonos and apnea shortly after the injection. [87] The authors felt that the rapidity of the respiratory depression and the abruptness of the onset of opisthotonic state could not be explained by any effect of the drug on cardiac muscle or peripheral blood vessels, and could best be explained by a direct effect of DPH on the central nervous system.

3. Behavioral and psychiatric changes.

Many of the reports of acute diphenylhydantoin (DPH) intoxication in man contain descriptions of distortions of perception and emotional state. Grosz [31] describes a patient having taken over 8 grams of DPH who underwent marked visual and auditory hallucinations. Laubscher describes delusions in his patient, a $4^1/_2$ year old child who had taken 2 grams of DPH [57] and Hoaken's patient described seeing bright lights and having the sensation of "worms in the head". [39] Peters [75] mentions "toxic and schizophrenic" psychosis in his patient. Most of these patients with acute overdosage of DPH are, as previously noted, hyperactive and described as being confused and disoriented. These phenomena are similar to the hyperactive, confused, and often psychotic states suffered by patients who are recovering from various types of sedative, for example, barbiturate intoxication. In DPH intoxication, however, these acute psychiatric phenomena seen to occur at the height of the intoxication rather than on recovery.

Unlike most other anticonvulsants, there is very little evidence that long-term DPH medication impairs mental abilities or alertness. One report describes improvement in behavioral and intellectual function in children after reduction in PDH dosage, [85] and there is one report of a patient who, upon recovering from acute severe DPH intoxication, showed sings of brain damage on psychological tests. [95] A recent carefully controlled study, however, could find no difference on psychological testing between a group of subjects on standard DPH dosage schedules, an controls. [7]

4. Seizures

Altrough DPH is one of the most effective anticonvulsants when administered over extended periods of time, there is considerable evidence that in acute intoxications it exacerbates or even produces seizures. Gruber in 1940 reported opisthotonic seizures in mice, rats, rabbits, and dogs after extremely large doses of the drug and in the course of other symptoms of intoxication. [32] Most of these seizures reported in man duringg acute intoxication have had prominent tonic components. Schereiner [91] described opisthotonic seizures in his 2 year old patient, both during the most severe stages of intoxication and during the recovery phase. Levy and Fenichel [59] report 3 cases with exacerbation of seizures during DPH intoxication and accompanying EEG abnormalities. Seizures were characterized by opisthotonic posturingg with momentary loss of consciousness that was often brief and frequently followed by tonic-clonic seizures. The severely intoxicated patient of Theil et al [95] suffered seizures characterized by a sudden cry, hyperventilation, sudden flexion of the upper extremities and extension of the lower extremities with the head being turned to the right, the tongue protruding, and pupillary dilatation. Patients of Hoaken [39] and of Blair et al [6] were described as having "jerking movements" in the extremities periodically during acute intoxication; these were probably seizure phenomena.

5. Tendon reflexes and focal neurological signs

Most cases of acute DPH intoxication have been described as having normal, brisk, or hyperactive tendon reflexes. [73] At least two cases of severe intoxication, however, were described as having areflexia. [95, 96] One of these patients expired, [96] the other, however, recovered after the use of dialysis. [95] It would appear that areflexia is uncommon and an extremely late stage of severe DPH intoxication. This, again, is consistent with animal work in which hyperactivity occurs until large doses of the drug are given.

Several instances of neurological abnormalities other than stupor and cerebellar dysfunction have been reported in patients suffering from acute DPH intoxication. Athetoid movements with continuous writhing of the extremities have been described. [39, 75] Another report contains an account of "swimming or writhing movements" and "snorting" in four children who had, had excessive doses of the drug. [73] There have been at least two reports of focal neurological deficit ascribed to DPH. Levy and Fenichel [59] described two cases who developed left hemiparesis and hypalgesia associated with severe EEG abnormality in the course of interest that Korey found DPH intoxication and which disappeared after the discontinuance of DPH. Morris, Fischer and Bergen [68] described two cases of hemiparesis occurring in young individuals who recovered completely upon withdra-

wal of the drug. Paresis of the legs with hyporeflexia has also been reported at the height of DPH intoxication. [83] There are no clues as to possible mechanisms by which the drug could induce these instances of focal cerebral dysfunction.

6. Treatment of acute DPH intoxication

It would appear only three specific points need be made about the treatment of acute DPH intoxication:

(1) There is no treatment for the ataxia of mild intoxication which is, in any case, not dangerous to the patient.

(2) In massive intoxication with semistupor, the use of analeptics is contraindicated. DPH is rarely dangerous as a central nervous system depressant. and the danger of cardiac arrhythmias being induced by combined DPH and analeptic effect is real. One of the fatalities of DPH intoxication. as noted above, has been ascribed to this combination of drug effect.

(3) The use of peritoneal dialysis should be strongly considered in a patient with a grave degree of DPH intoxication. This applies particularly to children who are in a comatose or semicomatose state. Two recent reports [2, 6] have documented fairly rapid recovery from severe DPH intoxication with the use of peritoneal dialysis accompanied by rapid drop in DPH blood levels.

7. Effects on peripheral nerve.

DPH has effects in physiological functions of the peripheral nerves. Toman [97] described the abolition of tre "supernormality" period following stimulation of a peripheral nerne and abolition of the consequent rebound spike. The drug was found to suppress the repetitive synchronized discharge to stimuli that had been found in peripheral nerves inmersed in isotonic sodium phosphate solution, and also to eliminate their spontaneous firing. Korey [51] described the reversal by DPH of the irritatbility of peripheral nerve preparation that resultsfrom diminution of calcium and magnesium ions in the surrounding solution. DPH did not affect normal nerve fibers but only those subjected to these abnormal environments. It is also of other more common signs of DPH to cross the membrane into the interior of the giant axon of the squid Later, Morrell and coworkers, [67] again studying isolated peripheral nerves, found that DPH administered systemically increased the threshold of the peripheral nerve to electrical stimulus of end organs or nerve endings and caused a decrease in the spike amplitude discharge even to super-maximal stimuli. They also found the abolition of rebound spike induced by long duration currents.

Trigeminal neuralgia has been treated with DPH with some success, [43] under the hypothesis that the drug would work by affecting the peripheral nerve conduction. Others have felt, however, that the favorable results in trigeminal neuralgia can better be explained by DPH effect on the synapse. When DPH is given intrevenously the effect on single neurons in the spinal trigeminal nucleus seems to be on the postsynaptic focal potential with only minimal effect on the presynaptic spike. [44]

Studies on peripheral nerve in man taking DPH have been confusing. Brumlik and Morretti [10] found no changes in the median nerve conduction time between patients receiving DPH and the normal controls.

Hopf,[42] however, testing the nerve conduction before and after administration of DPH found some slowing of motor conduction, particularly in those fibers that are normally slow conductors. A recent clinical study by Lovelace and Horwitz[64] described six patients on long-term DPH who showed clinical signs of peripheral neuropathy. The authors also report on 50 random cases receiving DPH and 20 areflexic individuals on DPH. Of the 50 random cases nine had areflexia in the legs, most of these patients showing abr normal serum folate in patients remes. It was of interest that of the 20 areflexic patients only one showed completely normal nerve conduction time and electromyography. Some of the patients with normal reflexes also showed delayed motor nerve conduction time.

In summary, despite abundant experimental evidence that DPH has some effect on the peripheral neuronal conduction, neuronal membrane permeability and synaptic transmission, the occurrence of peripheral neuropathy as a toxic symptom is rare. The presence of peripheral neuropathy as a toxic symptom is rare. The presence of peripheral neuropathy in these patients when it does occur may be related to abnormal folic acid metabolism which will be discussed in subsequent paragraphs.

II. Indirect Effects of DPH on Central and Peripheral Nervous System Functions.

In addition to direct effects on the central and peripheral nervous system, DPH can affect folate metabolism, carbohydrate metabolism and cardiovascular function, with occasional indirect effects on the nervous system.

1. Folic acid abnormalities

Many investigators in the past decade have studied the effects of anticonvulsants and DPH in particular, on the interrelated phenomena of altered folate metabolism, bone marrow abnormalities, hematologic and neurologic disordes. In an investigation of 54 epileptic patients on anticonvulsant medication 38% were found to have megaloblastic bone marrow and 7 of the 54 had macrocytosis in peripheral blood.[81] Another recent study has confirmed the finding that some patients (8%) on anticonvulsant drugs have high MCV values and 18% were found to have macrocytosis. Although the megaloblastic bone marrow and the macrocytosis is then not uncommon in patients on DPH, the incidence of anemia in a large series of patients taking DPH has been estimated as 15 to 75%, [5,22] Even rarer than the anemia are neurological disturbances whic hare presumably of the same etiology and accompany the anemia. Anand[1] describes one such case of an individual on DPH and Primidone who is described as having mild dementia, absent ankle jerks extensor plantar responses gross ataxia of legs ,and absent vibratory sense in the legs. This patient had a hemaglobin of 6 grams. Long et al[63] described another such individual on DPH, Ethotoin and Phenobarbital, also anemic, who showed stocking hypalgesia in both legs. Hansen et al[35] described an anemic individual with findings of peripheral neuropathy and Ungar[99] describes an individual with combined evidences of peripheral neuropathy and spinal cord dysfunction. A similar combination of neurological findings is described in two cases by Hawkins and Meynell.[37] Cases of peripheral neuropathy in patients on DPH, without anemia, have been described, as noted in previous paragraphs.

It has been postulated that these findings of peripheral nerve and spinal cord symptomatology in some patients on DPH are related to disturbed folic acid metabolism. Numbers of studies have shown that there is a very high incidence of subnormal motor nerve conduction ticeiving DPH,[44,46,49,64,79,80,81] although, of course, the vast majority do not show neurological abnormalities. In contrast, serum vitamin B_{12} levels are usually within normal limits. The cases of neurological dysfunction, particularly peripheral neuropathy, have improved with folic acid therapy and some of them had shown previous failures on B_{12} treatment.[1,35,37,63,99] Grant et al believes that folate deficiency is a fairly common cause of peripheral neuropathy and myelopathy of obscure origin, having found 10 such cases in one year.[28] They report that 3 of these cases with peripheral neuropathy improved with folic acid treatment but that cases with spinal cord abnormalities did not. Some have thought that low folate values, common in patients on DPH, result in anemia and neurological abnormalities only in those patients on a grossly deficient diet for a prolonged period. It has been demonstrated that DPH does interfere with the intestinal absorption of dietary folates. [40,86] It is of interest that Herbert in a study of experimental nutritional folate deficiency in a male volunteer over a period of $4\frac{1}{2}$ months did not find any objective signs of neurological deficit.[38] The same experiment, with thevolunteer taking DPH, would be of the utmost importance.

Improvement in patients' mental condition has been reported with the use of folic acid in those patients showing serum folate deficiency.[15,79] The relationship of the subnormal serum folate to seizure disorders is at present a confused subject. Reynolds has recently suggested[79,80] that folate deficiency is in some way tied to anticonvulsant effect citing the experience of Chanarin[14] of a patient who seemed to develop increased number of seizures with the administration of folic acid. Hawkins and Meynell,[37] however, in 1958 reported decreasing numbers of seizures in some of their patients who received folic acid therapy, a few of these results being fairly dramatic. Reynolds and coworkers[81] postulate that much of the dullness of patients on DPH and other anticonvulsants and even some psychoses may be the effect of folate deficiency on the central nervous system. This view has been recently challenged by Jensen and Olesen[46] who found 91% of a series of seizure patients (all "mentally deteriorated") under treatment with anticonvulsants to have subnormal serum folate levels although only one patient had a subnormal whole blood folate. They could find no evidence for folate deficiency and doubt the correlation of depressed serum folate with neurological abnormalities. They suggest that many symptomatic cases may have concomitant vitamin B_{12} deficiency.

2. Cardiovascular effects

Mercer and Osborne in a recent review [65] comment that their experience and that of other clinicians has been that DPH is a relatively safe drug with respec tto the cardiovascular system. Adverse cardiovascular effects after oral administration of the medication are negligible. Following intravenous administration, which is commonly used for cardiac arrhythmias and occasionally for status epilepticus, however, dangerous cardiovascular effects have occurred.

Studies in man an danimals show that the drug given parenterally does cause some depression cardiac output and depression of myocardial function. There is little eviden-

ce, however, that this fact is of routine clinical significance and only a few cases of possible congestive failure, secondary to parenteral DPH administration, have been reported.[65] Hypotension does occur in some cardiac patients given parenteral DPH apparently with reduction of peripheral vascular resistance as one probable mechanism. It has been shown in both animals and man that the drug does also have a direct actionon perioheral vessels. [47,66]

To April 1968 reports of 6 deaths shortly after intravenous DPH had been reported.[101] Of these individuals four had been suffering from digitalis toxicity and all were elderly. In some cases ventricular fibrillation was produced. Voigt[101] believes that the drug should not be given intravenously to patients with bradycardia or AV block. Very slow injection o fthe drug appears to be the best safeguard against fatal cardiovascular reactions. The risk of fatal arrhythmias with intravenous DPH also apparently is increased in the presence of hypoxia, or the use of analeptics.

3. Hyperglycemic nonketotic coma

It has been discovered in recent years from studies of experimental seizures in the rabbit that the administration of DPH produces a rise in blood sugar.[4] A study on dogs also showed the hyperglycemic effect, and use of carbon 14 labeled glucose showed that there was inhibition of the rate of tissue uptake of glucose in these animals.[89] Since this discovery several clinical reports have appeared of patients on DPH who developed rather striking elevations in blood sugar occasionally accompanied by stupor, coma, or marked alteration in state of consciousness. [17,25,74,88] In three of these reports blood sugar values ranged from 380 to 700 mgm%. Two of these individuals died with the metabolic syndrome of hyperosmotic nonketotic coma. In one patient the insulin response to glucose was delayed and subnormal while DPH was at a toxic level. No patients have been reported with permanent impairment of carbohydrate metabolism following the use of DPH. It is clear that not all patients with massive DPH toxicity have hyperglycemia, [2,6,96] but the explanation of why certain individuals are affected is unknown.

III. Laboratory Values Altered by DPH Medication

1. Electroencephalogram

Aside from the specific serum DPH levels, to be discussed later, the laboratory test most frequently altered by DPH medication is the electroencephalogram. In the normal therapeutic range, and without clinical signs of toxicity, there is little if any affect on the EEG patterns, normal or abnormal. [84] In DPH intoxication, however, induced by gradually rising blood and tissue levels of the drug as a result of oral medication, there is progressive slowing of the electroencephalogram. Apparently the first change is a slowing of the normal alpha rhythm. [84] As toxicity becomes more marked with the clinical symptoms of incoordination and altered mental status, as described in previous paragraphs, slower rhythms in the theta range (5-7 cycles per second), and some delta activity, appear in the electroencephalogram. [38, 45, 59, 83]

The presence of seizires in patient swith DPH intoxication syndrome hts been discussed previously. The electroencephalogram recorded in most these patients has been charaterized by slow frequencies, [59] but there is a recent report of one

case in a child with DPH intoxication in whom the EEG showed almost continuous 3 per second spike dome abnormality.[73] Other interesting EEG abnormalities reported during acute DPH intoxication are: (a) A flat EEG with spike dome bursts in a 2 year old child who suffered extreme toxicity with stupor, and opisthotonic seizures, but who recovered[91]; (b) EEG characterized by 14-16 cycles per second activity with frequent generalized bursts of 2-3 cycles per second activity in an adult who was in areflexic coma from a hugge dose of oral DPH and who also recovered.[95]

Dilantin apparently can occasionally cause marked EEG slowing accompanied by signs of CNS dysfunction as a manifestation of a generalized sensitivity reaction not associated with excess dosage, blood or tissue levels. The EEG abnormality in this case bore some resemblance to the "triphasic waves" seen in hepatic coma.[29]

The effect of intravenous DPH on the electroencephalogram is not striking. In a recent study in which the EEG was performed continuously before, during, and until one-half hour after injection of DPH, no EEG abnormalities were seen although the patient showed clinical signs of toxicity.[45] Riehl and McIntyre[82] found that intravenous DPH did produce EEG slowing but only confined to the zone of electroencephalographic abnormality that was present in the pre-drug state. No abnomalities in controls or in the unaffected hemisphere were found after the drug injection. Buchthal et al[12] studied the response of paroxysmal EEG abnormalities to intravenous I.V. DPH treatment and found that in only two out of six patients did the paroxysmal abnormalities decrease and then only for one two minutes. From these studies it is apparent that DPH efect on the normal EEG is dependent on longterm administration resulting in high blood and tissue levels.

2. Other laboratory values

A few biochemical values of blood, urine and cerebrospinal fluid can be altered by DPH medication. The cause of many of these findings is unknown and they are of no clinical importance as far as is presently known. That DPH can produce these effects is important knowledge, however, since many of these laboratory values could suggest disease entities.

The spinal fluid protein can apparently be raised during manifestations of DPH intoxication, one case with a spinal fluid protein of 140 mg% having been reported. Other cases have had only mild protein elevation.[76] This finding is of importance since the conjunction of ataxia and elevated CSF protein always suggests the possibility of a posterior fossa neoplasm. It is apparent, of course, that spinal fluid values have been determined in many individuals with DPH intoxication and have been found normal.

Serum protein-bound iodine can be depressed by longlterm DPH administration in the absence of intoxication.[13, 70] There is no change in the other parameters of thyroid function with the exception of the T_3 uptake chich is elevated.[71] There are no clinical signs of hypothyroidism. The quantity of thyroid hormone reaching the tissue is normal and it is thought that DPH interferes with the binding of thyroxin by plasma proteins. Fatigue and other symptoms, possible symptoms of hypothyroidism, in patients on DPH must not then be ascribed to hypothyroidism solely on the basis of depressed PBI.

It has been found that long-term DPH therapy may decrease basal plasma or urinary corticosteroids, [8, 16] although these findings have not been consistently corroborated. Patients on chronic DPH therapy, however, do not develop clinical adrenal cortical insufficiency. [16, 53] Sparberg [93] points out that the defining of a low baseline urinary corticosteroid excretion coupled with diminished response to ACTH stimulation may lead to an erroneous diagnosis of adrenal cortical insufficiency and if the serum PBI is low, a false diagnosis of panhypopituitarism may be made. These comments are particularly important since symptoms of fatigue and lack of energy are common in seizure patients on anticonvulsant medication.

The production ofhyperglycemia after large doses of DPH has been discussed in previous paragraphs. It is doubtful whether hyperglycemia in the absence of any evidence of DPH toxicity can be ascribed to the drug, but in the presence of such toxicity it must be considered. It is also of interest that plasma-free fatty acids were consistently elevated in animals after the intravenous injection of DPH, while hyperglycemia was being studied. [89]

IV. Neurotoxicity of DPH As Related to Blood Lavels and Dosage

Several studies have shown that DPH blood levels of less than 15 ug/ml are rarely associated with any toxic symptoms to the nervous system. Kutt and coworkers [54] have documented the fact that nystagmus on far lateral gaze is the usual first sign of neurotoxicity and is seen at a blood level of 20-30 ug/ml. At higher blood levels nystagmus appears on slight lateral deviation of the eyes, and is seen with the eyes in the neutral position at blood levels of over 50 ug/ml. Ataxia usually is seen at levels of 30 ug/ml and over; some disturbance in the state of consciousness frequently appears at levels of 40 ug/ml. It has been reported by many, however, that elevated blood levels are not universally associated with clinical neurotoxicity. [12, 45, 54] Buchthal et al [12] found, for example, that of patients with blood levels in the 30-60 microgram level, 24% had mild evidences of neurotoxicity, 50% had pronounced effects, but 26% had none. They also noted that of the patients with high DPH levels more side effects tended to occur in those who had recently been administered the drug than in patients on long-term administration. Jensen and Grynderup [45] have recently described three patients in whom DPH dosage was reduced after the finding of neurotoxicity, but concomitantly with disappearing signs of toxicity, serum levels rose for a period of time. Kutt and coworkers [54] present possible explanations for the occasional cases in witch clinical neurotoxicity does not correlate well with blood levels, and present three possibilities: (a) Different "neuronal susceptibility" as determined by patients' ager, pre-existing diseases, variations in the local circulation; (b) intoxication due to abnormal metabolites; (c) disproportion between blood level and brain tissue levels. A recent study has demonstrated, however, that in acute experiments on the rat, the DPH blood level was highly correlated with regional brain tissue levels of the drug. [58]

The relationship between the dosage regimen of patients on regular oral medication and the appearance of elevated blood levels and neurotoxicity is a much more difficult and uncertain question. Buchthal and coworkers [12] originally reported a linear relationship between the dose given by mouth and the serum le-

vel above the dose of 2 mgm/Kg, each milligram per kilogram resulting in a serum level of 3.3 ug/ml. This relationship occurred in patients who had not previously taken the drug ;seum levels of patients who had been on DPH for several years were much less closely related to dosage, and were in general much higher than those of patients newly begun on the drug. [12, 94] Other workers, however, have found more variation in blood levels from patients on standard DPH dosages. Loeser [62] reported that while average blood levels are higher with increasing dosage of DPH, correlation of blood level variance with dose is not statistically significant. The marked variation of peak DPH level from patient to patient could not, after long-term administration, he felt, be explained solely by differences in dosage. Two patients with daily dosages of below 6 mgm/Kg had blood levels of over 15 ug/ml. Triedman and Fishman [98] also failed to find a close correlation between dosage and serum level. They made the interesting observation that little correlation could be found between seizures control and height of serum DPH level. Jensen and Grynderup [45] found individual variation in the serum DPH plateaus ranging from 7 to 33 ug/ml in patients on a daily dose of 5 mgm/Kg.

The weight of evidence is, then, that there is marked individual variation in serum (and presumably tissue) levels of DPH on a similar dosage schedule, this fact reflecting variation in individual absorption and metabolism of the drug. Four cases have recently been reported of DPH intoxication with normal or low DPH dosage. [73] The reasons for these marked individual variations in blood levels on a similar oral regimen are unknown. One possibility is that DPH is administered often but not alwys in association with Phenobarbital (or other drug) which induces hepatic enzymes, speeds up metabolism of DPH, and thus lowers the blood level. Two recent studies on children have shown that those individuals on combined DPH and Phenobarbital medication did have lower DPH blood levels than those on DPH alone, although this fact seemed to have no correlation with seizure control [11, 102] There have been some recent suggestions that changes in the excipient or dispensing medium may alter absorption of DPH and resulting blood levels. [20, 102]

Some progress has been made in understanding a few pathological conditions in which high serum DPH values develop on normal doses of the drug.Kutt et al [55] have described a mother and twochildren who developed signs of toxicity with doses of 4 mgm/Kg and documented the cause of the toxicity as accumulation of unmetabolized drug resulting from insufficient parahydroxylation. They postulated that there was a genetically determined low ceinling in this family to the amount of DPH that the liver could metabolize. This low ceiling was specific to DPH in that the metabolism of barbiturates was normal .The same authors also documented the presence of neurotoxicity on low doses of DPH in patients with impaired liver function.[56] Some patients receiving INH develop DPH intoxication. It has been shown that only those individuals with genetically determined "slow inactivation" of the drug show this susceptibility to neurotoxicity. Dicoumarol can also apparently show the metabolism of DPH and induce toxicity at comparatively low dose levels.[34]

Summary and Conclusions

Diphenylhydantoin may have direct toxic action on the central or peripheral nervous system. Tempo-

rary cerebellar dysfunction is the commonest clinical sign, and can rarely be permanent. In massive doses DPH causes, in addition, agitated, semistuporous states often with various acute psychotic manifestations. Seizures may be precipitated. Depression of vital functions is rare and stimulants should not be used.

Long-term DPH administration on occasion can give impairment of peripheral nerve function.

Nervous system function can be adversely affected indirectly by DPH toxicity through three mechanisms: (1) Production of peripheral neuropathy on myelopathy with anemia secondary to DPH effect con folate metabolism; (2) shock or cardiac arrhythmia induced by intravenous DPH; (3) production of hyperglycemia nonketotic coma produced by DPH intoxication. Neurotoxicity of DPH is accompanied by abnormal EEG patterns; these usually consist of slow activity but various seizure patterns can also occur.

DPH can alter cerebrospinal fluid protein, protein bound iodine plasma and urinary corticosteroids. These findings probably have no clinical significance.

Afairly good correlation exists between DPH serum levels and degree of neurotoxicity although many cases with high DPH levels are free of clinical signs of toxicity. Only a rough correlation exists between dosage regimen and serum DPH levels maintained. It is known that in some patients concomitant administration of INH or Dicoumarol will slow metabolism of DPH.

RESUMEN

La difenilhidantoína puede ejercer una acción tóxica directa sobre el sistema nervioso central o periférico. El signo clínico más comunmente observado es la perturbación transitoria de la función cerebelosa, que rara vez se instala en forma permanente. En dosis masivas la DFH causa además estados de agitación y semi-estupor a mnudo acompañados de diversas manifestaciones psicóticas agudas. Puede precipitar convulsiones. Rara vez ocasiona la depresión de funciones vitales y no deben usarse estimulantes.

La ingestión de DFH por períodos prolongados puede en ocasiones dar lugar a trastornos de la función nervisa periférica.

Las funciones del sistema nervioso pueden ser afectadas indirectamente por la toxicidad de la DFH a través de tres mecanismos: (1) Producción de neuropatía periférica o mielopatía acompañada de aneemia como efecto secundario de la acción de la DFH sobre el metabolismo fólico; (2) shock o arritmia cardíaca inducida por inyección intravenosa de DFH; (3) producción de coma hiperglicémico no cetónico por la intoxicación de DFH. La neurotoxicidad de la DFH se acompaña de anormalidades en el electroencefalograma; habitualmente se traducen en una actividad lenta; pero también pueden observarse manifestaciones paroxísticas.

La DFH puede alterar las proteínas del líquido cefalorraquídeo, las proteínas plasmáticas ligadas al iodo y los corticoesteroides de la orina. Estos hallazgos probablemente no tengan significación clínica.

Existe una correlación bastante notoria entre los niveles de la DFH en el suero y el grado de neurotoxicidad, aunque en muchos casos que presentan altos niveles de DFH estén libres de todo signo clínico de toxicidad. Sólo existe una correlación poco precisa entre la dosificación y los niveles del suero en DFH. Es bien sabido que en algunos pacientes la administración simultánea de INH o Dicumarol enlentece el metabolismo de la DFH.

RÉSUMÉ

La dyphenilhydantoine peut exercer une action toxique directe sur le système nerveux central ou periphérique. Le signe clinique le plus courammet observé est la dérèglement transitoire de la fonction cérébelleuse, qui rarement s'installe d'une façon permanente. En doses massives la DPH cause des états d'agitation et de stupeur souvent accompagnés de différentes manifestations psychotique aigües. Elle peut précipiter des convulsions. Elle provoque rarement la dépression de fonctions vitales et on ne doit pas employer des stimulants.

L'ingestion de DPH pendant des périodes prolongées peut quelquefois provoquer des dérèglements de la fonction nerveuse periphérique.

Les fonctions du système nerveux peuvent être indirectement atteintes par la toxicité de la DPH par trois mécanismes: (1) Production de neuropathie periphérique ou myelopathie accompagnée d'anémie comme effet secondaire de l'action de la DPH sur le métabolisme folique; (2) shock ou arythmie cardiaque induite par injection intraveineuse de DPH; (3) production de coma hyperglycémique nonquétonique par l'intoxication de DPH. La neurotoxicité de la DPH s'accompagne d'anormalités dans l'electroencephalogramme; habituellement elles se traduisent par une activité lente, mais on peut aussi observer des manifestations paraxystiques.

La DPH peut altérer les proteïnes du liquide céphalorachidien, les proteïnes plasmatiques liées à l'iode et les corticostéroides de l'urine. Ces découvertes n'ont probablement pas de signification clinique.

Il existe une corrélation assez frappante entre les niveaux de la DPH dans le sérum et le degré de neurotoxicité; cependant plusieurs cas qui présentent des niveaux elevés de DPH sont libres de tout signe clinique de toxicité. Il existe seulement une corrélation peu précise entre la dosification et les niveaux de sérum en DPH. Oon sait bien que chez certains patients l'administration simultanée d'INH ou de Dicumarol ralentit le métabolisme de la DPH.

ZUSAMMENFASSUNG

Das Diphenylhydantoin kann eine direkte toxische Aktion auf das zentral oder periphere Nervensystem ausüben. Das am häufight klinisch beobachtete Zeichen ist dietransitorische gestörte Funktion des Cerebellum, das selten sich in permanenter Form einstellt. In massiver Dosis verursacht das DPHausserdem Stadien von Agitation y Balbbetäubung oft von verschiedenen akuten psychischen Manifestationen begleitet. Es können sich Konvulsionen überstürzen. Selten verursacht wird eine Depression der vitalen Funktionen, und es dürfen keine Stimulantien gebraucht werden.

Die Einnahme von DPH für längere Perioden kann gelegentlich zu Störungen in der peripheren nervösen Funktion führen.

Die Funktionen des Nervensystems können indirekt angegriffen werden durch Toxidität desDPHdurch drei Mechanismen:

1) Produktion von peripherer Neuropatie oder Myelopatie, begleitet von Anaemie als Sekundäreffekt der Aktion des DPH auf den folischen Metabolismus;

2) Schock oder Arrytmia cardiaca, hervorgerufen durch intravenöse Injektion von DPH;

3) Produktion von hyperglyschämischem Schock nicht Cetonisch, durch die Intoxitation des DPH, die Neurotoxidität des DPH wird begleitet durch Anormalitäten im Elektroenzephalogramm; gewöhnlich zeigt es sich in einer langsamen Aktivität, aber es können auch paraxsistische Manifestationen beobachtet werden.

Das DPH kann die Proteine des liquido cefaloraquitico, die plasmatischen Proteine, die an Jod und die Corticosteroide und die Corticosteroide des Urins gebunden sind, beeinträchtigen. Diese befunde haben wahrscheinlich keine klinische bedeutung.

Es besteht eine notorische grosse Beziehung zwischen den Nivellierungen des DPH im Serum und dem Grad der Neurotoxidität, obwohl in vieler Fällen, die hobe Niveaus von DPH zeigon, frei sinu von allen zelchen klinischer Toxizität. Es besteht nur eine Korrelation wenig prezizier bar zwischen der Dosifikation und den Nivellen des Serum des DPH. Es ist gut bekannt, dass bei einigen Patienten die Anwendung gleichzeitig von INH oder Diacumarol den Metabolismus des DPH verlangsamt.

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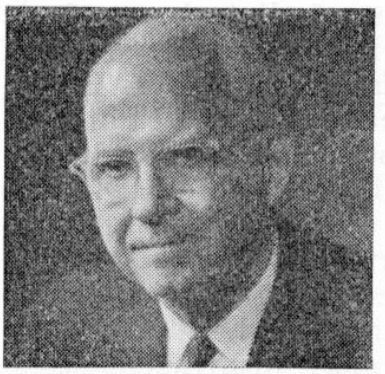

Teaching Neurology

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The objectives of the teaching of neurology are the instruction of the neophyte — the medical student or the house officer — in the diagnosis of disease of the nervous system and the treatment of patients with neurologic disease. These can only be learned by direct contact with patients, either at the bedside or in the clinic. This contact with the patient, however, is best preceded or at least accompanied by instruction in the fundamentals of the structure and function of the nervous system and knowledge of how disease affets the nervous system and what diseases cause neurologic manifestations.

The nervous system is an essential part of the living organism and neurologic diagnosis is a correlation of the data obtained from the study of the human nervous system in health and disease — a synthesis of all of the details obtained from the history given by the patient and an examination of him. Neurologic diagnosis is often considered to be difficult by physicias who do not specialize in clinical neurology. Most parts of the nervous system are inaccessible to direct examination and its intricate organization and integrated functions are difficult to comprehend on superficial observation. The major neurologic entities, however, can and should be diagnosed and treated by the physician in the general practice of medicine, and every practicing physician should have basic knowledge about nerologic diagnosis and treatment. Theories regarding the optimun modes of neurologic teaching have undergone change during recent years, but this is true also of medical education in general, and in fact of all education.

Historically, medical and neurologic education was first taught by lectures alone and then by lectures and clinical demonstrations, Neuroanatomy and neurophysiology were taught early in the curriculum, and often forgotten by the student when confroted by problems of neurologic diagnosis in the final years of his medical education. Personal contact with patients — opportunities to take a clinical history directly from the patient and his family, and to examine the patient personally — were not available. Changes, however, have been made in the medical curriculum. Possibly some of the changes have been made in response to student demand — students are more vocal about their interests and what they feel are their needs than they once were.

In most medical schools, at the present time, the basic sciences are correlated with clinical instruction. In carrying out such correlation in the study of disease of the nervous system, a course in neuroscience is offered early in the curriculum. The course gives instruction in basic neuroanatomy, neurophysiology, neuropathology and neurochemistry simultaneously with the study of clinical neurologic disease and its diagnosis and treatment. As an example, instruction is given on the structure, functions and pathology of the peripheral nerves at the same time that disease of the peripheral nerves is discussed and patients with such disease are presented to the students. This teaching continues during the first two years of the curriculum. Then in most medical schools, the student serves a clerkship during which he has patients with neurologic disease under his care for both diagnosis and treatment, under the supervision of clinical neurologists. In some mdical schools such clerkships in the various fields of medicine continue for two years, in others obligatory clerkships are held only during the third year, and the fourth year is an elective one in which the student can obtain more thorough instruction in some aspect of medicine in which he believes he has special interest. If the student wishes more training in the field of diseases of the nervous system, such a clerkship may be in clinical neurology, neurosurgery, pediatric neurology, or in more specialized work in neuroanatomy or one of the basic sciences or in fields such as neuroradiology, neuroophthalmology, or electroencephalography.

The above described approach to neurologic education seems to be a good one. Some details of it must be considered in greater depth, however, and certain warnings must be made.

The planning of the neuroscience course and its general supervision must be under the control of a clinical neurologist, who must ascertain that all important aspects of clinical neurology are included. The primary purpose of the course is the instruction of the student in the diagnosis and treatment of clinical neurologic disease. All important categories of neurologic disease, as well as neurologic complications of systematic disease, must be included. It is the experienced clinical neurologist who knows what conditions are of paramount importance.

If the course is under the supervision of a clinician, there may be a tendency to place insufficient stress on neuroanatomy, neurophysiology and the other basic sciences, and they may be taught superficially or briefly. Even though they are not taught as individual courses, the teaching in these must have adequate depth and breadth. Specific time must be given for laboratory as well as class room instruction.

The clinical aspects of the teaching must be emphasized. The student must know how to take a comprehensive neurologic history. Under certain circumstances this may be time-consuming and it may be necessary to obtain information from relatives and associates as well as from the patient. The history, however, is essential and often gives the key to diagnosis. The taking of the history is followed by the examination — physical examination, mental examination and neurologic examination. For the physician who deals with diseases of the nervous system, the neurologic examination is the essential part of the examination and it must be satisfactorily performed, complete, and carefully interpreted. For the physician dealing with diseases other than neurologic, the important essentials of the neurologic examination should be well learned and the physician should have sufficient experience so that the examination of neurologic functions will be routi-

nely included in the general physical examination. If such is the case, neurologic manifestations of systemic disease as well as primary diseases of the nervous system can be diagnosed and the entire patient cared for.

The basic concepts of neurologic disease can be learned from text books, but the actual diagnosis and treatment of such disease can be learned only from direct contact with patients, either at the bedside or in the clinic. Such contact, however, must be under the supervision and tutelage of a dedicated clinical teacher. It is important that this be observed and emphasized in every neurology teaching program, both undergraduate and postgraduate.

HISTORY OF MEDICINE

Dax's Law

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In the story of the localization and the lateralization of the so-called "centre of language", five names are prominent. Placed in order of time, but not necessarily of importance, they are: Auburtin, Broca, Duval, Dax père and Dax fils.

On April 4th 1864 the story opens at the Société d'Anthropologie de Paris in the rue René Panhard, when Dr. Auburtin gave an address entitled "On the seat of the faculty of language". Speech, he said, was a complicated activity mediated by an organ of pronunciation, a coordinating centre, and a means of transmission between these two. Lesions affecting each one of these structures alone, could interfere with speech Unlike Gratiolet, who believed that the brain acted as a whole, Auburtin was of the opinion that the centre for coordinating the movements peculiar to speech was to be found in the anterior lobes of the brain and nowhere else. As Dally's patient showed, speech can be destroyed in isolation. To support his belief, he quoted cases reported by Rostan, Lallemand, Heurteloup, Bernard, Boyer, Bonnafond, Sedillot, Macquet, and Bouillaud. Of particular interest was the patient of Cullerier at the Hôpital St. Louis, who had tried to shoot himself but merely blew away the frontal bones so as to expose the brain. He could still talk, but if any one pressed the brain lightly with a spatula, he temporarily lost his power of speech. This case called to mind a notorious beggar in the streets of Paris who used to allow passers by, if the consideration were great enough, to squeeze his exposed brain until he lost consciousness. Auburtin said that for a single contradictory case to be significant there must be a complete destruction of both anterior lobes. "If then the patient continued to speak, my doctrine would be shown up as fallacious, I believe no such case exists. In M. Bouillaud's service I studied over a long period of time a patient named Bache who had lost his speech... If when that man dies I find no lesion of the anterior lobes, I shall renounce my ideas. As far as I know, there has never been seen a lesion limited to the middle and posterior lobes, destroying the faculty of language".

Present at that meeting was the secretary of the society, M. Broca, When, a day or two later, there came under his surgical care at the Bicêtre, the man Leborgne, a feeble-minded and speechless hemiplegic of long-standing, who had developed an abscess of his leg, M. Broca invited Auburtin to see the patient with him. On April 17th Leborgne died. The brain revealed an old superficial lesion destroying the foot of the 2nd and 3rd frontal convolu-

Fig. 1. — Ernest Auburtin.

tions on the left. When it was shown at the next meeting of the Anthropological Society which was on the day following, and also at the Anatomical Society of Paris a little later, not much interest was evinced. But when a few months later another very similar case cropped up, where again at autopsy a comparable lesion was found, interest became aroused not only in anthropological circles, but throughout the medical profession of the world.

As Broca continued to collect hemiplegic cases with loss of speech —or "aphemia" as he called it— with an imposing collection of 22 post-mortem specimens, he found himself almost against his will, interrupting his surgical practice to be acclaimed as the prophet of cerebral localization, and the discoverer of the seat of the faculty of language.

The story now moves on three years to March 3rd 1864, when M. Duval described at the same Society two children with traumatic aphemia. In each case damage to the left frontal lobe could be demonstrated. In the discussion which followed, Broca said "I have been struck with the fact in my first aphemics the lesion always lay, not only in the same part of the brain, but always the same side — the left. Since then, from many post-mortems the lesion was always left-sided. One has also seen many aphemics alive, most of them hemiplegic, and always hemiplegic on the right side. Furthermore one has seen at autopsy lesions of F3 on the right side in patients who had shown **no** aphemia. **It seems from all this that the faculty of language is localized in the left hemisphere, or at least that it depends chiefly upon that hemisphere".**

At the next meeting of the Society — which was held on April 21st — Broca demostrated yet another brain with a leftsided lesion, the patient having had a traumatic loss of speech which was restricted to **"la tête, la tête"** and the particle **"oui".** Broca then revealed that a M. Dax, an obscure practitioner from Sommières in Provence, had complained to the Académie de Médecine that he (Broca) had neglected the work of his late father, who had known for a long time that lesions ablating the faculty of language always lay whithin the left half of the brain. Dax senior had apparently read a paper to this effect at the Congrès Méridional de Montpellier. "I don't like discussions about priority" said Broca "but several people said that I should have quoted Dax. I erred from ignorance. The original communication was not known, not even in Montpellier. I searched the literature and I also asked the Librarian of the Montpellier Faculté to have a look, but without success. The meeting

Fig. 2. — Paul Broca.

took place between July 1st and 10 th 1836, but there is no note about the Dax paper in the Revue de Montpellier". *

Broca then went on to elaborate his belief that the left half of the brain was particularly concerned with speech. He thought the left hemisphere in man to be better developed than the right. Perphas in sinistrals the centre for language would be in the rigth side. This would explain the exceptional cases of aphemia folowing disease of the hemisphere. If F3 on the left were atrophied from birth the child would learn to talk by way of the rigth hemisphere: this theory would explain the patient described by Moreau. Broca went on to say that probably **both** hemispheres play **some** part in language. The faculty of comprhending the connection between words and ideas belongs to both sides of the brain. Broca finished by saylng "far be it from me to divide man into two distinct beings like Meinard Simon du Peri in his "de Homine dextro et sinistro" (Leyden 1780).

Thus began the Broca-Dax controversy, which proved to be even more complex. Since a student, the vounger Dax had been intensely interested in "Alalia" or speech loss and applied to submit a Thesis upon this subject, but he was not allowed to do so. Patiently he collected case-material and evidence from the literature. He wrote a Mémoire which he presented to his local confrères in 1858 and again in 1860, entitled "Observations rendant à prouver la coincidence du dérangement de la parole avec une lésion de l'hémisphère gauche du cerveau". Later he sent it to the Académie de Médecine where it was received on March 24th 1863.

Dax **fils** was bitterly hurt by the fact that subsequent writers continued to pay no heed to his work, and to the credit due to his father. In July 1864 Charles Richet had publised in the Revue des deux Mondes a paper upon Aphasia in which the contribution of Dax **fils** and the discovery of Dax **père** were not mentioned. This too lead to another protest on the part of Dax though it did not appear until October 1865 in the Montpellier Médical. On Aprli 14th 1865 an article on Aphasia was published by Falret which did mention the work of Dax **père** et **fils** but in such terms as to infuriate the latter.

Meanwhile Dax junior had discovered in a bureau the manuscript written by his late father, and he published it as it stood in the **Gazette bébdomidaire de médecine** et **de chirurgerie** for April 26th 1865, In 1800, Dax **père** had apparently seen a cavalry officer with impaired memory for words after a sabre

* At that time there was no medical journal in the south, of France.

wound of the left side of the head. His second patient was the naturalist Brussonet who had lost his memory for words, proved to be due to a large ulcer on the surface of the left hemisphere. Dax had now seen three such cases, a coincidence which impressed him.

He subsequently collected more than 40 comparable cases without any exceptions coming to light, and he was able to add others from his library. From all this data he concluded that when the memory for words is impaired from brain disorder, one must look to the left hemisphere. He expressed the hope that his observations would prove useful in diagnosis and in treatment. Even when there is no actual hemiplegia, it is still possible to determine the site of the lesion provided there is a disorder of speech.

Dax **fils** then took up the story in an appendix to this paper. In his discussion of speech disorder it is obvious that he was including cases of more than one sort dysarthrias as well as dysphasias. Thus he was repeating the error that had for centuries bedevilled medicine, and indeed was destined to confuse neurologists for many years yet to come. Like the schoolmen of the middle ages Dax junior was inclined to ascribe aphasia io a paresis of the tongue. He adhitted that aphasies sometimes substituted one word for another, but Dax got round that difficulty by asserting that, unable to pronounce one word, the patient fumbles and gropes, and tries another and casier one. Dax retrieved some of his muddled thinking however, when he went on to speculate that the same cause which provokes a dyssynergy might sometimes interfere with the memory for words; and that in the present state of our knoyledge one cannot distinguish the two classes of case.

Thirteen years later Dax printed a little monograph on the topic of Aphasia. Once again he reproduced his father's paper, and by now he had collected from the literature 371 observations. The comments of Dax upon the relative neglect of his father's discovery were bitter indeed.

Arguments as to priority in the discovery that speechloss was specifically allied with lesions of the left hemisphere, ousted the more important conceptions of lef cerebral dominance and its association with handedness. Clear thinking upon this issue did not grow up until years later. Lélut commenting upon the younger Dax's report to the Académie, had said that that mysterious organ, the brain, would be even more mysterious if its two halves were found to subserve different functions. But Bouillau interpolated with a shrewd question —unexpected perhaps in one so prejudiced— "would it not be conceivable that we are "left-handed" so to speak, with regard to certain acts, such as, for instance, language?".

Despite the support of Baillarger (1965) contemporary medicine was rather slow to accord recognition of Dax's priority in this problem. Bouillaud with all his authority as Dean obstinately ignored not only Dax, but even the notion of a unilateral speech centre. Trousseau in his lectures kept referring to the discovery of the left-sided speech centre by Broca. This too provoked a letter of protest from Dax. Trousseau is said to have replied in two letters, generously acknowledging the debt due to the elder Dax. This correspondence —like the manuscript of the original text by Dax **père**— is missing But in the South of France there was a greater show of loyalty towards Dax. Thus in his **Thèse de Montpellier** en 1873, due recognition was paid by Trémolet.

It was probably Grasset however who, in France, first acknowledged publicly the claims of the two méridional physicians, and in 1873 he spoke boldly of "Dax's law".

It is of some interest to recall how the idea of a left hemisphere dominance quâ speech was accepted in

England. Hughlings Jackson, in one of his carliest papers which was published in 1864, stated that he viewed the problem from two different standpoints, which he called his "radical" element as opposed to his "conservative". His radical side urged him to the conclusion that the faculty of language resides on the left side of the brain. But a conservative respect for principles which he had long held, stood in the way. The one pointed to facts which he himself had observed independently, and which had been confirmed by Broca. The other side of him protested that the observations were not yet numerous enough. "Granting the duality of the brain, it is difficult to understand how disease of **one** hemisphere —be it right or left— can produce speechlessnes. If one hemisphere be the duplicate of the other (as the right eye is of the left) there ought to be disease on both sides in complete speechlessness". Jackson would therefore accept neither the old view that the brain is a double organ, nor the new one that the faculty of language resides in the left hemisphere only. "I wish to keep most clearly in view that "a great deal may be said on both sides".My object is to be a mere witness, especially as there are very great advantages in being neutral".

Jackson went on to pay a most warm tribute to Broca, and he was delighted that his own findings had tended generally to confirm those of so distinguished a man. Dax was not mentioned, but Jackson discussed briefly the differance between Broca and Trousseau. "M. Trousseau has seen but one case of hemiplegia on the left side with loss of speech, but he considers this quite enough to negative M. Broca's observations. With feelings of great respect for two such distinguished men, I should say that M. Trousseau's argument is a conservative, and M. Broca's radical one. M. Broca urges new facts — M. Trousseau appeals to established physiological principles... As I have before said, there are a great many advantages in being neutral".

Two years later Jackson again referred to this problem. On this occasion, he quoted the views of Moxon who explained the association of speechloss with paralysis of the right side by saying that only the left side of the brain is educated, though there is an "organ of language" on each side. Jackson regarded this as an important hypothesis, but differed from it in one respect. He considered that both sides of the brain were probably educated, but that the left one was the "one that begins to act," and that more automatic utterances would result from action of the right side only. He quoted an opinion that had been expressed by Gratiolet, to the effect that the frontal convolutions on the left side were in advance of those on the right in their development. "If this be so," said Jackson "the left side of the brain is sooner ready for learning. **It is the elder brother...**".

In his important paper "on the Nature of the Duality of the Brain", Jackson expanded these ideas at some length. This article did not apear until 1874, however, and really falls outside the historical events recorded in this present communication.
We may now briefly examine the identity of these five men, whose names are linked with this important chapter in aphasiology.

Unfortunately we know but little of Dr. Ange Duval except that he was a Surgeonin-Chief to the Navy, and Professor at the School of Naval Medicine in Brest.

Dr. Ernest Auburtin has actually been more neglected than Dax by historians of Aphasia. Auburtin was born in Metz in 1825 where his forbears were mirror makers .A former Chef de Clinique of the Faculty of Medicine, he practised in Paris at Nº 16 rue Saint Benóit, near St Germain-des-Prés. He was a nephew of Professor Lalemand of Montpellier. We are not sure what aspects

of medicine interested him particularly, but we know that he was doctor to the Princess Mathilde Bonaparte, cousin of the Emperor Napoleon III. Judging from an amusing entry in the Goncourt journals, he was also the medical attendant of Popelin. His main preoccupation was with anthropology, and he was a national associate of the newly formed Society. Obviously he was a deep thinker with a reflective turn of mind, and I like to think that it was he who really stimulated the interest of Broca into the topic of Alalia. He was intrigued with the implications of Gall's work as far as it had to do with speech. In this matter he was Gall's disciple once removed, for he took sides with Bouillaud, and indeed, married his daughter Elisa. Auburtin and his family inherited the Bouillaud property at Les Bergerons, near Roullet, Charente, situated between Angoulême and Bordeaux. There Auburtin died in 1895. Unfortunately there are no more Auburtins in medicine today but his grandson is the distinguished **Conseiller Municipal,** and the current **Maire** of the city of Paris.

Auburtin's original contribution has been overshadowed by that of Paul Broca,whose tremendous prestige made him a man impossible to overlook or sidestep. Paul Broca was born of Protestant stock in the little town of St. Foy la-Grande (Gironde), on the Dordogne, just nine years after Gratiolet. Broca's father was an Army Surgeon who had served through the campaigns of Napoleon. Paul Broca distinguished himself as a schoolboy, and by the time he went to Paris as a student in medicine he was already a scholar, a polyglot, a talented painter and an accomplished musician. So hard up was he that he toyed with the idea of emigrating to America, but instead he took a temporary and uncongenial job as a schoolteacher.

As a medical man Broca became well known as an anatomist and a surgeon, residing at no. I, rue des Saints-Pères, and he worked at the Hôtel Dieu, the Bicêtre, and the Salpêtrière, among other hospitals. While still an internist he took part in the 1348 revolution, turning down a commission and also the distinction of the Légion d'Honneur.

Broca's principal love was anthropology, and he was a founder member and the first secretary of the Société d'Anthropologie, Incidentally he had some difficulty in persuading the authorities that this new term "Anthropology" had no sinister political connotation, and had nothing to do with the "rights of man".

We pass over Broca's contributions to aphasiology which were merely incidents in the course of his remarkable career. Later in life he founded the University Department of Anthropology to house his great collection of skulls, and here again he had to dispel suspicions in high places — this time the Church. He published 5 massive volumes to support the thesis that high intelligence correlated with a broad skull, and that the French as a race possessed the widest heads in the world. During the Franco-Prussian war Broca commanded a field ambulance in the Jardin des Plantes. We recall how, during the Commune he smuggled bullion to the tune of 75 million gold francs in a hay-cart out of Paris to the government in Versailles. In 1880 he was elected to the Senate but did not live long to enjoy this distinction. At a banquet given in his honour Broca replied to the flattering speeches, "If I were superstitious I would think I was threatened with a tremendous sorrow, for never have I been so happy as now". Six months later, Broca was dead.

Finally we come to the two Doctors Dax. Dr. Marc Dax was born in 1770 in Tarascon, and took his diploma in Montpellier. After fighting a cholera epidemic in the Aigues, Mortes, he settled in the little township of Sommières (Gard) on the ri-

ver Vidourle as a general practitioner. Living as he did midway between Nimes and Montpellier, Dax was isolated from the main stream of Parisian medicine, though locally he was well respected as a family doctor. He worked on the staff of the town hospital for 37 years, published one or two papers, but evinced no interest in neurology except for his solitary contribution in 1836. He died a year later, at the age of 66 years, and was buried in the graveyard of the hospital.

His son Dr. Gustave Dax was born in Sommières in 1815, and like his father, qualified at Montpellier and practised in his home town. Like his father he also worked at the local hospital, but after 23 years service he was invited to resign. This extraordinary action may have been due to the fact that Marc Dax was a legitimist, in fact a Henriquinquiste. Boisson, the Mayor of Sommières and also its archivist, made no mention in his official history of the town of either Dr. Marc Dax or Dr. Gustave Dax. Why was this? Boisson was an Orleanist; his brother was the local pharmacist. Perhaps the reason lies here. Perhaps some time or other he fell out with Dax junior, who was obviously somewhat aggressive in temperament to say the least of it.

Dr. Gustave Dax died in 1898. To his sorrow his son Paul did not follow in a like career, and though he became a medical student, years went by without his taking his final examinations. He was of a literary bent, a poet and a playwright of some ability. He died quite suddenly on his honeymoon, presumably from that malady of lovers, subarachnoid haemorrhage.

Today the contributions of the two Doctors Dax are no longer forgotten in the world of Medicine. But even now the quiet little town of Sommières knows little of in two distinguished oppidans. No plaque adorns the wall of their dwelling in the Place du Bourguet, and though a member of eponymous streets are there, visitors will look in vain for a "rue des deux Docteurs Dax".

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On vacation...

Cannes

Located in the middle of the French Riviera whose sole name evoked sand, sun and leisure Cannes was our choice as a resting halt in a journey with a heavy scientific schedule.

This beautiful place with its crescent-shaped Gulf of Naples embracing the blue waves of the Mediterranean Sea would have remained a little fishing village if its charms had not captured the eyes of an outstanding British political leader, Lord Broengham, who, dazzled by its beauty, huilt a winter home there in 1834.

This aroused the interest of the English aristocracy in Cannes, and many followed his example, sking on the sunny seashores during the winter, with its icy torments, rain, snow and wind.

Nowadays it has become a famous summer resort and the seat of International Festivals of Film with world repercussion.

Arts and sports in their different expressions flourish in Cannes where many interesting events are always conflicting in attracting the tourist's attention.

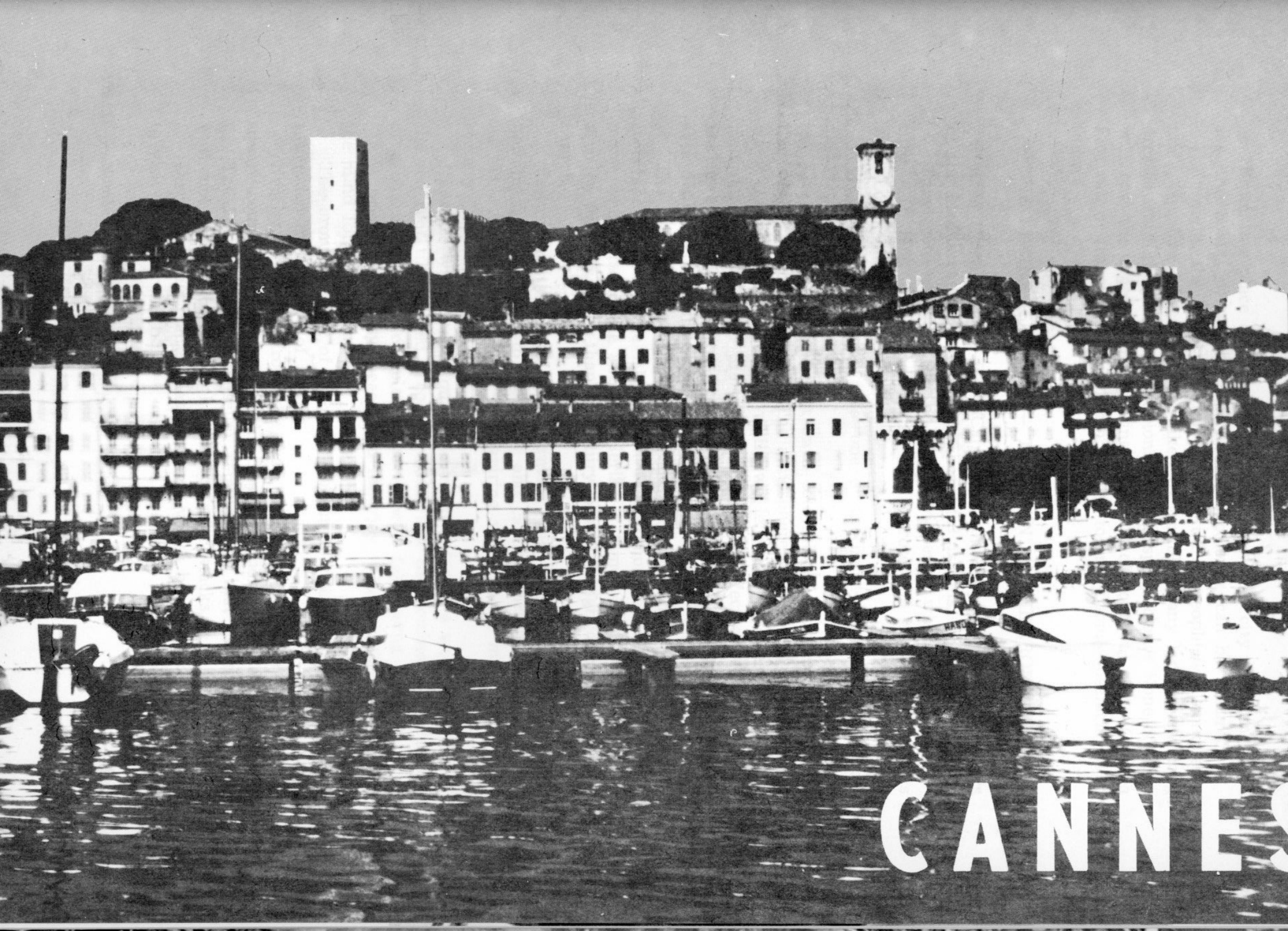
Day and night Cannes is full of life; its population has swelled with the human torrent that mean 100,000 tourists invading a city of 60.000 inhabitants, swimming in the morning or promenading in "La Croisette," a beautiful avenue by the sea, flanked by the wonderful buildings of modern Hotels, passing by the port in which yachts come and go or balancing in the waters and bringing more colour and gaiety to the scene.

At the end we find "Le Suquet", the old city, perched on a steep hill like and old postcard pasted on a modern panorama, giving a scent of the antique that adds charm to the environment.

"Le Suquet" is an enchanting place with twisting narrow streets that compels the explorer to climb stairs, open gates, always ascending, until one arrives at the highest spot where we meet the "Eglise Notre Dame d'Esperance", which was opened to public service in 1642, a year before Louis XIV the King Sun was born.

This charming relic of bygone days dominates with its square bell tower the dreamy scenery of "La Suquet".

In front of it concerts are given, known as "Musical Nights of the Suquet".


CANNES

From this place a beautiful view of the whole city of Cannes, the sea, the boats, all vibrating in luminous colours, can be admired.

At night, the "cafés" by the sea are full of people who conquer a table. equal to a bastion to be taken by assault. Many ladies wear long dresses while their male companions dress in sports clones None of them will end the night before visiting the Casino, going to some Cinema Festival, or traveling to the Lerin Islands to enjoy some spectacle given there.

THE LERINS ISLANDS. — THE MAN IN THE IRON MASK

At a short distance from Cannes surrounded by the clear waters of the Mediterranean sea, lie two beautiful islands.

They were named after the Monks of Lerins who in the 4th Century A.D. took the islands under their protection and whose abbots were Lords of Cannes.

To visit the islands was one of the most promising prospects during our stay in Cannes.

The sun was pouring light on a colorful panorama when we took the boat to go to the islands. The atmosphere was crystal clear and the wavy ocean gently rocked us while we left the port steering to Saint Honoret, the smaller of the two islands. The perfect curve of the Cannes'shore-with its buildings, palm trees, le Suquet, and the crowded port at a distance-shone in all its splender.

The island was becoming more and more real as we approached it. It is a delightful little island named saint honoret, in honage to the monk who founded the abbey of lerins, a famed center of intellectual activity that for more than a century provised high dignitaries of the church.

Nature in st. honorat is inharmony with a serene state of mind nothing is comparable to the noisy and cannes worldly.

The Abbey is in itself an inspiring view in the middle or green scenery.

Its white walls opened on ample arcades, facing a well kept garden; the red roof tiles placed a colour accent and the domincering presence of a charming belfry completed the Abbey's fascinating view.

A breath of beauty, peace, and innerjoy is sensed gy searching in the mind for perfection.

The bronze tongue of the belfry began to chant, and its vibrations resounded in the void of silence.

Nearby, emerging from the sea, a massive structure elevated its square countenance bathed by the rosy reflections of a setting sun.

The Fortress, now a museum, reminded us that the spiritual force was not enough to defend the Abbey from attacks.

Disrupting our contemplations came voices hurrying us to the boat to visit the other Island.

Its main attraction was the prison in which the Man in the Iron Mask was secluded.

While we, a noisy group of tourits, were approaching the Island, our thoughts flew back to the time when a young man was compeled to wear an iron mask for life and was brought to St. Margueritte, to remain like a legendary figure emerging sadly from the historical days of Louis XIV.

Who was he? Why was it a crime punished by death to discover his identity? Prior to this episode the Court of Louis XIV, the King Sun, was enjoying a period of unusual brilliancy, The King, 21 years old, was just married to Teresa of Austria, a beautiful Spanish Princess, The Royal couple was eliciting praise and admiration as they rode through Paris, the King handsome and manly on a white horse escorting his wife in a original chariot specially designed for the occasion.

A permanent spirit of festivity and gaiety prevailed at the court intensified by the marriage of the King's brother. "Monsieur," as he was called, Philippe, duke d'Orleans and Henriette of England, sister of Charles II. Cardenal Manzarin's death disrupted the succesion of happy events, and it has been noted by historians that it was some months afterwards that the Man in the Iron Masg entered like an unhappy shadow the life of the King Sun.

Let us hear the commentary of Voltaire, who always was haunted by the phantom of this sad life. (Le siècle de Louis XIV).

"Quelques mois après la mort de ce ministre, il arriva à l'isle Sainte Mtrguertte dans la mer de Provence, un prisonnier inconna d'une taille au-dessus de l'ordinaire, jeune et de la figure la plus belle et la plus noble. Ce prisonnier dans la route, portait un masque dont la mentonnière avait de ressorts d'acier qui le laissaient la liberté de manger avec la masque sur son visage, on avait ordre de le tuer s'il se decouvrait".

Thus Voltaire describes a young man with a distinguished look, who was brought to the island, his face covered with an iron mask, and with orders to kill him if he dared to take it off. The mask has a chin wich allowed him to eat without taking it off.

The Fort of Vauban where this unfortunate creature was imprisoned was contructed on a rocky soil facing the sea. It was made by order of Cardenal Richelieu as a political prison; a high round watch tower clearly speaks of some sentinels watching the sea, while a moat around the Fort makes it impossible for attacks or escape.

Arriving at the island we had to walk up a steep little road. The vegetation was beatiful, with many stands selling souvenirs, refreshments and cards displaying the prison of the Iron Mask.

Arriving at the Fort, we found some workers busily contructing a big stage just in front of the prison site of the tragedy of an unknown man it serves as a place for the enjoyment of diverse spectacles to be performed there.

We entered the prison and we felt an oppressive sensation invading our souls. A narrow and dark cell with a window profusely crossed by iron bars let the prisoner have the view of light freedom, with the wind playing on the waving sea, beyond his reach.

In spite of the stern condition in which he was kept, it is said that he was always addressed with high demonstrations of respect.

The stress of this wretched life must has been great. He tried to communicate with some people outside the prison, hurling through the window a silve plate, on which he scratched some words with a knife, towards a fishermen's boat.

Voltaire refers to this episode in the following way "Un jour le prisonnier écrivit avec un couteau sur une assiette d'argent, et j'etta l'assiette sur la fenêtre vers un bateaux, qui était au rivage, presque au pied de la tour, un pêcheur, a qui ce bateau appartenait, ramassa l'assiete et la porta au gouverneur. Celui-ci étonné, demanda au pêcheur. Avez vous lu ce que est écrit sur cette assiette, et quelqu'en l'a-t-il vue entre vos mains?

Je ne sais pas lire, répondit le pêcheur. Je viens de la trouver personne ne l'a pas vue" Ce paysan fut retenu jusq'à ce le gouverneur fut informé qu'il n'avait jamais lu, et que l'aassiette n'avait êté vue de personne. "Allez, lui dit-il, vous étes bien hereux de ne savoir pas lire".

In this way Voltaire tells us how the fisherman who took it and brought it to the Governer of the Fort, saved his life by demonstrating that he had never learned to read, and nobody else saw the inscriptions written in it. Otherwise he would have been executed at once.

Thus the doors of the mystery blocked for history the identity of the Man in the Iron Mask.

Those who knew what the truth was never revealedit Voltaire knew this fact from a realiable source. He wrote in 1750 that M. of Chamillart was the last Minister who shared this strange secret. The second Marechal de la Feullade, his son in law, told him that when his father-inlaw was dying, he knelt and begged him to tell him who was the Man of the Iron Mask.

Chamillartanswered him that this was a State secret and that he had sworn never to reveal it.

For more than a century and a half, this dramatic story was the object of commentaries throughout the world, becoming a sort of legend. Many were the historians that have made conjectures about the man behind the mask.

But it always was a sort of puzzle why it was such an important State-secret that no one could peer at his features.

This story enticed the wonderful imagination of one of the most famous French writers, who has excelled in historical novels. Alexandre Dumas, with his famous creation "The Three Musketeers" meddled

in the midst of the times of Louis XIV, and there were not one historical embroilment in which these bizarre "cavaliers", sword in hand, have not participated.

The Man in the Iron Mask deserved a book in a series of this kind.

Through his fertile imagination, Dumas solved the mystery, giving a reason why the prisoner had a distinguished look, why everybody addressed him with high respect, and why it was so important to erase his features from the living world.

According to Alexandre Dumas, when everybody wts celebrating the birth of Luis XIV who would become the King Sun, his father Louis XIII was called to the Queen's room where he was informed that a second son was just born. As the first twin had been already proclaimed King of France, and according to the medical dictum the last one to be born is the eldest, this may create a conflict and eclate future disensions and civil war. It was agreed to maintain this second delivery as a state secret, and the prince was condemned to an anonymous life Just a few persons knew it. The child grew secluded ignoring he could be King of France. Dumas built upon this a fascinating story mixing historical facts with fiction. The interwoven threads of intrigues in which his muskeeteers played an important role reached its climax when Louis XIV was kidnapped, and through a stratagem replaced by his brother, without anyone noticing the substitution. This was known by Fouchet who immedittely liberated the King and when both brothers faced each other for the first time, Louis XIV ordered that he be sent to the Island of Saint Margueritte, his face covered by an iron mask, never to be taken off from his head.

The silver plate thrown through the prison window, of the Fort Vauban, by the Man in the Iron Mask, was — in the Alexandre Dumas novel-recovered by Athos and his son Raoul, who read scratched in its back "I am the brother of the King of France, a prisoner to day, a mad man to-morrow. French gentleman and Christians pray to God for the soul and the reason of the son of your master".

"Advised by D'Artagnan they saved their lives by declaring that they were Spaniards and they didn't know a word of the French Language".

Even the product of a phantasy, the mystery that surrounded this legendary figure was more justified by Dumas' invention than from the version of many historians that placed behind the Iron Mask Count Mattieli, Eustache Dauger, a diplomatic Gremonville, or R. P. La Cloche, natural son of Charles II of Stuart.

"Whoever he may have been, his martirology ended in March 3, 1703 a la Bastille, where he was carried from the Island of Saint Margueritte, always under the supervision of the same man named Saint Mars who witnessed his death, 42 years have already pased since this unfortunate creature arrived masked at the island of Saint Margueritte. If he were a twin with the King of France, he would have 64

years when he died. We left the Fort Vauban casting a last look at the empty cell of that mysterious man. Outside, the huge out door theather has almost finished where the Royal Ballet of London will perform with its 60 dancers, and the French Ballet will represent "Nuits des Etoiles de l'Opera de Paris", will also be given the Opera Carmen of Bizet, and plays from Shakespeare.

May be when the starry sky shines over the players, and the Cannes lights place luminous dots along its curved shore, a silent spectator carrying an iron mask will sit among the spectators to rest his soul from his burdened life.

VALLAURIS.

A bus loaded with tourists headed for Vallauris, world known ceramic center which became famous because Picasso had in it his ceramie shop, where he turned out many of his beautiful ceramic pieces.

The bus traversed a hilly picturesque land with fresh green vegetation with a magnifent view of the sea at every turn of the road.

Reaching Vallauris, everyone left the bus gaily anticipating the joy of hunting for some decorative piece to bring back home.

A profusion of ceramic stores with glittering ware were waiting for us. Many of us were expecting to see the potters at work, which was very difficult, the store just sold the pieces and the workshop was not there.

In a place we saw at the back of the store an old kiln, and the lady in charge of it said that the potter was his son, who was also a musician who spent part of his time throwing ceramic pieces and playing in an orchestra in Cannes. She proudly showed us pictures and programs of his son's musical life.

The ceramic center was invaded by tourists whom we could see swarming through the street entering and coming out of the stores.

Many were asking about the location of the "Picasso Museum" one of the attractions mentioned in the booklet about Vallauris.

Passing by a beautiful old Church, was an entrance in which a plaque was announcing the Picasso Museum: We passed which seemed to be the ruins of a castle and in a room was a person in charge of the "Museum" surrounded by books prints, and slides from Picasso. The museum was just one room with a curved ceiling in which Picasso has painted a beautiful mural, about the War and Peace, a topic to which he has dedicated many thoughtful compositions. The curved ceiling seemed link these two trends of Humanity magnificently depieted in the two side's walls, while at the back we could see the four parts of the world streching the arm toward the Light.

We left this small town with a rewarding experience. Potters like God create many beautiful forms out of the Earth, vlessed by fire.

4th. OF JULY AT CANNES.

A wonderful weather seems to join the Bicentennial Festivities of the Independence of the United States.

The French National Marine Fragate "Suffren" stoped at Cannes and a resonant clustered bombing were saluting the United States in its glorious Independence Day.

At night it was a "Grand Gala Soirée" honoring the Bicentennial of the Independence at the Palm Beach Casino.

Cannes at night with its glittering lights, the stream of people, strolling its beautiful avenues by the Beach. The "Cafés" with tables filling the sidewalk where some singers play the guitars accompanying it with languorous voice.

Oon some days it, at the "Esplanade des Alliés" a Symphonic Concert can be enjoyed in the open, under the pleasant feeling of the breeze coming from the sea.

Coming back from one of them and still ringing in our ears the wonderful programme, of select clasics, we reentered the walking columm that always is bordering the sea, and a new conglomerate of diverse sounds invaded us with its enveloping presence. Music of all kinds drained from the luxurious Hotels, mixing with those of the radios that many of the walkers carried in their hands.

Passing by one of the most important Hotels crowded with an elegan concurrence sipping their cocktails we heard an orchestra whose members were enthusiastically singing, with an special pleasure like children who enjoy scandalizing the audience by being naughty

Ce soir nous dancerons
San chemisse et san pantalon...

These sentences were insistently repeated and we have walked far from there and we could still hear their singging "Ce soir nous dancerons... Sans chemisse et san pantalon..." like a bumblebee humming germinating a tthe warmth of other people's hearts.

This is Cannes, a mixture Saint and Sinner, historical and "avant garde" and snobbish artistical, musical and sportive, a brilliant Merry go Round dazzling in everyturn with news aspects of its multifarious life.

•NEWS

V Congreso Panamericano de Neurología

V Panamerican Congress of Neurology

V Congresso Panamericano de Neurología

Caracas-Venezuela
7 a 12 de Octubre de 1979

Auspiciado pela Federação Mundial de Neurología
Organizado pela Sociedade Venezolana de Neurología

COMITE ORGANIZADOR
ORGANIZING COMITEE
COMITE DE ORGANIÇÃO

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DR. MATIAS GONZALEZ M.
DR. ROLANDO HAAK B.
DR. REMY RADA
DRA. ISABEL ORTIZ DE MATOS

PROGRAMA PRELIMINAR

TEMAS PRINCIPALES

I "Estado Actual de las Enfermedades Vásculo-Cerebrales"

II "Neurología en las Primeras y Ultimas Etapas de la Vida"

III "Neurología Regional"

SIMPOSIUM

"Líquido Cefalorraquideo"

MESAS REDONDAS

a) Docencia en Neurología

b) Epilepsia

c) Terapéutica Neurológica

Figuras destacadas de la Neurología Continental Intervendrán en: Conferencias, Simposia y Mesas Redondas.

PROGRAMA SOCIAL

Caracas es una ciudad moderna, de bella ubicación geográfica e importante vida cultural, que ofrece todas las oportunidades para la elaboración de un interesante programa social durante el lapso del Congreso. La isla de Margarita, la Guayana Venezolana con el Salto "Angel" y los Andes, atraerán seguramente el interés de grupos turísticos, para quienes se organizarán excursiones inmediatamente antes o después de cumplirse el Programa Científico.

IDIOMAS

Los idiomas oficiales del Congreso serán: Español, Inglés y Portugués.

INFORMACION GENERAL Y SECRETARIA

CONGRECA, C.A.
Paso Subterráneo Hilton
Oficina 13
Parque Central
Caracas 101 - Venezuela
Apartado Nº 17422
Tif: 574.21.51

TRANSPOiTE

Viasa ha sido nombsada transportadora oficial de este evento.

Nota: para cualquier información, favor dirigirse a las agencias ICCA o de VIASA en sus respectivos países.

Agencia Oficial de Viajes:
Viajes Sir
Edf. San Germán, Local 5
Calle Acueducto, Sabana Grande
Caracas 105 - Venezuela
Apartado: 51364 - Caracas 105
Telex: 23335 AIRVI
Teléfono: 72.02.25

CUOTAS DE INSCRIPCION

	Participantes	Acopmpañantes
Hasta el 31-1-79	U$S 100 - Bs. 430	U$S 50 - Bs. 215
Del 31-1-79 al 31-7-79	U$S 120 - Bs. 520	U$S 60 - Bs. 260
A partir del 31-7-79	U$S 130 - Bs. 560	U$S 65 - Bs. 280

PRELIMINARY PROGRAM

MAIN TOPICS

I "Actual Concepts on Vasculo-cerebral Diaseases"

II "Neurology - Problems in Early and Final Periods of Life"

III "Regional Neurology"

SYMPOSIUM

"Cerebro-Spinal Fluid"

ROUND TABLES

a) Training in Neurology

b) Epilepsy

c) Therapy in Neurology

Relevant personalites in the field of. Continnental Neurology will be in charge to lectures, Simposia and round table of discussions.

SOCIAL PROGRAM

Caracas is a modern city, beatifully situated with important cultural activities, all of which offer an opportunity to develop an interesting social program during the course of the Conference.

The island of Margarita, the Guayana región with "Angel Falls" and the Andes will surely be attractive to visiting groups, for whom tours will be organized immediately before or after the Conference.

LANGUAGES

The official languages of the Congress will be: Spanish, English and Portuguese.

GENERAL INFORMATION AND SECRETARIAL SERVICES

CONGRECA C.A.
Paso Subterráneo Hilton
Oficina 13
Parque Central
Caracas 101 - Venezuela
Apartado Nº 17422
Telf.: 574.21.51

TRANSPORTATION

VIASA (Venezuelan Airline) has been appointed official transport of this event.

Note: For further information please coontact ICCA or VIASA offices in your respective countries.

Official Travel Agency
Viajes Sir
Edif. San Germán, Local 5
Calle Acueducto, Sabana Grande
Caracas, 105 - Venezuela
Apartado: 51364 - Caracas 105
Telex: 23335 AlRVI
Teléfono: 72.02.25

REGISTRATION FEES

	Active Membres	Accompanying Persons
Up to 1-31-79	U$S 100 - Bs. 430	U$S 50 - Bs. 215
From 1-31-79	U$S 120 - Bs. 520	U$S 60 - Bs. 260
From 7-31-79	U$S 130 - Bs. 560	U$S 65 - Bs. 280

PLANILLA DE INSCRIPCION
REGISTRATION FORM
FORMULARIO DE INSCRIÇÃO

CUOTAS DE INSCRIPCION
REGISTRATION FEES
QUOTAS DE INSCRIÇÂ

	Participantes **Active members** **Participantes**	**Acompañantes** **Accompanying persons** **Acompaphantes**
Hasta el 31-1-79 Up to 1-31-79 Até 31-1-79	U$S 100 - Bs. 430	U$S 50 - Bs. 215
Del 31-1-79 al 31-7-79 From 1 to 7-31-79 De 31-1-79 a 31-7-79	U$S 120 - Bs. 520	U$S 60 - Bs. 260
A partir del 31-7-79 From 7-31-79 A partir de 31-7-79	U$S 130 - Bs. 560	U$S 65 - Bs. 280

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Nome

Apellidos	**Nombres**
Surname	**Name**
Apellidos	**Nomes**

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Nationality .....
Nacionalidade

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Address .....
Endereço
.....

Fecha de llegada — Fecha de salida
Date of arrival ..... — Date of Departure .....
Data de chegada — Data de saída

Se incluye Giro
Enclosed is draft
Si inclui letra
Cheque
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Caracas 101 - Venezuela
Apartado Nº 17422
Tlt.: 574.21.51

International Rehabilitation Medicine Association

IRMA III

The Third International Rehabilitation Meeting was held in Basle, Switzerland from July 2-8, 1978. In his welcoming remarks, Dr. Wilhelm Zinn, Chairman, IRMA III, mentioned that Basle is a famous city with an old tradition of arts, science and trade. He promised an outstanding scientific program, as well as many, special social and cultural activities. He fulfilled every promise.

The outstanding symposia and work shops touched on virtually every subject requested by IRMA members. The social and cultural events were many, varied and different; something for everybody. The visits to the museums, especially the world-famous Basle Museum of Fine Arts, and a memorable evening of folk-lore and dining in Porrentruy, a charming little town in the Northwestern part of Switzerland, were, pehraps, the most exciting.

There was a serious attempt to bring together representatives of international agencies interested in Rehabilitation Medicine: The United Nations, World Health Organization, The International Federation of Physical Medicine and Rehabilitation, Rehabilitation International, The Council of World Organizations Interested in the Handicapped, and IRMA. This was manifest in the Opening Ceremony and the First Plenary Session as well as several formal and informal meetings throughout the week.

The Opening Ceremony at noon on Monday July 3, 1978, at the Congress Hall of the Swiss Industries Fair Center in Basle, The Mustermesse, was magnificent. The warm words of welcome by Dr. Wilhelm M. Zinn, representatives of the Swiss government and the medical community were interspersed with beautiful music played by a large symphony orchestra. Following the official opening of the Congress by Dr. Luis Ibarra of Mexico, President of IRMA, the orchestra played the world's premiere of the "IRMA Festival Overture for Large Orchestra" ("IRMA Festmusik fur Grösses Orchester"), composed especially for this occasion. This composition was presented as a gift to IRMA by the composer, the distinguished Swiss musician, Mr. Willy Berghamer, to be used in the opening ceremonies of successive IRMA Congresses.

At this time, Mr. Fréderic P. Walthard, Director General of the Swiss Industries Fair at Basle, extended an invitation to visit the First International Fair for the Rehabilitation and Integration of the Disabled (Rehamex 78). More than 70 exhibitors from 12 countries exhibited their products on personal equipment for the disabled as well as devices for treatment, beds and couches, locomotion aids, training and professional rehabilitation, and special installations and architectural design. for the living quarters of the disabled. In addition, more than 40 private and public organizations from Switzerland, the Federal Republic of Germany and Austria presented their programs in the Social Exhibition of Rehamex-78, and the exhibitors were available at all times to discuss their methods of integrating the handicapped into Society.

There was also an Exhibition of Works of Art by physicians, their families, and also of permanently disabled persons. This exhibition was designed to show the talents adn widespread interests of IRMA members as well as of their patients. The fair covered an area of approximately 100,000 square feet and was opened to the public as well as to the Congress members and their families.

The were more than 1300 official registrants for IRMA III. They attended 25 scientific and 5 plenary sessions and 25 summaries of the scientific sessions. The number of invited international scientists and medical specialists, interested in Rehabilitation Medicine, has never before been duplicated and will be hard to surpass in future congresses. These sessions were recorded on tape and may be purchased by members.

The closing ceremony at noon on Saturday, July 8, 1978 was informal. President Ibarra introduced the newly elected Officers and Members of the Executive Committee of IRMA for 1978-82 and announced that each of the 62 representative nations should appoint two councillors for this period. Dr. Christopher Evans of the United Kingdom, the new Secretary, requested the cooperation of all IRMA members, as did Dr. P.J.R. Nichols, United Kingdom, Editor of International Rehabilitation Medicine, the Official Journal of the IRMA. He reminded the IRMA. He reminded the IRMA III spearkers that they should submit their papers to their official journal first.

EXECUTIVE COMMITTEEE IRMA 1978 - 1982

President ..... Dr. Wilhelm Martin Zinn, Switzerland
President-elect ..... Dr. Herman J. Flax, Puerto Rico, USA
Past President ..... Dr. Luis Guillermo Ibarra, México
Vice-President ..... Dr. George G. Burniston, Australia
Secretary ..... Dr. Christopher Evans, UK
Deputy Secretary ..... Dr. Joaquim Rezende, Brazil
Treasurer ..... Dr. William J. Erdman, USA
Deputy Treasurer ..... Dr. Pierre Lambert, France

MEMBERS

1) Dr. M. P. Cameron, Canada
2) Dr. Miguel Rangel, Colombia
3) Dr. W. Schmidt-Kessen, German Federal Republic
4) Dr. Luigi Caldana, Italy
5) Dr. H. Wilmot Dennis, Liberia
6) Dr. Iwao Yokoyama, Japan
7) Dr. U. Daranond, Thailand
8) Dr. Franjo Gracanin, Yugoslavia

Dr. Herman J. Flax of Puerto Rico, U.S.A., President-elect and Chairman IRMA IV, invited everyone to help make IRMA IV in San Juan, Puerto Rico as successful as IRMA II in Basle. Finally, Dr. Ibarra invested Dr. Wilhelm M. Zinn with the IRMA Presidential badge for 1978-82.

Dr. Zinn spoke of the need to increase the membership, especially from the Eastern Countries of Europe. He emphasized the importance of the admission of IRMA as a full-fledged International Member of the Council for International Organizations of Medical Sciences, where IRMA will act as a consultant

in Rehabilitation Medicine to this important international medical organization. He also pointed out the need to support the new IRMA Journal, "International Rehabilitation Medicine". Finally, he thanked the members for their attendance and cooperation in IRMA III.

The Congress adjourned on a happy note. The organizing committees did their work well, and IRMA II will be difficult to surpass. Everyone agreed, despite the cold weather and the expensive Swiss franc, that the welcome was warm, and they were amply rewarded for their participation.

The next Agenda topic was **Future Activities.** Dr. André Van Gestel, Executive Secretary of the International Federation of Physical Medicine and Rehabilitation, invited the Assembly to attend the 8th International Congress in Stockholm, Sweden, May 26-30, 1980. The central theme is, "Disability - Prevention and Management by Rehabilitation Medicine".

The Secretary reported on IRMA's contribution to "1981-UN International Year for Disabled Persons". Only a few Councillors responded to a call for proposed plans for this year. Their replies were bound and presented by Dr. Ibarra to Mr. Esko Kosunen, Secretariat International Year for Disabled Persons, United Nations, at the First Plenary Session. IRMA is committed to participate in this important UN proclamation, and each councillor and each country should strive to carry out the objectives, especially the first and the fifth, namely. "Helping disabled persons in their physical and psychological adjustment to society", and "Promoting effective measures for the prevention of disability and for the rehabilitation of disabled persons". These are clearly areas in which medical expertise will be required to achieve the objectives.

IRMA will now take a more active part in the work of the CIOMS. Dr. H. J. Hachen and Dr. W. M. Zinn were designed by the Executive Committee to continue as IRMA representatives. They will attend meetings in Geneva and elsewhere, whenever possible, and will prepare a report for the 1980 IRMA Assembly meeting.

The Executive Committee decided not to request admission of IRMA into the Council of World Organizations Interested in the Handicapped (CWOIH) at the present time. The majority of these organizations are not medical. Also, the International Federation of Physical Medicine and Rehabilitation is a member, and the Committee considered the IFPM&R to be an able spokesman for Rehabilitation Medicine.

The Medical Commission of Rehabilitation International will hold a future meeting in Brighton, England prior to the Second European Conference of Rehabilitation International on September 17, 1978; and in Geneva, Switzerland on March 20-23, 1979. IRMA is well represented on this Commission with four Executive Committeemen, two Councillors and five Members. The meeting in Geneva will be held in conjunction with IRMA, IFPM&R, and CIOMS at the WHO headquarters. This meeting will continue the reunion of these international organizations for Medical Rehabilitation held during IRMA III.

The XIVth Congress of Rehabilitation International will be held in Winnipeg, Canada, June 22-27, 1980. Dr. K. A. Jocheim, Past-President RI, invited all the IRMA members to attend and participate in this meeting.

The Assembly voted for Puerto Rico as the **Site for IRMA IV in 1982.**

The members of the **Executive Committee** were elected.

The President-elect, Dr. Herman J. Flax, becomes Chairman of the Organizing Committee for IRMA IV in San Juan, Puerto Riso, USA. The exact date will decided later.

There was no **New Business** and no **Resolutions** were presented.

Dr. Ibarra presented the new Secretary, Dr. Christopher Evans to the Assembly. Dr. Evans requested the cooperation of the Councillors and Members. He stated that "News and Views" vill be published in Puerto Rico for the remainder of this year. Starting 1979, "News and Views" will be published in Switzerland by Eular Publishers and distributed apart from The Journal to all paid-up members. He urged all members to recruit their medical colleagues for IRMA as well as send in news items. He reminded the IRMA Councillors that they must poll the individual members of their respective countries for the purpose of electing two Councillors for the new term, 1978-82. As soon as possible he should receive these names for future contact.

Dr. Ibarra then invested Dr. Zinn with the Presidential seal. Dr. Zinn pledged to continue the able work of his predecessor. With the help of the Councillors and the Members he will strive to increase the prestige of IRMA in International Rehabilitation Medicine. He thanked the Assembly for participating in IRMA III and wished them all a safe voyage home.

The next meeting will be held in Stockolm, Sweden, duringg the 8th International Congress of the International Federation of Physical Medicine Rehabilitation. The meeting was then **adjourned.**

HERMAN J. FLAX, M.D.

President--elect of the International Rehabilitation Medicine Association, (IRMA), Dr. Herman J. Flax, graduated from the Medical College of Virginia in 1940 and received the degree of Master of Medical Sciences for graduate work in Physical Medicine from the University of Pennsylvania in 1952.

Additional training was completed at the Workmen's Compensation Center, Toronto, Canada under Dr. Harold D. Storms, and the Institute of Physical Medicine and Rehabilitation in New York City with Dr. Howard A. Rusk. He organized the PM&R Services of the State Insurance Fund for Injured Workmen at the Professional Hospital in 1949, the Veterans Administration Hospital in 1951, Clínica Dr. E. Fernández García Chest Disease Hospital in 1952, and Clínica Dr. M. Juliá Psychiatric Hospital in 1952, all in Puerto Rico.

Dr. Flax is Chief, Rehabilitation Medicine Service, San Juan Veterans Administration Hospital and Rehabilitation, University of Puerto Rico School of Medicine. He is a Diplomate of the American Board of Physical Medicine and Rehabilitation, Fellow of the American College of Physicians, of the American Academy of Physical Medicine and Rehabilitation, the American Academy for Cerebral Palsy, the Stroke Council of the American Heart Association, a member of the Canadian Association, of PM&R, the Sociedad Española de Rehabilitación, and other medical and auxiliar y medical societies. He is a past-president of the Section of PM&R of the Puerto Rico Medical Association and of the American Congress of Rehabilitation Medicine. He served as Secretary of IRMA from 1974-1978.

Dr. Flax has published numerous papers on many different subjects in Physical Medicine and Rehabilitation. He was married to the late Dra. Josefina Guarch and has three children, Hjalmar, Judy and Jennifer.

THE PAVLOVIAN SOCIETY

To All Members of the Pavlovian Society

Dear Friends:

The program and arrangements for the Pavlovian Society Meeting are fast approaching completion.

I am pleased to announce that through the cooperation of Dr. Anthony Reading our meeting Noverber 16-18 will be co-sponsored by the Department of Psychiatry, College of Medicine, University of South Florida. This has made possible obtaining Category I Credit for the Physician's Recognition Award of the American Medical Association. The actual number of credit hours has yet to be determined.

The program has developed in a most exciting fashion. Some of the highlights are:

1. The meeting will be dedicated to Professor Curt P. Richter who will present an overview of his work.
2. Professor J. Z. Young will attend and present an overview on "Memory as a Selective Process".
3. Dr. Roger Ray has put together a symposium on marine mammal behavior which will include as participants some of the world's most active scientists in this field.
4. Dr. Joseph Wolpe will present an overview on "Behavior Modification".
5. Dr. Dave Randall has brought together the top scientists in the country for the symposium on cardiovascular conditioning.

TOURETTE SYNDROME ASSOCIATION Inc.

GENERAL MEMBERSHIP MEETING

October 7, 1978

RESEARCHERS REPORT ON TOURETTE STUDIES AT NIMH

Eric Caine, M. D., who became affiliated with the University of Rochester Medical Center in June, 1978, joined his former colleagues from N.I.M.H. for a presentation of research findings resulting from their involvement in Tourette investigations over the past three years. Dr. Caine had helped to direct these efforts at the Section on Experimental Therapeutics of N.I.M.H. He stressed the importance of the Association in helping the illness to become better known, and thereby aiding patients to be diagnosed. Dr. Caine introduced the speakers and served as moderator for the program. At the outset, their criteria for the diagnosis of G. T. S. were reviewed. They are:

1.) Multiple motor and vocal tics.
2.) Onset before the age of 14.
3.) Waxing and waning course.
4.) Gradual replacement of old symptoms with new ones.

Ms. Linda Nee, M. S. W., began working with Tourette patients in October 1975. She indicated that most of their patient population had come to N.I.M.H. as a result of publicity engendered by our Association. Her report was based on data accumulated on the first fifty cases. Of these, 42 were male, 8 female. Three black families were part of this original group. The patients came from much the same geographical area as other patients at the National Institutes of Health: 38 % from Maryland, 12 % from Virginia, 10 % from D. C., and 40 % from elsewhere. Their age range was 8 to 51, with 42 % between 10 and 14.

The religious background was similar to that at N.I.H. as a whole: 10 % Jewish, 38 % Catholic, 46 % Protestant, and 6 % other. About half of the ancestors were from Eastern Europe, half from Western Europe. Seven families had some American Indian ancestry. Twenty of these patients had learning disabilities of the group, 15 had a positive family history of full blown Tourette Syndrome, 16 had a history of family tics, and 18 had no family history of tics or. G.T.S. Where a positive family history of G.T.S was found, the mode of inheritance has not been made clear as yet.

Clinical differences were found when the family history was taken into account. With a positive family history of G.T.S. there was 93% success with haloperidol; with a family history of tics there was 70% sucess with haloperidol; with no family history of either, there was only 43% success with the same medication.

Sleep disturbances after the onset of the illness, and prior to the use of medication, have been reported by this group, and are currently being studied. Obsessive-compusive behavior is also being studied.

Christy Ludlow, Ph. D., a speech pathologist who has worked on linguistics and language disorders, explained that when she was asked to study vocal tics, there was no guide for doing so. Much of her work has been directed toward developing a methodology for their study. She listed seven categories of vocal tics: lingual, laryngeal, exhalation, nasal, copralalia, labial, and jargon. The lingual, made by tongue movement, is the most frequent, laryngeal is next in frequency, and exhalation next. She stated that, contrary to the popular press, copralalia is not the biggest problem.

Patients were found to be most prone to vocal tics when asked to tell a story about a picture. The tics occur mostly at the beginning of sentences and at breaks, and with words that do not contain information such as prepositions. They generally do not occur with nouns and verbs.

The vocal problems of patients with G.T.S. have been contrasted with those of stutterers, and differences have been found. Thus far, the researchers do not find a relationship between vocal tics and motor tics, and both have to be carefully measured. The effectiveness of Haldol on motor and vocal tics also appears unrelated. Dr. Ludlow urged that the patient be carefully observed at all times of the day, and at different drug levels, in order to begin to understand the vocal aspects of G.T.S.

Ronald Polinsky, M.D., who is a neurologist currently in charge of the Tourette investigations at N.I.H., spoke about the drug studies that have been done there. Although haloperidol is the treatment of choice it has many possible side effects, and there are also patients who don't respond to it. For these reasons various other medications have been tried. They are: Clozapine, an antipsychotic (of the benzodiazepine family) which is thought to block dopamine receptors and to be free of the risk of tardive dyskinesia. In a double-blind, crossover study on 7 patients, no difference in motor tics was observed during the period on the drug and the period on placebo. The side effects of clozapine were: drowsiness, low white blood cell count, increased salivation, and tachycardia. It has since been taken off the market due to fatal reactions to the drug in Europe.

Chlorimipramine (also known as Anafranil), a tricyclic antidepressant which blocks reuptake of serotonin, was given a controlled trial with six patients using double-blind ,cross-over studies. The results were negative. Desipramine was also given a controlled trial and the results were negative. In each of these studies, there was no difference in

symptoms when the patient was on medication and when he was on placebo.

Although Haloperidol is the treatment of choice, other neurotransmitter substances need to be studied: glutamate, gaba, norepinephrine, acetylcholine, and serotonin. Relationships have been postulated between dopominergic systems and acetylcholine. Dr. Polinsky indicated he hoped to study these.

Currently, a protocol is bening constructed for the study of Lecithin. They expert in the future to investigate what happens when dopamine is blocked and when it is stimulated. They will also analyze HVA, the metabolite of depamne in the brain. Examination of HVA in the blood and urine can give evidence of whether there is a dysfunction of the dopaminergic sys- In addition to the pre ceeding, they expertc to conduct research on tardive dyskinesia. The outpatient clinic at N.I.M.H. will continue to study and provide treatment to patients.

Carl Merril, M.D. works on basic biochemical genetics. He firts became interested in G.T.S. after seing Dr. Van Woert's report in the New England Journal of Medicine linking Tourette's to Lesch Nyhan's disease. In Lesch Nyhan, an enzyme — HGPRTase is either missing or defective. In G.T.S. the enzyme appeared to be unstable. Dr. Merril studied this in several different ways, including a new method called two dimensional electrophoresis, which is used to separate proteins and to study the purifed enzyme. He could not detect a defect in the enzyme system. His future plans are to study the white blood cells of Tourette patients for their genetic information.

Michael Ebert, M.D., who is Head of the Section on Experimental Therapeutics, gave an overview of the clinical research unit pointing out that it made up of an interdisciplinary group of specialists with many different kinds of training and this is especially needed in an illnes as complex as Tourette Syndrome. He talked of the ways in which researchers try to track down a neurochemical problem. One way is to try to find homogenous groups; that is, groups that share the same symptoms, because this may be a clue to'the biochemical problem. Another way is to accumulate data on the neurotransmitter systems. This is done via drug trials, and by studying the neurochemical systems. The latter is difficult to do because nerve endings are complex, and the important elements to analyze —the synthesis, storage, release and activation o receptors —are not easily accesible. Presently, activity of brain chemicals is ascertained by the measurement of the metabolites of these chemicals in the CSF and urine.

The techniques available to researchers are imperfect at present, according to Dr. Ebert. In order to come to a conclusion about a biochemical abnormality, many kinds of data wil have to be put together. There is the hope that, at some future time, brain scans may be developed which could be used to study brain chemicals, making this type of research more practicable.

Dr. Ebert called Tourette Syndrome one of a group of fascinating disorders in which higher function, behavioral disorders and disorders of motor function are involved. Scientists are interested in these because they will teach us more about the function of the brain.

Dr. Eric Caine elaborated on the treatment philosophy at N.I.M.H. Haloperidol is considered the drug of choice and it is administered when the illness is not tolerable to the patient and his family. It is given in very low doses until the minimum effective dose is reached. There is no attempt to eliminate all the symptoms. The dose is raised or lowered based on symptom severity. They try, on a regular basis (every three to six months) to reduce the

medication in order to watch for tardive dyskinesia. Patients are encouraged to live a full life, to explain the illness to their peer, and not to let it limit them.

Dr. Caine reviewed the possible side effects of haloperidol: dystonic reactions, kathisia, akinesia, drowsiness, (giving the medication a night helps to avoid this symptom), mental dulling, depression, weight gain, and tardive dyskinesia. The latter is an involuntary movement disorder caused by long terms use of antipsychotic drugs. At MIMH they have seen three cases of tardive dyskinesia. One of these cases was a patient who had received 50 mg. of haloperidol for three and a half years. Dr. Caine said patients who are on Haldol for twenty yearse may be at risk for tardive dyskinesia. This is not a reason not to take it, in Dr. Caine's opinion, but to use it carefully and to take time off the drug.

Other therapies for G.T.S. were briefly commented on. Dr. Caine said Pimozide may be useful, but may also carry the risk of tardive dyskinesia. Chlorimipramine was not found to be useful. They hope to be able to try choline in the near future.

Behavior modification, according to Dr. Caine, is difficult to evaluate because it fails to consider the spontaneous variations that are part of G.T.S. The same has been true for psychotherapy. However, since this a chronic disease which plagues people's lives, psychotherapy might help some individuals to deal better with it .This has to be decider on an individual basis.

The discussant for this program was Dr. Thomas Chase, Director of Scientific Research at N.I.N.C.D.S. and a member of the Medical Advisory Board of the Tourette Syndrome Association. Dr. Chase noted some special difficulties in triyng to undesrtand Tourette Syndrome. These are:

Widespread misinformation.

The lack of certainty about the genetic involvement in G.T.S. (Some cases appear to be genetically determined and this seems to affect response to medication, and may influence the expression of the illness).

The need to develop appropriate methodologies for the study of G.T.S.

What was missing from the program, in the opinion of Dr. Chase, was an answer to the question "What really goes wrong in this illness?" He asserted that basic information is badly needed-the kind that should be forthcoming from the brain bank-in order to try to answer this question.

Dr. Chase reminded the audience that at the time in 1975 when he was approached by Betti Teltscher to serve on our advisory board, G.T.S. was virtually unheard of, and almost no research was going on. Now researchers are beginning to look at this syndrome in an expert way. Educational efforts aimed toward the public and profesionals must continue, and attempts must be made to interest more scientists. He ended his talk by congratulating the Tourette Syndrome Association for the excellent work it has done to date in educating the public and physicians about this disorder, and in fostering research.

EXCERPTA MEDICA

Travel Award 1979

The Trustees of the Excerpta Medica Foundation announce with great pleasure that applications may now be submitted for their Travel Award for 1979. The Award, which lasts for a period of three months and covers travel and hotel costs, is open to all categories of medical specialists. However, only candidates born during, or after, 1943 will

be considered. If married, the recipient may also be accompanied by either husband or wife. The closing date for the receipt of applications is 1st March 1979. People wishing to be considered for this Award should write to:

Mr Kenneth Ellison Davis

Travel Award Office

Excerpta Medica Foundation

P.O. Box 1126

1000 BC Amsterdam

The Netherlands

enclosing:

a) Curriculum Vitae (plus a recent photograph).
b) List of publications, plus reprints.
c) Two letters of recommendation.
d) A statement of approximately 250 words indicating how the Award would be used.

The Award will be conferred upon the recipient at a formal ceremony to be held in The Netherlands at an appropriate date in 1979.

Previous recipients of the Excerpta Medica Travel Award:

1973 — Robert W. Rodieck, M. Sc., Ph. D.

lately Reader in Physiology, Department of Physiology, Faculty of Medicine, The University of Sydney, New South Wales, Australia.

1975 — Erik Juhl, M.D.

Head of the Liver Unit, Division of Hepatology, Medical Department, Copenhagen Kommunes Hospital, Hvidovre, Denmark.

1977 — Robert H. Anderson, B. Sc., M.D., M.R.C. Path.

Reader in Cardiac Morphology, Cardiothoracic Institute, Brompton Hospital, The University of London, London, United Kingdom.

SOCIETY FOR NEUROSCIENCE

9650 ROCKVILLE PIKE
BETHESDA, MD 20014

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NEUROSCIENCE NEWSLETTER

VOLUME 9, NUMBER 4

December 1978

David H. Cohen, Editor - G. Gurvitch, Managing Editor - Published quarterly and distributed by the Society.

HIGHLIGHTS OF THE ST. LOUIS COUNCIL MEETING

Approval of 354 new membership applications (214 Regular, 124 Student, 16 Affiliate) and 96 changes of status (9 Regular to Emeritus, 85 Student to Regular, 2 Sdudent to Affiliate). Total Society membership now stands at 5,656.

Approval of three new chapter petitions: Central Illinois, Rhode Island, and Tampa Bay Area. The Society now has 59 chartered chapters.

Affirmation of interest in undertaking Society production of saleable audiovisual continuing education programs. Report on further investigations due at April 1979 Council meeting.

Approval of Stephen Max as Finance Committee chairman, John Blass a Social Issues Committee chairman, Jerome Sutin as additional 1979 Program Committee member and Special Interest Dinners chairman, Alan Epstein as additional Education Committee member. (For complete committee listings, see Vol. 9, Nº 3, September 1978 **Neuroscience Newsletter).**

Approval of proposal to offer members subscription discounts on as many relevant journals as will participate in the program, beginning as early in 1979 as possible.

Review of: 1978 Short Course on Neuroanatomical Tchniques; International Brain Research Organization and its plans for a 1982 World Congress; joint SN/National Paraplegia Foundation grant application to NINCDS for support of three scientific meetings on regeneration in the CNS; September SN Conference on Projecting Future Needs of Neuroscience; Annual Meeting Press Room.

Selection of 1979 Nominating Committee: Drs. T.N. Wiesel (President), W. Maxwell Cowan (Past-President), Ira B. Black, Brenda A. Milner, and Louis Sokoloff.

Approval of the 1977-78 Treasurer's Report, including the General Operating Budget for 1978-79 of $ 183,194, exclusive of Annual Meeting expenses. (The Treasurer's Report will appear in the March **Newsletter).**

Approval of the Finance Committee recommendation that nonstudent Society annual dues for individual members be raised from $ 25 to $ 35 beginning with 1979 dues (except in the case of those who have already paid their 1979 dues. See details, p. 3).

Consideration of suggestions from members at the November 6 Business Meeting.

A straw vote on the proposal that the Society dispense with slide presentations and have only symposia and posters at Annual Meetings was defeated by about 3:2 on the floor of the Business Meeting. Both Council and the Program Committee tend to favor what seems to be a natural evolution toward increased poster presentations, while leaving the slide option open. Council will consult with the 1979 Program Committee Chairman, Larry Kruger, regarding the symposia/poster format and other programming options, and will discuss the issue further at their April 1979 meeting.

It was suggested at the Business Meeting that the Society establish a committee to "watchdog" the appearance of unnecessarily restrictive federal regulations that could seriously hinder research or clinical application. Council declined to create another committee, preferring to execute its responsibility in this matter through Officer response to individual problem cases, and through the Society's affiliation with the Coalition for Health Funding. Council directed that an article informing members about Coalition activities be printed in the **Newsletter.** (This item will apper in the March issue).

SOCIETY FOR NEUROSCIENCE CONFERENCE: PROJECTING FUTURE NEEDS OF NEUROSCIENCE

Under the auspices of the Society for Neuroscience, 21 neuroscientists and 57 representatives of Federal agencies and scientific associations met in Washington, D. C., for three days (September 25-27, 1978) to assess the research and training needs of neuroscience and their future funding. Of central concern was defining the major considerations in developing an adequate base of hu-

man resources, technological capability, and budgetary support for the optimal growth of neuroscience. There are few guidelines for the forward planning of national scientific programs; the Conference thus represented an important step in implementing such a planning effort in neuroscience.

Planning for future needs is obviously a complex problem and must allow for unanticipated scientific and budgetary developments. In this context, the participans discussed such issues as research support formats and their relative merits; training needs and support in relation to available resources; higt-cost technology in neuroscience; the relationship between flexibility and stability in research funding; and the optimization of neuroscience supported through interagency cooperation. Each topic was approached by first considering the relative effectiveness of current and past mechanisms, and then debating what mechanisms might be most appropriate for the future. Effort was also directed toward exploring the complex budget formulation and appropriation processes, and discussion focused particularly on the decision-making mechanisms of program planning, project review and grant award at such agencies as the NIH Institutes, ADAMHA, and the NSF.

Clearly emerging from the discussion was the fragmentary nature of our data regarding the base of support for neuroscience research, the distribution of scientits within the broad field, etc. Such deficiencies in part relate to the interdisciplinary nature of the field and the fact that "neuroscience" has not been clearly defined and often is not specifically identified in the available funding and human resource statistics. Effective planning for the future will require a more accurate and comprehensive data base, the development of which should be a high priority.

The conferees made specific recommendations on each of the topics considered. These included, for example, the creation of a Science Bank modeled after the Federal Reserve Bank to assure funding stability by buffering acute decreases or delays in research support; a continuing effort to identify under-investigated and under-funded areas of neuroscience research; the value of coupling broad interdisciplinary expertise; the need for increased funds for equipment replacement; and the fostering of interagency cooperation to maximize the effectiveness of limited fiscal resources for neuroscience research support.

A summary of the Conference proceedings will be published in a future **Newsletter,** and a full report of all the deliberations and recommendations will hopefully be ready for publication in the late spring of 1979. We invite the membership to review these presentations and to respond to them, since the success of future planning efforts is dependent upon input from the entire neuroscience community.

Barry H. Smith and
David H. Cohen

FUTURE MEETINGS

January 26-28, 1979, Galveston, TX

The Society's Galveston Chapter will sponsor the First Galveston Neuroscience Symposium, entitled "Information Processing in the Nervous System — Communication Among Neurons and Neuroscientists". A Friday afternoon session will consider events at the level of the membrane, and will feature presentations by Drs. Arthur Brown, Douglas Eaton, Jeff Barker and Susumu Hagiwara. Drs. Allen Selvers-

ton, Paul Adams, Pablo Rudomin and Forrest Weight will consider the synaptic level on Saturday morning; and the circuit level wil be discussed by Drs. Theodore Bullock, Kenneth Naka, William Kristan and George Moore on Saturday afternoon. Considerations at the behavioral level will be given by Drs. John Fentress, Harold Pinsker, Fred Miles and Robert Grossman on Sunday morning. A special Friday evening program will be given by Prof. Mario Bunge of the Foundation and Philosophy of Science Unit of McGill University. A Keynote Address will be presented after a Banquet on Saturday evening by Prof. Arnold Mandell of the Univ. of California, San Diago.

Attendance at the Symposium will be by **advanced registration.** All interested members of the Society are invited to obtain additional information and registration forms from Dr. Glenn V. Russell, Dept. of Anatomy, Univ. of Texas Medical Branch, Galveston, TX 77550 (713/765-1146).

April 1-4, 1979, Zichron Ya'acov, Israel

24th OHOLO Biological Conference on Neuroactive Compounds and Their Cell Receptors. In English. Invited papers only. For further information, contact Mrs. Haya Ophir, Secretary to the OHOLO Conferences, Israel Inst. for Biological Research, P.O. Box 19-Ness-Ziona, Israel.

May 7-9, 1979, NINCDS (Bethesda, MD)

The Intramural Program of the National Institute of Neurological and Communicative Disorders and Stroke will sponsor an International Symposium entitled "The Role of Peptides in Neuronal Function", to be held May 7-9, 1979, at the National Institutes of Health reservation in Bethesda. The three-day meeting will draw together investigators from diverse disciplines for a comprehensive review of peptide research as it relates to the field of neurolobiology.

The first day will include presentations on the anatomy ant physiology of peptirergic neurons, as well as the synthesis and secretion of peptides. The second day will begin with a discussion of peptide-mediated communication in the nervous system, followed by reviews of the neurobiology of specific peptides, including angiotensin, somatostain, substance P, vasoactive intestinal peptide, luteinizing hormone releasing hormone, thyrotropin releasing hormone, olfactory system peptide, bag cell hormone and neorodepressing hormone. The final day will be devoted entirely to the pharmacology, physiology and potential clinical application of opioid peptides.

Among the invited participants are: H. Kosterlitz (Aberdeen, Scotland), S. Snyder (Baltimore, MD) R. Walter (Chicago, IL), J. Martin (Boston, MA), J. Phillis (Saskatoon, Sask., Canadá), J. McKelvy (Dallas, TX), J. J. Dreifuss (Geneva, Switzerland), F. Margolis (Hoffmann - LaRoche, Netley, NJ), and S. Said (Dallas, TX).

The Symposium is being organized by Drs. Jeffery Barker and Thomas Smith of the NINCDS Laboratory of Neurophysiology. Those interested in attending should contact either Dr. Barker or Dr. Smith, Bldg. 36, Room 2C02, NIH, 9000 Rockville Pike, Bethesda, MD 20014 (301/496-2414).

July 1979, Tokyo, Japan

The Association for the Psychophysiological Study of Sleep (APSS) will hold its Third International Congress the last week in July 1979, in Tokyo, locally organized and hosted by the Japanese Sleep Research

Society. Requests for meeting and travel information should be addressed as follows:

From the Americas: Christian Guilleminault ,M.D., Sleep Research Center, Stanford Univ. School of Medicine, Stanford, CA 94305.

From Asia: Kazuo Azumi, M.D., Tokyo Metropolitan Inst. for Neurosciences, 206 Masashidai, Fuchu-City, Tokyo, Japan.

From Europe: Michel Billiard, M. D., Service de Physiopathologie des Maladies Nerveuses, Cliniques Saint-Eloi et de Chauliac, 34059 Montpellier, France.

July 30 - August 3, 1979, Oxford, England

The Pharmacology of Thermoregulation Fourth International Symposium will include review lectures and free communications. For further details and reservations forms, write to Prof. A.S. Milton, Dept. of Pharmacology, University Medical Buildings, Foresterhill, Aberdeen AB9 2ZD, Scotland; or to Dr. P. Lomax, Dept. of Pharmacology, UCLA School of Medicine, Los Angeles, CA 90024, USA.

August 5-10, 1979, Boston, MA

4th Congress of the International Society of Electrophysiological Kinesiology. March 5 deadline for submission of papers. Address inquiries to Dr. Carlo J. De Luca, Children's Hospital Medical Center, 300 Longwood Ave., Boston, MA 02115.

August 22-24, 1979, Michigan State Univ., E. Lansing

American Phyciological Society special meeting on the "Relation Between Brain Neurotransmitters and Endocrine Fuctions". The Endocrine Society and the Society for Neuroscience will be Guest Societies, whose members may submit abstracts and register for the meeting at the same rate as APS members. The call for papers will be mailed Feb. 1, with an abstract submission deadline of Apr. 2. Request forms from the APS, 9650 Rockville Pike, Bethesda, MD 20014 (301/530-7165).

July 13-19, 1980, Budapest, Hungary

XXVIII International Congress of Physiological Sciences. The scientific program wil include free presentations (short communications, posters, and films), symposia, and invited lectures, in 15 sections. The deadine for registration and submission of abstracts is December 31, 1979. Address inquiries to the Secretariat, XXVIII International Congress of Physiological Sciences, MOTESZ, Congress Bureau, **H-1361, Budapest,** Pf. 32, Hungary.

NEUROEPIDEMIOLOGY

MINUTES OF THE WORLD FEDERATION OF NEUROLOGY RESEARCH COMMITTEE ON NEUROEPIDEMIOLOGY

IOWA CITY, IOWA, U.S.A.

June 15, 1978

The meeting was called to order at 12:30 p.m. The following individuals were in attendance:

A. Leviton
A. Eldadah
Z. Stein
M. Susser
G. Beringer
V. Marshall
C. Sullivan
J. Annegers
R. Loewenson
L. Kurland
B. Visscher
N. Halsey
R. Lerner
S. Shafer
M. Leske

S. Kunitz
J. Torner
A. Hauser
J. Kline
P. Spiers
D. Bunnell
M. Gregerman
D. Friyd
J. Handke
R. Malmgren
M. Wernstock
S. Lamm
E. Millner
R. Detels
Dr. Schoenberg chaired the sesion

Dr. Schoenberg began by reviewing the program elements of the Research Committee and reported on discussions which took place at the previous meeting held in Los Angeles in April of this year. Specific details of this earlier session are included in this mailing.

Discussion at the present meeting centered around three items: (1) development of acceptable standars of nomenclature, (2) training in neuroepidemiology, and (3) scientific meetings in neuroepidemiology. Particular difficulties in the classification of neurological diseases encountered in the forthcoming 9th revision of the Internacional Classification of Diseases were highlighted by Dr. Schoenberg. Although the international coding scheme poses several difficulties, the adaptation for use in the United States should address these deficiencies. Dr. Leonard Kurland, who worked on the development of the U.S. adaptation, briefly described the situation. If any members of the Research Committee have particular comments concerning the codes, please note them on the appropriate form and return this form directly to Dr. Schoenberg. These comments will be forwarded to the World Health Organization and hopefully wil be considered in the future revisions of the classification scheme.

Dr. Schoenberg then described educational programs in neuroepidemiology. One component of this program, a set of four videotapes, was highlighted at a scientific exhibit shown at the Society for Epidemiologic Research meeting. These tapes are available on 3/4" color videotape cassettes and review the application of epidemiology in the analysis of clinical problems in neurology and neurosurgery. For requests within the United States, the tapes may be obtained without charge on a loan basis from the National Medical Audiovisual Center (Annex), Distribution Section, Station K, Atlanta, Georgia 30324. Foreign orders for the videotapes should be sent directly to Dr. Schoenberg. The enclosed brochure entitled "Neuroepidemiology" describes these tapes in more detail. Educational opportunites supported bi the NINCDS include the National Research Service Awards, providing both institutional and individual research training fellowshisps in neuroepidemiology for U.S. citizens. The individual fellowships are limited to postdoctoral students, while the institutional awards include possible provisions for both predoctoral and postdoctoral students. Sponsoring institutions may supplement the income of fellows involved in the program. The World Health Organization also provides support for fellows who are not U.S. citizens but who want to study neuroepidemiology in the United States. A comprehensive textbook on neuroepidemiology will be published by Raven Press during 1978. With regards to courses in neuroepidemiology, Dr. Schoenberg noted that atetemps will be made to offer such a course at a future meeting of the American Academy of Neurology. There appears to be considerable interest in a presentation dealing with clinical trials in neurology. Dr. Schoenberg will also contact Dr. Leonard Schuman, University of Minnesota, with regard to the possi-

bility of presenting a neuroepidemiology course at the epidemiology summer sesion in Minneapolis in the future. Dr. Shafer mentioned the International Cardiovascular Epidemiology Course held annually, and noted that a similar program might be very useful in the area of neurological epidemiology. The Research Committee will look into this matter.

In discussions with Drs. Roger Detels and Jim Gale, past and present Presidents of the Society for Epidemiologic Research, there appears to be considerable interest in having a session on neurological epidemiology a part of the forthcoming meeting of the Society for Epidemiologic Research to be held in New Haven in June, 1979. If any members of the Research Committee have particular suggestions concerning the organization and content of such a session, they should contact Dr. Schoenberg. An outline of the proposed symposium is icluded in this packet.

Future meetings of the World Federation of Neurology Research Committee on Neuroepidemiology will be held anually in conjunction with the American Academy of Neurology and the Society for Epidemiologic Research. In addition, we shall hold sessions during the Pan American Congress of Neurology and during the World Congress of Neurology. The Research Committee would also be pleased to participate in other regional meetings of the World Federation of Neurology.

The importance of liaison with other scientific societies was emphasized. Such contacts will be initiated with the International Epidemiological Association. At the conclusion of the meeting, those present volunteered for work on following committees:

I. Devolopment of Standars of Nomenclature and Classification.

   A. Hauser; R. Malmgren; L. Kurland; S. Kunitz.

II. Identificacion of Available Data Resources Registries.

   A. Eldadah; R. Lerner; S. Kunitz; L. Stein; J. Torner; L. Kurland; D. Fryd.

III. Standard Methodologies for Research Surveys J. Handke; R. Lerner; A. Hauser; Z. Stein; J. Torner; R. Malmgren; B. Visscher; S. Shafer; E. Millner; V. Marshall; R. Detels; D. Fryd; R. Loewenson; M. Leske.

IV. Training in Neuroepidemiology.

   A. Eldadah; T. Chin; M. Susser; Z. Stein; G. Beringer; D. Bunnell; C. Sullivan; M. Greberman; L. Kurland; R. Detels; J. J. Annegers.

V. Exchange of Information.

   A. **Newsletter** - G. Beringer.

   B. **Liaison** - A. Eldadah; M. Susser; A. Hauser; E. Millner; V. Marshall; M. Greberman.

VI. Directory of Personnel for Consultation.

   A. **Development of Directory** - C. Sullivan; D. Bunnell; D. Friyd.

   B. **Individuals volunteering for inclusion in the directory** - M. Susser; A. Eldadah; J. Handke; C. Sullivan; R. Lerner; S. Kunitz; D. Bunnell; A. Hauser; J. Torner; R. Detels; D. Friyd; R. Loewenson.

VII. Facilitating Research - Unusual Disease Patterns - Migrant Studies.

Name	Countries
M. Susser	U. K., Netherlands, Israel, various others.
Z. Stein V. Marshall R. Detels	S. E. Asia, Africa
L. Kurland R. Loewenson	Japan, Chile, South America, S. E. Asia

A list of these committees is included in this mailing. For those of you who would like to participate in the function of these committees, please enter your nome on the appropriate section of the form and return in to Dr. Schoenberg.

The meeting adjourned at 2:00 p.m.

Respectfully submitted,
Bruce S. Schoenberg, M. D., M.P.H. Secretary, World Federation of Neurology Research Committee on Neuroepidemiology.

COURSE PROPOSAL FOR THE AMERICAN ACADEMY OF NEUROLOGY

COURSE TITLE: Clinical Trials in Neurology.

COURSE DESCRIPTION: This course is intended to provide clinicians with an understanding of how clinical drug trials are carried out and how to evaluate their results. Lectures will be given to illustrate general principles of drug trials. These didactic presentations will be followed by practical workshops for small groups. Faculty will include a recognized clinical expert in the particular field as well as a biostatistician or epidemiologist. Participants will learn about funding sources for drug trials, how to select subjects and controls, and how a proper clinical trial must be designed to give meaningful results. Also, clinical trials carried out recently for some of the major neurologic diseases and symptom complexes will be reviewed (e. g., stroke, seizures, movement disorders, and myasthenia gravis).

COURSE OUTLINE

9:00 A.M. - 10:30 A.M.

I. Principles of Clinical Trials (Lectures).
   - A. Epidemiologic considerations.
   - B. Biotatistical considerations.

10:30 - 12:30

II. Practical Aspects of Clinical Trials.
   - A. Organization of Clinical Trials.
     1. Coordinating center.
     2. Clinical center.
        a. role of participating investigators.
     3. Starting and stopping trials.
        a. ethical aspects.
     4. Publications and publicity.

B. Use of Drug Trial Data|Support of Studies.

1. Food and Drug Administration.
2. National Institute of Neurological and Communicative Disorders and Stroke.
3. Pharmaceutical Industry.

2:00 - 5:00

III. Workshop Sessions.

A. Cerebrovascular Disease.

1. Epidemiologist.
2. Neurologiost.

B. Convulsive Disorders.

1. Epidermiologist.
2. Neurologist

C. Movement Disorders (Parkinson,s disease, spasticity, dystonia).

1. Epidermiologist.
2. Neurologist

D. Myasthenia Gravis.

1. Epidermiologist.
2. Neurologist

SYMPOSIUM PROPOSAL FOR THE SOCIETY FOR EPIDEMIOLOGIC RESEARCH

June, 1979

Neuroepidermiology: Methodologic Problems and Solutions.

I. Presentation of Problems.

A. Uncommon Disorders.

B. Difficulty in Diagnosis.

II. Presentation of Practical Solutions.

A. Records - Linkage Systems.

B. Registries.

C. Studies of Geographic Isolates.

D. Studies in Urban Settings.

E. Studies in Rural Settings.

III. Discussion.

BOOK REVIEWS

CLINICAL CONCEPTS OF NEUROLOGICAL DISORDERS

Edited by James F. Toole, M. D.
Professor of Neurology
Chairman, Department of Neurology
The Bowman Gray School of Medicine of Wake Forest University
Winston - Salem, North Carolina
The Williams & Wilkins Company - 428 E. Preston Street, Baltimore, Md. 21202· U.S.A.

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CONTENTS:

2. Headache and Head Pain ..... Donald J. Dalessio

3. Paresthesiae, Pain and Peripheral Neuropathy ..... Elliott Mancall

4. Weakness, Fatigueand Muscle Wasting: Disorders of the Motor Unit .... Justiniano F. Campa and T. R. Johns.

5. Disorders of Locomotion .... Larry A. Pearce.

6. Episodic Loss of Consciousness: Syncope, Seizures, and Narcolepsy .... L. James Willmore, B. Joe Wilder, and R. Eugene Ramsay.

7. Hysteria, Anxiety, Depression, and Related Neurotic States ..... Arthur W. Epstein.

8. Amnestic Syndromes and Disorders of Expression ..... D. Frank Benson.

9. The Bedside Assessment of Stupor and Coma ..... John H. Caronna.

10. Ischemic Cerebrovascular Syndromes ..... H. J. M. Barnett.

11. Hemorrhagic Cerebrovascular Syndromes ..... John S. Meyer.

12. Computerized Axial Tomography in Neurological Diagnosis ..... John E. Lee and William H. Stuart.

Index .....

Prof. Toole stated that the contributors to this volume geared their presentations to medical students and house officers training in general medicine.

The topics were chosen to provide a core of information concerning the nervous system vhich would be useful to the non-neurologist.

As much as possible, have been emphasized ambulatory and outpatient evaluations and have approached each subject as a physician would; first considering the presenting complaints, then the examination of the patient followed by laboratory findings, management, and a short but up-to-date bibliography so that the interested reader can pursue each topic in greater depth.

The volume begins with interviewing and screening techniques for defining neurologic disorders and continues with consideration of common abnormalities such as headache, weakness, paresthesias, and gait disturbances. There are special considerations of episodic disturbances such as syncope, convulsions, and cerebral vascular disease.

A section of special interest is a chapter on differentiation of neurologic disease from functional disorders.

The diagnosis and management of disorders of cortical function including amnesia, disorders of expression, stupor, and coma are particularly relevant for internists. Cerebral vascular disorders are singled out for special attention and a final chapter on the use of computerized cranial tomography in medical and neurologis practice is included because of the enormous impact of this diagnostic innovation on the delivery of care to patients suffering with disorders of the head and brain.

Finally Dr. Toole said that he is specially pleased to have been able to assemble the work of such an outstanding group of neurologists who are above all, bedside clinicians, therapeutically oriented, an who have broad experience in internal medicine and neurology.

The authors of this book have achieved their aim to expound in a clear and precise way the modern concepts, about the essentials problems of clinical neurology that interest the especialist and internist as well.

It is a book to be highly recomended.

Prof. Dr. Víctor Soriano.