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Editorial

El alcohol (Ethanol) constituye para la humanidad entera uno de los problemas más graves que desde largo tiempo la afecta. Es el opio de occidente.

Muchísimas personas lo ingieren y sufren ellas de su acción tóxica que incide tanto en lo físico, en la esfera psíquica y en el medio social, a veces con consecuencias trágicas para los demás.

El alcoholismo, para quien lo padece, implica una situación patológica crónica que le exige ser asistido toda la vida. Se estima que en el mundo se encuentran en esta situación veinte millones de personas. Francia anualmente pierde cuatro mil de sus habitantes por delirium tremens y diez mil por cirrosis hepática alcohólica.

La adicción al alcohol es muy antigua. Siempre se menciona en relación con él a Noé y a Baco. Alejandro de Macedonia murió prematuramente sin haber consolidado su Imperio por haberse agravado el estado febril con que enfermó en Asia, por una prolongada borrachera. Tiberio el Emperador era un bebedor de tal magnitud que lo llamaban "biberius".

La vida recreacional de Occidente admite entre sus elementos continuamente presentes, la bebida alcohólica, con marcada tolerancia en el medio social, frente a los desarreglos de conducta de quien hace abuso de la misma. La severidad es de mucho más entidad en lo que atañe a otras drogas siendo algunas de ellas quizá menos peligrosas que el alcohol.

En la lucha contra la plaga del alcoholismo se siguen distintas tendencias. Se aprovecha de productos con los cuales se acondiciona un estado de repulsa al vicio, son "curas de desagrado". Los elementos más empleados son la apomorfina, la cianamida, el antabus (Bisulfato de Tetraltildurea). Los resultados positivos se aprecian en el 70 % de los ensayos. Pero debe consignarse que una vez que se suspende el tratamiento, la recaída aparece invariablemente.

Se recurre hoy a la psicoterapia con respuestas favorables en un 50 %, es decir en una proporción equiparable a la de las enfermedades mentales en general. No se pretenden curas radicales sino un alivio de la situación con disminución de cantidad y frecuencia de la ingestión del tóxico y reducción de sus efectos perniciosos, teniendo en cuenta que el tratamiento debe ser hecho por vida.

Mencionemos que existe en parte en lo que atañe al comportamiento de las personas adictas una cierta dependencia genética.

El modo de operar del alcohol sobre el encéfalo es directo, es decir no se hace mediante los productos de su metabolismo. Actúa aumentando la resisten-

cia eléctrica de la membrana celular, disminuye también la transmisión sináptica y la movilización de cationes. Parece que los efectos más importantes ocurren por inhibir el alcohol a la Formación Reticular en la acción moduladora que incide sobre las vas aferentes y eferentes.

El alcohol en el organismo se metaboliza y se quema en forma por demás peligrosa. Su oxidación está asociada a la de los ácidos ribonucleicos con lo cual queda dicho que se afecta la estructura celular fundamental. Se llega en esta forma a la necrosis celular del hígado y del páncreas. Quemándose el alcohol se quema y destruye también estructuras esenciales del cuerpo.

Deseamos expresar nuestro agradecimiento al magnífico grupo de autores que han contribuido a este número con su profundo conocimiento y vasta experiencia, en uno de los tópicos más complejos de la neurología. Sus brillantes conceptos serán de utilidad para nuestros lectores enfrascados en la solución, comprensión y manejo de uno de los más complicados pacientes que un especialista debe enfrentar.

Es un placer para nosotros el anunciar que nuestro cuerpo de Editores y Consejeros, se ha visto enriquecido con la incorporación de especialistas de renombre mundial como el Dr. R. Hassler de Alemania, Dr. Tchabischer de Austria, el Dr. Kreindler de Rumania, Dr. Refsum de Noruega, el Dr. Schnidt de la URSS. Ellos serán un gran estímulo para nuestra Publicación y con estas palabras les brindamos nuestra más cordial y afectuosa bienvenida.

Dr. VICTOR SORIANO.

Editorial

Alcohol (Ethanol) constitutes one of the most serious problems for all mankind, having been affected by it over a long lapse of time. It is the opium of the west.

Many people ingest it and suffer from its toxic effects, which not only affects the physical, psychic, but also the social sphere, sometimes causing tragic consequences for other people.

Alcoholism implicates a chronic pathologic situation for those who suffer from it and obliges them to continue taking it for the rest of their lives. It is estimated that there are twenty million persons in the world who find themselves in this situation. France loses four thousand of its inhabitants yearly through delirium tremens, and ten thousand by alcoholic hepatic cirrhosis.

Addiction to alcohol is very ancient. It is always mentioned in relation to Noah and Baco. Alexander of Macedonia died prematurely without having consolidated his empire as the fever he contracted in Asia got worse, by a prolonged state of drunkenness. Tiberius, the Emperor, was such a tremendous drinker that he was called "biberius".

The life of recreation in the west admits alcoholic drink among its continually present elements, with marked tolerance in social circles, in the face of the disorderly conduct of those who make abuse of the same. The consequences are much more severe than in other drugs, some of them probably less dangerous than alcohol.

In the battle against the plague of alcoholism, different trends are followed. Advantage is taken of products with which a repulsive attitude to vice is acquired, in the way of "displeasure cures". The elements which are mostly employed are apormophine, cyanamide, antabus (Tetratilduran bisulfate). Positive results are estimated in 70 % of the tests. But it should be stated that once the treatment is suspended, relapse invariably takes place.

Nowadays pyschotherapy is applied with favorable response in about 50 %, that is to say, in a comparable proportion to that of mental illnesses in general. There is no pretense of radical cures, but the situation is alleviated with a decrease in the amount and frequency of ingestion of the toxin and reduction of pernicious effects, taking into account that the treatment should be done all through life. We shall mention that there exists a certain genetic dependence which in part applies to the behavior of addicts.

The way alcohol works on the encephalon is direct, that is, it is not by means of the products of its metabolism. It acts increasing the electric resistance

of the cellular membrane. It also diminishes the synaptic conductivity and the mobilization of kations. It would seem that the most important effects occur through the ingestion of alcohol in the Reticular Formation in the modulating action which acts on the afferent and efferent passages.

Alcohol in the organism metabolizes and burns in a very dangerous way. Its oxidation is associated with that of ribonucleic acids which affect the fundamental cellular structure. In this way it reaches the cellular necrosis of liver and pancreas. As the alcohol burns, essential structures of the body are also burned.

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

It is for us a pleasure to announce that our body of Editors and Advisers has been enriched with the incorporation of world known specialists as Dr. R. Hassler from Germany, Dr. Tchabischer from Austria, Dr. Kreindler from Rumania, Dr. Refsun from Norway, Dr. Schmidt from URSS. They will be a great stimulus for this Publication and with these words we give them our most hearty and affectionate welcome.

Dr. VICTOR SORIANO.

Ethanol and the Nervous System Experimental Neurophysiological Aspects

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In a recently published review of the effects of ethanol on the nervous system [40], based largely on literature available up to mid-1967, it was necessary to conclude that our understanding of these effects was rather fragmented. There was a considerable amount of information about effects of ethanol on the whole organism, much less about its physiological effects on individual neurones, still less about the biochemical or biophysical interactions with subcellular components, and almost no bridging of the gaps between these three levels of action. In the three years following, a number of developments have added substantially to our understanding of the cellular mechanisms, and have helped explain some of the findings in the whole animal. The present review will concentrate on these newer findings and their significance.

Actions of ethanol on the integrated nervous system

In the review cited [40], it was suggested that many of the major actions of ethanol on the nervous system resulted from decreased responsiveness of the midbrain reticular formation, both to direct electrical stimulation [7] and to indirect stimulation via collaterals from afferent sensory pathways[32]. This could apparently account for the many observations of alcohol-induced reductions in sensory acuity [50] and in cortical evoked responses to sensory stimulation [25, 30, 56]. It would also provide an explanation for the decreased span of attention to environmental stimuli [19, 59], the disinhibition of emotional expression [29] and the progression of drowsiness, sleep and coma produced by increasing doses of ethanol [61, 62]. Possibly as a direct consequence of the action on pathways originating in the reticular formation, or perhaps as a secondary effect of the decrease in wakefulness, ethanol produces a number of changes in autonomic tone which resemble those found during sleep, including vagally mediated increases in peristalsis and gastrointestinal secretion, and cutaneous vasodilatation. It also appears to block ascending impulses from the midbrain which lead to hypothalamic and neurohypophyseal release of vasopressin [16], oxytocin [23] and gonadotropic hormones [70]. Impairment of the cortical activating function also appears to explain the typical effects of ethanol on the EEG, including a tendency to synchronization, increase in amplitude, and shift toward lower frequency distribution [13, 34].

At the same time, descending modulatory discharge from the reticular formation is also impaired by ethanol. As a result, ethanol initially facilitates many spinal reflexes [77] by removal of inhibitory tone [37, 44], but also impairs muscular coordination by abolishing differences in inhibitory control of agonist and antagonist muscle groups [45, 48]. Positional alcohol nystagmus or PAN [3] similarly appears to result from the removal or reduction by ethanol of inhibitory brainstem influences on sensory organs in the semicircular canals since obstruction or removal of one or more canals abolishes the

corresponding components of PAN [21, 54].

In contrast, direct excitability of cortical cells, spinal motor neurones, or primary sensory pathways is, on the whole, much more resistant to ethanol than are these modulatory sistems. Consequently, measurements of cortical excitation thresholds [7], axonal conduction [47] or transmembrane ion fluxes underlying the action potential [2, 55] were generally thought to show little change except at ethanol concentrations which are associated with deep intoxication in the intact subject.

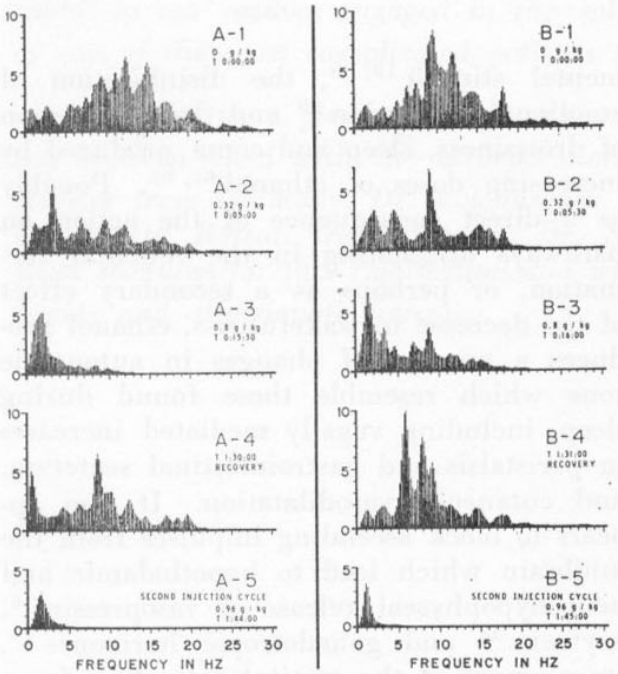

Fig. 1. — *Alcohol-induced changes in frequency spectra of the left frontoparietal EEG in the undisturbed (left column) and alerted (right column) preparation. A-1, B-1: control state, no ethanol. Ethanol doses shown in A-2, A-3 and A-5. T indicates time from start of experiment, in hr:min:sec. Ordinate indicates the activity (energy) in arbitrary units. (From E. K. Sauerland and R. M. Harper [68]. Reproduced with kind permission of the authors and of Academic Press, Inc., publishers of* Experimental Neurology).

Recent work has confirmed portions of the picture presented above, refuted others, and generally added a little more detail to it. For example, quantitative analyses of the shifts in EEG frequency and power-density spectra under the influence of ethanol [51, 68] (Fig. 1) support the conclusions reached by earlier workers. The picture has been extended by the observation [68] that apparently the same effect of ethanol is demonstrable in the EEG of animals in which the influence of the midbrain reticular formation has been excluded by complete precollicular transection (Fig. 2). It was suggested that ethanol may be acting directly on the cortical cells generating the EEG, or on thalamic pacemakers. Other possibilities must also be considered. Hippocampal stimulation can in turn control the rhythm of thalamic electrical discharge [49], so that primary ethanol effect on the hippocampus can not be excluded. Also, Story *et al.* [74] suggested that the differential effects of ethanol on cortical electrical response to direct electrical stimulation and to afferent sensory stimulation might best be explained by depression of cortical interneurones mediating sensory input into deeper layers of the cortex. In view of later studies of ethanol effects on spinal interneurones (to be mentioned below), this suggestion merits further attention, perhaps by studies of single-unit activity in deafferented slabs of cortex *in situ*.

The inhibition, by ethanol, of oxytocin and vasopressin release in post-partum women has again been demostrated most convincingly. By cannulation of a mammary duct and measurement of the intraductal pressure changes, Cobo and Quintero [9] showed that blood alcohol levels over 200 mg/100 ml. sharply reduced the milk-ejection response to suckling by the infant, but caused no change in the dose-response curve to intravenously injected oxytocin. Fuchs [22] observed the same phenomenon in lactating rats. Weight gain by the suckling young was used as an index of milk-ejection, and increasing doses of ethanol over 1 g/kg were found to give progressively greater reduction of milk yield. In contrast ethanol had no effect on the milk-ejection response to exogenous oxytocin. Both groups therefore concluded that ethanol blocks the release of oxytocin in response to afferent stimuli. These studies reinforce the conclusions of earlier ones [23, 80], with the added advantage that mammary duct contraction is considered a more specific indicator of circulating oxytocin than is the response of the post-partum uterus.

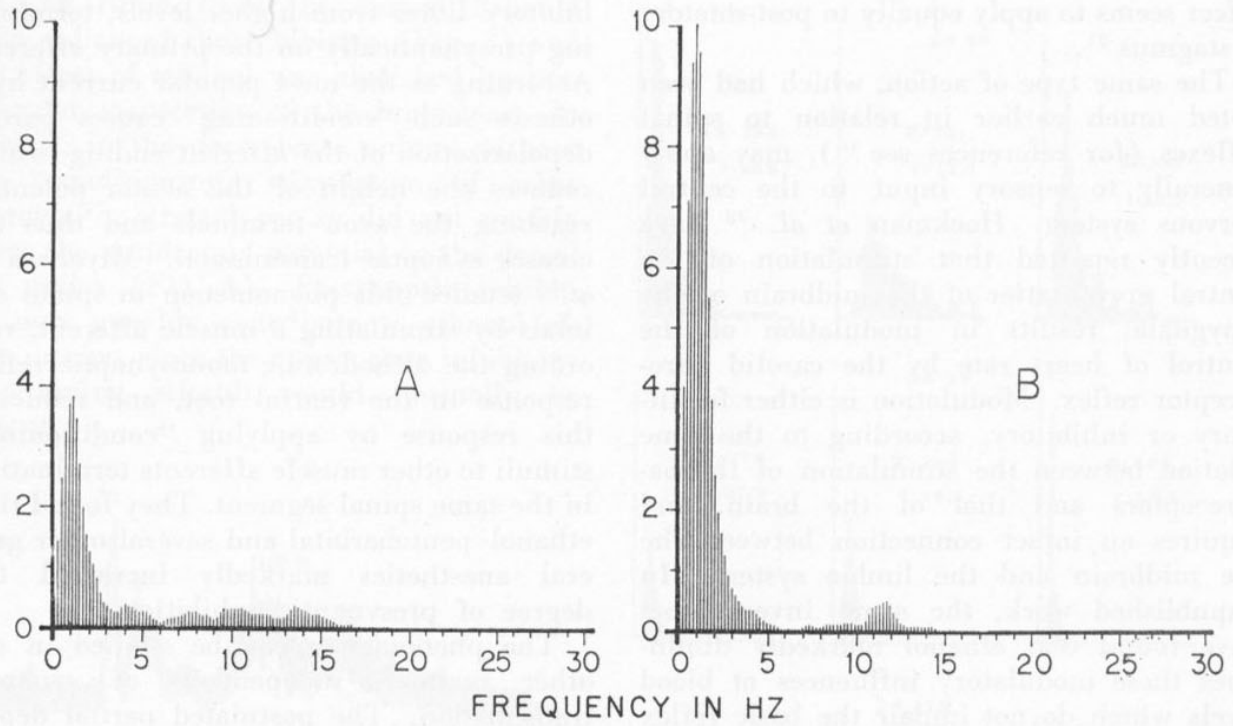

Fig. 2. — *Effect of ethanol on the frequency spectrum of the left frontoparietal EEG in a preparation with complete precollicular transection. Ordinate shows the amount of activity (energy) in arbitrary units. A: no ethanol; B: ethanol 0.33 g/kg, showing marked increase in activity in the 0.2-2 Hz frequency range. (From E. K. Sauerland and R. M. Harper* [68]. *Reproduced with kind permission of the authors and of Academic Press, Inc., publishers of* Experimental Neurology).

These studies do not help, however, to explain how ethanol inhibits the release of oxytocin or vasopressin. Bissett and Walker [6] had shown that injection of nicotine could cause release of vasopressin and thus terminate ethanol-induced diuresis. The effect of ethanol was therefore not on the secretory cells themselves, but on the pathways by which neural stimuli reach them. Further clarification of the action of ethanol will require examination of the effect of ethanol on the secretory process after production of selective lesions or local stimulation at various levels in the pathways between the primary sensory afferents and the secretory cells, or micro-iontophoretic application of ethanol at the same levels. It is obviously difficult to do this with respect to pathways as complex as that leading to oxytocin secretion. Perhaps it is not too surprising, therefore, that more studies of this type have been made with respect to analysis of ethanol effects on reflexes, and on sensory evoked potentials in the cortical electrogram.

Effects of ethanol on reflexes

Further support has been provided for the view that positional alcohol nystagmus results from suppression of tonic inhibitory influences on the vestibular sense organs or afferent pathways. In a most ingenious experiment, Oosterfeld [64] determined the effect of zero gravity produced by parabolic flight in high-speed aircraft, or 2-3 x g produced by flying in a tight circle, on the intensity of PAN in humans and rabbits. In confirmation of the suggestion by Nito *et al* [62], Oosterfeld showed that gravity, and not deflection of the cristae, is indeed the effective stimulus. Weightlessness abolished both phases of PAN, while high gravitational force restored PAN I during the interval between PAN I and PAN II, in which nystagmus is normally absent. The effect of moderate doses of ethanol is apparently to reduce the threshold of effective stimulation, by reducing inhibitory modulation of the response to the constant normal gravitational stimulus. This disinhibitory

effect seems to apply equally to post-rotatory nystagmus [31].

The same type of action, which had been noted much earlier in relation to spinal reflexes (for references see [40]), may apply generally to sensory input to the central nervous system. Hockman *et al.* [33] have recently reported that stimulation of the central grey matter of the midbrain or the amygdala, results in modulation of the control of heart rate by the carotid baroreceptor reflex. Modulation is either facilitatory or inhibitory, according to the time relation between the stimulation of the baroreceptors and that of the brain, and requires an intact connection between the the midbrain and the limbic system. In unpublished work, the same investigators have found that ethanol markedly diminishes these modulatory influences at blood levels which do not impair the basic reflex itself.

A more detailed understanding of the cellular basis for these effects on reflexes is provided by three recent studies [17, 53, 69]. One mechanism of impairment of reflexes is that of presynaptic inhibition at the axon terminal of the afferent neurone, produced by "conditioning" stimulation of certain other afferent fibres or of descending inhibitory fibres from higher levels, terminating presynaptically on the primary afferent. According to the most popular current hypothesis, such "conditioning" causes partial depolarization of the afferent ending, which reduces the height of the action potential reaching the axon terminals and thus decreases synaptic transmission. Miyahara *et al.*[53] studied this phenomenon in spinal animals by stimulating a muscle afferent, recording the orthodromic monosynaptic reflex response in the ventral root, and reducing this response by applying "conditioning" stimuli to other muscle afferents terminating in the same spinal segment. They found that ethanol, pentobarbital and several other general anesthetics markedly increased the degree of presynaptic inhibition.

The phenomenon can be studied in another manner, independent of synaptic transmission. The postulated partial depolarization of the afferent terminal lowers the intensity of additional depolarizing stimulation of the terminal needed to trigger an antidromic action potential back along the same fibre, and the longer-latency dorsal root reflex. Sauerland *et al.*[69], using this technique in intact animals produced presynaptic inhibition of trigeminal afferents by "conditioning" stimuli applied to de-

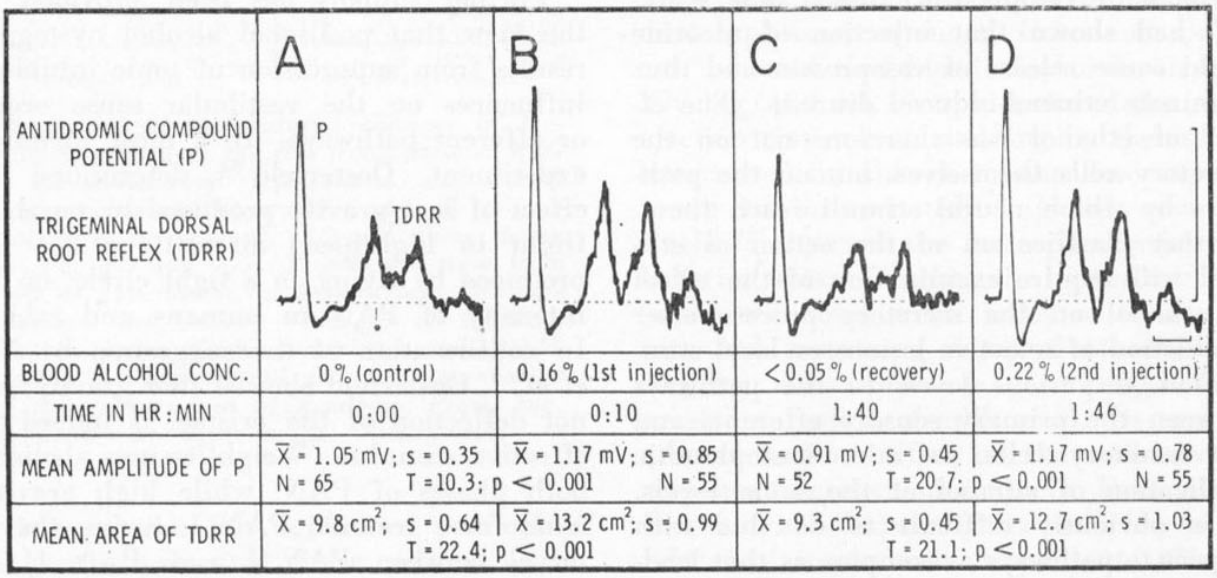

Fig. 3. — *Ethanol-induced changes of antidromic compound potential (P) and trigeminal dorsal root reflex (TDRR) in the intact brain. Discharges were elicited by single stimuli to the spinal trigeminal nucleus and recorded from the ipsilateral infraorbital nerve. Amplitudes of P and the areas of TDRR were measured with reference to the baseline level (broken lines marked *). Calibration bars: amplitude 1 mv, time 2 msec. (From E. K. Sauerland, N. Mizuno and R. M. Harper*[69]*. Reproduced with kind permission of the authors and of Academic Press, Inc., publishers of* Experimental Neurology.)

scending fibres from the cortex. Ethanol again enhanced the inhibition (Fig. 3) and this effect of ethanol was abolished by precollicular transection of the brainstem. In contrast, in the decerebrate animal without any "conditioning" stimulation of other afferents [17], ethanol *per se* did not modify either the antidromic potential or the dorsal root reflex (Fig. 4). Presynaptic inhibition may possibly contribute to ethanol effects *in vivo*, since the appropriate inhibitory conditioning stimuli would normally be present.

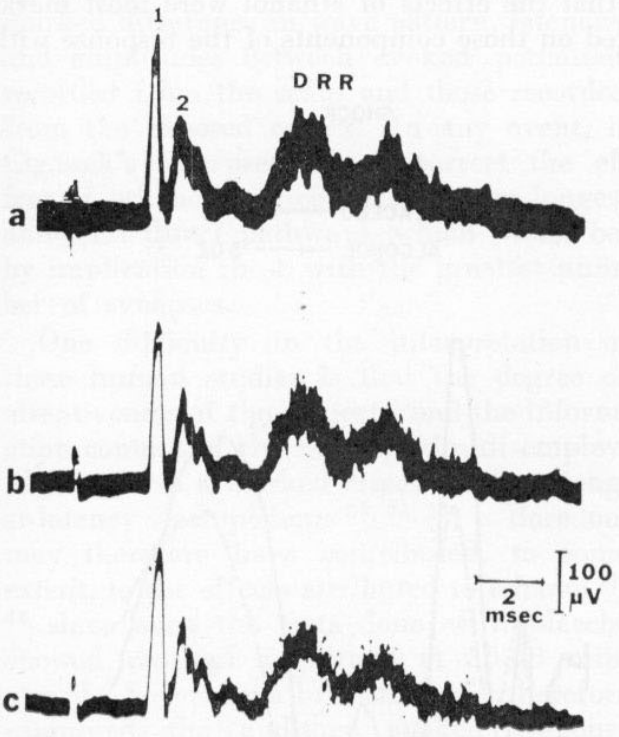

Fig. 4. — *Responses in soleus nerve to cord stimulation in base of ventral horn, in the absence of "conditioning" stimulation (compare with Fig. 3). 1 and 2: antidromic responses; DRR: dorsal root reflex. a: control; b: 5 min after 0.9 g/kg ethanol; c: 30 min after ethanol. 8-10 superimposed traces in each record. (From E. Eidelberg & D. F. Wooley [17]. Reproduced with kind permission of the authors and of* Archives Internationales de Pharmacodynamie.)

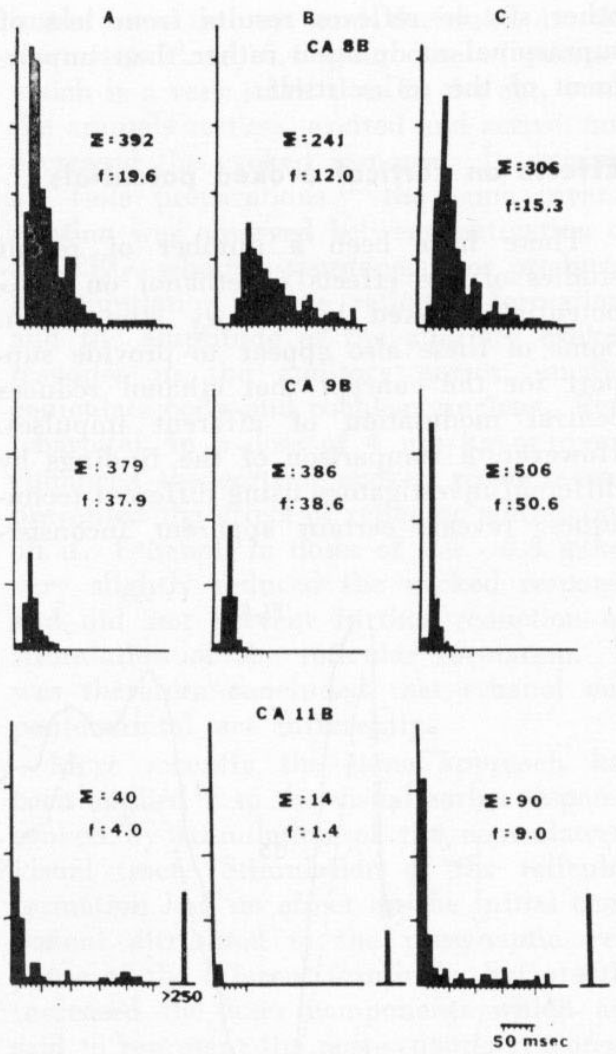

Fig. 5. — *Interval histograms of spontaneous activity of three different interneurones. A: control; B: 1 min after 0.3 g/kg ethanol; C: 6 min after ethanol. Abscissae: small divisions = 10 msec intervals. Ordinates: relative distribution of spikes. E = number of spikes in 10 sec epochs; f = mean firing frequency. (From E. Eidelberg and D. F. Wooley [17]. Reproduced with kind permission of the authors and of* Archives Internationales de Pharmacodynamie.)

On the other hand, even in the decerebrate animal, ethanol in quite low doses did markedly decrease the firing rate of spinal interneurones (Fig. 5) and the excitability of motor neurones. As a result, orthodromically recorded ventral root responses to dorsal root stimulation were reduced, polysynaptic responses more so than mono-synaptic [17]. This would adequately explain the finding, for example, that ethanol markedly reduced sexual reflexes in the cord-sectioned rat and dog [27, 28], at concentrations which had much less effect on the flexion and crossed extension reflex, and none on the tendon jerk [27]. It could also account for the observation that in the intact subject the major effect of moderate doses on the patellar tendon reflex [77] and

other simple reflexes results from loss of supraspinal modulation rather than impairment of the reflex itself.

Effects on cortical evoked potentials

There have been a number of recent studies of the effects of ethanol on EEG potentials evoked by sensory stimulation. Some of these also appear to provide support for the concept that ethanol reduces central modulation of afferent impulses. However, a comparison of the findings by different investigators, using different techniques, reveals certain apparent inconsistencies which make it difficult to draw firm conclusions.

Gross *et al.* [25] had observed in human subjects that a small dose of ethanol, about 0.5 g/kg, caused a reduction in amplitude of all components of the evoked response recorded from the mid-scalp region after auditory stimultation by a standardized click. Lewis *et al.* [46], using a dose of 1.25 g/kg, found quite similar changes in the responses evoked in the same region by visual stimulation and by electroshock to the finger (Fig. 6). Both groups found that the effects of ethanol were most marked on those components of the response with

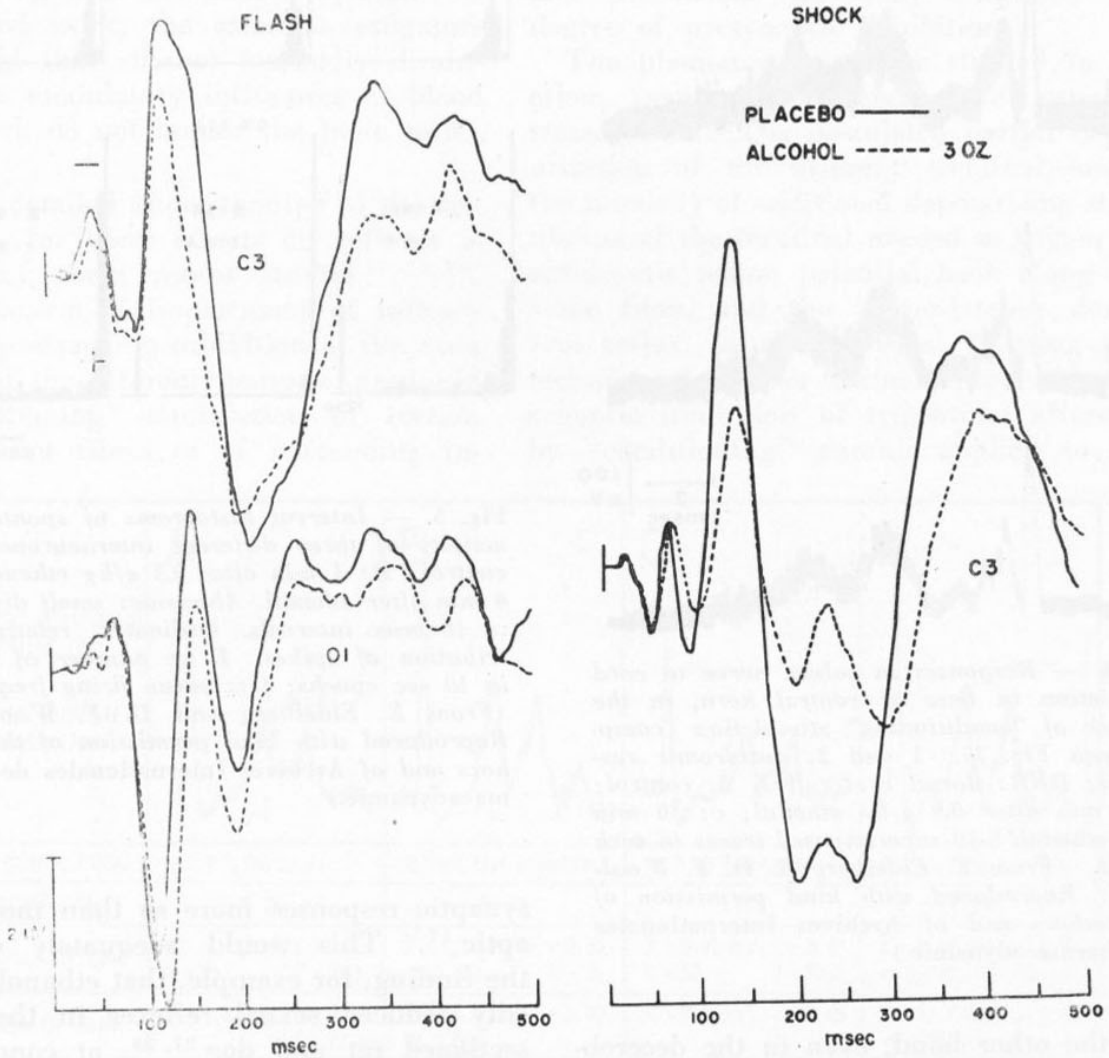

Fig. 6. — *Composite evoked EEG responses to light flash (left) and finger shock (right) following administration of ethanol or placebo. Each composite is the sum of 100 responses from each of 9 subjects. C3, recording from mid-scalp area; 01, recording from occipital region; reference electrode attached to ear. (From E.G. Lewis, R.E. Dustman and E. C. Beck* [46]. *Reproduced with kind permission of the authors and of Elsevier Publishing Co., publishers of* Electroencephalography and Clinical Neurophysiology.)

latencies of over 50-80 msec, which they considered to represent impulses conveyed extralemniscally via the reticular formation and the diffuse thalamic projections to the association cortex.

Ciganek [8] has pointed out that all three of these evoked responses (auditory, visual and sematosensory) have the same set of component deflections, and he therefore questions whether any of the components, even those of the shortest latency, represent primary afferent impulses. Some investigators even seriously question whether they are cortical potentials at all, because of the marked difference in wave pattern, latencies and amplitudes between evoked potentials recorded from the scalp and those recorded from the exposed cortex. In any event, if Ciganek's interpretation is correct the effect of ethanol is greatest upon the longest and least direct pathways, which would be, by implication those with the greatest number of synapses.

One difficulty in the interpretation of these human studies is that the degree of attentiveness of the subjects, and the information content of the sensory stimuli employed, also have a marked effect on these longer-latency components [39, 73, 75]. Boredom may therefore have contributed, to some extent, to the effects attributed to ethanol [25, 46] since even the tests done with placebo showed reduced amplitude at 30-60 minutes [25]. Soveri and Fruhstorfer [72] therefore examined the auditory evoked response under conditions of deliberate attention or inattention to the stimuli. The mean amplitude during the inattentive state was reduced to less than half its control value by ethanol in a dose of 0.52 g/kg. Deliberate attentiveness increased the amplitude, proportionately more under ethanol than in the control tests, but not enough to compensate for the effect of the alcohol. Similar studies are currently in progress in this laboratory.

To a considerable extent, this factor has already been taken into account in studies of evoked potentials in experimental animals. In unrestrained cats with chronically implanted electrodes, the evoked response of the auditory cortex to click stimuli was increased in amplitude when the animals were drowsy, and decreased in the alert state [58]. A 0.4 g/kg dose of ethanol, which is a very small dose in the cat, made the animals restless, excited and active, and decreased the evoked response. In encéphale isolé preparations [76] the same inverse relation was observed between activation of the EEG, whether spontaneous or produced by stimulation of the reticular formation, and the amplitude of the auditory evoked response in the auditory cortex, medial geniculate body and cochlear nucleus. Pentobarbital, in a dose of 4 mg/kg or more, enhanced the cortical evoked response and prevented the effect of reticular stimulation on it. Ethanol, in doses of 0.4 - 0.8 g/kg, very slightly reduced the evoked response and did not prevent further reduction on stimulation of the reticular formation. It was therefore concluded that ethanol and pentobarbital act differently.

More recently the same approach has been applied [57] to the visual cortex response evoked by stimulation of the contralateral visual tract. Stimulation of the reticular formation had no effect on the initial component attributed to the presynaptic response of the afferent terminals, but greatly increased the later components which are said to represent the post-synaptic responses of the cortical neurones. Pentobarbital, in doses of 2-32 mg/kg, caused progressively greater reduction in the post-synaptic components, but the decrease could be partially offset by stimulation of the reticular formation. Ethanol, in doses of 0.1 - 0.6 g/kg, also reduced the late components in the absence of reticular stimulation, but stimulation of the reticular formation restored the response completely. Again it was concluded that ethanol and pentobarbital act differently.

All of these studies [57, 58, 76] require comment on at least two points. First, the doses of ethanol and of pentobarbital did not cover corresponding parts of their respective dose-response curves. Pentobarbital was used in a series of doses which produced effects ranging from ataxia and sleep to light surgical anesthesia, while the doses of ethanol were such as to produce mild excitation to drowsiness. The results of Nakai & Domino [57] show that at the highest dose of

ethanol the evoked response was apparently beginning to decrease even in the presence of reticular stimulation. If one or two higher doses had been used, the results with ethanol might well have parallelled those with pentobarbital. Indeed, Guerrero-Figueroa *et al.* [26] have reported that local responses evoked by direct stimulation of the midbrain reticular formation and limbic system were progressively reduced during alcohol intoxication in cats with implanted electrodes. This matter deserves to be examined further.

The second comment relates to some of the techniques employed, and the validity of the inferences drawn from evoked response studies. In none of the work cited above were blood gases monitored, and blood pressure readings, though taken, are not actually presented. It is reasonable to assume that efforts were made to keep the preparations as physiologically normal as possible, but it should be emphasized that changes in perfusion and oxygenation of the cortex can markedly affect its electrical responses, and drugs such as ethanol can have considerable effect on cerebral circulation. This is especially important when one is dealing with responses such as the auditory evoked response, in which the relation between the surface waves and intracellullar electrical events is not yet established. Because of this, it is unwise to conjecture on the mechanisms or significance of the effects of reticular stimulation on the evoked potentials themselves, but it is probably legitimate to use *change* in these effects under ethanol as an empirical index of ethanol action on the reticular neurones, particularly if coupled with measurement of the threshold for effective reticular stimulation.

Underlying mechanisms

Acetylcholine release.

Several of the effects of ethanol noted above involve mechanisms in which acetylcholine plays a role. It is generally accepted that synaptic transmission in the spinal cord is cholinergic, and an increasing body of evidence [11, 20] supports the idea that at least some portions of the reticular activating system and of the primary sensory pathways, right up to cortical level, are also cholinergic. The finding that both ethanol and pentobarbital decrease the release of acetylcholine by eserinized brain cortex slices *in vitro* [41, 43] therefore appeared consistent with the observed actions on these neural systems *in vivo*. An apparent difficulty was that ethanol did not inhibit acetylcholine release when the slices were stimulated by a high concentration of K^+ in the medium, while other effects of ethanol, such as reduction of oxygen uptake, were much greater in the stimulated slices. This problem has now been resolved. In as yet unpublished work in this laboratory, ethanol was found to inhibit acetylcholine release when the brain slices were stimulated electrically, rather than by high K^+. The difference from pentobarbital proved to be quantitative rather than qualitative.

However, there still remains the apparent discrepancy between these results and those obtained by use of rat and frog nerve-muscle preparations [24, 36, 63]. There is evidence of *in*creased acetylcholine release from the motor nerve endings under the influence of ethanol, during the resting state (spontaneous miniature end-plate potentials) as well as in response to nerve stimulation (end-plate potentials). The explanation may lie in the techniques used. Nerve-muscle junctions are fairly tightly apposed structures, and diffusion of extraneous materials from the incubation medium into the synaptic cleft requires a significant time. With higher concentrations of ethanol the period of increased release of acetylcholine lasted only a few minutes or seconds, and was followed by failure of release due to nerve block [24]. With lower concentrations, the rate of ethanol diffusion would be lower and it would probably take longer to reach the stage of impairment of action potentials in the nerve ending. Since the observations with each concentration of alcohol lasted for 10-15 minutes or less, the most evident change is the early increase in acetylcholine release. On the other hand, brain slice incubations were carried on for 90 minutes [41], so that the inhibitory effect predominated; conceivably a short period of exposure to

ethanol might have shown increased release, and this can be tested experimentally. *In vivo*, capillary circulation ensures that diffusion occurs over much shorter distances, and the temporal separation of stimulatory and inhibitory actions is probably minimal.

Catecholamine release.

..In the earlier review [40] reference was made to conflicting reports about whether or not ethanol caused discharge of catecholamines from central adrenergic terminals. It was suggested that the disagreement might be explained by the finding [10] that increased release under the influence of ethanol is demonstrable only of the simultaneous resynthesis is prevented, as by *a*-methyltyrosine. This has recently been confirmed by direct measurement of norepinephrine levels and turnover rate in rat brain, in the presence and absence of ethanol [4]. Corrodi [10] suggested that inhibition of vasopressin release by ethanol is mediated by release of norepinephrine from hypothalamic terminals of fibres originating in the midbrain. More recently, and perhaps somewhat unexpectedly, it has been suggested that adrenergic neurones also subserve such other inhibitory functions as the production of sleep and synchronization of the EEG. Smith *et al.* [71] reported that low doses of propranolol decreased the duration of sleep caused by a 4 g/kg dose of ethanol in mice. Mardones *et al.* [51] observed that pretreatment of rabbits with reserpine prevented the EEG synchronization produced by ethanol in a dose of 1 g/kg. In all these studies, ethanol was given under conditions in which it could be normally metabolized to acetaldehyde, which is known to be an effective releaser of catecholamines. These effects of ethanol in the central nervous system may therefore possibly be indirect ones, caused by acetaldehyde.

5-Hydroxytryptamine metabolism.

A similar suggestion has received considerable attention recently, with respect to cerebral metabolism of serotonin. Several groups of investigators [5, 12, 18] have shown that ethanol alters the metabolic pathway of norepinephrine, serotonin and other substrates of monoamine oxidase. The initial product of deamination is an aldehyde intermediate, which is then normally oxidized to acidic end-products, including vanillylmandelic acid and 5-hydroxyindoleacetic acid (5-HIAA). During the metabolism of ethanol and acetaldehyde, the coenzyme NAD is reduced to $NADH_2$, which favors the formation of the respective reduced end-products, 3-methoxy-4-hydroxyphenylethylglycol and 5-hydroxytryptophol (5-HTOH) in the liver. The same effect can result from the blocking of aldehyde oxidase by acetaldehyde formed from the ethanol. The discovery of a tiny but measurable level of alcohol-oxidizing activity in brain [66] lent some support to the idea that local production of acetaldehyde in the brain might be enough to influence these reactions. Recently it was reported that 5-HTOH injected directly into the cerebral ventricles had observable effects on the visual evoked response and on behavior [67], raising the possibility that some of the effects of ethanol might he mediated through these metabolic alterations.

Against this view, however, is the report that the brain enzyme which produces 5-HTOH differs from the corresponding enzyme in the liver, in that it uses the co-factor $NADPH_2$ rather than $NADH_2$[14], and the metabolism of ethanol generates only $NADH_2$. Addition of ethanol to liver slices *in vitro* results in a clear shift of serotonin metabolism away from 5-HIAA to 5-HTOH, but with brain slices this does not occur [15]. *In vivo* studies of the metabolism of ^{14}C-serotonin injected directly into the caudate nucleus, and of turnover of endogenous serotonin in the brain, have failed to show any deviation from 5-HIAA to the 5-HTOH pathway under the influence of ethanol. The balance of evidence at present, therefore, is against this pathway playing a significant role in the mediation of ethanol effects in the brain.

Cell membrane alterations.

The strongest evidence obtained to date, concerning cellular mechanisms of ethanol

action, is of a biophysical nature. Earlier reports [2, 55] had indicated that ethanol increased membrane resistance in the squid axon, impairing the ion fluxes responsible for production of the action potential. This has been supported by recent observations in the giant axon of the lobster [35]. Even more interesting is the evidence of a similar increase in membrane resistance in motor neurones of the cat spinal cord [17] and in the post-synaptic membrane in rat skeletal muscle [24], at ethanol concentrations much lower than those used in studies on crustacean nerves. These findings provide a much stronger basis for explaining the inhibitory effects of ethanol on neuronal excitability, action potentials, and synaptic transmission. Moreover, the relatively greater effects on smaller neurones with a higher surface-to-volume ratio would account for the selectivity of ethanol action such as the greater sensitivity of mammalian motor neurones than of crustacean giant axons, and the still greater sensitivity of spinal [17] and cortical [74] interneurones and the reticular formation.

Mayer *et al.* [52] reported that the velocity of axonal conduction in the ulnar nerve is decreased during the rising phase of the blood alcohol curve in man. Re-examination of the data of Low *et al* [47] reveals the same effect. This might seem to imply an effect of ethanol on the space constant of the axon membrane. However, it is much more likely that this change in conduction velocity reflects the change in limb temperature which may follow ingestion of the alcohol [47, 65].

Finally, the inhibitory effect of ethanol on active transport of cations across neuronal membranes [38,42] provides an additional factor contributing to the selectivity of action of ethanol. Small neurones with high firing rates will become depolarized to the point of unresponsiveness much sooner than larger cells, given the same degree of inhibition of active transport by ethanol.

SUMMARY

Recent studies have strengthened the view that many actions of ethanol on the nervous system result from impairment by alcohol of modulatory influences exerted by the brainstem reticular formation on both afferent and efferent pathways. The main cellular basis of this effect appears to be an increase in electrical resistance of the cell membrane, which has been observed in mammalian neurones at alcohol concentrations corresponding to mild intoxication *in vivo*. Together with impairment of synaptic transmission, and impairment of active transport of cations, this provides a clearer understanding of the complex picture of acute intoxication.

RESUMEN

Estudios recientes sustentan la hipótesis según la cual los efectos más importantes del etanol sobre el sistema nervioso se explican por la acción inhibidora del alcohol sobre la modulación ejercida por la formación reticular del tronco cerebral tanto sobre las vías aferentes como eferentes. La base celular de este efecto, parece ser el aumento de la resistencia eléctrica de la membrana celular, que ha sido observado en neuronas de mamífero con concentraciones de alcohol correspondientes a una intoxicación moderada *in vivo*. Este efecto y también la disminución de la transmisión sináptica y del transporte activo de los cationes permiten comprender con mayor claridad el complejo cuadro de la intoxicación aguda.

RÉSUMÉ

Des résultats récemment publiés supportent l'hypothèse que beaucoup des effets les plus importants de l'éthanol sur le système nerveux s'expliquent par l'action inhibitrice de l'alcool sur la modulation exercée par la formation réticulaire du tronc cérébrale, tant sur les voies afférentes que sur les voies efférentes. La base cellulaire de cette action inhibitrice est apparemment l'augmentation de la résistance électrique de la membrane cellulaire, qu'on a récemment noté dans les neurones du mammifère avec des concentrations d'éthanol qui correspondent à une intoxication modérée *in vivo*. Cet effet, aussi bien que la diminution de transmission synaptique et du transport actif des cations, donnent une compréhension plus complète des complexités de l'intoxication aiguë.

ZUSAMMENFASSUNG

Neuere Ergebnisse stärkten die Ansicht, dass viele Wirkungen des Äthanols auf das Nervensystem durch eine alkoholbedingte Hemmung der Modulationsfunktionen des Retikulärsystems des Hirnstammes auf afferente sowohl wie efferente Bahnen entstehen. Die wichtigste zelluläre Basis für diese Wirkung scheint in einer Zunahme im elektrischen Widerstand der Zellmembran zu liegen, wie es in Warmblütlerneuronen mit Alkoholkonzentrationen, die einem milden Rausch in vivo entsprachen, beobachtet wurde. Zusammen mit der Hemmung synaptischer Transmission und der Hemmung des aktiven Kationentransportes ermöglicht diese Beobachtung ein besseres Verständnis des komplexen Bildes akuter Alkoholintoxikation.

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Genetic Aspects of Alcohol Drinking Behaviour

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Genetic research of alcoholism may have its origin in the genetotrophic theory presented by Williams [31] in 1947, which he together with his collaborators [32] developed further, and tried to support it with animal experiments. The word genetotrophic implies that alcoholism is a genetic disease, because it is thought to arise fundamentally from nutritional deficiences which, in turn, are genetically controlled. Many scientists, Popham [25] in particular, have criticized Williams' theory and demonstrated certain weaknesses of the genetotrophic theory. The thoughts have anyhow proved rather fruitful to alcohol research. On the other hand one has tried by means of animal experiments to construct a biological model of the heritability of alcohol drinking behaviour, as well as the metabolic and psychophysiological factors correlating with drinking. The genetotrophic theory has undoubtedly also given the initiative to some twin studies on drinking behaviour.

Studies on Laboratory Animals

The first ones to start cross-breeding experiments with albino rats showing different alcohol drinking habits were Mardones *et al.* [19] They calculated the correlation between parents and offspring, which showed that hereditary factors regulate spontaneous drinking.

Since those studies biometrical methods have developed quite a lot. A complete genetic analysis of a behaviour component, e. g. alcohol consumption, in fact requires quite extensive cross-breeding experiments. The method of biometric analysis based on generation means is described by Bruell [4] and a corresponding method for behaviour research, the diallel cross analysis, was described by Jinks & Broadhurst [15] and Broadhurst [3]. These methods enable us to analyse the share of genetic variance and environmental variance from total variance, and the possible dominance, overdominance, heterosis and maternal effect. The figures obtained by means of this analysis are theoretically fairly reliable, and the analysis may be continued to estimate the number (k) of relevant genetic components, the segregation units. For this the characteristic under review has to be hereditarily additive, the effect of the single loci have to be quantitavely equal, and the loci must combine freely. This can be tested by means of scaling tests. It seems probable that only rather few materials fulfil these qualifications when strictly implied.

An important problem of genetic alcohol research based on animal experiments is an accurate determination of the phenotype. It is obvious that the results of a genetic analysis totally depend on the method used when determining the phenotype. The alcohol drinking behaviour of the test animals has usually been tested by free choice experiments where the animal can choose between standard food, water and a weak (5-15 % v/v) alcohol solution simultaneously. The phenotype has been defined by either alcohol preference (the amount of alcohol consumed as percentage of total

fluid consumption), or by the alcohol consumption figure (the amount of alcohol consumed in milligrammes per unit of body weight). Eriksson has criticized the use of the preference figure in many of his papers [6, 8, 9] and demonstrated that the preference ratio is a misleading measure because it is directly dependent of total fluid consumption which fluctuates with secondary factors, such as room temperature, the quality of the food offered, the diuretic effect of alcohol etc. The figure for the body weight (mg/1000 g) is free from such amount of alcohol consumed per unit of sources of error, and it shows clearly the physiological or pharmacological effect of alcohol.

Fuller [13] has studied the concentration of alcohol solutions used when defining the phenotype, and he has demonstrated that different inbred strains of mice show different concentration preferences. According to Fuller the phenotype of spontaneous drinking behaviour should be defined by means of six different concentrations offered. The preference readings thus obtained are then used to calculate the alcohol score which can be used as a measure of the phenotype. Later Cicero and Myers [5] have presented experimental results which show that a single test solution can be employed, if the concentration preference of different animals or strains is defined by using a concentration series rising by 1 % a day and starting with a 3 % concentration. A single test percentage is then selected which is 3 percentage points greater than the concentration just above the selection threshold, defined as the highest concentration at which the alcohol solution constitutes half of the animal's total fluid intake. However, Eriksson [8] has demonstrated experimentally, that rat strains at a certain concentration level, i. e. 5-10 %, tend to drink roughly the same absolute amount of alcohol per unit of body weight, the level of which is determined individually or according to the strain to which the subjects belong. The same feature may be found in the material presented by Thomas [29], who tested the alcohol preference of the inbred mouse strains C57BL and DBA. If one calculates the amount of alcohol consumed per unit of body weight, one would find that it remains roughly the same over a large concentration area, although it is naturally in different levels in the different strains. From a physiological and pharmacological point of view the amount of alcohol consumed per unit of body weight (mg/1000 g) is important. This is best taken into account when using a test solution, the concentration of which is so high, that even those subjects with the highest alcohol preference may drink alcohol according to their full physiological capacity without having to exceed their normal fluid requirement. For the rat a concentration of 5-10 % is suitable, but for some mouse strains with a very high alcohol preference (C57BL) one should use a concentration higher than 10 % in free choice experiments. Many secondary factors also have an effect on the definition of the phenotype. Mardones [18], Lester [17] and Eriksson [8] cite several papers which show that the composition of the food affects the alcohol consumption of the animals and thus their phenotype figures. Myers [21] and Eriksson [8] have also carried out experiments which show that the temperature of the environment affects the alcohol preference. According to the experiments carried out by Eriksson [8] when the temperature rises (5-32°C), rats start to drink weaker solutions, but the amount of alcohol consumed per unit of body weight rises only slightly. An important factor affecting the phenotype figure is the age of the subjects. Wallgren and Forsander [30] have demonstrated that old rats have a higher alcohol preference than young rats. This feature was found in both sexes in the rat by Eriksson and Malmström [11]. Goodrick [14] and Eriksson [8] have found that the rise of alcohol preference with age is partly ostensible being a result of a combined effect of diminishing total fluid consumption and slowly rising alcohol consumption. Previous experience of alcohol drinking also influences the phenotype reading obtained in a free choice experiment, as has been demonstrated in many papers. Thus, it is obvious that different methods of defining the phenotype may very strongly affect the results and their interpretation. One has to consider this when comparing the rather

conflicting results presented by various authors.

Mardones *et al.* [19] demonstrated with their cross-breeding experiments with albino rats the strong positive correlation ($r = +0.416$) between the alcohol consumption of parents and their offspring. They divided the parents into four groups according to alcohol consumption. This method does not correspond to present day methods in genetic biometry, so it is not possible to carry out a real genetic analysis of the material or draw any conclusions. Later Mardones [18] published another paper where he described how he developed two strains of rats differing in their consumption of alcohol. A genetic analysis of these strains was never carried out, although Mardones with his collaborators did many extensive comparative studies with these animals. McClearn and Rodgers [20] investigated the preference for 10 percent ethanol in mice of two inbred strains (C57BL/Crgl and A/Crgl) and in F_1, F_2 and backcross generations derived from them. They described only the distribution of the drinking behaviour, but later Brewster [1] completely reanalysed the same material biometrically. He demonstrated that the summative additive effect (d) assumed a value of 0.16 which was significantly greater than zero ($p < 0.001$), thus, confirming the polygenic mode of inheritance. He estimated the heritability, which came to 82 percent indicating that over 80 percent of the variation in ethanol preference in the strains was due to genetic factors.

Correspondigly Fuller [13] performed a genetic analysis of ethanol preference using four inbred mouse strains (C57BL/6J, C3HeB/FeJ, A/J and DBA/2J) and F_1 hybrids derived by crossing the strains non-reciprocally in a half-diallel cross. Brewster [1] reanalysed the material biometrically and showed that the ratio of the additive genetic variance to the total phenotypic variance is high, 86 %, and the average dominance ratio assumes the value of 0.67, confirming that dominance was incomplete. Further analysis confirmed that non-allelic interaction was absent and that there was some dominance, the parental strains differing in the frequency of dominant alleles.

Eriksson [7] has published an experiment, where by outbreeding selected two genetically different lines of rat, marked differences in alcohol consumption between the sexes and the strains were evident by the eight generation. Selection was reflected in the regression coefficient 0.75 which accounts for 66 % of the total variance. The heritabilities differed significantly in the two sexes, heritability coefficient (h^2) for the males being 0.26 and for the females 0.37. Eriksson [9] has further studied by cross-breeding experiments the influence of parents of different sexes to the alcohol consumption of the offspring, and found the correlation between parents and offspring to be 0.40 ($p > 0.01$), but this correlation exists mainly between the mothers and their female offspring. Eriksson and Pikkarainen [12] studied the alcohol consumption of two inbred mouse strains (C57BL and CBA). Strain differences in voluntary alcohol consumption explained 69.4 percent of the total variance of the males, and 94.2 percent of that of the females; which indicates that the genetic strain differences are more pronounced in females. Brewster [1] made a genetic analysis of preference for 5 percent alcohol in a free-choice situation by means of a 2×2 diallel cross involving the Maudsley Reactive (MR) and non-reactive (MNR) rat strains and an F_1 generation derived by reciprocally crossing rats of the two strains. In defining the phenotype Brewster applied both the alcohol preference score. The genetic mechanism governing voluntary alcohol intake emerged as an additive polygenic system with a high heritability, 71 %, and a complete dominance 0.97 in the direction of high ethanol intake. Preference scores gave a similar picture but with no dominance.

Eriksson [10] has recently studied alcohol consumption of inbred mouse strains and their F_1, F_2 and F_3 offspring and backcrosses B_1 and B_2 in a free-choice situation, during which the drinking behaviour was motivated by adding 0.0034 % of crystalline saccharine to the alcohol solution and in addition 0.002 % of quinine sulphate to the water. Biometrical analysis showed a striking dominance in the males ($d = 1.1$) to the non-drinking direction with slight

overdominance. In females the dominance was partial ($d = -0.53$). The fact that offspring of C57BL have higher alcohol preference caused significant difference ($t = 6.1$; $p \times 0.001$) between the F_1 offspring of reciprocal crosses. Estimation of heritability showed that in the males 74 % and in the females 92 % of the variance in ethanol consumption is due to genetic factors. The most striking point was that the segregating units were indicated to be strongly coupled as demonstrated by the F_1, F_2 and F_3 generation means. Thomas [29] has compared the C57BL and DBA mouse strains and their F_1 and F_2 hybrides as well as their backcrosses as to their ethanol consumption when the ethanol was offered in 8 different concentrations in a certain order. According to the results it would seem that the offspring are intermediate, but no genetic analysis was carried out.

Many authors have considered that the sexes are equal as to their ethanol consumption [1, 13, 27]. In these studies the preference score has been used as a measure of the phenotype. Eriksson [7] and Eriksson and Malmström [11] have demonstrated with rats that the females drink more ethanol per unit of body weight than the males. Eriksson and Pikkarainen [12] have also found in inbred mouse strains that the females of the drinker strain C57BL consumed more alcohol than the males. Brewster [2] has also shown that female rats (of the RHA, RLA and RCA strains) drink more alcohol than the males. Eriksson states that higher alcohol consumption of the female rats can be demonstrated only in those strains which have a high preference reading.

Experiments have also shown that the drinker strains are less homogeneous as to their phenotype than the non-drinking strains. Most authors [1, 13, 27] have come to the conclusion that the genetic mechanism regulating alcohol consumption is polygenic and additive. Some crossbreeding experiments with inbred mouse strains have produced a dominance in the non-drinking direction [10, 27], whereas other experiments have produced a similar dominance in the drinking direction [1, 13]. This indicates that the loci in different strains vary as to their strength. Similarly it has been demonstrated [10] that there exists a linkage. It has also been found that at least some strains show a clear sex difference and that a part of the factors influencing drinking behaviour are sex-linked. On the other hand it has been shown rather consistently that the ratio of genetic variance, the heritability, is high in both mice and rats. But it seems also evident that depending on the species and strains there may be several genetic mechanisms regulating alcohol intake in the test animals. This is in accordance with those studies which show that animal strains differing in their behaviour also differ in consumption of ethanol (Brewster) [2], as well as those which state that animal strains with different drinking habits also differ in general behaviour (Poley *et al.* [24] and Royce *et al.* [28]).

Studies on Human Beings

When considering how important a social political and national economical problem alcoholism is, its etiology has been studied relatively little. Particularly scant is research in the part played by hereditary factors in the etiology of alcoholism. A research in this field would seem most naturally done by means of the classical twin to find twin populations stable and representative enough. The Scandinavian countries, where people are less mobile, are fairly well suited for this purpose and almost the only twin studies fulfilling the requirements of biometries have been carried out in Scandinavia.

Kaij [16] made a rather extensive twin study in Sweden. The author defines chronic alcoholism as based solely upon three criteria, a) a pathological desire for alcohol, b) a physical dependence on alcohol, and c) the occurrence of black-outs during intoxication. The author's sample consists of 214 consecutive probands from the official registers of abusers of alcohol in two southern Swedish counties. The probands were members of 174 male twin pairs born between 1890-1939, of which 48 were monozygous (MZ) and 126 dizygous (DZ). The author personally examined 292 twins in their homes. In addition, 32 of

the MZ pairs were subjected to psychometric testing. The twins were divided into 5 classes of drinking habits based upon a) information obtained from the official registers, and b) information supplied by personal examination. 54.2 % of the MZ probands had partners who were also probands as compared with 31.5 % of the DZ probands. By the method of using degrees of concordance and discordance it is shown that MZ pairs had significantly more similar drinking habits than DZ pairs, both according to official information and to the compound classification. With some reservation the results were regarded as a support of an assumption that drinking behaviour is influenced by genetic factors and that such factors greatly determine the appearance of chronic alcoholism. The intrapair comparison of the test performance of the MZ twins did not demonstrate any convincing signs of intellectual deterioration in the twins who had more advanced drinking habits than their co-twins. Further, no clinical diagnosis including organic mental defect proved to be related to more advanced drinking habits by intrapair comparison.

Recently Partanen, Bruun and Markkanen [23] published a very extensive and versatile twin study where they tried to answer the question: To what extent can variations in drinking behaviour and in alcoholism be attributed to variations in genetic factors and to what extent to environmental factors? The subjects studied comprised 902 Finnish male twins of 28 to 37 years of age. Probably this is the largest sample ever employed in a twin study. Zygosity diagnosis was based on a combination of 10 anthropological measures and serological analysis. 172 of the twins were found to be monozygous (MZ) and 557 dizygous (DZ). The authors state clearly the weaknesses involved in the zygosity determination and indicate the magnitude and type of errors introduced as a result. Much information was obtained respecting the consumption of alcoholic beverages, and of cigarettes and coffee, taste preference, diet, the social psychological aspects of the relationship between twins and a great variety of other personal and demographic characteristics. A personality descriptions and a number of intelligence tests were also made. The quantifiable drinking variables were: Density, Amount and Lack of control.

Density is a factor expressing indicators of frequency of drinking and amount reflects the quantity of alcohol consumed per drinking occasion. Lack of control is a factor felt to be roughly equivalent to dependency on alcohol.

Partanen, Bruun and Markkanen [23] sum up the most important findings into the following points. Of the drinking variables, Frequency and Amount show significant heritability, $H = 0.27$. Lack of Control and Social Complications seem to be predominently environmentally determined. A linear combination of Amount and Lack of control, and to a lesser degree, of Density, has a considerably higher heritability than any of the single drinking variables. Further, their data suggest that the choice of the population noticeably affects the magnitude of heritability estimates. Consistently higher heritabilities were obtained among the younger pairs than among the older in personality and drinking variables, with the exception of Amount. There seem to be no hereditary connections between heavy use of alcohol on the one hand, and consumption of coffee, tobacco or taste preferences on the other. Various environmental factors were found to be associated with magnitude of pairwise MZ differences in density and lack of control. Amount seems to be relatively independent of the variables studied.

Popham *et al.* [26] has criticised the basic assumptions when estimating heritability by saying: "Physical differences evoke different responses on a cultural basis. To take a necessarily oversimplified example, in American society there is a general tendency to negatively value small size and positively value large size. Such interactions between physical characteristics and social attitudes will tend towards concordance in the treatment of MZ twins and discordance in DZ twins even when the pairs are reared apart [11]. Undoubtedly one may speculate like this, but that - contrary to the opinions expressed by Popham later in his paper,- diminishes the importance of twin studies. Probably the genetic-environmental inter-

action presented by Popham is less important than most other environmental factors which may be clearly estimated.

On the basis of the studies referred to above it seems obvious that alcohol consumption in both laboratory animals and man is at least partly regulated by a hereditary mechanism. Future research must concentrate on an accurate precising of the genetic models and the connecting of drinking behaviour to other behaviour components. Nichols and Hsiao [22] have succeeded in selecting two rat strains on the basis of their susceptibility to morphine addiction, and to show, that the strain susceptible to morphine is spontaneously also more susceptible to alcohol addiction than the other strain avoiding morphine. This finding may suggest, that the general structure of the CNS and its susceptibility to drug dependence is genetically determined.

SUMMARY

Since the beginning of the 1950's genetic alcohol research has grown into an important field of biological alcohol research. Modern methods of genetic biometry enable us to analyse the genetic background of drinking behaviour of test animals. One may estimate the share of genetic variance, dominance ratio, heterosis, overdominance and maternal effect by cross-breeding experiments, as well as estimate the number of relevant hereditary factors. The author cites studies which deal with problems concerning definition of phenotype, and he claims, that the best measure of drinking behaviour is the amount of alcohol consumed per unit of body weight.

Most of the experiments were carried out with inbred mouse strains, and these experiments show that approx. 70-90 % of the variance in drinking behaviour is of genetic origin. Cross-breeding experiments have shown that the factors influencing heredity are additive. Some authors have found a dominance in the drinking direction, others in the non-drinking direction. Experiments with rats have also shown that there exists a clear genetic component, although its share of total variance is smaller than in mice. Drinking habits of laboratory mammals seem to be regulated by several hereditary mechanisms which are different in different strains. There are also references to sex differences in drinking habits, which indicate that heredity may be sex-linked.

Some studies on humans with monozygous twins suggest that drinking behaviour is partly genetically regulated. The provisions and reservations stipulated by the material are dealt with. Finally the author expresses an opinion of a more general genetic susceptibility to drug-dependence.

RESUMEN

Desde 1950 las investigaciones genéticas relacionadas con el alcohol se han transformado en un importante campo de investigación biológica. Modernos métodos de biometría genética nos permiten analizar el "background" genético del comportamiento resultante del consumo de alcohol en animales de experimentación. Puede estimarse la cuota de variación genética, las relaciones de dominancia, la heterogeneidad, la sobredominancia y el efecto maternal y la cantidad de factores hereditarios importantes. El autor cita estudios dedicados a problemas relacionados con la definición del fenotipo y sostiene que la mejor manera de medir el comportamiento resultante del consumo de alcohol es determinar la cantidad de alcohol consumido por unidad de peso del cuerpo.

La mayoría de los experimentos fueron realizados en la familia de ratones y los resultados obtenidos indican que un 70-90 % de la variación en el comportamiento es de origen genético. Los experimentos de cruza han demostrado que los factores que influencian la herencia son complementa-

rios. Algunas experiencias evidencian una dominancia en el sentido de la ebriedad, otras en el sentido contrario. Los experimentos realizados en ratas también demuestran que existe un claro componente genético, pero su proporción dentro de la variación total es menor que en ratones. El hábito de la bebida en mamíferos de laboratorio parece ser regulado por mecanismos hereditarios que difieren en las diversas familias. También surgen referencias a las diferencias de sexo relacionadas con el hábito de la bebida que indican que la herencia podría estar relacionada con el sexo.

Algunos estudios realizados en seres humanos con mellizos monozigotas y dizigotas sugieren que el comportamiento de las personas adictas a la bebida está en parte regulado genéticamente. Se exponen las condiciones establecidas para el procesamiento del material. Finalmente el autor expresa su opinión, según la cual habría una mayor predisposición hereditaria con respecto a la dependencia de las drogas.

RÉSUMÉ

Les facteurs génétiques dans le comportement de consommation de l'alcool.

Depuis le début de 1950 les recherches génétiques de l'alcool ont joué un rôle important dans les recherches biologiques de l'alcool. Les méthodes modernes de la biométrie génétique donnent la possibilité d'analyser chez les animaux de laboratoire le fond génétique du comportement de consommation de l'alcool. A l'aide de croisements expérimentaux on peut calculer le degré de la variation héréditaire, les relations de la dominance, hétérogéneité ou sur dominance, l'affectation maternelle et estimer la quantité des facteurs héréditaires importants. Sont exposées des recherches concernant des questions se reliant á la définition du phénotype et on présente le point de vue, que la meilleure mesure du comportement de la consommation est la quantité d'alcool consommée par unité de poids du corps.

La plupart des expériences a été faite avec des lignées de souris procrées intérieurement, ces expériences démontrent, qu'à peu près 70-90 % de la variance du comportment de consommation est génétique. On a démontré avec des croisements expérimentaux, que les facteurs influençant l'hérédité sont de genre additif. Certaines recherches démontrent la dominance vers l'ivrognerie et d'autres vers la tempérance. On a aussi démontré avec des expériences faites avec des rats l'existence d'un clair composant héréditaire, quoique sa part dans la variance totale est plus petite que chez les souris. Chez les mammifères de laboratoire de nombreux mécanismes héréditaires semblent réglementer la consommation, ils diffèrent selon les lignées. On a aussi exposé les constatations sur les différences de consommation entre les sexes, qui indiquent la transmission héréditaire liée au sexe.

On expose aussi des recherches se basant sur la comparaison faites entre des hommes jumeaux monozygotes et dizygotes. En vertu de ces recherches le comportement de la consommation partiellement génétique semble clair. On expose les conditions établies par le traitement du matériel. Pour finir on présente un point de vue de la plus commune prédisposition héréditaire a l'égard de la dépendence de drogues.

ZUSAMMENFASSUNG

Genetische Faktoren beim Alkohol-Trinkverhalten.

Die genetische Alkoholforschung ist seit 1950 ein wichtiges Gebiet in der Alkoholforschung geworden. Die heutigen Methoden der genetischen Biometrik geben die Môglichkeit den genetischen Hintergrund des Trinkverhaltens an Versuchstieren zu analysieren. Durch Kreuzungsversuche kônnen die Mengen der erblichen Varianten, die Dominanzkoeffizienten, Heterosis oder

Superdominanz und der mütterliche Effekt bestimmt werden, man kann auch die Mengen der wirkenden Erbfaktoren schätzen. Es wird über Untersuchungen berichtet, bei denen man Fragen behandelt die mit der Phänotypenbestimmung zusammenhängen, weiter wird die Ansicht vorgebracht, dass das beste Mass des Trinkverhaltens die getrunkene Menge/Körpergewicht ist.

Grösstenteils sind die Tierversuche mit Inzucht-Mäusestämmen durchgefuhrt worden, und sie zeigen, dass ca. 70-90 % der Varianz des Trinkverhaltens genetischen Ursprungs ist. Durch Kreuzungsversuche hat man gegeigt, dass die die Genetik beeinflussenden Faktoren additiver Natur sind. Einige Versuche zeigen Dominanz in Richtung Trunksucht, andere wieder in Richtung Abstinenz. Auch mit Rattenversuchen hat man das Vorhandensein einer deutlichen erblichen Komponente gezeigt, obwohl ihr Anteil an der Totalvarianz kleiner ist als bei Mäusen. Es erscheint, dass das Trinken bei den Laboratoriumsäugetieren von vielen genetischen Mechanismen geregelt wird, die unterschiedlich sind bei verschiedenen Stämmen. Es ist auch über die festgestellten Unterschiede beim Trinkverhalten der beiden Geschlechter berichtet worden, welche auf eine geschlechtsgebundene Genetik hinweist.

Auch über an Menschen durchgeführte Untersuchungen, die sich auf das Vergleichen der monozygotischen und dizygotischen Zwillinge gründen, wird Bericht erstattet. Auf Grund dessen scheint eine genetisch bestimmte Trinkgewohnheit eine Tatsache zu sein. Über die Bedingungen die die Behandlung des Materials voraussetzt wird berichtet. Zum Schluss wird die Ansicht über eine allgemeine erbliche Bereitwilligkeit bezüglich Drogensucht ausgesprochen.

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The General and Intermediary Metabolism of Ethanol

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Abbreviations

AcH — Acetaldehyde
ADH — Alcohol dehydrogenase
DHAP — Dihydroxy acetone phosphate
GP — Glycerol phosphate
GPD — Glycerophosphate dehydrogenase

The manner in which alcohol is absorbed, distributed, and metabolized has been reviewed previously,[30] and this paper focuses only on the more recent contributions. The alcoholic fatty liver has been reviewed recently [12] and is not included. References have been restricted to review articles or to the latest paper in any series which cites the earlier literature; unfortunately such a restricted bibliography often fails to credit the original investigators properly. The words alcohol and ethanol are used interchangeably.

Metabolism of Ethanol

Pathway of Alcohol Metabolism.

The accepted pathway for alcohol metabolism is: Ethanol acetaldehyde acetic acid, and a further metabolism of the latter as acetyl CoA through well-established normal pathways. Animal tissues contain several enzymes which utilize acetaldehyde (AcH) as a substrate in vitro, but none of these alternate reactions has been implicated in alcohol metabolism in vivo. The most recent addition to this list is a condensation-decarboxylation reaction between *a*-ketoglutarate and AcH to form 5-hydroxy-4-ketohexanoic acid.[24] This reaction was discovered originally by following the fate of labeled alcohol in liver homogenates [1] and the reaction does take place in vivo in the presence of high concentrations of AcH.[31] However, it cannot be detected during alcohol metabolism in vivo, [31, 32] and the fate of the alcohol carbons generally parallels acetate metabolism.[1] At present there is no substantial evidence for an alternate pathway of alcohol metabolism. The small differences in the rate of CO_2 formation from alcohol and acetate in the intact rat [22] may be due to an inhibition of acetate metabolism by the liver during alcohol metabolism [17] whereas no such inhibition occurs when acetate alone is administered.

Oxidation of Alcohol to AcH.

The slowest reaction in the metabolism of alcohol is its oxidation to AcH by alcohol dehydrogenase (ADH), primarily in the liver. Von Wartburg [27] has found an atypical ADH in 20% of the Swiss and 4% of the English population which is more active than the normal ADH and has a lower pH optimum. Chemical modification of the amino groups at the active site of horse liver ADH produces a more active enzyme.[20] Livers containing the atypical ADH oxidize alcohol 5 - 6 times faster in vitro than normal, while individuals with the atypical ADH in their livers oxidize alcohol 40 - 50 % faster than do normals.[27] ADH is not a typical adaptive enzyme since its activity is increased relatively little if

at all by the administration of alcohol, [9, 11] and the chronic administration of alcohol has only a relatively small effect on the rate of alcohol metabolism in vivo. [9, 18]

Alcohols can also be oxidized to aldehydes in vitro by catalase plus H_2O_2 as well as by the microsomal drug metabolizing enzymes. The adaptive increase in this microsomal system following alcohol administration [11] explains the increased tolerance to barbiturates by alcoholics, but the participation of this system in alcohol metabolism in vivo is not yet clear. The oxidation of ethanol by the microsomal system does not seem to account for much of the alcohol metabolized by a normal animal, but it may be responsible for the increased rate of alcohol metabolism sometimes observed in chronic alcoholics.[11]

Oxidation of Alcohol by the Liver.

The end product of alcohol metabolism in the liver seems to be acetate since: 1) the amount of acetate leaving the liver is more than 50 to 80 % of the amount of alcohol being oxidized [14, 33] and 2) between 75 and 100 % of the O_2 consumed by the liver is required to oxidize the alcohol to acetic acid. [4, 14] There is little or no formation of CO_2 from alcohol in the liver, and the production of all CO_2 by the liver practically ceases during alcohol metabolism. [4, 23] Citric acid can be formed, but its oxidation by the liver is inhibited 75 % during alcohol metabolism; [33] in the absence of a functional citric acid cycle the acetate cannot be oxidized further. The liver acetyl CoA and ATP concentrations are maintained normally during alcohol metabolism. [33] Presumably the oxidation of alcohol hydrogens through the respiratory chain provides adequate energy for the liver in the relative absence of a citric acid cycle.

The mechanism by which the DPNH, formed in the cytosol during alcohol metabolism, passes its electrons to the respiratory chain in the mitochondria remains obscure. Presumably another substrate accepts the hydrogens from DPNH in the cytosol, and the reduced substrate passes into the mitochondria where it is then reoxidized by a mitochondrial enzyme. All of the substrate pairs which might function as such a hydrogen shuttle (lactate/pyruvate; GP/DHAP; malate/oxalacetate; *B*-hydroxybutyrate/acetoacetate) become more reduced during alcohol metabolism, [7, 33] and all might participate in the transport of hydrogens into the mitochondria to varying degrees. The hydrogens from alcohol seem to flood all systems capable of reacting with DPNH.

While the oxidation of some substrates by isolated mitochondria is inhibited by alcohol, it should be emphasized that such in vitro studies differ from the conditions in vivo in at least two important ways. 1) Since isolated mitochondria do not oxidize alcohol, the electron transport chain is not preempted in vitro by hydrogens coming from alcohol, and 2) some in vivo effects of alcohol may be due to AcH rather than alcohol.

Oxygen tension in the liver is normally low, and the rate of alcohol metabolism by a perfused liver is much higher when the perfusing blood is completely oxigenated.[5] This suggests that the rate of alcohol metabolism in the intact animal may be determined by the O_2 supply to the liver as well as by such factors as ADH activity and hydrogen transport mechanisms. Hepatic blood flow is unaffected or increased only slighty by alcohol,[14] and the total O_2 consumption by the liver is unchanged during alcohol metabolism. [14] The increased rate of alcohol metabolism which is produced by fructose administration [25] has been attributed to biochemical effects on hydrogen transport within the liver cell, but it may also be due to the 30 % increase in hepatic blood flow and the 60 % increase in hepatic O_2 consumption which is produced by the fructose. [25]

A most impessive 4 to 5-fold increase in the rate of alcohol metabolism is found in patients with a genetic glucose-6-phosphatase deficiency.[27] If the normal individual utilizes most of the oxygen supplied to the liver to oxidize alcohol to acetic acid, then such a major increase in the rate of alcohol metabolism must involve either: 1) a greater oxygen supply to the liver; 2) a very effective coupling of the oxidation of al-

cohol with the reduction of some other substrate, and the reoxidation of the other substrate extrahepatically; or 3) the oxidation of alcohol itself extrahepatically. In the absence of glucose-6-phosphatase, excess glycogen accumulates in the liver and blood pyruvate is elevated. The high rate of alcohol metabolism in such patients might be attributed to an increased production of pyruvate by the liver and a concomitant coupling of the oxidation of the alcohol with a reduction of the pyruvate. However, an increased oxygen supply to the liver is also possible. Whether the excess liver glycogen could be reduced in such patients by feeding alcohol has not yet been determined.

Congeners. [6]

The biological effects of different alcoholic beverages have traditionally been attributed to the ethanol content alone, but recent studies have demonstrated that the congeners in some beverages also have biological effects. The higher alcohols are more intoxicating than ethanol, [28] and they affect some metabolic reactions in the same way as ethanol but at much lower concentrations; the congeners in bourbon also produce electroencephalographic changes.

Metabolic Alterations Produced by Alcohol

If we assume that all of the oxygen consumed by the liver during alcohol metabolism is used to oxidize alcohol to acetate, the immediate consequences of alcohol metabolism on other liver functions should be profound. Theoretically: 1) no O_2 would be available to metabolize any substrate other than alcohol and AcH; 2) the citric acid cycle would stop functioning; 3) the respiratory chain would be fully utilized in oxidizing the hydrogens from ethanol and AcH; 4) all of the acetate produced by the liver would be metabolized further by other tissues; and 5) oxidative reactions involving fatty acids, amino acids, carbohydrates, etc., in the liver would be suspended until most of the alcohol had been removed. Anaerobic reactions and reductive processes could continue and possibly be intensified.

The effect of alcohol metabolism on other metabolic reactions in the liver is not as extreme as pictured above, but there is undoubtedly a shift toward reductive processes for other substrates while alcohol is being oxidized. Numerous laboratories [4, 14, 23, 33] have found an increased lactate/pyruvate and *B*-hydroxybutyrate/acetoacetate ratio during alcohol metabolism. These changes presumably reflect a similar increase in the DPNH/DPN ratio [33] but not TPNH/TPN. Fatty acid oxidation is inhibited while the reductive process of fatty acid synthesis is enhanced by alcohol. [2] Biogenic amines are normally deaminated, and the resulting aldehyde is further oxidized to the corresponding acid; in the presence of ethanol metabolism the biogenic aldehyde is reduced to its corresponding alcohol.

The metabolic alterations produced in the liver by alcohol metabolism could be expected to occur at relatively low alcohol concentrations. The Km for the oxidation of alcohol by man in vivo [15] is 2 mM (0.009 %), and the rate of alcohol metabolism is relatively linear above 0.04 %. [26] The concentration of acetate in blood during alcohol metabolism is also independent of higher blood alcohol concentrations. Hence the rate of oxidation of alcohol to acetate by the liver is already maximal at no more than 40 mg % blood alcohol, so that higher blood levels would prolong the effect without intensifying it. Except for the liver and possibly the kidney, other tissues lack the ADH enzyme and are unable to oxidize significant amounts of alcohol; tissues lacking ADH would not be expected to have a strong "reducing atmosphere" during alcohol metabolism. However, they are affected by the events occurring in the liver; heart muscle, for example, utilizes more acetate and lactate but less free fatty acids during alcohol metabolism.

Carbohydrate Metabolism.

Lundquist [13] has reviewed the metabolism of carbohydrate under the influence of eth-

anol. The utilization of galactose is decreased 50 % during alcohol metabolism, and this is attributed to an inhibition by DPNH of the enzyme which converts UDP-galactose to UDP-glucose. One-half of the fructose molecule normally is converted via glyceraldehyde (and presumably glycerate) to lactate and pyruvate. In the presence of alcohol, the formation of lactate and pyruvate from fructose is reduced markedly, glucose formation is increased correspondingly, and small quantities of sorbitol are formed. Conversely, the oxidation of sorbitol to fructose is inhibited by alcohol.[8] The alteration in fructose metabolism is attributed [13] to an inhibition of the oxidation of glyceraldehyde to glycerate by the same DPN-requiring enzyme which is involved in oxidizing AcH to acetate. Clearly the oxidative steps in fructose metabolism are inhibited during alcohol metabolism, and the glyceraldehyde moiety (as well as the DHAP) can be converted to glucose without any oxidative steps being involved.

Glycerol metabolism by the liver is slowed by alcohol, and GP accumulates more than it does from the administration of glycerol alone. [21, 34] GP also accumulates in the liver during alcohol metabolism in vivo or in liver slices, and this is intensified by the simultaneous addition of fructose [25] or glycerol. [21] The GP can be formed under these circunstances from fructose [10] or endogenous glucose by the reduction of DHAP with DPNH; [34] it can be formed from glycerol by a simple phosphorylation with ATP. However, the removal of GP requires an oxidation to DHAP by the mitochondrial GPD. During alcohol metabolism the respiratory chain in liver mitochondria is largely preempted by the oxidation of hydrogens from alcohol and AcH, and the GP therefore accumulates.

Thyroxine treatment increases the activity of the mitochondrial GPD enzyme. and this prevents the alcoholic inhibition of glycerol metabolism as well as the accumulation of GP, [21, 34] but it does not affect the rate of alcohol metabolism.[21] Presumably, the increased GPD activity after thyroxine allows more of the GP hydrogens to be oxidized by the respiratory chain in competition with the hydrogens coming from alcohol. If the total oxidative capacity of the respiratory chain or the total O_2 supply to liver is not increased by thyroxine, the rate of alcohol metabolism cannot be increased by thyroxine. The rate should theoretically be decreased by the competition with GP, but it would be unchanged if the hydrogens utilized to form GP from DHAP came initially from the alcohol or AcH. Dihydroxyacetone can be metabolized to GP, and this reductive process is increased during alcohol metabolism. [10] The increased availability of GP may also contribute to the alcoholic fatty liver since it is required for the synthesis of triglycerides and phospholipids.

Hypoglycemia and Gluconeogenesis.

Alcohol inhibits gluconeogenesis as well as the conversion of glycogen to glucose and would therefore, be expected to produce hypoglycemia.[16] Children and fasting adults are susceptible to alcoholic hypoglycemia, but well-fed adults maintain their blood sugar following alcohol administration. Plasma insulin levels are relatively normal during alcoholic hypoglycemia, and the lack of a glucagon response suggest a deficiency in liver glycogen. The effect is, therefore, obtained when liver glycogen stores are low and the rate of gluconeogenesis in the presence of alcohol is too slow to meet the peripheral requirements for glucose.

Ethanol inhibits glucose formation in liver from many substrates; the degree of inhibition varies with the experimental conditions and the species studied. The results are consistent with a partial block in the oxidation of other substrates during alcohol metabolism. For example, the conversion of lactate (but not pyruvate) to glucose is inhibited 65-70 % during alcohol metabolism [7, 10] because the lactate cannot be oxidized as readily to pyruvate. [10] When the oxidation of alcohol is minimized by pyrazole or the use of a tissue with little ADH activity (kidney), the alcohol no longer inhibits gluconeogenesis from lactate. [10] A relatively small (25-30 %) inhibition of gluconeogenesis from serine and alanine [7, 10] can be attributed to a conversion of more

of the pyruvate formed from these substrates to lactate instead of to glucose.[10] GP accumulates when dihydroxyacetone or glycerol is administered during alcohol metabolism and the decreased gluconeogenesis from these substrates can be attributed to a slower oxidation of this metabolite.

A controlling step in the conversion of pyruvate to glucose is the reduction of 3-phosphoglycerate to 3-phosphoglyceraldehyde (the only redox step in the process). In the absence of alcohol, an excess of pyruvate can compete with the 3-phosphoglycerate for available hydrogens (3-phosphoglycerate accumulates and metabolites beyond this step decrease) and thus inhibit its own conversion to glucose to the point where it is a less effective substrate than lactate; such an inhibition can be reversed by supplying additional hydrogens from alcohol metabolism.[7] With lactate as substrate in the presence of alcohol the 3-phosphoglycerate is reduced readily,[7] but the initial oxidation of lactate to pyruvate is also inhibited and the overall conversion of lactate to glucose is, therefore, reduced. Hence the effect of alcohol metabolism on gluconeogenesis is consistent with and explained by a reducing atmosphere in the liver.[30]

Alcohol Effects on Brain

Since alcohol is not oxidized by brain, any effect that it exerts in this organ cannot be attributed to a shift toward reductive metabolic pathways. Wallgren has recently reviewed the biochemical effects of alcohol in the central nervous system,[28] as well as the possible mechanism by which alcohol produces its intoxicating effect.[29] The most striking conclusion from all of these studies is that alcohol has relatively little effect on any of the biochemical parameters studied so far, and that high concentrations of ethanol (e. g., 0.4 % or more) are often required to elicit any effect at all. This emphasizes the fact that intoxicating levels of alcohol per se do not disrupt the normal metabolic pathways in the brain in any major way. It is the metabolism of alcohol rather than the alcohol per se which modifies liver metabolism and probably produces liver damage. Conversely it is the alcohol per se, rather than any metabolism of the alcohol, which is probably responsible for the intoxicating effects in the brain.

Small amounts of AcH reach the brain via the bloodstream, and it is possible that the effects of alcohol on brain function are really due to AcH. The major reasons for a skeptical approach to a key role for AcH in producing intoxication are: 1) blood levels of AcH required to produce intoxication are much higher than are obtained during alcohol metabolism and this is especially true in the dog where very low levels of AcH are maintained in the blood even though the dog is obviously intoxicated; 2) the relative pharmacological effectiveness of a series of aldehydes with increasing chain length does not parallel the corresponding alcohols;[29] 3) blood AcH levels do not parallel blood alcohol levels or the symptoms of intoxication.[28]

If the effect of alcohol on brain function is really due to alcohol per se, rather than to AcH or to a major effect on brain metabolism, then the alcohol must exert some kind of biophysical effect. The most obvious possibility is an effect on the neuronal or synaptic membrane, i. e., an orientation of the alcohol molecule with respect to the polar and non-polar layers in such a way that the normal control of ion transport is mildly disrupted.[29] Pauling[19] has proposed a theory of anesthesia in which the chemically unreactive (non-hydrogen bonding) type of anesthetic forms hydrated microcrystals (clathrates) with water molecules in the brain. These microcrystals are stabilized by trapping charged protein side-chains and solute ions and they prevent the free movement of ions and other molecules. This in turn decreases the conductance of the electrical network and restricts the electrical activity of the brain to an unconscious state even though the exciting mechanism continues. Pauling further proposed that the narcosis resulting from the cooling of the brain results from a stabilization of natural clathrate structures at low temperatures (27°C), and that Mg ++ acts as an anesthetic by participating in and stabilizing the hydrogen bonded framework of such microcrystals. Alcohol would also be

expected to participate in the hydrogen bonded framework of hydrated microcrystals. In ways yet to be established, alcohol seems to interfere with the orderly arrangement of ions in and around membranes - mildly at intoxicating levels and more severely at narcotic levels.

SUMMARY

The only known pathway for the metabolism of alcohol in the intact animal is via acetaldehyde to acetic acid, and the latter is the end product of alcohol metabolism in the liver. While the microsomal drug metabolizing enzymes are increased by the administration of alcohol, they are not primarily responsible for the oxidation of alcohol. The oxygen supply to the liver may be a limiting factor in determining the rate of alcohol metabolism, and most of the oxygen consumed by the liver during alcohol metabolism is used to oxidize alcohol to acetate. This markedly curtails the metabolic activity of the citric acid cycle in the liver, increases the DPNH/DPN ratio, and causes a shift toward reductive processes for other substrates while alcohol is being oxidized. This in turn inhibits the utilization of galactose and glycerol and alters the metabolism of fructose by the liver. Alcohol metabolism provides additional hydrogens for the reduction of 3-phosphoglycerate to 3-phosphoglyceraldehyde in the process of gluconeogenesis, but it also prevents the oxidation of and/or causes the reduction of some gluconeogenic substrates and thereby inhibits the conversion of such substrates to glucose. Hygpoglycemia results when liver glycogen is depleted and gluconeogenesis is inhibited by the alcohol.

In contrast to the liver, alcohol is not oxidized by the brain, and there is no well-defined disruption in metabolic pathways in this organ. It is the metabolism of alcohol (rather than the alcohol itself) which modifies liver metabolism, while it is the alcohol per se (rather than alcohol metabolism) which affects the brain. The effect of alcohol on brain function does not appear to be due to acetaldehyde. It can be postulated that alcohol physically modifies the membrane and/or its immediate environment, but our knowledge is too limited for this to be very meaningful.

RESUMEN

El único mecanismo conocido del metabolismo del alcohol en el animal intacto, transforma el acetaldehido en ácido acético, siendo este último el producto final del metabolismo del alcohol en el hígado. En tanto que las enzimas microsómicas que metabolizan las drogas son aumentadas por el consumo de alcohol, no son fundamentalmente responsables de la oxidación del alcohol. El oxígeno que llega al hígado puede ser un factor que limite la determinación del ritmo del metabolismo del alcohol y la mayor parte del oxígeno consumido por el hígado durante el metabolismo del alcohol es utilizado para oxidar el alcohol transformándolo en acetato. Esto limita significativamente la actividad metabólica del ciclo del ácido cítrico en el hígado, aumenta la relación de DPNH/DPN y da lugar a un empuje reductivo de otros procesos mientras se produce la oxidación del alcohol. Esto a su vez inhibe la utilización de galactosa y glicerol y altera el metabolismo de la fructuosa en el hígado. El metabolismo del alcohol proporciona hidrógenos adicionales para la reducción de 3-fosfoglicerato a 3-fosfogliceraldehido en el proceso de glucogénesis; pero también evita la oxidación y/o causa la reducción de algunos sustratos gluconeogénicos inhibiendo así la conversión de estos sustratos en glucosa. La hipoglicemia se produce cuando el glicógeno se agota y la gluconeogénesis es inhibida por el alcohol. Contrariamente a lo que sucede en el hígado, el alcohol no es oxidado por el cerebro y hay una ruptura no

definida de las vías metabólicas en este órgano. El metabolismo del alcohol (más que el mismo alcohol) es lo que modifica el metabolismo hepático, en tanto que el alcohol en sí (más que su metabolismo) es lo que afecta el cerebro. El efecto del alcohol sobre la función del cerebro no parece deberse al acetaldehido. Puede postularse que el alcohol físicamente modifica la membrana y/o sus adyacencias inmediatas pero nuestros conocimientos no nos permiten atribuirle gran significación a este fenómeno.

RÉSUMÉ

Le seul mécanisme connu du métabolisme de l'alcool chez l'animal sain, transforme l'acétaldéhide en acide acetique, ce dernier etant le produit final du métabolisme de l'alcool dans le foie. D'autant que les enzimes microsomiques que les drogues métabolisent sont augmentées par la consomation de l'alcool, ne sont pas responsables fondamentalment de l'oxydation de l'alcool. L'oxygène que arrive au foie peut être un facteur qui limite la determination du rythme du metabolisme del'alcool, et la plus grande partie de l'oxygène absorbé par le foie durant le metabolisme de l'alcool est utilisé pour oxyder l'alcool, le transformant en acetate. Ceci limite d'une façon significative l'activité métabolique du cicle de l'acide citrique dans le foie, augmente la relation du DPNH/DPN et donne lieu a une poussée réductrice des autres processus, pendant que se produit l'oxydation de l'alcool, celui-ci a son tour inhibe l'utilisation de galactose et glicerol et altère le métabolisme de la fructuose dans le foie. Le metabolisme de l'alcool proportionne des hydrogenes additionels pour la reduction de 3-phosphoglycerate a 3-phosphoglyceraldehide dans le processus de glucogenese; mais aussi evite l'oxydation et cause la reduction de quelques substituts gluconeogeniques en inhibant ainsi la transformation de ces dérivée en glucose. L'hipoglycemie se produit quant le glycogène s'épuise et la gluconeogenese est inhibée par l'alcool. Contrairement a ce qui se produit dans le foie, l'alcool n'est pas oxydé par le cerveau et il y a une rupture non définie des voices mètaboliques dans cet organe. Le metabolisme de l'alcool (plus que l'alcool lui même) est ce qui modifie le metabolisme hèpatique, en tant que l'alcool en soi (plus que son metabolisme) est ce qui affecte le cerveau. L'effet de l'alcool sur la fonction du cerveau ne parait pas être du a l'acetaldehide. On peut en deduire que l'alcool physiquement modifie la membrane ou ses adjacences immediates, mais nos connaissances ne nous permettent pas d'attribuer une grande signification a ce phénomène.

ZUSAMMENFASSUNG

Der einzige bekannte Weg des Abbau's von Alkonol beim intakten Tier führt über das Essigsäure. Die Letztere ist das Endprodukt des Alkoholabbau in der Leber.

Während die mikrosomatischen, Drogen abbaunenden Enzyme duch die Zuführung von Alkohol zunehmen, sind sie nicht verantwortlich in erster Linie für die Alkoholoxydation. Das Sauerstoffangebot an die Leber mag ein beschränkender Faktor sein im Sinne der Begrenzung der Alkoholabbaurate und der Grossteil des Sauerstoff, den die Leber während des Alkoholabbau verbraucht, wird benützt um Alkohol zu Essigsäureverbindungen zu oxydieren. Das beschneidet in merklicher Weise die Aktivität des Stoffwechsel des Zitronensäurezyklus in der Leber, vermehrt das DPNH/DPN Verhältnis und verursacht eine Veränderung zu Gunsten von Reduktionsprozessen anderer Substrate während Alkohol oxydiert wird. Das verhindert seinerseits die Verwendung von Galaktose und Glyzerin und verändert den Abbau des Fruchtzucker durch die Leber. Der Alkoholabbau liefert zusätzlichen Wasserstoff für die Reduktion

des Triphosphorglyzerin zu Triphosphorglyzerinaldehyd im Prozess der Glykogenerzeugung, aber dies verhindert auch die Okydation und/oder verursacht die Reduktion von manchen Glykogen erzeugenden Substraten und verhindert dadurch die Verwandlung solcher Substrate in Glukose. Es entstent ein Tiefstand des Blutzucker, wenn das Leberglykogen erschöpft ist, und die Glykogenerzeugung duch den Alkohol vernindert ist.

Im Gegensatz zum Vorgang in der Leber wird Alkohol durch das Gehirn nicht oxydiert und hier-zeigt sich eine nicht gut geklärte Störung der abbauvorgänge in diesem Organ. Es ist der Abbau des Alkohol / mehr als der Alkohol selber / der den Leberstoffwechsel verändert, während es der Alkohol an sich ist / mehr als der Alkoholabbau / der das Gehirn angreift. Die Alkoholwirkung erscheint nicht in der Hirnfunktion weil Essigsäurealdehyd vorhanden ist. Es kann behauptet werden, dass der Alkohol die Membranen und / oder ihre unmittelbare Umgebung physikalisch verändert, aber unsere Kenntnis darüber ist zu beschränkt, um wirklich bedeutungsvoll zu sein.

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Some Biochemical effects of Ethanol on CNS*

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I. INTRODUCTION

It is a well known fact that major part of EtOH research carried out in laboratory animals and humans as well, refers rather to effects, as on liver, kidney and, to a lesser extent, on CNS than to intrinsic mechanisms of physico-chemical, biochemical, or phisiopathological nature. Perhaps it is due to this circumstance that at present it is difficult to formulate a general theory on alcoholism as such. The diversity of results on the effects of EtOH, e. g. on the respiration of nervous tissue, makes it necessary to pose previously certain basic problems of EtOH action on biochemical processes of CNS. Some of these aspects are as follows: (') The form and lapses in which the animal or human organism receives the EtOH. Within the great differences existing in the diverse species, there would exist three forms for the study of EtOH : acute alcoholism produced by the administration of one or more high doses of alcohol; chronic alcoholism in which the effects derive on one hand from the alterations induced by EtOH in important organs of the economy of close functional and biochemical relation with CNS (liver being the most important) and on the other from the effects of EtOH on the brain "per se" and finally lifelong permanent alcoholism where the generations consume exclusively EtOH solution. This last form, which we call "filial" has been studied at our Institute of Experimental Medicine since 1949 and at this time we are working with the 44-45 "alcoholic generations" (which consume 12 % alcohol v/v exclusively). (") Another fact refers to the circunstance that the quality of metabolite or depressant of the alcohol —irrespective of the dose offered to CNS— has not been sufficiently elucidated. A priori, one could assert that EtOH complies with most of the molecular and biochemical requisites to be considered a CNS metabolite; further the confirmed existence of enzymes which handle its oxidation (alcohol-NAD-oxidoreductase) and of its immediate product, the CH_3CHO (aldehyde + NAD –oxidoreductase), as we shall see below. On the other hand, it appears evident that EtOH, same as other alcohols of higher molecular weight, administered at high doses has a depressant action on CNS, i. e. "non-metabolic effects" which would eventually be explained by the high oil water partition coefficient and lipid solubility of these compounds (alcohols). In this respect, Pauling [63] maintained that alcohols and in general toxic matters of CNS could form hydrate microcrystals of the clathrate type, composed of alcohol or depressant molecules with surrounding water and the charged side of proteins which would presumably affect the structure of diverse CNS enzymes and the mobility of certain molecules which vitally integrate the nervous cells, hence the depressant effect.

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A priori, it could be suggested that at low doses EtOH would act as a metabolite in CNS, preferentially in areas such as brain cortex, M. R. F., hypothalamus, cerebellum, to quote only the most explored; the respective neurons and glia cells would have the enzymatic capacity to manage EtOH metabolically" (intracellularly). On the other hand, ethanol at high dose would condition its depressant effect occurring preferentially at membrane level (cellular, mitochondrial, etc.), phenomena which would occur to a lesser extent with low doses. The problem arises when we attempt to determine what is a low dose (perhaps 100 to 120 mg 100 ml of blood, 70 mM), what produces CNS excitement, or what constitutes a high dose (200-250 mg/100 ml blood) that provokes a frankly depressant effect.

This general statement is a mere hypothesis, still awaiting the experimental work for its eventual confirmation or rejection.

Lately, certain important reviews and monographies have been published about general and cellular effects of EtOH, containing neurobiochemical aspects [23, 40, 52, 59, 95, 96, 97, 98, 99].

II. NEUROBIOCHEMICAL STUDIES

Respiratory process

The study of EtOH effect on respiration appears to be basic in an organ as CNS, it being so aerobiotic and glucose-dependent. In this respect various techniques have been used: measuring of O_2 consumption in encephalon "in vivo", thus the findings of Hine et al. [36] and Fazekas et al. [21] show that alcohol levels of 300 mg/ml blood or more, diminish O_2 consumption of the human brain. The "in vitro" studies offer different results depending on the CNS area studied (generally brain cortex), on the quality of slice, "in repose" or "stimulated" (KCl 10 mM or electrically), and on the character of alcoholism: acute, chronic or filial.

In accordance with Quastel and his group [4, 5, 24], Wallgren and his group [54, 88, 89, 90, 92], Sutherland et al. [81], it could be asserted that EtOH at low concentrations (e. g. 20 mM) increases lightly the QO_2 of brain cortex slices "in repose". However when respiration is stimulated by K+ or electrically even in presence of glucose as substrate, EtOH even at the level above mentioned inhibits respiration. In "in vitro" measurings of brain cortex, hypothalamus and cerebellum of "alcoholic generation (38th to 44th) rats", Egaña et al. found a definite decline of QO_2 in Ringer-bicarbonate-11.4 mM or 22.8 mM EtOH; this descent is especially notorius in brain cortex and cerebellum in repose and with highest dose of alcohol [13]. EtOH action "in vivo", in turn has been studied, offered to slices in conjunction with some of the so-called specific subtrates of CNS: glucose, glutamate, *gamma*ABA, pyruvate; Sutherland et al. [11] in acute alcoholism experiments, report an increase of QO_2 in brain cortex even at 56 mM EtOH, having as co-subtrates glucose, glutamate, pyruvate and acetate. During the first 15 minutes of incubation there is an increase which disappears later. Egaña and Rodrigo [73] in experiments "in vitro" in which EtOH is associated to one of the above mentioned co-subtrates have found in the CNS of "alcoholic generations" an increased QO_2 in presence of EtOH + glucose, glutamate or pyruvate with the *gamma*ABA action being less notable, at least in brain cortex and cerebellum. It is to be mentioned that normal animal brain responds differently from that of the alcoholic generation, at equal EtOH concentration; see TABLE I. It should also be stated that what is found in adult CNS is not strictly similar to impuber or newborn CNS, be it normal or of "alcoholic generation". There have been attempts to discover the mechanism through which EtOH acts on neuronal respiration and in this respect the experimental answers are varied: (') the use of [14 C] - ethanol and the study of $^{14}CO_2$ yield gave contradictory results: Sutherland et al. [82] reported that brain slices convert EtOH in CO_2, a statement contradicted by Masoro et al. [55] who disclaim such conversion (brain 0 %, as against liver 15-28 %, kidney 17-29 % of conversion $*EtOH \rightarrow *CO_2$). It should be mentioned that Bartlett et al. [3] stated —21 years ago— that there could occur a first dehydrogenation of the EtOH without completing its

TABLE I

Effect of Exogeneous Substrates on Diverse CNS' areas; adult rats normal and 40th - 41st alcoholic generations: $\frac{mu \text{ atom oxigen}}{mg \text{ protein}}$

Normal	EtOH / glucose D	EtOH / glucose C	EtOH / Glutamate D	EtOH / Glutamate C	EtCH / *gamma*ABA D	EtCH / *gamma*ABA C	EtCH / Pyruvate D	EtCH / Pyruvate C
Brain cortex	2.77 ± 0.71	1.61 = 0.6	2.57 ± 0.9	1.30 ± 0.4	2.07 ± 0.6	1.91 ± 0.8	3.74 ± 1	2.73 ± 0.53
Hypothalamus	3.76 ± 1	1.62 ± 0.36	3.82 ± 1	0.95 ± 0.2	3.82 ± 1	0.9 ± 0.01	2.33 ± 0.4	0.89 ± 0.24
Cerebellum	1.18 ± 0.55	1.08 ± 0.18	1.02 ± 0.15	0.64 ± 0.1	0.79 ± 0.22	0.47 ± 0.01	1.70 ± 0.26	0.90 ± 0.2
40.th - 41.st Alcoholic generation								
Brain Cortex	2.10 ± 0.8	2.04 ± 0.6	2.32 ± 0.5	2.23 ± 0.7	1.27 ± 0.33	2.02 ± 0.81	2.8 ± 0.9	2.65 ± 1
Hypothalamus	1.86 ± 0.7	2.08 ± 0.9	2.10 ±	1 ± 0.3	2.46 ± 0.9	1.63 ± 0.4	2.23 ± 0.5	1.10 ± 0.3
Cerebellum	1.05 ± 0.29	1.18 ± 0.3	0.80 ± 0.2	0.67 ± 0.1	0.79 ± 0.27	0.79 ± 0.3	1.88 ± 0.4	0.99 ± 0.3

Warburg vessel; Ringer - Bicarbonate initial pH 7.5; gas phase O_2 95 % - CO_2 5 %. EtOH : two concentrations *D* = 11.4 *mu* mole / ml incubation medium and *C* = 22.8 *mu* mole / ml. Substrates : glucose 10 mM; glucamate 10 mM, *gamma*ABA 1 mM and pyruvate 10 mM; the substrates were located in the main vessel from the beginning of the experimento "Blanks" EtOH both *D* and *C* with the four substrates respectively, run in each experiment; mean and S. D. Experiments on "impuber" and new born have been also carried out both in normal and "alcoholic generation" (see Ref. 73).

TABLE II

Uptake of EtOH "in vitro" of diverse CNS' area, adult rats normal and "alcohol generation": $\frac{M \text{ EtOH}}{mg \text{ protein}}$

	Normal D	Normal C	Alcoholic Generation D	Alcoholic Generation C
Brain Cortex	0.46 ± 0.1	0.12 ± 0.2	0.63 ± 0.2	0.98 ± 0.3
Hypothalamus	0.92 ± 0.1	1.54 ± 0.6	1.28 ± 0.6	2.1 ± 0.1
Cerebellum	1.29 ± 0.3	1.94 ± 0.5	1.58 ± 0.4	2.98 ± 0.8

The experimental condition are identical to Table I; EtOH determination : enzymatic (alcohol - NAD - oxidoreductare) method; incubation time: 70 minutes; Warburg vessel. Determination with impuber and new borm animals have been also carried out; see Ref. (73).

oxidation to CO_2, a theory which further complicates the problem (''). On the other hand the effect of ethanol on the mitochondrial cerebral respiration has been analyzed; again in this aspect we encounter conflicting results. Quastel and his group [5, 24] assert that the mitochondrial respirations is relatively insensitive to concentration of alcohol that considerably depresses K+ –stimulated respiration of rat brain cortex, and further that the first product of EtOH oxidation, acetaldehyde inhibits mitochondrial respiration to the same exent as that of brain cortex slices, De Gregorio et al. [15] have confirmed the inhibition of mitochondrial respiration (''). The relation of CNS'ADH content and the respiratory process is analyzed further and it can be stated that it is confirmed that the brain contains this enzyme (iv). Finally it should be remembered that certain authors (Rubin et al. [75], Lieber et al. [53] and Tephly et al [84]) have called the attention to the existence of microsomal alcohol-oxidation system; this is fully proven in the liver and it would represent a different route of ADH-ethanol degradation, it being a peroxidasic reaction in which H_2O_2 generated through a microsomal enzyme in which NADPH –oxidase would act. The existence of such system in the normal CNS has not been described as yet (v), Lastly, we believe that the actual EtOH uptake capacity of the CNS has relation with the respiratory process. In this respect Burbridge et al. [11] have published CNS ethanol uptake facing this metabolite and exogenous co-subtrates glucose appearing with the greatest output not only as regards EtOH uptake "in vitro" but also EtOH $\rightarrow$ CO_2 conversion. On our part, we have communicated results of EtOH uptake "in vitro" by brain cortex, hypothalamus and cerebellum of alcoholic generations, areas which show a higher uptake compared with that of the control rats, see Table II [73].

Oxidative phosphorylation

EtOH and homologous alcohols of low molecular weight do not affect the P : 0 ratio of mitochondria of rat brain at doses capable of producing "in vivo" an acute intoxication, or, at least a depressant activity [81]. However, Rehak et al. [67] when working under equal conditions find that CH_3CHO and other homologous aldehydes depress the P : O ratio in far lower concentration than required to obtain similar effects in rat liver mitochondria. If we consider that CH_3CHO is a product of EtOH metabolism in the organism, we should expect that both compounds would produce the same uncoupling effect "in vivo", unless the number of intermediary reactions in which CH_3CHO intervenes, surpasses greatly those described for ethanol [95] which would cause that the acetaldehyde be metabolized at a greater speed, being degraded while forming from EtOH [14, 94].

These facts are in accordance with the accumulation of CH_3CHO observed in humans after the administration of disulphiran, a drug which blocks the degradation of this compound and produces a certain degree of uncoupling of the oxidative phosphorylation and mitochondrial respiration of rat CNS "in vitro" [87]. The concentration at which both types of results are obtained, would be similar.

Acetaldehyde

A parallelism between the degree of alcoholic intoxication and the acetaldehyde concentration in blood, cannot be established [93], since this hardly reaches high levels because it undergoes a metabolic remotion far superior to its formation speed starting from EtOH. McLeod found in rats that at levels of 40-60 *mu* g of CH_3CHO per ml blood no functional alterations are observed. A level of 100 *mu* g/ml is needed to produce a severe depression of short duration [58]. In any case, there is a close relation between acetaldehyde concentrations in the blood and in nervous tissue which it enters very easily.

The actions of acetaldehyde on CNS cause alterations as increase of acetylcholine and acetoin levels [6, 7] or non-specific inhibition of monoamino oxidase [86]. Ridge [68] in studies carried out in rat brain "in vivo" found an aldehyde dehydrogenase an enzymatic system capable of oxidizing acetaldehyde by

means of a coupled reaction through NAD to the reduction of pyruvase to lactate. This is in accord with previous findings of Kiessling [49] who reported the inhibitory effect of the oxidation of pyruvate in preparation of rat brain mitochondria; this has not been the case with other substrates tested, as glutamate, succinate and *alpha*-ketoglutarate.

This reduction of pyruvic acid, coupled to the oxidation of acetaldehyde, would block the entrance of the former into the citric acid cycle. In this respect, Berry and Stotz [6] indicate that rat brain homogenates incubated in presence of acetaldehyde, exhibit a decrement in the citric acid formation. Moreover, Higgins [35] found that due to this fact the metabolism of glucose moves to the path of NADP-dependent phosphogluconate.

Alcohol NAD : oxidoreductase (ADH)

In connection with this zinc-enzyme (ADH, EC 1.1.1.1) [85] which catalizes the reversible oxidation $EtOH \rightleftharpoons CH_3CHO$, we may say that the scant studies on the subject carried out in the CNS show contradictory results. Some authors come to the conclusion that CNS does not possess ADH [86], however Dewan [16, 17], Raskin et al. [66] and recently Egaña et al. (histochemical method) have established its presence in brain, although in lower quantities than in liver. These last authors [20] have been able to ascertain a quantitatively different distribution in brain cortex, hypothalamus and cerebellum, the levels in animal of alcoholic generation being greater than in normal. Nevertheless, although its enzymatic activity is low, we cannot disregard the importance of the participation of brain ADH in the metabolism of ethanol. In fact, Raskin and Sokoloff [66] indicate that this brain mechanism which permits the oxidation of alcohol, can indeed play a significant role in the pathogenesis of neuronal disorders with the chronic ingestion of ethanol.

Although Sutherland et al. [82] and Burbridge and Coworkers [11] have indicated that the brain is capable of oxidizing ethanol, other attempts made [3, 51, 55, 90] have not achieved to determine the metabolization of ethanol in brain tissue. However, these negative results do not constitute an evident proof of the absence of brain ADH; as after incubating rat brain cortex slices of rat under [14C-1]-ethanol [3, 55], the acetaldehyde formation has not been measured but only the production of CO_2, fatty acids and cholesterol, whereas it is quite probable that the formation of earlier intermediates also takes place [93].

On the other hand, certain authors [86] attempting to measure the enzymatic activity of brain ADH by means of the Bonnichsen and Brink [8] method, described, for liver, have failed due to the fact that this is a procedure based on the spectrophotometric reduction of NAD and does not have sufficient specificity, nor sensitivity when applied to tissue of low ADH content, such as brain and which further contain many other enzymatic systems which also work NAD/NADH, as indicated by Raskin and Sokoloff [66] who, starting from the reduction of lactic aldehyde have been able to detect in the soluble fraction of rat brain, significative quantities of ADH with kinetic properties and response to inhibitors very similar if not identical to those obtained for liver ADH.

Carbohydrates and proteins

Häkkinen and Kulonen [31] have studied the effects of ethanol "in vitro" and found an increase in the rate of consumption of glucose and formation of pyruvate and lactate in the soluble proteic fraction of rat brain homogenate of previously alcohol-treated rats. Similar results have been obtained when using fructose, mannose and glucose-phosphate. Previous findings of Wallgren and Kulonen [90] indicated further that rat brain cortex slices incubated in presence of ethanol (0.087 M) increased the oxygen and glucose consumption. Nevertheless, "in vivo" a different situation arises, derived from the action of acetaldehyde "per se", a compound delivered and fixed with great facility in brain tissue, diminishing the NAD/NADH relation which affects not only the anaerobic glycolysis but also the oxid-

ation of the citric acid cycle [35] of considerable importance in the energetic CNS supply. This can be explained further that the energy requirements are diminished on account of the ethanol interference with functional activity of brain tissue [93].

In connection with the effects of EtOH on the proteic metabolism, Kanüke et al.[48] pointed out that ethanol diminishes the exchanges of aminoacids in cerebral cortex slices. On the other hand, Häkkinen et al. [30] describe a general diminution of the amino acid content in rat brain cortex slices incubated in presence of ethanol, while during the period of intoxication by ethanol, they show an increase in the levels of glutamate and aspartate [28]. Finally, Quastel [64, 65] using EtOH in concentrations of 0.92 % obtains a disminution of 40-50 % in the incorporation of radiactive glycine in brain tissue. All these phenomena are probably related to the interferences of ethanol in the ATP/ATPasa system, indispensable for the utilization of the energy arising from the cellular metabolism.

Active transport of Na+ and K+; ATPase studies

Due to the close relationship —at least in the CNS— between the active transport of Na+ and K+ on one hand and ATPase on the other, both aspects will be analyzed in conjunction. Since the pioneering work of Skou [79] we are aware of the existence of an enzyme in the nerve cell membranes which hydrolizes ATP to ADP and Pi, which is stimulated by Na and K cations in presence of $Mg^{2}+$. We know that CNS contains at least four types of ATP –phosphohydrolase: DNP – activated enzyme of mitochondrial localization (Rosie [74]); Na+ and K+ activated enzymes located on the mitochondria membrane surfaces [1,32], microsomes [32, 43], nerve endings [10] synaptic membranes [10] neurons and neuroglia [13] brain cortex, etc.; $Mg^{2}+$ – activated ATPase of a similar location of the former Naidoo et al. [62], Tanaka et al. [83] and $Ca^{2}+$ - activated enzyme [62], Hess et al. [33]. For complete details on ATPase, see reviews by Seller [78].

Kalant and his group [38, 39, 45, 47] have communicated that EtOH inhibits the transport of Na+ and K+ across the cell neuron membranes and compare this inhibition to that corresponding to EtOH on extra oxygen consumption induced by electric stimulation. Järnefedlt [42, 43] in turn found that EtOH inhibits the Na+ - K ATPase of CNS and the possibility of a competitive action of K+ in presence of EtOH has been indicated. In conjuction with the inhibition of EtOH on the active transport and on the (+ K–) - ATPase, Wallgren and his group [91] pointed out that ATP turnover is not altered. Lately, Sun et al. [80] reported that Na+ - K - ATPase is more considerably inhibited by EtOH at concentrations ranging from 43 to 2568 mM than the Mg-activated ATPase.

The importance of these studies of ATPase and the inhibiting action of EtOH of the breakdown of ATP as also the inhibition of Cr -P breakdown, resides in the fact that the resulting ADP is lesser during the alcoholic intoxication and as a consequence the nervous cells would not have a stimulus for their respiratory process on one hand and further that there would be an inhibition of the active transport of Na and K cations tied to the availability of ATP from the neuron [40, 91]. Finally it should be mentioned that K+ "in vivo" counteract the action of EtOH; in this respect it is supposed that the inhibition on Na+ - K - ATPase is mediated by Na+; EtOH would increase the inhibitory effect of Na+ at the K+ side of the enzyme [12, 38, 40].

Neurotransmitters

It appears quite clear that EtOH acts on the neurotransmission within the CNS, at least on certain chemical metabolites or cerebral constituents traditionally considered neurotransmitters. The most important are - ACh, NA, 5-HT, *gamma*ABA. Obviously the effects of EtOH has been analized on the synthesis, degradation, spontaneous liberation of neurotransmitters, their reuptake, their intermediate metabolism followed by traced molecules, etc.

The problem arises within the study of the effect of EtOH on neurotransmitters not

so much from the analysis of effects, but: a) due to the action mechanism and of the quality of the neurotransmitter e. g. for ACh the facts would be different for *gamma*ABA and b) to the mechanism of action of EtOH on the neurotransmitting function "per se".

Regarding point a) an example could illustrate the problem: the role of acetylcholine. Nachmansohn [61] has lately collected the new concepts of cholinergic neurotransmisson. He claims e. g. that ACh is not a neurotransmitter between two cells, never liberates extracellularly, its action taking place intracellularly within the excitable membrane (ACh-receptor protein); the ACh would induce a conformational change of the protein and phospholipids with possible $Ca^{2}+$ ions bound to protein. This would result in a permeability of the membrane permitting the movement of thousands of ions per mol of ACh release intracellularly from its "stable bound" to "labil bound" and "free" forms. Thus, these observations alter to a certain extent our understanding regarding the manner in which neurotransmission takes place during the conduction of the nerve impulse, interneuronal in the junction nerve-muscle. Until these phenomena are not clearly understood we cannot comprehend the action of substances as EtOH which, in certain cases, has evident effects on certain so-called CNS' neurotransmitters.

Acetylcholine

There exist but scant studies on the action of EtOH on CNS.ACh; the most important ones were reported by Kalant and his group [44, 46] : 0.5 % EtOH does not increase the spontaneous liberation of brain cortex slices "in vitro" in spite of the fact that it has been established that the enzymatic mechanism of its synthesis is not altered and that in presence of K+ in the incubating medium 1 % ethanol has no effect on the liberation of ACh. In relation to the synthesis of ACh an important event is represented by the work of Ammon et al. in the sense that EtOH administered "in vivo" does not affect brain CoA but it does so in the liver; these authors pose an erroneous explanation since they suppose that EtOH is not oxidized to CH_3CHO in the brain [2].

While it is true that there exist studies on the reinforcement of ethanol effect on ACh, e. g. in the muscular contraction (Sachved et al. [76, 77]) or in the neuromuscular transmission of both pre- and postsynaptic routes (Inoue et al. [37]), important as they are –same as finding on brain cortex "in vitro" –they do not contribute to explain the EtOH action on the neurotransmitting action of ACh and its metabolism .

Catecholamines and 5-HT

Gursey et al. [25] announced ten years ago that both NA as 5-HT descend in rabbit brain under the effect of EtOH, a finding which has been questioned by various authors (Duritz et al [18], Haggendal et al. [26]). These authors question the results concerning NA, Dopamine and 5-HT; moreover, Bonnycastle et al. found an increase in the cerebral 5-HT [9].

Other authors have worked on aspects not related to the neuroamine content, its liberation and reuptakes we refer to the intermediary degradation of these neurotransmitters, thus Maynard et al. [56] have studied the mechanism of inhibition of MAO activity "in vitro" : it diminishes in liver but not in brain mitochondria. This latter fact is mistakenly interpreted by the authors as due to a supposed non-existence of ADH in CNS.

Lastly, there appear as a fact of difficult interpretation in terms of local effect of EtOH on CNS, the results obtained in experiments carried out "in vivo" with NA and 5-HT labelled, injected in the animal "in toto".

gamma - Aminobutyric Acid

We are acquainted beforehand with three fundamental facts in relation with *gamma* ABA and CNS neurotransmission : its existence in the brain in greater quantity than

in other organs of the economy (Roberts et al. [69, 70, 71, 72]), its metabolic role, since it supports the respiration and oxidative phosporylation of certain CNS areas (Me-Kahn et al. [57], Egaña [19]) and its possible neurotransmitting role in nervous structures ranging from crayfish stretch reflex to brain cortex of the monkey (Roberts [71]). The binding effect or *gamma*ABA on ACh action has also been indicated. This action requires the intervention of Na+ (Kuriyama et al. [50]. The effect of EtOH on *gamma* ABA of CNS has been investigated by means of the following methodology : its content, EtOH administered to rats and mice increase by 34-46 % the *gamma*ABA content (Häkkinen et al. [27, 28, 29, 30], Mouton et al. [60]). Also, Häkkinen et al. [28, 29] have established that brain slices "in vitro" under the action of EtOH increase their *gamma*ABA content, a finding which is contradicted by other authors [22, 34]. These differences have been explained as refering to the different alimentary stage of the animal, since in fed animals EtOH does not produce an increase. As to the active transport of *gamma*ABA, this has been investigated "in vitro" by Iversen et al. [41] and Cerda et al. [12], authors who showed in experiments with [14c - 1] - *gamma*ABA; the presence of glucose in the incubating medium has no effect on *gamma*ABA uptake; the EtOH (0.8 v/v) however stimulates the *gamma*ABA uptake by 75 %. It is thought that the effect of ethanol on the activite transport of *gamma*ABA, in abscence of glucose, is not directly tied to the transport of K+ and Na+ (Cerda et al. [12]). These authors have established that EtOH (1.6%) inhibits the activity of glutanic decarboxylase [12].

III. CONCLUDING REMARKS

1. In the analysis of the effect and neurochemical mechanism of EtOH on CNS, certain postulates would appear acceptable : either as a metabolite and/or as a depressant it depends on the dose offered to neuroaxis and on the mode of administration. It is also acceptable that a great part of such effects are not due to EtOH "per se" but to acetaldehyde, a more active (and toxic) compound than EtOH itself. The effects vary, according to species, mode and dose of administration (acute, chronic or filial "alcoholic generation") and particularly to the CNS area analyzed (brain cortex, hypothalamus, cerebellum, M. R. F., etc.).

2. Whilst the process of EtOH oxidation by CNS it not fully elucidated, there is a general agreement to admit that the first and most important product of its oxidation is acetaldehyde, a compound of more toxic effect than EtOH itself.

3. It could be supposed that EtOH migh act in two areas of the cell: the cellular membrane and the intracellular compartmentilization membranes. In the former on the ATPase Na+ - K - Mg^{2}+ activated system and possibly on mitochondrial and microsomal level. In any case, the effect of EtOH on CNS differs fundamentally depending on whether it acts by itself or associated with co-substrates, at least in experiments in respiration "in vitro".

4. Lately it has been evidenced that CNS has alcohol-NAD: oxidoreductase activity of a possibly unequal distribution within the neuroaxis.

5. EtOH causes the deviation of pyruvate from the citric acid cycle, an ergogenetic fact unfavorable for the neuron, accentuated if we consider that even in the absence of a P:O uncoupling effect, ATP could not deliver freely its energy, owing to EtOH inhibition of the APTase system.

6. As regards EtOH effect on the neurotransmitters of CNS, certain facts related to the ACh liberation, 5-HT and NA con- of ^{14}C-NA, ^{14}C-5-HT, are known; an intent of the brain, excretion of catabolites crease of cerebral *gamma*ABA content, a diminution in the formation of *gamma*ABA starting from precursors (glut), etc., all of which makes us assume that in alcoholism, whatever its form, the neurotransmission of CNS is affected.

7. It is conceivable that the ingestion of EtOH in "filial" form by generations, acts as a conditioner of certain neurobiochemical alterations of the neuroaxis, at

least, as far as the respiratory chain and EtOH uptake by CNS are concerned.

IV. ACKNOWLEDGEMENTS

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SUMMARY

A light revision of certain aspects of EtOH action on the CNS is offered, underlining (') its effect on the respiratory chain of certain encephalon areas which depends, amongst other factors, on the dose and mode of ethanol offer to CNS and on the presence of co-substrates (specific of the neuron), (") the presence of alcohol-NAD : oxyreductase in the nervous tissue, (''') the action of alcohol on the central neurotransmitters and ('''') the effect of filial ingestion (during 42 or more generations) of EtOH on the CNS biochemical indexes.

RESUMEN

Se dan a conocer algunos aspectos de la acción del EtOH sobre el SNC; (i) se pone cierto énfasis sobre los efectos en la cadena respiratoria de determinadas áreas del encéfalo (corteza cerebral, hipotálamo, cerebelo), efectos que dependen de la dosis de EtOH ofrecida al tejido nervioso y de los substratos específicos que actualmente utilicen las neuronas; (ii) sobre la existencia de Alcohol-NAD-óxidoreductase del encéfalo; (iii) la acción del EtOH sobre neurotrasmisores centrales y (iv) se analiza el efecto de alcoholismo filial y permanente (42 ava A. G. ratas y procedentes) sobre algunos índices bioquímicos de SNC.

RESUME

Une revision légère de certains aspects de l'action d'EtOH sur le système nerveux central est offerte, soulignant (') son effet sur la chaîne respiratoire de certaines regions de l'encéphale que depend, entre autres facteurs, de la dose et la façon d'offre de l'ethanol au système nerveux central et de la présence de co-substrates (specifiques de la neurone), (") la présence de'alcoole-NAD: oxyreductase dans le tissue nerveux, (''') l'action de l'alcoole sur les neurotransmetteurs centrals et ('''') l'ingestion filiale ,pendant 42 ou plus de generations) de l'EtOH sur les indexes biochemique du système nerveux central.

ZUSAMMENFASSUNG

Eine leichte Durchsicht von gewissen Aspekten der EtOH aktion auf das zentrale Nervensystem ist angegeben, hervorhebend (') deren Wirkung auf die Atmungskette von gewissen Gehirnflaechen, die, unter anderen Faktoren, von der Dosis und der Anbietungsmethode von Ethanol an das zentrale Nervensystem und von der Anwesenheit von Co-Substraten (spezifisch des Neurons) abhangen, (") die Anwesenheit von Alkohol-NAD : Ozyreductase im Nervengewebe, (''') die Aktion des Alkohols auf die zentralen Neurosender und ('''') die Wirkung des Filialgenusses (wahrend 42, oder mehr Generationen) von EtOH die biochemischen Douter des zentralen Nervensystems.

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Chemical Changes of Ethanol in the Body

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As a rule, the alcohol (ethanol) present in the human body has been imbibed. Some alcohol may be absorbed by the skin, or inhaled in the form of alcohol vapours, but no large amounts can enter the body by these routes. The alcohol consumed is absorbed into the blood from the oral cavity only to a minimal extent. Most of it reaches the stomach, where it stays for a short or long time. Alcohol is not resorbed into the blood there. The conditions for the resorption are much better in the small intestine. The digest of the stomach reaches this part in small portions, which here come into contact with a large surface possessing a dense capillary network. In the small intestine, the alcohol is resorbed quickly by a normal diffusion process [4, 10]. The rate at which the alcohol reaches the blood depends on the concentration gradient between the intestinal fluid and the blood, and the diffusion distance. Thus the structure and the morphology of the capillary net of the mucosa has a great influence on the resorption rate.

The retarding effect of food on the resorption of alcohol has been studied by numerous investigators [37, 52, 54]. Tuovinen found that food rich in protein and carbohydrate delayed the resorption and that food rich in fat had the same effect, only to a smaller degree. In Fig. 1 are shown the results of an experiment on the effect of different kinds of foodstuff on the resorption phase of the blood alcohol curve. It has been assumed that the food produces its effect by decreasing the evacuation of the stomach content into the gut.

The alcohol resorbed in the intestine is carried by the blood to all parts of the organism. In the capillaries of the various organs, it diffuses through the cell walls. The brain, liver and kidnies, which are richly supplied with blood, very quickly attain equilibrium between the blood and the tissue fluid; this is not the case in some other tissues. However, at a certain time after the alcohol has been consumed it is evenly distributed in the water phase of the whole body. Consequently, the alcohol concentration of the blood provides a good

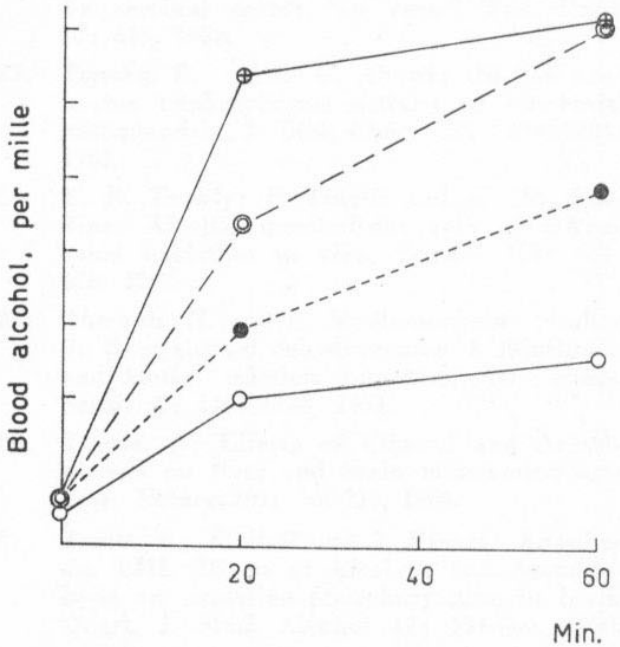

Fig. 1. — *The resorption phase of the blood alcohol curve after consumption of different kind of food.* +——+ = *alcohol without food,* O——O = *alcohol, butter and bread,* ●——● = *alcohol and potatoes, and* O——O = *alcohol and meat (according to Tuovinen* [52]*).*

picture of its concentrations in other fluids and organs, including the nervous system. The alcohol content of the body can be expressed by the following equation, presented by Widmark [54].

$$A = p \times c_0 \times r ,$$

in which A is the total amount of alcohol consumed in grams, p is the body weight in kg, c_0 the blood alcohol content at "zero" time in parts per thousand, and r a factor that expresses the proportion of the body in which the alcohol is distributed. This space is equal to the water phase of the body. The formula provides that the alcohol is distributed in the body immediately after consumption. Since part of the alcohol has been oxidized when the distribution is in equilibrium in the organism, the amount metabolized has to be taken into account in calculations.

As was shown in 1919 by Mellanby [37], the elimination of alcohol from the body occurs at a constant rate until the alcohol concentration attains a low level. Most of the alcohol ingested is oxidized in the body. Only a small part is eliminated unchanged, by the urine, with the sweat, or evaporated through the breath.

According to Widmark [54], the ideal blood curve assumes the shape indicated in Fig. 2. During the first phase of the curve, the absorption of the consumed alcohol from the intestinal tract dominates the curve, and the blood alkohol rises sharply. The resorbed alcohol is distributed by the blood throughout the body, and diffuses in the capillaries from the blood into the cellular fluids. Alcohol oxidation has already begun at this stage. After the lapse of a certain period the resorption from the intestine is in equilibrium with the distribution and the oxidation, and the blood curve is flat. Subsequently, the resorption rate diminishes, as most of the alcohol has been resorbed; when the distribution is faster than the resorption, a sharp fall in the blood alcohol concentration is observable, lasting until all the alcohol has been evenly distributed in the organism. A continuous decrease in the blood alcohol concentration then takes place, and the slope of the curve is a function of the rate of alcohol oxidation.

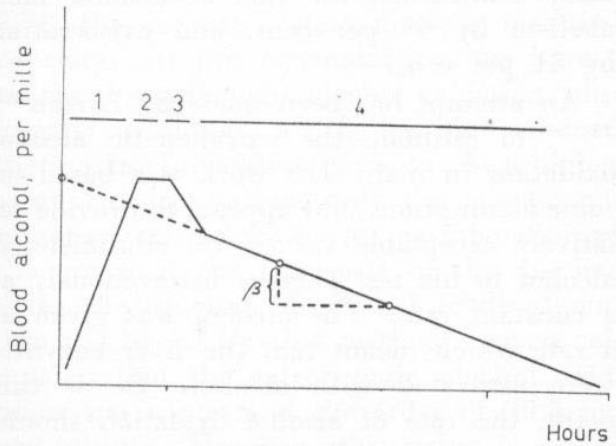

Fig. 2. — *The ideal blood alcohol curve. 1 = resorption phase, 2 = plateau, 3 = diffusion equilibration and 4 = elimination phase (according to Widmark [54]).*

The rate of alcohol oxidation is usually expressed as the fall in blood alcohol concentration during one hour. This is the B_{60} value, and it has been measured by many researchers in different countries. Some of the values arrived at are listed in Table 1. At moderate alcohol concentrations, the rate of alcohol oxidation is constant, although it has been reported that it is elevated at higher concentrations [11].

TABLE 1. Elimination rate of blood alcohol in man.

Author	Country	$B60^1$
Coldwell and Smith [9]	Canada, 53 *	13
Ninane and Brakel [41]	Congo, 10	13
Prag [43]	England, 30	13
Alha [1]	Finland, 42	13
Ponsold and Heite [42]	Germany, 1655	17
Widmark [54]	Sweden, 30	15
Newman and Lehman [40]	U.S.A.	14

* number of persons investigated.

A number of reports quite clearly show that some persons are capable of metabolizing alcohol more than three times as quickly as the average person [22, 39]. Under certain conditions some compounds such as fructose, and some amino acids can accelerate alcohol oxidation, but not to any high degree [20, 55].

Batelli and Stern [3] of Geneva seem to have been the first to provide a clear de-

monstration that different organs in the body can oxidize alcohol. They found that the liver from many species of animal has a high capacity to metabolize alcohol, but that to some extent the kidneys could also effect the oxidation. In the same year, Hamill [18] showed that a rabbit heart perfused with a Ringer solution containing alcohol removed a part of the alcohol during the experiment. Fisher [12] made a similar observation some years later in experiments with cat hearts, as did Klewitz [25] with rabbit hearts.

The Danish scientist Lundsgaard [35] has clearly demonstrated the dominating role played by the liver in the oxidation of alcohol in the body. In one experiment, he studied the rate of alcohol oxidation in a perfused cat liver, and in another the breakdown of alcohol in the hind limb of the animal. In the liver perfusion, the concentration of the alcohol decreased quickly, and at a constant rate (Fig. 3). In the ex-

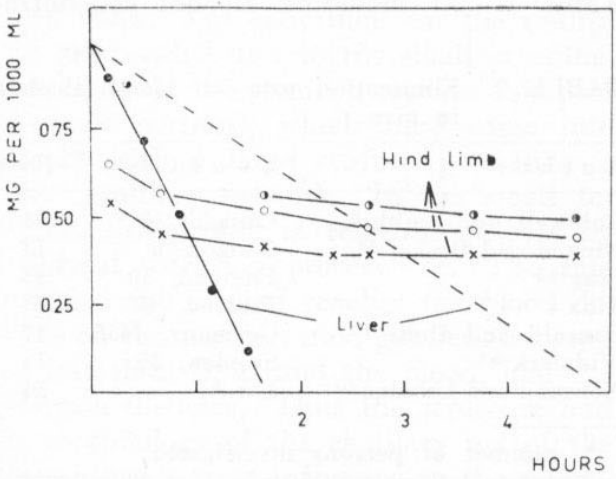

Fig. 3. — *Alcohol concentration of the blood during perfusion of cat liver and hind limb. The dotted line is corrected for liver weight and volume of the media. (Lundsgaard [35])*

periments with perfused limb, the alcohol concentration was hardly influenced at all. After the diffusion balance between blood and intracellular medium had been established, only a very slow fall in the alcohol concentration was observable. In these experiments, difficulty was encountered in comparing the alcohol oxidation rates in the liver and the hind limb, but in later experiments with eviscerated cats, Lundsgaard [34] found that these animals could eliminate alcohol at a rate amounting to no more than about 10 per cent of that of the intact ones.

Clark *et al.* [8] have studied the way in which alcohol is oxidized in normal dogs, and in hepatectomized or eviscerated animals (Fig. 4). They found that hepatec-

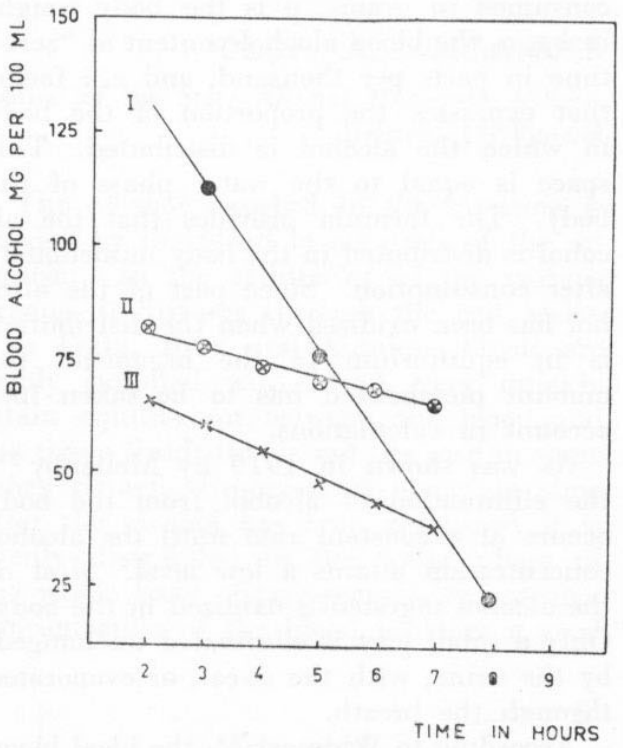

Fig. 4. — *Alcohol concentration of the blood of dogs treated in different ways after alcohol administration. I represents untreated, II eviscerated and III hepatectomized animals (Clark* et al. [8]).

tomy diminished the rate of alcohol metabolism by 69 per cent, and evisceration by 81 per cent.

An attempt has been made by Larsen [27, 28, 29] to estimate the extrahepatic alcohol oxidation in man. His work was based on some assumptions, but appears to provide relatively acceptable values. He administered alcohol to his test persons intravenously at a constant rate. The alcohol was given at a rate which meant that the liver enzymes were saturated with alcohol. Below this point, the rate of alcohol oxidation should be proportional to the alcohol concentration in the blood. This was also the case, as is observable from Fig. 5. After two hours of infusion, the rate of the alcohol administra-

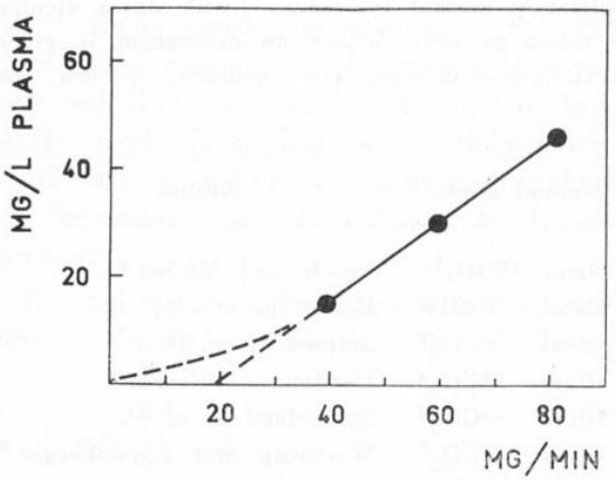

Fig. 5. — *Rate of intravenous alcohol infusion in man, plotted against plasma alcohol concentration. The dotted line across origon represents the expected course of the line on the infusion of very small quantities of alcohol (Larsen [59]).*

tion was increased, and again increased after another two hours. The concentration of alcohol in the blood plasma was measured at all three rates. If the concentration of alcohol in the blood is plotted against the infusion rate, a straight line results. However, if this line is extrapolated, it does not pass through the orego. Larsen explained this by making the assumption that there are two active sites of alcohol oxidation, one hepatic, and one outside the liver. These two sites are saturated with alcohol at different concentrations. The extrahepatic site is saturated even at a low alcohol concentration, less than the lowest applied in the experiment. At a concentration of 10 mg of alcohol per litre blood, i. e. 0.2 mM, the enzyme system displays maximal capacity. At this concentration, we have a maximal extrahepatic alcohol oxidation, plus hepatic oxidation, which has not attained the maximal oxidation capacity. At a higher alcohol concentration, only the hepatic elimination can increase. An extrapolation of the curve at the intersects of the abscissa gives the amount of alcohol oxidized outside the liver. By this method, Larsen calculated that the extrahepatic alcohol oxidation was a mean of the order of 20.5 mg per minute. However, this value is rather high, much higher than reported in experiments with hepatectomized animals.

A great variety of techniques have been applied in studies of the site of extrahepatic alcohol oxidation, and thus the results are not always comparable. Table 2 relates to the capacity of some organs of the rat, horse, pigeon, and man to oxidize alcohol. The metabolic capacity quoted has been calculated on a liver capacity equal to 100. The liver and the kidneys are the most active tissues in the metabolizations of alcohol. Some authors have reported that the highest activity is present in the liver, but others have found more than twice as great an activity in the kidneys as in the liver, calculated per unit of tissue weight. However, this depends upon the method employed for measurement of the activity. If the disappearance of the alcohol is measured, the liver is the most active organ, but since the breakdown of the alcohol there is limited to acetate, the production of carbon dioxide is consequently small in comparison with that in the kidneys, where the rate of alcohol oxidation is less, but instead proceeds completely to carbon dioxide, without the accumulation of intermediates. Muscles, except for cardiac, diaphragm and skeletal muscle, are, according to most researchers, capable of oxidizing small amounts of alcohol. Earlier, most investigators were unable to observe any alcohol metabolism in the brain. By the application of a sensitive technique however, Raskin and Sokoleff [44] discovered that the brain oxidized small amounts of alcohol; they were also able to enrich and characterize the alcohol dehydrogenase there. The presence of alcohol dehydrogenase has also been detected in the retina [26]. Schmidt and Schmidt [47], Spencer *et al.* [50] have found that small amounts of alcohol dehydrogenase are also present in the stomach and intestinal mucosa in the fat depots, pancreas, and lung tissue.

Alcohol dehydrogenase does not exist in normal blood, but the enzyme has been found there in some liver diseases. Schmidt *et al.* [48] have observed increasing amounts of the enzyme in acute and chronic hepatitis. Wolfson *et al.* [57] have induced liver demage in experimental animals by means of carbon tetrachloride, and found that alcohol dehydrogenase appeared in the blood some hours after administration of this

TABLE 2. Comparative capacity of organs from different animal species to break down alcohol. The metabolic activity of the liver is taken as 100. Where an estimation is given, but no figures appear in the original text, +++ is high, ++ medium, + low, and O no activity.

Liver	Kidney	Brain	Intestine	Heart	Muscle	Spleen	Method used	Author
100	3		0		0		slices, ^{O}EtOH[1]	Leloir and Muñoz [30]
100		100					slices, EtOH[2]	Burbridge *et al.* [7]
100	127	0			2		slices $^{14}CO_2$[3]	Masoro *et al.* [38]
100	272	1		9	3		slices $^{14}CO_2$[4]	Bartlett and Barnet [2]
+++		+					slices $^{14}CO_2$[5]	Sutherland *et al.* [51]
100	256				3-7	8	slices $^{14}CO_2$[6]	Wartburg and Eppenberger [53]
100	21				+	+	mince, EtOH[7]	Batelli and Stern [3]
100	0.2	0	0-3	0	0		mince, ADH[8]	Schmidt and Schmidt [47]

1. Q_{EtOH}, *mul* of ethanol, as gas, disappearing per mg dry tissue in 1 hour at 37°.
2. Ethanol disappeared in *mug* per mg fresh tissue in 2 hours, temperature not stated.
3. Per cent of ^{14}C-ethanol converted to $^{14}CO_2$ in 3 hours at 37.5°.
4. Total counts of expired $^{14}CO_2$ per 100 mg dry tissue in 2 hours at 38°.
5. $^{14}CO_2$ formation from 1-^{14}C-ethanol in 3 hours at 37.3°.
6. $^{14}CO_2$ formation from 1-^{14}C-ethanol per g dry tissue in 1 hour at 37°.
7. g ethanol disappearing per 100 g tissue in 1 hour at 40°.
8. Soluble ADH calculated in Büchner's units.

compound. After two days, the enzyme disappeared from the blood. However, it is difficult to understand how the alcohol could be oxidized in the blood by alcohol dehydrogenase, even if the enzyme were present there. The enzyme also needs NAD as a coenzyme, and a system which reoxidizes the reduced coenzyme. Such a system is not present in the blood.

Scheggia *et al.* [45] have found an enzyme capable of oxidizing alcohol in the blood of alcoholics. The enzyme was not identical with alcohol dehydrogenase, but was a peroxidase. It has not been proved whether this enzyme possesses any function in the oxidation of alcohol in the intact organism.

The alcohol is not oxidized completely in the liver to carbon dioxide, but only to an intermediary step. This was demonstrated by Lundsgaard [36] in 1938. He found that when a cat liver was perfused with blood containing alcohol, the respiratory quotient was depressed from 0.69 to 0.37; he believed that this depended upon incomplete oxidation of alcohol. At the same time the alkali reserve of the blood decreased indicating the formation of an acid, which Lundsgaard assumed to be acetic acid (Fig. 6). A year later, Leloir and Mu-

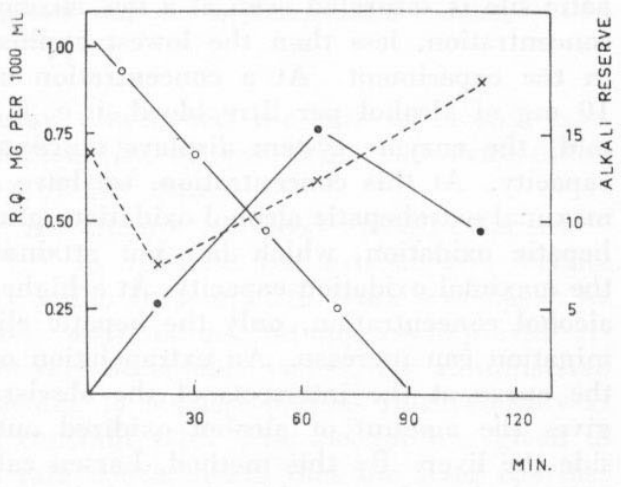

Fig. 6. — *The rate of oxidation and influence of ethanol on the respiratory quotient and alkali reserve of the blood during perfusion of an isolated cat liver.* O——O *Ethanol concentration in the blood.* +——+ *respiratory quotient* .——. *alkali reserve. (Lundsgaard* [36]*)*

ñoz [30] made similar experiments with rat liver slices, and showed by means of a colour test that the acid formed was in fact acetic acid. This has been subsequently confirmed by different techniques applied by Forsander and Räihä [16] and by Lundquist *et al.* [34].

A small part of the alcohol formed undergoes further metabolism in the liver. By the perfusion of labelled ethanol through a rat liver, and subsequent analysis of the organic acids formed, Forsander and Räihä [16] found that carbon from ethanol was incorporated not only in ethanol, mainly in *B*-hydroxybutyrate. but also in lactate and in pyruvate, and in intermediates of the citric acid cycle (Fig. 7). A small proportion of the alcohol is also oxidized to carbon dioxide, as is indicated in Table 3.

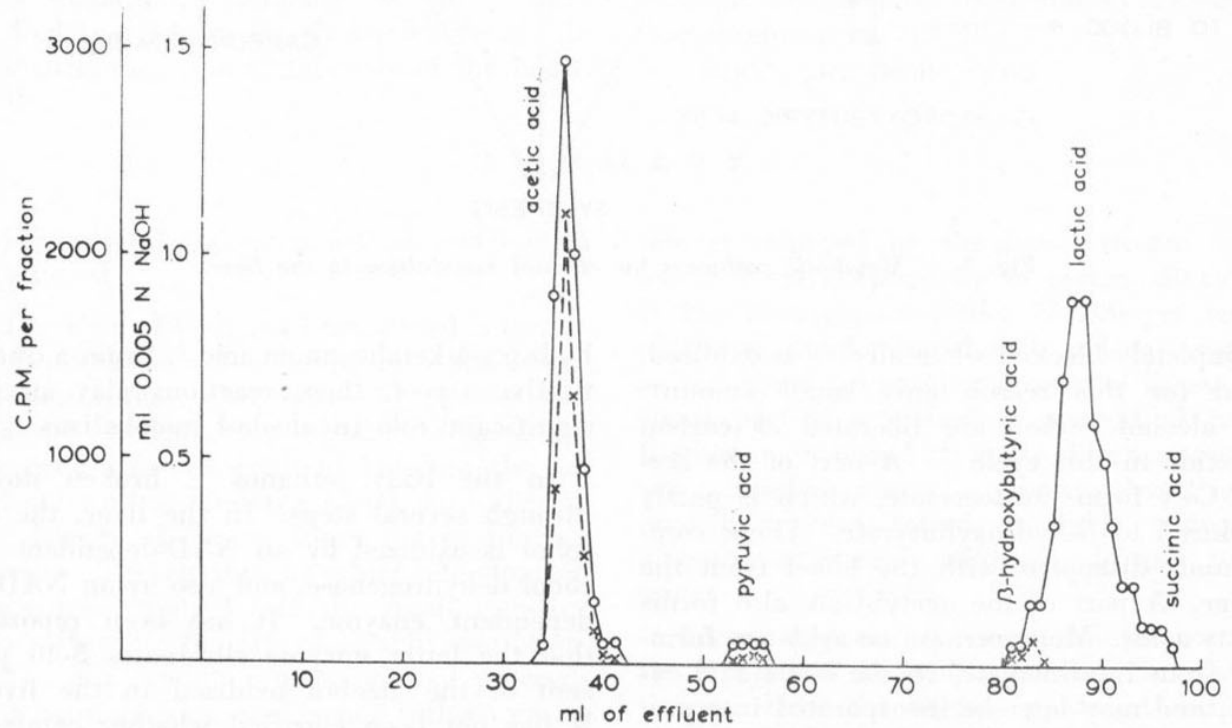

Fig. 7. — *The organic acids in rat blood after* FJ *min. circulation perfusion of an isolated rat liver with blood containing 1-C* ^{14} *ethanol. The acids were separated on a silica gel column and eluted with increasing concentrations of butanol in chloroform.* O——O, *amount of organic acid in the fractions,* × - - - - ×, *the radioactivity of the fractions.*

TABLE 3. Oxidation of labelled ethanol to carbon dioxide during one-hour perfusion of the liver and hind limb of a rat (Forsander [13]).

Perfusion	as CO_2 per cent	oxidized per cent ethanol
Liver	1.8	26
Hind limb	2.4	—
Liver + hind limb	8.1	—

Labelling from ethanol has also been found in fatty acids [49], in proteins and amino acids [21], in glycerol and glycogen [46]. According to these findings, the intermediary metabolism of ethanol proceeds in the liver in the following way: Fig. 8.

Ethanol is oxidized over acetaldehyde to acetate, which is for the most part carried away with the blood stream. A minor part of the acetaldehyde is also transported by the blood from the liver. A small proportion of the acetate forms acetyl-CoA, which can be metabolized in different ways. In the liver, acetyl-CoA does not seem to be formed direct from acetaldehyde, as in some bacteria, but from acetate. The acetyl-CoA can condense with oxaloacetate to citrate, and undergo oxidation in the citric acid cycle. This pathway is, however, almost

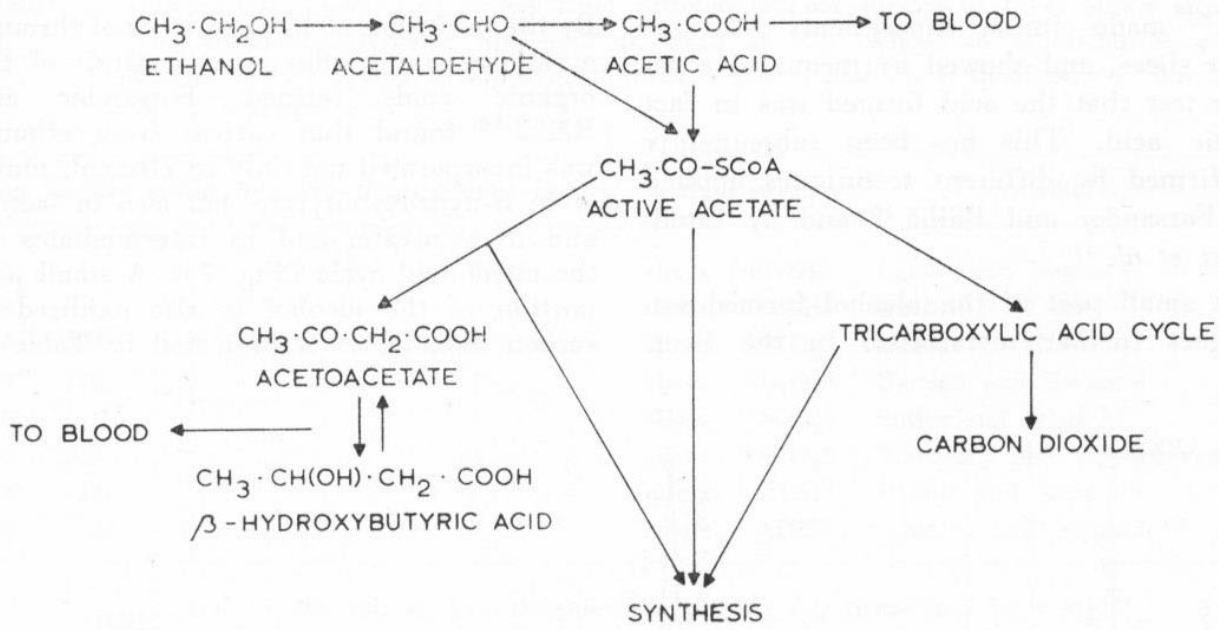

Fig. 8. — *Metabolic pathways for ethanol metalolism in the liver.*

completely blocked when alcohol is oxidized, and for this reason only small amounts of alcohol carbon are liberated as carbon dioxide in this cycle [15]. A part of the acetyl-CoA forms acetoacetate, which is partly reduced to *B*-hydroxybutyrate. These compounds disappear with the blood from the liver. A part of the acetyl-CoA also forms fatty acids. Moreover, amino acids are formed from intermediates in the citric acid cycle, and may later be incorporated into protein. Glucose and glycerol may also be formed from intermediates in this cycle.

It has been reported that between 75-100 per cent of the ethanol oxidized in the liver may be found as acetate [30, 34, 56]. The remainder must have been metabolized via the pathways described. As yet, it has not been clarified which are the most important routes, but it seems probable that under certain conditions the oxidation in the citric acid cycle is quite intensive (Lindros, unpublished results). The synthesis of fatty acids is insignificant during ethanol metabolism, and the formation of ketone bodies is not increased to any great extent [32].

Alcohol is also esterified to a low degree, and excreted by the urine as ethyl sulphate [6] and as ethyl-glucunoride [24]. Acetaldehyde may undergo condensation reactions and react with pyruvate, forming acetoin [23]. Together with *a*-ketoglutarate, it can form 5-hydroxy-4-ketohexanoic acid [5]. From a quantitative aspect, these reactions play an insignificant role in alcohol metabolism.

In the body, ethanol is broken down through several steps. In the liver, the alcohol is oxidized by an NAD-dependent alcohol dehydrogenase, and also by an NADP dependent enzyme. It has been reported that the latter enzyme eliminates 5-20 per cent of the alcohol oxidized in the liver. It has not been clarified whether catalase, which can in a coupled artificial system metabolize alcohol, has any role in the *in situ* alcohol oxidation. Aldehyde dehydrogenase seems to be responsible for the oxidation of acetaldehyde [33], although some other enzymes present in the liver are well capable of oxidizing the aldehyde.

It has been calculated from the rate of alcohol oxidation in the human body that alcohol can cover about two thirds of the energy need of a normal man [13]. When ethanol is oxidized to acetate in the liver, one third of its energy content will be liberated. It is possible to calculate from the oxygen consumption of the liver that ethanol monopolizes most of the oxidation processes there. When the acetate is oxidized extrahepatically, the remaining two thirds of the energy of the alcohol molecule is liberated.

Acetate is a normal substance in the body, and is readily oxidized in many tissues [19]. The rate at which acetate is broken down in the muscular tissue is dependent upon the acetate concentration, and the functional state of the tissue [17]. The higher the concentration, and the more work the muscle performs, the more intensive is the acetate oxidation. Very little work has been done on the quantitative extrahepatic utilization of the acetate produced during ethanol oxidation. Lindeneg *et al.* [31] have studied the way in which acetate from ethanol influences the metabolism of the heart. This investigation was made by the heart perfusion technique. A calculation made from the result obtained indicated that about 20 per cent of the oxygen consumption of the tissue was utilized for oxidation of the acetate. The remainder was utilized for the oxidation of free fatty acids, lactate and unknown compounds.

Alcohol oxidation can cover a large part of the basal metabolism of the body. This metabolism must, to a great extent, occur through extrahepatic oxidation of the acetate produced in the liver.

SUMMARY

The general and intermediary metabolism of ethanol.

The alcohol (ethanol) consumed is resorbed from the small intestine into the blood. The resorption takes place by normal diffusion. The rate of the uptake depends on the concentration gradient between the intestinal content and the blood, and also on the density of the capillary net of the gut mucosa. The rhythm by which the stomach content is emptied into the small intestine also influences the rate of alcohol resorbtion.

The elimination rate of ethanol proceeds at a constant rate and is not influenced by work or by body temperature. Compounds such as fructose and some amino acids have been reported to increase the rate of oxidation under certain conditions.

Alcohol is oxidized mainly in the liver. Extrahepatically only 5-20 per cent of the consumed alcohol is metabolized. Next to the liver, the kidneys are most active in alcohol oxidation. The alcohol is oxidized to the acetate stage in the liver and the acetate is removed by the blood stream and oxidized extrahepatically to carbon dioxide. It has been reported that 75-100 per cent of the oxidized ethanol is found as acetate in the blood originating from the liver. A small part is esterified to acetyl-CoA and further metabolized in many different pathways. Carbon atoms originating from ethanol have been found in lipids, glucose, glycerol, colesterol, amino acids and proteins.

Acetate appears as a normal substance in the body, and is readily oxidized in many tissues. How the acetate produced during alcohol oxidation is utilized has, however, not been thoroughly studied. According to one report the heart used about 20 per cent of its oxygen consumption for acetate metabolism.

As an energy source, alcohol is able to stand for a large part of the basal metabolism of the body. Evidently this mainly occurs through extrahepatic oxidation of the acetate produced in the liver.

RESUMEN

El alcohol (etanol) consumido es absorbido por el intestino delgado y de allí pasa a la sangre. La absorción se produce por difusión normal. La cuota de asimilación depende del cociente de concentración entre el contenido intestinal y la sangre y también de la densidad de la red capilar de la mucosa intestinal. También influye sobre la cuota de absorción de alcohol el ritmo del pasaje del contenido estomacal al intestino delgado.

La cuota de eliminación del etanol transcurre a un ritmo constante y no es influida por el trabajo o la temperatura del cuerpo.

En determinadas condiciones se ha observado que los compuestos tales como la frutosa y algunos amino-ácidos aumentan el ritmo de oxidación.

El alcohol se oxida fundamentalmente en el hígado. Fuera de allí se metaboliza solamente del 5 al 20 por ciento del alcohol consumido. Le siguen en importancia los riñones en cuanto a la actividad relativa a la oxidación del alcohol. Este es oxidado hasta el estado de acetato en el hígado y este acetato pasa a la corriente sanguínea y es oxidado fuera del hígado transformándose en dióxido de carbono. Se ha observado que el 75 al 100 por ciento del etanol oxidado se encuentra en forma de acetato en la sangre proveniente del hígado. Una pequeña parte es esterificada transformándose en acetil-CoA y posteriormente se metaboliza a través de diferentes vías. Los átomos de carbono provenientes del etanol han sido hallados en lípidos, glucosa, glicerol, colesterol, aminoácidos y proteínas.

El acetato aparece como una sustancia normal en el cuerpo y es rápidamente oxidado en diversos tejidos. No ha sido estudiada en profundidad la forma como es utilizado el acetato producido durante la oxidación del alcohol. De acuerdo a un informe el corazón utilizó alrededor del 20 por ciento de su consumo de oxígeno para metabolizar el acetato.

Como fuente energética, el alcohol puede cubrir gran parte del metabolismo basal del cuerpo. Evidentemente esto se da fundamentalmente a través de la oxidación extrahepática del acetato producido en el hígado.

RESUME

Le métabolisme général et intermédiaire de l'éthanol.

L'alcool consommé est résorbé de l'intestin grêle au sang. La résorption se fait par un processus normal de diffusion. La quantité d'assimilation dépend du degré de concentration entre le contenu intestinal et le sang et aussi de la densité du réseau capillaire de la muqueuse. Le rythme auquel le contenu de l'estomac se vide dans l'intestin grêle influence aussi la quantité de résorption d'alcool.

La quantité d'élimination de l'ethanol se fait à un degré constant et n'est pas influencée par le travail ou la température du corps. Il est rapporté, que quelques composants comme le fructose et certains acides aminés augmentent en certaines circonstances la quantité d'oxidation.

L'alcool est principalement oxidé dans le foie. Seulement 5-20 % de l'alcool est métabolisé extrahépatiquement. Après le foie les reins sont les plus actifs dans l'oxidation de l'alcool. Dans le foie l'alcool est oxidé seulement en acétate. L'acetate formé est transporté par le sang et oxidé extrahépatiquement en carbone dioxide. Il a été rapporté, que de 75 à 100 pour-cent de l'éthanol oxidé se trouve en acetate dans le sang laissant le foie. Une petite partie est estérifiée en acétyle-CoA et métabolisée dans plusieurs voies différents. On a trouvé du carbone provenant d'éthanol dans les lipides, la glucose, le glycérole, le colesterole, les acides aminés et la protéine.

L'acétate est une substance normale dans le corps et est faciliment oxidé dans maints tissus. L'utilisation de l'acétate produit pendant l'oxidation de l'alcool n'a pas été très étudiée. On a trouvé dans une recherche que le coeur employait à peu près 20 % de sa consommation d'oxygène au métabolisme d'acétate.

L'alcool peut couvrir une grande partie du métabolisme de base du corps. Pour une grand partie cela doit se passer par une oxidation extrahépatique de l'acétate produit dans le foie.

ZUSAMMENFASSUNG

Der Haupt-und Zwischenstoffwechsel von Äthanol.

Der konsumierte Alkohol (Äthanol) wird vom Dünndarm ins Blut resorbiert. Die Resorption erfolgt durch einen normalen

Diffusionsvorgang. Der Grad der Aufnahme hängt vom Konzentrationsgradienten zwischen Darminhalt und Blut ab, der Ausschüttung des Mageninhaltes in den Dünndarm hat ebenfalls einen Einfluss auf den Grad der Alkoholresorption.

Die Eliminierungsrate von Alkohol geht in einem konstanten Mass vor sich und wird durch Arbeiten oder Körpertemperatur nicht beeinflusst. Es wurde berichtet, dass einige Verbindungen, wie Fruktose und einige Aminosäuren, unter Umständen den Grad der Oxydation erhöhen kônnen.

Der alkohol wird hauptsächlich in der Leber werden nur zwischen 5 und 20 % des konsumierten Alkohols umgebaut. Neben der Leber sind die Nieren höchst aktiv in der Alkoholoxydation. In der Leber wird der Alkohol lediglich zu Acetate oxydiert. Dieses gebildete Acetat wird durch den Blutkreislauf abtransportiert und ausserhalb der Leber zu Kohlenstoffdioxyd oxydiert. Es wurde berichtet, dass zwischen 75-100 % des als Acetat im Blut vorliegenden, oxydierten Alkohols die Leber mit dem Blut verlässt. Ein geringer Teil wird zu Acetyl-CoA verestert und in vielen verschiedenen Stoffwechselwegen weiterverwendet. Kohlenstoff aus Äthanol wurde in Lipiden, Glukose, Glyzerol, Colesterol, Aminosäuren und Proteinen gefunden.

Acetat ist eine ganz gewöhnliche Substanz des Körpers und wird in vielen Geweben leicht oxydiert. Die Verwertung des während der Alkoholoxidation gebildeten Acetats wurde noch nicht so oft untersucht. In einer Arbeit wurde ermittelt dass das Herz ungefähr 20 % seines Sauerstoffbedarfes für den Acetatstoffwechsel aufwendet.

Der Alkohol kann einen grossen Teil des Grundstoffwechsels des Körpers decken. Dies muss in grossem Uhfang durch Oxydation des in der Leber erzeugten Acetats ausserhalb der Leber geschehen.

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Ethanol and Central Nervous System

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Alcohol, as one of luxury goods, has been loved and used widely by mankind since olden times, and at the same time its harmful effects are as old as human history, too. Originally, the word alcohol comes from "al-kohl" in Arabic, which meant dissociation of spirit. Man makes use of alcohol to cheer up his spirits, make himself at home and be drunk with joy. Alcohol is an indispensable adjunct of ceremonial occasions and in ancient times it has been used in the course of medical treatment. If man uses alcohol moderately and timely, it will bring him more happiness, but if one uses it without regard to time and place, unhappiness in his future life can easily be expected. Alcohol takes part in the happiness and unhappiness of man, and the working part of it is surely his central nervous system.

I. The Working Mechanisms of Alcohol to Central Nervous System

Alcohol is a sort of general anesthetic. The basic attitude of this anesthetic to the central nervous system is observed at neuron or at synapse. That is to say, if we steep a neuron of a frog in physiological sodium chloride solution mixed with alcohol, in proportion to its density a fall of membrane potential through depolarization will be observed and impulse conductivity of neuron will be restrained [1]. On the other hand, as for the effect toward synapse, at superior cervicale ganglion of a rabbit, obstraction of impulse conducting by alcohol is observed [2]. As a biochemical change in cooperation with this neurophysiological ones, the enzyme consumption of a slice extracted from the cerebral cortex of a rat is reported to be promoted by low concentration alcohol and be restrained by high concentration alcohol [3, 4].

Among central nervous system, cerebral reticular activation system responds most sensitively to alcohol and this change is thought to be the basic effect to central nervous system [5, 6].

II. Effect of Central Nervous System mainly to Physical Functions

Spinal reflex accelerates at low blood alcohol concentration and is restrained at high blood alcohol concentration. Acceleration of reflex at low concentration is not observed in spinal animal or anesthetic animal, so it is understood because of its indirect effect resulted from inhibition by alcohol to spinal reflex inhibition system of superior central nervous system. On the other hand, monosynapse or polysynapse reflexes of a spinal cat are both restrained at over 0.5 mg/ml blood alcohol concentration [7]. This fact suggests that inhibition when high concentration works directly for the spinal cord.

It is well known that when drunk cooperative movements of skeletal muscles declines. As indexes of drunkenness we test equilibration or flattery movements, one of the reasons of which is because of such effect of alcohol [8]. In the test of not opening eyes and putting fingertis, of both hands together, the rate of agreement falls

by comparatively little alcohol [9]. As the co operative movements are physiologically complex, overall functions, the working realm of alcohol is also complex. It is thought to be a result of alcoholic effects to many reflex arcs involving from the deep sensation receptor to the cerebellum, but detailed mechanisms have not yet been revealed [10, 12].

As one of involuntary cooperative movements caused by alcohol there is nystagmus. This indicates a pattern particular to alcohol.

Alcohol from the viewpoint of anticonvulsive effects resembles other general anesthetics or sleeping drugs. These effects are vividly observed as inhibition effect against cramps of little animals caused by electroshock, auditory stimulus or convulsive central nerve system stimulants [13, 15].

Respiration is slightly and transitorily promoted by small or mediocre quantity of alcohol and restricted or stopped by toxic dose of alcohol (over .0 mg/ml blood alcohol concentration) [16].

Electroencephalograph shows varied changes by blood alcohol concentration. Generally in man or in animals, *a*-wave activation is observed at low concentration but at high concentration mean frequency of *a*-wave declines and slow spindle wave is observed. This change at high concentration is said to resemble the ones in the fall of inspiratory oxygen partial pressure or in hypoglycemia rather than normal sleep [17, 18]. And the induced electric response in the cerebral cortex of a cat by electric stimulus is promoted when low blood alcohol concentration (5 to 25 mM) injected into local mini-artery and is inhibited when high blood alcohol concentration (over 50 mM) [19].

III. Effect of Central Nervous System mainly to Mental Functions

About the effect of alcohol to the range of vision, visual acuity, color sensation, etc., has been given attention from old, but these changes have much quantative and qualitative individual differences, so an agreed conclusion has not yet been obtained. In flicker-test, however, a fall of discrimination power is observed.

The sense of smell and that of taste are said to become dull by a small quantity of alcohol [20]. On the contrary the auditory sensation is hard to be influenced. But the sense is in close connection with the concentration of consciousness, so in daily life it is strongly influenced by the change of attentiveness indirectly.

Alleviation of pain sensation by alcohol is well known empirically, and also proved experimentally [21].

One of the sensory effects of alcohol easily overlooked, there is inhibition of fatigue feeling. In heavy labour, a little quantity of alcohol is said to encourage us. In fact, total muscular momentum seems to increase momentarily in low blood alcohol concentration. For reason of this it is considered that alcohol is a source of energy or that alcohol promotes blood circulation. However experimentally, increased of momentum by these effects is not so significant, so disappearance of fatigue feeling is considered to play the leading role.

Alcohol lowers thinking power. Especially the more complex and higher thinking process, such as calculation, association, concentration of consciousness, time perception etc., they are, the more easily they are inhibited. Moreover the more fresh memories are, the more easily they are deprived of. These thinking processes are improved by taking alcohol moderately, but sometimes realized subjectively as though in fact only deterioration is observed. In very simple memorial or thinking activities, however improvement is actually observed by a little quantity of alcohol [22]. On the other hand in case of complex thinkings, when they are prevented by extreme tension or anxiety, alcohol inhibits the preventive functions and makes them recover their own original activities, so activates in appearance. The TV master that can speak smoothly only when a little drunk is subject to this case. This fact, as is mentioned in the later part, is related to the tranquilizing effect of alcohol.

Emotion is managed by the cerebral limbic system, which is considered as phylogene-

tically or anatomically lower center than that of thinking. Alcohol displays complex effects to the mind by inhibiting reticular activation system as mentioned above, and this is most obviously observed in emotion. A crying drunkard, a merry drinker or a vicious drinker, etc., are good examples. In general, alcohol makes people have a more guilty conscience, individual characters to be magnified and emphasized and flowing of feeling become free and wild. In such a fact it has ever been discussed that perhaps alcohol may be explained to be a stimulant to central nervous system. But such a hyperthymic effect is found in the stage of excitation in anesthetic induction by all sort of general anesthetic, and is not a unique effect of alcohol. For similar reasons, sexual desire is often accelerated by alcohol. On the contrary, erection or ejaculation reflex are inhibited similarly to other spinal reflexes [23].

Alcohol has also the effect of inhibiting extreme awakening of consciousness and relax tension-anxiety. The mechanisms of tranquilizer effect have not yet been fully elucidated neurophysiologically or biochemically. But as is mentioned later it can be proved behavioral-scientifically in experiment on animals.

In pneumoencephalography, lateral ventricle of every kind of alcoholics is large, especially in delirium tremens, Korsakoff's psychosis and alcoholic hallucinosis. The heavier drinker he is, the larger lateral ventricle he tends to possess. The reason why lateral ventricle of every kind of alcoholics is large is that the brain has atrophied because of long-dated and large quantitative drinking, and as the result of that, lateral ventricle has been enlarged [24].

IV. Personalities of Alcoholics

As Sherfey pointed out, alcoholics are never attributed to a single personality-type or mental disorder, but are, from their origine, attributed to an abnormal behavior connected with some personality-types or mental disorders. Kant has classified alcohilcs into the next three groups from their personality characteristics [25].

1) Emotional immaturity and Dependency.
2) Insecure Feeling, Remarkable Self-Consciousness and Intense Tension.
3) Eagerness to get Personal Importance.

Type 1) is the so-called dependent type and problems are often found in growth history, especially in parent's attitudes for bringing up their children. Type 2) belongs to the so-called isolated type, unsociable and delicate from childhood, often manifests neurotic symptoms of every kind before becoming a drinker. Type 3) is eager to get personal importance and is passive-aggressive.

On the basis of these clinical experiences, many scholars using various tests strive to classify alcoholics from personality side. Hewitt, using MMPI, found the psychopathic tendency with antisociality. Manson, using MMPI and Cornell Selectic Index, found evident anxiety, quick-temper, over-sensitivity and maladjustment especially troublesome in human relations [26]. Klebanoff, using TAT, found marked uncertainty and imperfect feeling and for this reason many of them present psychoneurotic responses [27].

Moreover, many scholars used Rorschach Test, too. Although Klopfer and others stated finding not a special impression, Halpern and others found from this test immaturity of emotional development and lack of adaptability [28]. And Buehler and others pointed out lack of spontaneity, fall of tension tolerance and duration of evident anxious feeling [29]. Toda compared Rorschach Test among two groups, Solitary drinker and Social drinker. The former showed as a whole poor Rorschach protocols and in point of personality characterized by over-sensitive human relations full of anxiety, maladjustment caused by unbearable nihilistic feeling, self-abandonment, sinful feeling, etc. [30] The latter showed rather rich responses but, in point of personality, manifested oral-erotic tendency in all aspects of human existence and all human relations are characterized by infantile feeling and need for approval.

In our studies, too, alcoholics as a whole have been pointed to have poor thought inhalt, immature inner-control and poor sympathy [31]. Kato and Nishio, through Maladjustment Scale (Fisher), found emotional immaturity. Arai and others, administrated MMPI and Zondi Test as well as Rorschach Test, observed emotionally disturbed personality tendency, deterioration of socio-cultural level and extra-panitive tendency from Rosenzweig P-F Test. The Social drinker is said to have a higher aspiration level and the Solitary drinker a lower aspiration level [32].

As mentioned above, we have discussed the effect of alcohol on the central nervous system. We cannot say that the study in this area has been accomplished yet. Nowadays alcoholics in every country are increasing rapidly, so we hope to obtain many rich results in the study of this area.

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Alcohol and Nervous System with special reference to the Enolic Neuropathies

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Introduction

The enolic neuropathies, both central and peripherical, appear in our midst with a high incidence, whether by themselves or fully playing an assistant roll, mainly in the pathogenesis of some neuropathies of diabetic, tuberculous, nutritional or toxic origin.

The statistics known with reference to the encephalopathies, mielopathies and radiculopathies do not allow the alcoholic ethiology to be fully known because of the late concomitance with other processes. This does not occur with the peripherical forms, mainly those that are not cranial.

In the statistics a frequency is given of 3.95 % of polyneuropathies in proved alcoholics, which is a figure similar to ours reaching approximately 4.2 %. Respecting statistics concerning encephalopathies, also in alcoholics, the figures are unusually lower, 0.7 %, considering all the different kinds of clinical forms. Within the casuistry of our neurological patients, the enolism is 24 %, considering anamnesis valid.

Statement

In our midst it is not easy to appraise the incidence and magnitude of alcoholism. If a group of alcoholics is taken, for example, the risk is that of only grouping those in whom the gravity of the lesion or its complications have made it necessary to make a consultation. Nevertheless, during recent years, both purely enolic and ethylic who do not pay any attention to their own alcoholic ingestion, has apparently increased. This is usually the case of well-to-do people who drink because of the "social custom". On the whole they are well nourished and with scarce possibilities of any lack. They are not subject to physical fatigue and they do not even consider themselves enolists, due to the fact that the alcoholic ingestion is made during meals, as if it formed part of the meal.

Classification

The manifestation of encephalic alcoholism can be grouped in the following way: (according to the classification of Girard and coll. [8–9, 14] with some differences and cases added by us)

1) ACUTE INTOXICATION: Confusion and onirical stages.

   A) Epileptic form with electroencephalogram not decidedly intercritically abnormal.

   B) Clinical liberation of an asymptomatic dysrhythmia, principally in the phychomotor forms.

2) SUB-ACUTE ENCEPHALOPATHIES: With ventricular-stem lesions and of the Circuit of Papez.
   A) Gayet-Wernicke type.
   B) Korsakoff type.

3) METABOLIC ENCEPHALOPATHIES:
   A) Delirium Tremens.
   B) Porto-Cava type
   C) Alcoholic epilepsy.
   D) Crisis in alcoholics without acute access.
   E) Alcoholic abstinence.
   F) Pellagrous encephalopathy and possible lack of other vitamins.
   G) Alcoholic hypoglycemia.

4) CEREBRAL ATROPHIES:
   A) Marchiafava-Bignami type.
   B) Morel's laminar esclerosis.
   C) Cerebellar form (archicerebellar, paleocerebellar, neocerebellar).
   D) Non-especific neuronolisis of the encephalon, with or without gliosis.

5) LESS FREQUENT FORMS OF MECHANISM NOT ALWAYS ESTABLISHED:
   A) Central pontine desmyelinization (CPD).
   B) Symmetrical necrosis of the putamen (SNP).
   C) Pallidal necrosis.
   D) Necrosis of the intercerebral commissures.
   E) Difuse or local desmyelinization.
   F) Alcoholic porfirinosis.

6) MYELOPATHIES
   A) Anterior horns.
   B) Back Tracts.
   C) Anterolateral cords.
   D) Mixed spinal forms. Pseudoesclerosis.

7) POSTERIOR RADICULOPATHIES: (Rare).

8) CRANIAL NEUROPATHIES:
   A) Optical and/or retrobulbar neuritis.
      A') Ophthalmoplexic, neuritical and muscular forms.
   B) Neuritis of VII pair (rare).
   C) Neuritis of VIII pair.
      C') Auditive rare.
      C") Vestibular more frequent.

9) PERIPHERICAL NEUROPATHIES.

10) RETRACTILE MYOPATHIES - MYOATROPHIES:
   A) Pseudomyastenias.
   B) Liberation of a latent myastenia.

ACUTE INTOXICATION: Confusion, convulsive symptoms, ataxia, liberation of sphincters. The neuropathological lesions are: Congestion and oedema at the level of the cerebral and cerebellar cortex and central grey nuclei. These lesions have been found in their pure forms or concomitantly to visceropathies or metabolopathies. The syndrome of abstinence can form a psychologic and neurological picture similar to that of an acute intoxication.

Sub-Acute alcoholic encephalopathy

Gayet-Wernicke Type: This type of pathology presents its highest incidence in unnourished alcoholics, not always for a long period of time. It is also seen often in the course of another different type of complications as delirium tremens, or in the case of cure by disulphiram. Different causes other than alcohol show figures around 5 to 15 %.

Symptomatology: From the general point of view, asthenia is found, also adinamia and loss of weight. In the digestive area, anorexia, nausea and vomits are the most observed symptoms.

As to the symptomatology derived from the sphere of the nervous system, we will say that on some occasions, the commencement is sub-acute and accompanied by headaches, slowness in ideation, descent of vigilance, confusion.

However, on other occasions, the commencement can be acute due to a glucidic surcharge, of apoplectiform type or mental confusion, anterograde amnesia, Korsakoff type. Consciousness may present different grades of disturbances from bradipsychia to stupor. Sometimes onyrism, zoopsias and agitation are seen. The psychiatric picture evokes the lesion of the mamillary, talamic bodies and cingulum.

Ocular paralysis. This seen in 20 to 50 % of the cases. Paralysis of the Oculo Motor, in general dissociated, that is: without participation of the intrinsic musculature, symmetrical or not. Paralysis of the Abducens, Paralysis of function, isolated or associated (vertically, laterally, convergence). Internuclear paralysis with loss of convergence and optokinetic reflex, being able to be intermittent during the commencement.

The photomotor reflex can be slow or abolished, but the Argyll-Robertson sign is never present.

The eye fundus is normal, although oedema of the papilla and even hemorrhages can be seen.

The nystagmus is frequent and precocious.

The cerebellar syndrome is frequently observed, principally at the beginning, but it can also be sequelar alone. The pneumoencephalographic observation reveals a cerebellous atrophia [4, 5].

Muscular hypotonia is rarely seen. The hypertonia is more common and this varies with time. It may be absent during the period of rest and appear with passive movements, increasing with the extension of these (Hypertonia of opposition).

Corea. Pseudoparkinsonian syndrome.

Cases of descerebrated rigidity (Magnus and Klein) or rigidity of decortication, are seen. Tetanoid forms with hypertonia at predominance of the axial musculature with pseudomeningeal picture and trismus.

Babinski with hyperreflexia may be added. Generalized epilepsy. Prehension. Gestual perseverance, noises, movements with tongue and mouth.

Hiccough. Vegetative alterations such as tachycardia, hypotension, hyperperspiration, alterations of a respiratory type, hipo or hypernatremia.

It can be associated with polyneuritis, retrobulbar optical neuritis, heart insufficiency, pellagra, other alcoholic encephalopathies, subdural haematoma, Marchiafava-Bignami [15–16], centropontine myelinolysis, etc. [3, 19, 21, 22].

Complementary examinations: The dosage of Thiamine is not reliable. The colorimetric method has the peculiarity of giving high figures in blood, if the organism has ketonic acids or aspirins, for example. As for the chromatographic and enzymatic methods, both are reliable. The figures are 275 micrograms per ml. and 0.5 mg. per 100 ml. respectively.

Hyperpyruvicemia is also seen in intoxication with heavy metals and metaloids, in nodose periarthritis and diabetes. Also in bronchogenic carcinoma, hepatic cirrhosis and lack of vitamin B12.

However, there does not exist any relation between the gravity of the picture and the pyruvicemia which can even be normal. The pyruvicemia descends with treatment only in those cases which were not treated; furthermore, it can be that it does not get rapidly down to normal by giving Thiamine.

The test of hyperpyruvicemia by glucidic surcharge is risky.

As to the transcetolasic activity of the erythrocytes, this is disturbed with the insufficiency of Thiamine.

The LCR is normal.

The EEG depends on the grade of alteration of consciousness.

Evolution: The prognosis is bad, in general fatal. The sequelas can be the syndrome of Korsakoff, the cerebellar syndrome and oculomotor paralysis.

Pathologic Anatomy: It concerns bilateral and symmetric lesions in the grey formation around Ventricle III, the cerebral aqueduct and Ventricle IV. The mammiliary bodies are always injured and they are often atrophic and hemorrhagic. These anatomic lesions are also seen in the localizations previously mentioned, and further-

more in quadrigeminal bodies, principally inferior, vestibular nucleus and dorsal vagus. It can also be that there are injuries in the Median and Dorsal nucleus of the Thalamus, Bulbar Olives, the Pulvinar, Striatum, Locus Ceruleus and Locus Niger.

As to the clinical correlation, we will say schematically that the hypothalamic lesion would be what is responsible for psychic disturbances, the mamilliary lesion of the Korsakoff syndrome, the oculomotor paralysis by the periaqueductal and internuclear lesion by posterior longitudinal tract.

The vestibular disturbances are through the direct lesion. However, the cerebellar syndrome is not easily explained in certain patients in whom the anatomopathological lesions are not evident, it being clear that it is not so in the case of atrophy of the Purkinje cell or in other formations [5].

With the microscope it is possible to differentiate lesions of a vascular type which are the first to appear and which dominate in the acute forms. Arteriocapillary hyperplasia of the three membranes is seen (pseudoglomerular) in capillary adventitia. Vascular pseudo-eruption without neoformation. It is associated with delamination and hyalinization which permits to speak of angionecrosis. Sometimes the alterations of the intima are very severe. Hemorrhage in general is not present, but when it does exist, it can become considerable. When death occurs slowly it is replaced by pigmentary deposits [4].

The vascular and neural lesions do not superpose neither as to their topography nor in their intensity with the neural alterations which are sometimes mild and sometimes serious as we have already explained. In Mamillary bodies, for example, ischemic lesions exist which could not exist in the vestibular nuclei or Vagus Dorsal. They vary from one case to another. Some neurones can be intact; others, however, can be laden with hyperchromatic lipids or pigments. In the chronic forms, the nucleus is seen to be excentric, with granulovascular degeneration, chromatolysis, neurolysis, disintegration of the Golgi apparatus, tigrolysis and alteration of the Nissl granules. Sometimes in the mamillary bodies, absence of neuronal depopulation is found, and on the other hand, an aspect of pseudohypercitosis. The neurones increase in volume, they are polyhedral and eosinophilous. The Nissl substance is lost in the periphery, with an granulomatous aspect, and a yellow pigment (Lipofuosin) [21] is observed. Ovoid, vesiculose, eccentric nucleus with prominent nucleoli. The lesion takes the median zone of the Mamillary bodies and it is not accompanied with architectonic alteration. The mamilo-thalamic tracts are respected, but other neuronal populations are swollen or disappear. There are zones of demyelinization and it can be thought that the neuronal suffering is the retrograde consequence of the lesion of the processes of the neuronal cells.

In what it does to the glial modifications, we think that they have no proportion with the vascular ones. It is important in the slow forms where there is an astrocytarian reaction, hyperplasia, anarchic hypertrophia. Astrocytes with fibrillar aspect or degenerate necroties. Microglial reaction. At times, as we will see, there exists astrocytic indemnity and great lesion of the oligodendroglia [18].

Concerning the myelinic alterations, we will say that these are exceedingly precocious, with clinical forms which can be specific.

The reasons which would explain the different topographs of these alterations would seem to either the presence of nuclei ontogenically more precocious with different metabolism or the presence of zones lacking in hematoencephalic barrier. This latter case would also explain the difference between children and adults.

Fisiopathology: The alterations produced by alcohol are partly due to a lack of vitamin B1. Alcohol produces an increase in the need of it and at the same time a decrease in its absorption.

In the experiment the same lesions are reproduced as in the human organism.

The alcoholic encephalopathy is due to the acute and massive lack of vitamin B1. In experimental form, no signs appear until 70 % of Tiamine have been lost for the great encephalopathy.

Minor scarcities of this substance, but

more prolonged, would produce peripherical neuropathies, without necessarily giving it an identical mechanism.

Pathogenic effect of thiaminic lack in the brain: In this aspect the transport of the Na ion in the central axon plays an important role. It turns out to be the coenzyme with area of influence coincident with the topography of the illness, indispensable for two systems: the carboxylase of the ketonic acids and transcetolase. Obviously the blockade of either of these two systems could provoke lesions.

The carboxilase is extremely important in the metabolism of the ketonic acids (ketoglutaric). It maintains the cerebral rate of ATP and of Acetilcoenzyme A.

On the other hand, it is doubtful as to whether the increase of the pyruvic acid and that of the cerebral pyruvates can correlate with lesions at this level.

The transcetolase would be more important in the experimental order.

The chart of transcetolase activity coincides with the topography of the illness. The renal insufficiency which is complicated with encephalopathy and neuropathy diminishes the transcetolase activity without the intervention of Thiamine.

The carboxilase activity increases in a parallel way with the regression of symptoms by way of Thiamine. The transcetolase makes it slower. In experimental encephalopathies, rates of reduced glutation have been seen. Both mechanisms are not incompatible. Other shortages have also been mentioned, vitamin PP, B2, A, C, but they are linked more with peripherical neuropathies.

All the lack of vitamins, except thiamine or vitamin B12, are null or scarce in the pathogenesis of the human encephalopathy Nevertheless, some lacked signs of shortage of thiamine and are thiamine-resistant and would respond on the other hand to vitamin B12 or to folic acid. As we have seen before, the thiaminic dosage is of difficult appraisal in the interpretation of its values.

The hepatic lesion creates situations such as the following: There exists sufficient thiamine, but not very active due to the alteration of the apoenzyme of protide nature, in which the synthesis needs the normal hepatocyte and the contribution of protidic anabolizants as vitamin B12 and folic acid.

Korsakoff type: Important bilateral alterations are observed in the circuit on which the Hypothalamus-Mammillary Body-Thalamus-Cingulum with relation to the emotion and memory, principally of recent cases, are related:

The lesions are gliovascular and neuronal, preferably situated around the Sylvius aqueduct, between the Posterior Hypothalamus and the IV Ventricle. The mammillary tubercules are the most frequent structures and intensely affected, and it is observed that they are retracted, reddish and with intense gliovascular reaction, but in some cases with neuronal indemnity, which justifies the possible reversibility of the process when the ethiology is, for example, of extreme scarcity.

Frequently it is also observed that the lesion reaches the thalamic nuclei principally the Dorsomedian and its connections [18].

Metabolic alcoholic encephalopathy

Delirium Tremens: In this case the anatomopathologic lesions are somewhat inspecific including vascular, petechial and congestive lesions, oedema with late varied lesions.

Porto-Cava Type: The lesions of the nervous structures in this case are probably produced by the high tenor of the amoniac in the portal blood flow in view of the subjacent hepatic disfunction and in general lines are of the type of those previously described: neuronal depopulation, gliosis, vascular lesions, petechial and hemorrhages [4].

Alcoholic Epilepsy: The pure forms are disputable. Excess of alcohol favours the crisis in epileptics, but it cannot be spoken of as an alcoholic form. Alcohol diminishes the convulsive threshold. In predisposed individuals the crisis can be brought about

only with excess, with pathologic EEG. The crisis is produced in 12 to 48 hours following the ingestion. In other cases convulsive crisis are produced by abstinence.

Crisis in alcoholics without acute excess or abstinence: Neither the clinical nor the EEG reveal peculiarities, that is, there is lack of paroxysms. The crisis are not frequent and often during the night. The mechanism is unknown. In some cases, it is possible to discover cortical atrophies through the pneumoencephalogram.

Alcoholic pellagrose neuropathy: The three "D"s are not noticeable at present: Dermitis, Diarrhoea, Demency. What is hardly likely to lack is the dermopathy frequently photosensitive. Dermatological and mucous signs are seen, Delirium, desorientation, agitation and hallucinations.

The histological lesion reveals neuronal lesion without gliovascular lesion nor necrosis. Swollen cells with their eccentric nuclei and central chromatolysis. They offer the aspect of retrograde degeneration. The pontine nuclei principally take the formations of the trunk, and eventually the posterior hypothalamus, medulla spinal cord and peripherical nerves. There is also a lesion at the level of the cortex in the Best cells. Cerebellar pathology is also observed, not very frequently; spinal cord, very frequent and peripherical neuropathies.

The origin of this picture would be by multidefficiency with domination of lack of nicotinic acid, vitamin PP, difficulty in the transformation of tryptophane at the level of the digestive tube by the bacteria, defficiency of Vitamin B6 which is important for that transformation, lack of essential proteins and presumed alteration of the genetic code, the same as in other alcoholpathies (DRN-DHN).

From the clinical point of view and to emphasize what has previously been convened, the following can be found: delirium, confusion, agitation, balance disturbances, retropulsion, dentate wheel, muscular jerks in hand and face, hypertonia of opposition, catatonia, hyper- or hypo-rreflexia, sensitive or sensory alterations [2].

At present they are seen in hospices or psychoneurotic patients, and even in places with defficient dietetics and in patients undergoing prolonged therapeutics in which the aspect of shortage is not taken care of, or in social catastrophic situations, such as wars, etc.

Alcoholic hypoglycemia: It is seen in chronic and undernourished alcoholics. It gives the impression of common drunkenness, coma, hallucinations, convulsions, trismus, perspiration, hypothermia, There could be depletion of the neoglucogenesis. Alcohol reduces the hepatic formation of glucose starting from pyruvic acid and alanine.

Cerebral atrophies

Marchiafava - Bignami Type: The *primary* degeneration [24] of the Corpus Callosum is a rare complication of alcoholism and was originally described in men addict to red table wine [15–16]. Its frequency is very low in certain races, as for example the negro race [3]. Its dominion is observed in patients of the male sex, and is frequently associated with undernourishment. Effected also in experimental form. [24].

The original description was effected in 1903, year in which Marchiafava - Bignami [15–16] studied a clinical picture characterized by a demency associated with a convulsive state, in three alcoholic patients. Until Sumsden's work in 1970, 88 cases were studied.

It being difficult to find characteristic semiological elements which interpret the attack of the Corpus Callosum, an apraxial syndrome with inespecific state of demency, associated or not with a generalized hypertonia, bending in the brachial extremities and extensor in crural extremities accompanied with opisthotonos and trismus, should suspect a lesion of the same.

The clinical picture is proteiform and includes psychic and emotional disturbances, delirium and mental confusion, convulsive attacks, diverse grades of trembling, rigidity, paralysis, apraxia, aphasis and reflexes of suction and of prehension. The duration is varied, of several weeks to a few months, the cure being feasible. It is not possible to explain the clinical expres-

sion of the illness, exclusively by the lesion of the Corpus Callosum, but furthermore by the presence of more extensive cerebral lesions. The diagnosis in life results practically impossible, being in general of the presumptive cases [4].

This picture is given exclusively in grave alcoholics and as part of the mechanism product, the capillary alteration at the level at the hemato-encephalic barrier, could be admitted with certain doubts.

The pathologic anatomy shows symmetrical areas of demyelinization [11], joining at the level of the Corpus Callosum, above all on the Median Line which commences usually in the anterior zone and later extends towards the posterior region and with less frequency to the Anterior Commissure or in other parts of the White Substance.

Microscopically, two forms of this necrosis and central demyelinization of the Corpus Callosum are described: In the first place, intense demyelinization which gives the impression of necrosis. Myelinic destruction. Free fat fagocytes with granulose bodies. Fragmentation and disappearance of cylindroaxis. Poor glial reaction. Tissular edema, vasodilatation and vascular proliferation without neoformation. Capillaries with endothelial thickening which produces obstruction of the same. The vascular alteration described is less intense than in the Wernicke illness. Lesions with cavitary aspect, pseudocystic when the granular bodies and edema [11] decrease.

The second type includes intense simple demyelinization. Decoloration of myelinic sheath with eventual fragmentation. Axons relatively conserved. Less abundant granulose bodies. Do not lead to cavitation, but they do to atrophy of the Corpus Callosum. The lesions can take the white hemispheric substance in symmetrical form. It respects the internal capsule and the foot of the radiant corona. Sometimes there is a lesion found in the anterior white commisure. In other cases demyelinization of median cerebellar peduncles are seen without centropontine affection. The decussation of the optic nerve, the optical bandlets, the bulbar olives, the cerebral peduncles and the oval center are structures which are sometimes affected. The cylindroaxis are conserved better than the medular fibers of these areas and concomitant reactions are observed of the macrophages and somewhat less of the astrocytes, oligodendrolysis with low content of cytochrome oxidase and high in porphyrins.

According to some authors [10] divers grades of recuperation are presented if the abstinence of alcohol is maintained, and also good nourishment, but in due form the prognosis of this affection, mistakenly attributed to Italian wines is very severe as one third of the cases die during the first or second month, the cases of cure given by other authors being doubtful and not controlled.

Morel Laminar Sclerosis: In this entity the morphology of the lesions is given by a proliferation of the neuroglia with laminar disposition, principally in the third layer of the cerebral cortex, preferably frontal localization [20]. In the clinical picture, the following dominate: trembling, alterations of the rhythm of sleep with behavioural disturbances, undefined gait, agnosia and convulsions [14].

Alcoholic cerebellar atrophies: Usual cerebellar syndrome in acute intoxications-Gait disturbances. Ataxia in the defficient encephalopathies is in all the cases the symptomatology rapidly reversible. As we have said, the pathological anatomy is not congruent with the severity of the clinical picture.

In chronic alcoholism, on the other hand, there exists degenerative lesion with perdurable cerebellar alteration. However, the cerebellar atrophy in some cases can take its course without symptomatology.

From the point of view of the pathological anatomy [18] there is a cortical atrophy limited to the anterosuperior part, vermis and adjacent zone of hemispheres and to floccule and nodule. Neuronal rarefaction in granular layer. Degeneration of the Purkinje cells. Astroglial proliferation in molecular layer. Neuronal lesions in the bulbar olive possibly retrograde. The dentate nucleus is found usually undamaged. The pneumoencephalograph shows atrophy of the paleocerebellum [23].

As to the clinical manifestations the following are observed: gait ataxia, discreet incoordination, intentional tremor of lower extremities, and more discreet in upper extremities. It can follow a progressive evolution, or regressive or standstill in some of the stages. The major incidences are seen in middle-aged men. It can often be associated with tremor through lesion of the central grey nuclei. Apparently there is no relation to any type of avitaminosis.

Infrequent forms of mechanism not explained

Symmetric necrosis of Putamen: Observed by Osonoff and coll. in a child who at three years of age took 250 c.c. of cognac. We have seen the pallidal degeneration in a person with antecedents of pronounced enolism [1].

Central Pontine Demyelinization or Centropontine Myelinolysis: It is mainly characterized by foci of demyelinization or myelinolysis in the rostral region of the Protuberance [3, 21]. Described in alcoholism [23] it is seen in cases of pure undernourishment, even in children [25]. Approximately in 50 % of the cases, it is seen associated with divers illnesses, which is the case in: Urlian fever, tuberculosis, parasitosis, leukemia, Hodgking, Sclerodermia, diabetes, gastrectomy, appendicitis, chronic renal insufficiency, subdural abscess, cranio-encephalic injury, hepatopathies, hyperemesis gravidarum. Furthermore, hydroelectric alterations are frequently observed. It appears at any age.

As to its pathological anatomy, it deals with a limited lesion only or predominantly in the protuberance. Macroscopically it is an area of a greyish colour. Microscopically there is a disappearance of the myelin in the zone with an integrity of axons and neurons (fundamental dissociation). There can be cavitation by necrosis. Rarefaction of oligodendrocytes. Pycnotic degeneration and lipidic overstrain. As to its topography, we say that it is centroprotuberantial, not superposable to vascular territory. Symmetric and concentric [20]. In general of free limits. Sometimes multiple foci and pseudospongiosis are found. In 2/3 of the cases, it would deal with minor asymptomatic forms. It can be associated with Wernicke syndrome, but keeping each entity its proper individuality [19–20].

Attention is called to the fact that in all instances, the patients have died after a period of intensive treatment, and that the illness was not discovered till 1959.

The clinical manifestations depend on the extension which the process can reach. We have seen the appallic syndrome of Kretschmer and Achinetic Mutism [1]. In spite of not knowing the descriptions referring to associations between Centro-pontine Mielinolysis and Marchiafava-Bignami illness, it is possible to affirm that these have been clinically observed, but on the other hand, the association between the latter and the Wernicke syndrome have been described. And we remind our readers that the anatomo-pathological alteration of M. B. is dominantly myelinolytic - that is to say, the pathogenic interpretation of these demyelinizations is complicated.

The context is emphasized of metabolic alterations which accompany the aforementioned cerebral lesions, among which we shall mention: Hepatic insufficiency, hydroelectrolitic alterations, increase of proteic and lipidic catabolism and disturbance of the saccharometabolism, and also alterations of endocrinal type and of metabolism of calcium and phosphorus and of the hypophyseal, thyroidea, suprarrenal and gonadal functions.

Other demyelinizations: Demyelinizations and necrosis of the putamen can exist, also of the cortex, demyelinizations of the cerebellum and median cerebellar peduncle. The diagnosis is usually very difficult even in symptomatic forms. On some occasions there can exist the great pseudo-bulbar syndrome: alteration of deglution, mutism, emotional liberation, spasmodic laughter and crying. Pyramidal quadriplegia (in flexion) can be added. State of aquinetic pseudomutism. If it returns, it can leave dysarthia, intentional tremor. There can be confusion, transitory coma. Terminal coma is the rule. There can be loss of corneal reflex, ocular movements, attitude of decerebration. The

LCR is normal and there can exist a slight increase in the albumina and cells. Its installation is rapid, and death occurs in one to four weeks. As the definition is of an anatomical type, it does not correspond to speak of possible improvements.

POSTERIOR RADICULOPATHIES:

The rarity is simply repeated of these pictures such as was done in the preceding picture. Cervical braquialgias and ciatalgias are frequent, with positional component, so often in an alcoholic.

CRANEAL NEUROPATHIES:

Frequently associated with other manifestations. Present in chronic alcoholics, smokers. Undernourishment and the existence of other toxic pictures favour such. There are present: ophthalmoplegias, rarely pure facial paralysis, trigeminal neuralgias and glossopharyngeal, cochlear and vestibular changes - optical retrobulbar neuritis and optical or optochiasmatic neuropathy.

The clinical manifestations of the optical neuropathy are given for disturbances of sight in colors, alterations in the visual field: central scotoma or cecal centre. Precocious alterations of the visual acuity. All this can present a brusque commencement. The eye ground which at the beginning is normal, presents in the course of evolution, swelling, sometimes hemorrhages, temporal or total paleness. The lesions always bilateral, can be asymmetric. All these alterations lead to definite blindness. The mechanism is nutritional and is essentially due to insufficiency of vitamins and other insufficiencies.

PERIPHERAL NEUROPATHY:

The polyneuropathy is frequently seen in chronic ethylists, principally endolics, with years of alcoholic ingestion in large amounts. In clinic history it is usual to gather the antecedents of a digestive affection as a starting point of the neurological manifestations of peripherical type. In other cases this circumstance is not present, but in general they are often patients in a defficient state of nutrition and in a very bad state on the whole [8–9].

The commencement of the ethylic neuropathy and with less frequency, the enolic, may be in some cases insidious [6] beginning with dysesthesia, paresthesia, tingles and cramp during the night. Global loss of strength can be added, also tiredness, difficulty in going upstairs, decrease in labour capacity.

In other cases the commencement may be brusque, presumably due to the addition of some factor of a vascular type, which is the case in the "Saturday night paralysis", frequent in the Radial upon supporting the head with the arm while sleeping. The association of an important ingestion of alcohol with an infectious process can be the liberating factor of a polyneuropathy of acute or sub-acute commencement, which can be ascending, reaching grave quedriplegias. They are sometimes Giullain-Barré's syndrome with all its characteristics. It should not be forgotten that in these acute cases with generalized pain, one of the components is constituted by the lesion of the muscular fibre [7, 8]. The alcoholic myopathy [12, 13] complicates the picture by the grave paresis and atrophies that can provoke severe alterations of gait. The ulcerous mutilant acropathy are not very frequent. Other times myasthemic syndromes are observed that can be latent pictures liberated by alcohol. In this type of patients it is the psychic manifestations which can call the attention, with amnesia alterations loss of attention and concentration capacity, or the well known Korsakoff psychosis, or cerebellar signs, tremor, or monosymptomatic apraxia (Primary degeneration of the Corpus Callosum, which we have already described). In the ethylist, the pain awakened by the compression of the muscular masses or of the nervous distances should be put on the track of neuropathy. In the state period, the objective changes are added to the subjective disturbances of the sensitivity. The patient can already now only complain of tingling. In some cases fulgurant pains are added with night exacerbation. These pains are accompanied with tactile numbness to the objective examination, hyperalgesia in the picture of painful

anaesthesia or a free alteration of the tactile sensitivity, which is also thermal and painful. The causalgiform syndromes are not infrequent. In that concerning the deep sensitivity this can be seen alternated with hiccough or apallesthesia and akinesthesia, but not in such an evident way as in other polyneuropathies. These grave alterations of deep sensibility that can reach a pseudotabetic form, should remind one of the medullary lesions of funicular degeneration type, not infrequent in alcoholics with atrophia of the gastric mucosa, alterations of the intestinal passage, dooping phenomenon, mal-absorption and malnutrition.

Sensitive loss can take an aspect of stocking in lower extremities, but it is not openly symmetrical or is more evident in certain nervous territories [2].

In what concerns motility, this is found to be affected in a variable way. Flaccid paralysis is usual, which affects preferently the muscles of the anteroexternal region of the leg, with "ballant" and "stoppage" foot in the gait. Paralysis can take hold of the flexor muscles of the foot, the quadriceps, and as it has already been said, can be ascending with paralysis of the abdominal, spinal paralysis, and that of upper extremities.

Muscular hypotrophy is more accentuated in the lower extremities. There is pain in the muscles on palpation, and they are indurated.

The tendon reflexes, principally the patellar and the achylian are abolished in the state period, but in the first moments, as occurs in other polyneuropathies, they can be alive.

The skin of legs and feet of these patients becomes dry, fragile, cold and shiny. The acrocyanosis or ochre pigmentation of the skin are not infrequent. The nails are alterated with increases of thickness, striation and onychogryposis. The feet become emaciated but atrophy of the muscles of the feet is not as important as in other polyneuropathies. Sometimes they take on the aspect of certain stages of mutilant ulcerous acropathies.

We should call attention to the possible appearance of ulcero-mutilant acropathy in alcoholics. Of possible presentation, but rare, in the polyneuropathy in general by traumatic factor (footwear) or physical-chemical aggression (hot water bags - keratolytic) constitutes the most important discovery in the Bureau Barriere syndrome. They are old alcoholics, middle-aged, undernourished, belonging to the social class of poor means and who usually do heavy work, many times in damp places and without appropriate footwear. None of them present family antecedents - in other words, added pictures of alcoholism. That is, without forgetting the frequency of alcoholism in the patients with syringomyelia, Thevenard's disease, leprosy, etc.

An examination shows the loss of a global sensibility in the form of a stocking, with trophic alterations of both feet. The skin takes on an ochre colour, it is thin and dry. The nails are deformed. Arthropathies appear with the type of neurogenic arthropathy. The motor alteration is not important, but hypotrophy is seen in the leg muscles and atrophy in the foot muscles. The foot takes on a rigid aspect and the movements of the toes are seen to be limited. Over the hyperkeratotic zone in the sole or plantar side of the toes, a blister forms, and later an ulceration of sanious edges that does not heal and commonly not painful. The ulcer gets infected and advances toward deep tissues with osseous and articular lesion and posterior amputations.

This lesion has been attributed to an alteration of the raquidian ganglia with neuronal destruction and fibrosis. Nevertheless, in some patients polyneuropathy combines with the lesion of the raquidean ganglion, fact which is seen in the decrease in the nervous conduction, although in some cases studied by means of electromyography, we have not found any open signs of muscular denervation.

It must not be forgotten that porphyrial neuropathy can be central whereas the peripherical is the more frequent in these patients.

In the ethylists with neuropathies, the following examinations should not be omitted: hepatic and cardiac function, complete study of the gastric intestinal and pancreatic function.

The cerebrospinal fluid is normal or the albumina is slightly increased. We have seen in chronic alcoholics with acute intoxication, albumino - cytologic dissociation and an increase of the gamma globulins in the electrophoretic course.

The electromyographic study and that of the velocity of nervous conduction effected in proved alcoholics without clinical neuropathy (Bischop and coll. 1972) shows a decrease in the velocity of conduction and in 60 % of them, an increase of polyphasic potentials without open signs of denervation [17].

In proved polyneuropathies we have seen a clear decrease in the velocity of nervous conduction in the internal Popliteal (OT) and External Popliteal nerves. In the upper extremities, the affection is not so evident.

The signs of denervation are not so clear, but potentials can be seen which indicate denervation of anterior tibial (OT), peroneus largus, gastrocnemius, principally if the compressive factor is added. The increase of the lyphasic potentials is simple, exceeding 20 % of the total. The maximum voluntary effort permits poor interferences to be seen. In the case of myopathy the electromyelograph will give the characteristic signs of this, but sometimes presents itself in proximal form.

In the pathogenesis in the pure forms is admitted as we have previously analysed, lactic pyruvic acid with inversion of its index, these factors being varied in cases of great chemical, metabolic pathogeny, as occurs in the formation of porphyrins related or not to alcohol, in diabetes, in toxic neuropathies, principally the thallic and plumbic, a special clinical appearance in the cases to which methylism is added.

The physical variances which provoke alterations of the axon or of the myelina are peculiar, and they also modify the evolutionary course of a paralysis caused by another illness such as facial or frigoral paralysis.

It is worthy of emphasizing that in primary acute enolytic intoxications, the alterations are practically exclusive and dominant in the Central Nervous System, as we have seen.

SUMMARY

A commentary is made of the different causes and pathogenic mechanisms of the diverse alcoholic neuropathies.

The following have been considered: acute intoxication, the sub-acute with its different sub-types, Gayet-Wernicke and Korsakoff, all the forms of alcoholic encephalopathies of metabolic type, cerebral otrophies. Also we have considered the forms of less incidence and mechanism, not totally clear, the myelo and radiculopathies, the craneal and peripherical neuropathies, the myopathies and myoatrophies and the myastenic or pseudomyasthenic forms.

RESUMEN

Se hace comentario de las diferentes causas y mecanismos patogénicos de las distintas neuropatías alcohólicas.

Ha sido considerado lo siguiente: intoxicación aguda, la subaguda con sus diferentes subtipos, Gayet-Wernicks y Korsakoff, todas las formas de encefalopatías alcohólicas de tipo metabólico, atrofias cerebrales. También hemos considerado las formas de menor incidencia, con mecanismo no totalmente aclarado, las mielo y radiculopatías, las neuropatías craniales y periféricas, las miopatías y amiotrofias y las formas miasténicas y seudomiasténicas.

RESUMÉ

Nous avons fait un commentaire des differentes causes et mecanismes pathogeniques des distinctes nevropathies alcooliques.

Nous avons consideré l'intoxication aigue, la subaigue avec ses differentes formes, Gayet-Wernicke et Korsakoff toutes les formes d'encephalopathie alcooliques de type metabolique, atrophies cerebrales. De même nous avons consideré les formes de moindre incidence, de mecanisme non complétement éclairci, les mielo et radiculopathies, les nevropathies craniennes et peripheriques, les myopathies et amyotrophies et les formes myathéniques et pseudo-myasthéniques.

ZUSAMMENFASSUNG

Es werden die verschiedenen Ursachen und pathogenen Mechanismen der verschiedenen alkoholischen Neuropathieen komentiert.

Folgendes wurde behandelt: akute Intoxikation, die subakute in ihren verschiedenen Subtypen, Gayet-Wernicke und Korsakoff, alle Formen alkoholischer Enzephalo pathieen von Stoffwechselcharakter, zerebrale Atrophieen. Wir haben auch die weniger häufigen Formen behandelt, mit nicht ganz aufgeklärtem Mechanismus, die Myelo - und Radikulopathieen, den Kopf betceffende und periphere Neuropathieen, die Myopathieen und Myoatrophieen und die myasthenischen und pseudomyasthenis chen Formen.

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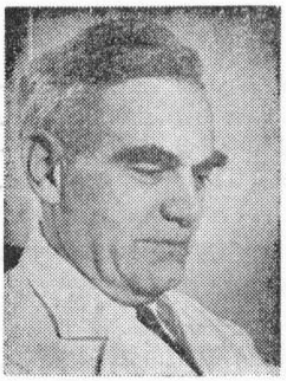

The Future of Neurology

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"The meek shall inherit the earth". As prediction, these words have often been used to preach against pride, as though the kind of humility which is preoccupied with legacy were not the blandest arrogance. Perhaps we should merely take them for advice, instead. When we dare to read the future, we should be humble. Loren Eiseley [1] said, "The future may be guessed at, but only as a series of unknown alternatives". He then quoted Henry Phillips [2] of the Massachusetts Institute of Technology as having expressed this dilemma succinctly: "What will happen five minutes from now is pretty well determined, but as that period is gradually lengthened a larger and larger number of purely accidental occurrences are included. Ultimately a point is reached beyond which events are more than half determined by accidents which have not yet happened. Present planning loses significance when that point is reached..."

Even the Lord that greatest Physician, seems to have had trouble with prognostication if we rely on Holy Writ. We read in Genesis, Chapter 2, verses 16 and 17, the Lord told Adam: "Of every tree of the garden thou mayest freely eat: But of the tree of knowledge of good and evil, thou shalt not eat of it: for in the day thou eatest thereof, thou shalt surely die". And though he partook, we are informed in Genesis, Chapter 5, verse 5 that "all the days that Adam lived were 930 years".

The millennia since Genesis have seen us to an advanced stage of civilization where horoscopes and similar moonshine, are appearing in the daily press. With prognostication of such quality, who needs fortune cookies? How can the future be anticipated except with an eye to the past? There are advantages to having been around the track though it means having reached the decrepit age, which is these days is said to be after 30. The most important thought I can bring to young peers is that they prepare to be competent and responsible. Competent and responsible men and women do not find the future so formidable that they cannot face it with equanimity, even without prediction. I shall try to outline the possibility. Although I shall be speaking of neurology, what I have to say applies to medicine in general. We are all in the same boat.

The ways of becoming a specialist became circumscribed during my career. The simplest method —and I mean simple— was to fall into ignorance of all else, in other words to constrict intellectual horizons. What is known about the function and malfunction of the nervous system in relation to what could be known is limited, though no one is in possession of all of it. Yet there are some who become specialists by reason of limitation. We all have to contend with this pull toward simplicity on entering a specialty, but no specialty is a limited field. It is required that the whole be carried into the part. Neurology is a branch of Internal Medicine, Internal Medicine a branch of General Medicine which is subdiscipline of Life. Specialization is made necessary by human limitation, but its danger should always be kept in mind. I suppose Shaw was in this vein when he said: "No man can be a specialist without being in a strict sense an idiot" Even though the field of Neurology is so broad that no one encompasses all of it,

falling into ignorance on all else removes one from the roster of the responsible. Striving for ever widening horizons, against the traffic, develops character, as work develops muscle.

The usual pedagogy does little to encourage or even sustain breadth. The medical student is faced with a vast heap of information but rarely hears that he is expected to be broadly oriented. In fact, such breadth as he brings with him usually is discounted or ignored. Perhaps the clearest evidence is the almost total lack of interest displayed in his ability to express himself. His particular responsibility appears to be to incorporate information and regurgitate it on request, condensed and annotated. This parrotting trivializes mentality.

Another example might be cited in the examinations students are exposed to, including specialty board examinations. These generally reinforce the idea that memorized knowledge will get them where they want to go. Examinations can be rated according to their function as the learning experiences they indeed should be. Most examinations are dismal failures as learning experience. They do not even separate sheep from goats as usually they are designed to do. Such studies as are available demonstrate little relationship between grades and achievement in medicine. They seem, rather, suited to keeping pearls from swine. I do not line up with those opposing any appraisal of discipline or qualification. I strongly support it. But whatever techniques are employed I want them to reinforce a healthy educational philosophy. Examinations in general are not constructed as learning experiences nor to measure correct action in practice, which depends largely on proper discipline.

Wilfred Trotter [3] said it as well as it had been said in his superb essay on Emergency, which applies not only to emergency but to all of practice: "When we turn to consider the emergencies in the strict sense of the term with which the doctor has to deal, we find we are still in a region where personality at least holds its own in comparison with technical equipment. For the more urgent the call for decision and action, the more important are character, the slowly matured power of judgement and a grasp of fundamental principle, and the less trustworthy are more detailed knowledge and executive skill". This is my message.

Learning does not begin nor stop in medical school any more than it began or halted with college. Nevertheless professional training is responsible for many of the attitudes and much of the orientation of physicians. The most able physicians use what they have learned everywhere: at home or abroad, and even at school, and are sustained by their never ceasing development.

The biblical admonition "Physician, heal thyself", suggests the procedural method. You cannot help somebody until you can help yourself. A physician functions well when, in the very broadest sense, his health is good. This kind of health transcends merely physical health. Drawing on his wherewithal of good feeling to apply knowledge to the concerns of others, his major therapeutic tool is always himself. A doctor is truly bereft without this kind of health and his propensity to give is threatened when for any reason his own emotional or intellectual supplies are in disarray. In medical practice, there is no way to give from an insufficiency.

The analytical method of developing a nodding acquaintance with the unconscious, particularly one's own, isn't beyond the capability of anyone interested. It helps to keep in good repair a sense of humor, and in one's own behavior there will be found quite enough to amuse. In growing older, the accent is on growing rather than aging, in never-ceasing development. When health is good and growth is ongoing, the chances for becoming commendably free of fear and comfortable with uncertainty are enhanced.

The future is always uncertain. Among other uncertainties are patients and their behavior, and it is our primary responsibility to become comfortable with them. A prior requirement is still to be comfortable with oneself, for unless one is, one is comfortable with no one, certainly not patients who are ill and demanding. The physician in good health welcomes happenings out of the ordinary since they lead to advances in the discipline. But it is in the nature of

things to settle into routines, and to resist change. Whitehead gave one of his illuminating pronouncements on this particular topic when he said: "The art of progress is to preserve order amid change, and to preserve change amid order. Order is not sufficient. What is required, is something much more complex. It is order entering upon novelty; so that the massiveness of order does not degenarate into mere repetition; and so that the novelty is always reflected upon a background of system".

To indicate what young neurologists face let me cite a few of the changes in a lifetime, which in themselves contain the seeds for research. Early in my neurological career, neurosyphilis constituted some ten per cent of admissions to the general hospital. The advent of penicillin changed all that, and neurosyphilis has become so rare that our young peers are baffled by it, when one or another patient evades a penicillin absolution.

The virtual disappearance of neurosyphilis has called for changing concepts about certain neurological function. It has been taught that appreciation of vibration and position travel together and are conveyed in the spinal cord via the posterior columns. As anyone who continuously examines these functions knows, their deficits usually are dissociated, the appreciation of vibration being afflicted considerably more often and to a greater degree. It appears likely that the historical statement about vibration and position was predicted on disorders of the posterior root, a notorious locale for the attack of the spirochete of syphilis.

I thought I had made this discovery until I got to ruminating about it, and remembered that Netsky [4] had predicated the separate conduction of vibration and position in the spinal cord on the basis of a study of the pathology of syringomyelia. My experience with the relative disappearance of neurosyphilis leads me to agree with Netsky on clinical grounds.

With the disappearance of tabes dorsalis, shooting pain naturally attracted less and less attention. Migrating pain is found not infrequently in multiple screlosis and diabetes. Those who knew the pain of tabes dorsalis tend to ignore it in these other afflictions, perhaps because it is nowhere so obtrusive. It could be that this indifference has led to a similar orientation in our juniors. Whatever the case, it represents a disservice to patients, who appreciate physicians who know how their disease operates. It is a great comfort for the patient to know that his physician knows.

It has been interesting to follow the development of concepts about "stroke", which became more treatable during my career. One aspect was that when no occluded vessel was found in the brain to go along with an ischemic softening, the phenomenon of vasospasm was sometimes invoked, until the demonstration of the occlusive disease in the arteries traversing the neck.

The concept of vasospasm was very nearly discarded when all the mayhem was found in the neck, the terra incognita of medicine during my career. The swing of the pendulum is almost always too far in medical conception; dichotomous thinking is a luxury not to be indulged, in biological operations. Intracerebral arteries have little if any inervation and their intrinsic contractability was considered unimportant in symptomatology. But cerebral vasospasm does occur. It is again engaging attention with the unfolding of the prostaglandins story.

Recent work has suggested a mechanism similar to that of transient ischemic attack operating in the mononeuritis of diabetes and in (what is diagnosed as) thrombosis of spinal cord arteries, where intervening vessels e. g. between aorta and the spinal cord or nerve, have not yet received the scrutiny they deserve. Perhaps some of you will look into this.

I can't forebear the mention of an unresolved dilema, because many consider it to have been solved, namely the treatment of subarachnoid hemorrhage. The results of conservative treatment in the era before the neurosurgeons entered the arena appears to be comparable [5] with those obtained with surgery. Slosberg [6] is the modern exponent of conservative therapy in subarachnoid hemorrhage. Most neurosurgeons excepting only a few continue to operate.

With each patient suffering subarachnoid hemorrhage decision must be taken and as

Kant said this has to be "on the basis of knowledge sufficient for action but insufficient to satisfy the intellect". Sir William Gowers well over a half century ago said this about decision in medicine: "We must always remember it is the balance of evidence that determines diagnosis. The sciences concerned with disease deal largely with probabilities, almost wholly so in internal medicine. The probability varies in degree, but it usually falls short of certainty. We must learn to take probability as our guide. We have to act. To act, we must decide, and to decide we must weigh the evidence, and deal with the probable as if it were certain. Sometimes we shall be wrong, but generally we shall be right; if we hesitate between two opinions we shall be powerless. Remember that also in practical life, in dealing with patients, the habit of discerning the probability and acting decisively is all-important. Nothing is so necessary to every practitioner as the confidence of his patients. To gain that, he must manifest some measure of confidence in himself. If you must wait before forming even a probable opinion, at any rate be decided in delay. Remember, decisive hesitation is far wiser than hesitating decision". Decisions like these call mainly on character, the slowly matured power of judgement and a grasp of fundamental principle. Detailed knowledge is not as helpful as we often think.

A change in neurological practice was experienced as the nutritional neurological states became rare in the United States. Polyneuritis which had been associated most often with alcohol addiction and pellagra became less. Today alcohol remains a consideration in diagnosis but polyneuritis is more often associated with latent diabetes and other conditions such as carcinoma. It is a curious observation worth pursuing that covert disturbance of glucose metabolism rather than severe diabetes is most often associated with the severe neurological peripheral syndromes.

Much was written about sciatica during my youth and what was done to the sciatic nerve, like so much of what was considered therapy, doesn't bear mention in polite society these days. Sciatica has metamorphosed mainly into the syndrome unstable lumbar disc, for which surgery is becoming increasingly replaced by conservative treatment.

What cervical hyperostosis was thought to be during my early career, is at best a guess. The disability was likely considered together with that produced by compression of the median nerve beneath the carpal ligament, and both thought of as nerve root or brachial plexus syndromes.

Drug problems like the poor are always with us. Several decades ago they were the result of the barbiturates and bromides and other addicting substances; today neurologists see mostly the dyskinesias and zombie states, the result of inconsiderate use of a whole series of substances, which George Day has included under the heading of "jollification drugs". One of my most important functions became to take people off drugs that had been prescribed. In fact some of my greatest therapeutic triumphs were achieved in this way. The amount and variety of drugs ingested in these times is fantastic, and the relief obtained by their withdrawal, especially in the aged, gratifying.

As a young physician, I had the useful experience of observing a wardful of patients undergoing insulin shock therapy several times weekly for a half year. I'm not sure it was useful for patients but I surely learned a good deal about the manifestations of hypoglyceria, not to be confused with those of epilepsy, a differentiation which still seems to baffle many. Insulin shock therapy was long since abandoned but its effects became a part of my clinical acumen.

I thought we had also outgrown the lobotomy era, but of late there have been signs of recrudescence. There is a tendency in succeeding generations to discount the work that has gone before. The statistical support currently being put forth for leukotomy is strangely analogous to that put forward on the previous go around, even though area of brain destruction has varied. Those experiencing the original holocaust are not going to admit of this procedure on any other basis than the most rigid selection of patients, each one of them con-

sidered as 100 per cent. Nor will the statistical approach suffice. I cite a quotation from Thomas Carlyle at every opportunity because it is wonderfully apt in the clinical situation, "A judicious man looks at statistics not to get knowledge but to save himself from having ignorance foisted on him".

These are a few of the changes in Neurology in my professional lifetime, there are a whole host of others. Our young colleagues can expect to have an analogous experience. They need to prepare to expect change. You have sensed the shift in thinking that was required with each of them, not only therapeutically but conceptually. Every advance opens up new vistas that we ought to be prepared to exploit. One cannot do this from any other stance than that that nurtures continuing growth; a vintage neurologist will not do. Whitehead said: "Our rate of progress is such that an individual human being, of ordinary length of life, will be called upon to face novel situations which find no parallel in his past. The fixed person, for the fixed duties, who, in older societies was such a godsend, in the future will be a public danger".

Does training foster our remaining students in perpetuity or do we suggest to our junior partners that fact collecting will see them through? Observing the development of oneself and one's peers will help to derive the answer. Watching people grow older reveals that many age rather than grow. This particular way of growing old is an etiological factor in certain forms of senility [7, 8].

A career as specialist should not set the doctor apart emotionally from his clientele. The latter's concerns also require of us a continuing broadening of interests to know what is transpiring in areas other than medicine whether they involve the affairs of the lowliest or those of the captains and kings. There is every reason why a neurologist as an expert in the vagaries of the master organ should develop this general competence. Why else would he enter this particular specialty? Surely not to trivialize the mentality as increasing departmentalization tends to do.

A benevolently skeptical approach is useful. Optimism is possible as long as one maintains health including to be sure an enlarging mind. Things may be in a hell of a mess but if so they are bound to interest anyone who has health.

It requires no foresight whatever to know that the patient will remain the reality of medicine and the clinical method a superior approach. Lack of appreciation of the clinical method usually indicates it was but honored in the breach in training when the temptation is considerable to play with gadgets. Scientific medecine often occupies the student to the exclusion of practical art, as we become more scientific we seem to become less understanding of the human dilemma. These need not be opposed.

Robert Hutchins [9] remarked that: "Training will always be seductive if only because it puts little strain on the mind of the teacher or student. The trouble is as John Dewey pointed out it is always obsolescent. And the rate of obsolescence is higher now than at any time in history. René Dubos has remarked that the more technical a society is the less technical its education has to be".

Currently, medicine is undergoing a sorting of priorities. With the profession increasingly subject to direction from outside, there is bound to be more attention on patient care. This is likely to result in some reorientation particularly of the work ethic. In freely-wheeling practice, physicians have put in as much time as the traffic will bear, for all practical purposes allowing themselves to be governed by the traffic. This may have been devotion to duty, but as often it indicated loss of direction. Few if any of the charges hurled against the profession have concerned the important problem of working beyond capacity. It would constitute my main indictment.

A recommendation I would like to proffer is for every young physician to determine within a reasonable period of time the limitations of his tolerance, and to take steps to remain within his realistic capacity. Obviously, everyone has a limit beyond which he cannot give fair measure to his patients.

Good practice cannot be guaranteed by excellence of training. We are well aware that it may not accompany the acquisition

of detailed knowledge or executive skill, talents that I do not by any means deprecate. They are important but hardly require the lion's share of training they now receive. As Trotter said, more important are character and the slowly matured power of judgement and grasp of fundamental principle. It would augur well for the future if these were given the best attention in schools of medicine and in training programs. Since fine young people are attracted to medicine it can be predicted with confidence that their careful nurture will allow them to appreciate for themselves why there can be no better therapeutics than the mature physician.

This brings me again to what constitutes fair measure and I will have done. I do not believe fair measure consists of pill peddling and I'm sure neither do you. An index of maturity in the physician is in the paucity of drugs his patient receives. It is a desperate situation indeed when the doctor unaware of his inadequacy, strives to redress it with prescriptions. There is no substitute for the physician who knows himself, in the final analysis the best therapeutic instrument.

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The exemplary life of Elizabeth Blackwell first woman medical doctor in the world

About 120 years ago there did not exist a woman boasting the title of Doctor in Medicine, nor was there a female medical student who attended lecture-halls where classes were held for future physicians.

The study and practice of Medicine was exclusively for men, and therefore prohibited for women.

We will dedicate this article to the heroic life of the first woman, Elizabeth Blackwell, who due to her indomitable will and spirit of sacrifice, opened up the way of her congeners to this noble profession: a weak woman who brought about one of the most extraordinary revolutions in history, without aggresiveness, without discursive activity, no high-sounding attitudes. Her best argument was her style of life, her best weapon, that of her own perfectioning.

IN HER INFANCY, THE ONE WHO WAS TO BECOME THE FIRST WOMAN DOCTOR INSTITUTES A DIFFICULT FUTURE FOR HERSELF

Little Elizabeth Blackwell was in deep thought. Her imagination proyected itself towards the future, trying to glimpse into what she would be when she was grown up. A dense mist clouded her desires, and the future seemed impenetrable. With her face resting in her little hands, and sighing, with half-opened eyes, she exclaimed: "I don't know what I will be, but I do believe that it will he something really difficult". In her little body, she felt the flame of conquest of one who aspires to defy all difficulties with a really important objective.

Some restless nature must have taken hold of the little girl, as she outlined the most intricate events in order to be able to fulfill her desire.

The Blackwell family lived in Bristol, England, where the father had a sugar refinery. Samuel Blackwell, a man of great liberal spirit, showed special preference to little Elizabeth, the third-born of his daughters, who was very similar to him in character.

Samuel Blackmell had a great respect for human individuality, which extended to all without exception, putting special emphasis on the children, whom he helped in building their own personality. It is not strange that Elizabeth should deeply love this good and comprehensive person.

WITH HER FAMILY, SHE EMIGRATES FROM ENGLAND TO AMERICA

She was only eleven years old when her father decided to emigrate with his family to America. After living for six years in New York, fortune took wings for the industrious Samuel, and on the border of ruin, he decided to seek new horizons in a small city, called Cincinatti on the border of Ohio, which had the reputation of being flourishing.

The long tiring journey was detrimental to his health, and soon after arrival, he died due to an infection of the biliar ducts.

This was a tremendous blow to Elizabeth. She had lost her father and great friend, and as for the family, their bread-winner. After much discussion, it was decided that the three eldest daughters should earn their living, taking charge till the boys were in a condition to take on this responsibility. Therefore they opened up a small school for girls and Elizabeth taught.

While she was in Kentucky doing this work, in an unusual way fate took another course. One hot tiring afternoon, Elizabeth was fulfilling the sad task of visiting a friend, who was waning away with cancer. From those lifeless lips, words were uttered that were decisive in her life. They were: "Frequently I have asked myself why it is that these women who are always occupied in the care of patients, are not permitted to become doctors. If I had been treated by a woman doctor, perhaps my illness would have been better understood". And looking at her visitor, the extenuated features spat at her: "Why don't you study Medicine?" Elizabeth felt the impact of the question as an aggression to her sensitive nature. Would she be a doctor? The prospect of contact with sick people, the horror of bleeding wounds, the pustules and the respeated vision of death, made her refuse vehemently such a passing idea.

Nevertheless, several weeks after her friend's death, this question followed her without mercy. "Why don't you study Medicine?" She struggled against this suggestion with all her strength. "The idea only of having to work on the physical structure of the human body, affected with different illnesses, filled me with disgust" she wrote years later, remembering this stage in her life.

SHE DECIDES TO BE A DOCTOR, BUT THE SCHOOLS OF MEDICINE DID NOT ACCEPT WOMEN TO BE ADMITTED

But the idea attracted her and repelled her at the same time, until suddenly her spirit was enlightened. Would this not be the opportunity to do something really difficult? Would this be a worthy objective to which I can employ all my energy: Her fate was decided: she would be a doctor.

With firm determination, she started what was for her, a path sown with thorny difficulties.

The family's doctor tried to suavely dissuade her, explaining to her that it would be very difficult for any Medical College to admit her as a pupil.

But he did not refrain from saying that the best were in Philadelphia. Full of hopes, Elizabeth travelled to Philadelphia, with money industriously earned with her work. Her first step was to request to be inscribed in the most important Medical School in that city.

Bit by bit her ambitions were cast down, as one after another of all the Medical Schools denied her request for admission.

She realised that it was very difficult to stand on her feet in a world which until then, was only reserved for men, When the last of them closed the door in her face, Elizabeth decided to try her luck in New York, but alas! there again, time and time again her hopes were dashed to the ground.

Some had pity on her obstinate attitude, and gave her to understand that if she attained her aim, it would cause a real revolution, but nevertheless, they spoke encouraging words to her.

If at the beginning, Elizabeth had doubted as to the idea of being a doctor, this constituted her main objective now, and she would not give in until she had attained her intent. This aim had assumed the nature of a sacred mission, which she could never abandon.

But fate which had put her to such a hard test, also granted her a small light which encouraged her on her way.

Dr. William Elder, distinguished doctor of Philadelphia, had something in common with her father, and respected the rights of every human being. He was very well known as he had always pleaded for the rights of women. This doctor gave her hospitality in his home, and not only did he give her friendly advice, but also instructed her in different aspects of medicine.

At the same time he tried to get her into some Medical College in Philadelphia, under his responsibility. As he failed in this intent, he decided to write to a friend of his childhood, who was Dean of a small Medical School, which is now known as Hobert College, in Geneva, state of New York.

His letter perplexed the Dean: A woman, student of Medicine

He did not want to slight his friend, but thought he would have to scheme the best way to get out of this problem.

He wrote to say that he, on his part, would not put any difficulty in the way, but that he thought it appropriate that the matter should be solved by the students themselves.

Therefore this problem would be submitted to voting by the students. He hubbed his hands happily, as he was sure that the students would vote negatively, but what was his surprise when everything to the contrary occurred.

HER ADMISSION IN A SCHOOL OF MEDICINE

Under the date of October 20, 1847, the assembly of students unanimously expressed the following:

"It is resolved that one of the principles of the Republican Government is the universal education of both sexes, and that the request for admission

of Elizabeth Blackwell to be a member of our class, counts with our entire approval, and upon extending our unanimous invitation, we promise that our conduct will never cause her to repent of having attended this Institution".

With this really excellent document, of gentlemanly and courteous wording, the first woman student of medicine in the world gained admission.

The youths faithfully fulfilled their promise, their behavior was respectful, and without further fuss, they accepted Elizabeth in a natural way as another companion in their class.

Nevertheless, her exploit was not considered favorable by everybody: there were members of the Faculty who did not conceal their disgust, and the people of that town looked upon her with disdain, as if a monster were passing by.

Many owners of boarding houses indignantly denied her hospitality, but with her dignified conduct and dedication to study, these suspicious attitudes were overcome, and when the time came for graduation, the people were proud of her.

But with this, she had reached only one stage of the line of conquest at which she had aimed.

DR. BLACKWELL ASPIRES TO BECOME A SURGEON

The next step she wanted to take was equally difficult for a woman. She wanted to be a surgeon. With this in mind, she embarked for France, with the object of specializing in surgery.

She had only graduated three months when, full of hope, she arrived in Paris. There again, the unfriendly eyes of prejudice hemmed her in.

No hospital nor clinic in Paris wanted to accept her, even though she carried her very well earned title of Doctor in Medicine.

With Spartan fortitude she bore this new opposition to her desires. She was determined to study, and would do it at all costs. So she kept her title and her pride in the bottom of her bag. and inscribed in the great Hospital de la Maternité of Paris, as a student in midwifery. She did not mind having to fulfill all the tasks required for that, such as scrubbing floors, making beds and being subject to rigid discipline. She was in a hospital ward and nothing would prevent her from getting experience in Obstretics and Feminine Surgery.

When she reached what she considered as the culmination of her studies, adversity again submitted her to a hard test. In her care for a baby with an infection, she contracted an eye infection, which left her blind in her left eye.

As a castle of cards, her dreams of practising surgery fell to the ground.

SHE INAUGURATES HER OWN HOSPITAL ESPECIALLY FOR WOMEN AND CHILDREN AND THE FIRST MEDICAL SCHOOL FOR WOMEN

She then decided to return to New York and to fully dedicate herself to practise General Medicine. Although she was prepared to face this task, the environment in New York was such that it was not ready to receive her. No Hospital nor Clinic wanted to accept her patients. Another person other than Elizabeth Blackwell, would have given up such an arduous task, but each of fate's defiances signalled her a goal to attain. Therefore, simply because her patients were not accepted, and having the title and experience which capacitated her for such, she inaugurated a Dispensary, to attend the folk.

Four years later, she opened the doors of her own Hospital, a "Hospital for women and children".

Her brave efforts started to give the best results. Medical Schools had become less reticent to receive women amongst their students. Her own sister,

Emily, had been accepted in "The Western Reserve Medical School" and had received the title of Doctor in Medicine together with another student by the name of Zachenska. Both joined enthusiastically in Elizabeth's work to help her establish a Medical School for Women, as an annex of the Hospital. She had already been directing the hospital for eight years.

In this hospital for the first time, the Hygiene Professorship was created and occupied by Elizabeth herself, the pioneer woman doctor.

In all parts of the world, whenever a woman receives with emotion the title of Doctor, she should lift up a vote of gratitude to this woman who opened for them the Medical lecture halls.

It was twenty years since Elizabeth had received her title, had opened a Dispensary, a Hospital for women and children, and a School of Medicine for those of her own sex. It would seem that her work had reached its climax and it could remain in this condition in a well organized routine.

SHE ESTABLISHES A SCHOOL OF MEDICINE FOR WOMEN IN LONDON

But the creative activity had become in Dr. Elizabeth Blackwell, the oxygen for her life. Thus, leaving the School of Medicine in her sister Emily's hands, she declared: "The pioneer stage has finished... Throughout the Northern States, the free access and equality of rights has been secured for women in the Medical Profession."

She packed her bags and went to England in 1869 to finish her mission in the land where she was born, in Bristol, in a long ago February of 1821.

There she inaugurated "The School of Medicine for Women of London". She had the security of a pilot who has guided the ship of his life through many storms on the sea of experience.

She was only 48 years old and was the first woman doctor, and she had opened hospitals and medical schools in two countries. With real human understanding in the realm of feminine spirit, she summed up her ambitions in these few words: "To be able to see that all human beings be born, and nourished in the right way, and to be better educated".

She died in 1910, at the age of eighty nine years, and as her tombstone indicates, she was "The first woman in modern times to qualify in Medicine" (1849).

DISCRIMINATION IN MEDICAL EDUCATION

When the reluctance to receive women as medical students was on the wane, and women were being admitted in important universities, it was thought that there was no need to continue keeping medical schools exclusively for the female sex. Emily Blackwell proposed to annex her Medical School to the Cornell University. This institution refused her offer, but opened its doors to the feminine element in 1899; then the University for Women inaugurated by Elizabeth, thinking that it was not necessary any more, closed its doors. Nevertheless, the time had not yet come for mixed teaching. The Universities which accepted coeducation of men and women in Medicine, took discriminatory measures as follows: in some, the women sat at the back of the lecture hall; in others, they attended separate classes, while in others they had to sit behind a screen.

Furthermore, many doctors would not consult with their female colleagues.

THE PRESENT TRIUMPH OF WOMAN IN THE MEDICAL PROFESSION

Now that woman has conquered an honorable place in the annals of Medicine, outstanding for her refined quality of intelligence and her devotion to the care of patients' lives, and now that the barrier of sex has been surmounted and only counts with the moral quality and intelligence in the service of humanity, we must give homage by means of these lines, to the valiant woman who suffered all the disappointments and difficulties reserved for those chosen to bear the heavy burden of the pioneers.

The way opened by her is trodden today by thousands of women, many of whom honor the medical class with their talent, occupying the highest hierarchies.

The International Association of Medical Women was founded in 1919, and has affiliates in 34 countries, and members in all the world. It has been built up, thanks to this woman called Elizabeth Blackwell, first woman doctor in the world, who opened up hospitals, and inaugurated Universities in America and England, and was the first one to dispose of four years for the medical career, which until then was done in two years, created by the professorship of Hygiene.

The Greek Mythology, on considering Hygia, daughter of Esculapius, god of health, provided undoubtedly women's place in the annals of Medicine.

Perhaps Hygia smiled complacently from Olympus at the unfortunate and triumphant life of little Elizabeth, who conquered for herself and millions of women who followed in her footsteps, the Doctorate in Medicine, illuminating the austere lecture rooms of the Faculties in all the world with her grace and intelligence.

Prof. VICTOR SORIANO.

• Book Reviews

A TEXTBOOK OF NEUROLOGY

By H. HOUSTON MERRITT
840 pp., ill. Lea & Febiger
Philadelphia — 1973

Recently the 5th Edition of the Textbook of Neurology by Prof. H. Houston Merritt was published. He is an outstanding figure in that speciality, for his eminence in his educational posts and in the direction of institutions and societies; his professional status of the famous Dilantin in the Treatment of Epilepsy, which wrought the transformation of the social marginated that were the epileptics, in people with all possibilities to develop within the social circle in which they have to live. Mention must also be made of his books and other publications which enrich the medical libraries in all the world, and other attributes of which he is worthy.

His book, consisting of 840 pages, fulfills the author's purpose: that the reader may find all that concerns illnesses of the Nervous System, described in a precise, concise and orderly way, without omitting any useful knowledge of all that has been attained up till now. In this way, the inquisitive reader finds ample satisfaction in the reading.

The Figures and tables placed within the text contribute towards the hierarchy of the publication. The first 204 which are well chosen, demonstrative and necessary, correspond to graphic material of different authors, who are authorities in the field. The tables, which are also numerous, 136, with statistic data, make it easy for the reader to rapidly take hold of fundamental knowledge of the subject. In this way, the book is also useful for every one who wants to make the most of brief periods of time.

Each topic under consideration is followed by a list of very well chosen and appropriate references, which are useful to the reader who endeavors to increase his knowledge in particular aspects. If the chapters are extensive and of great practical importance, with significant sub-titles, the bibliography is also grouped in accordance with those sub-titles. We shall mention the example of Vascular Diseases of Brain and Spinal Cord, in connection with Clinical Considerations, and the references are classified as follows: Premonitors and Initial Symptoms; Examination of the Patient; Neurovascular Examination; Laboratory Data; Prevention of Stroke; Treatment, Phase 1-Saving Life, Phase 2-Rehabilitation.

Outstanding neurologists participate in topics in which they are authorities, employing the characteristic techniques of the book, that of giving the maximum information with clarity in the least space possible. Thus Virus Infections is in the Hands of Prof. Donald H. Harter; Vascular Diseases of Brain and Spinal Cord, corresponds to Prof. James F. Toole; Developmental Defects and Diseases to Inborn Metabolic Defects, to Prof. Harry H. White; Muscles, Diseases of Collagen Tissues in the chapter of Degenerative and Heredodegenerative Diseases to Prof. Lewis P. Rowland; Diseases of the Myelin Sheath to Prof. Charles H. Poser and Convulsive Disorders to Prof. Gilbert H. Glaser.

All these are very important themes by authors of recognized specialization in same. We thus consider that this new edition of the book by Prof. H. Houston Merritt on which we are commenting, is magnificent. We recommend it to all those interested in the knowledge of the Sciences of the Nervous System, and to all doctors who wish to be up to date in Neurology.

Dr. Víctor Soriano.

EPILEPSY HANDBOOK

By LOUIS D. BOSHES, M. D. and
FREDERIC A. GIBBS, M. D. — 1973

This is a book written by outstanding authorities on the subject, the former in the clinical field and the latter in electroencephalography, who is author with his wife of the famous "Atlas of Electroencephalography". He was also one of those specialists who established what is fundamental in clinical electroencephalography, correlating certain aspects of E. E. G. records with

special pathological cases, with singular meaning for diagnosis, prognosis and treatment. We mention Petit Mal Variant Epilepsy and Akinetic Seizures; Diencephalio (Thalamio and Hypothalamio) Epilepsy with Fourteen and six per second positive spikes, Anterior Temporal Lobe Seizures; The Clinical Importance of the electroencephalogram in sleep, etc.

The purpose of the book is to teach vivid experience, in concise form, with the maximum of clear and definite opinions, correcting and clearing doubts that arise in the reader's mind. It does not expound largely on problems of basic mechanism, but provides rich practical information about all the situations which arise when making clinical epilepsy. They express it clearly at the end of the preface: "The busy doctor needs, and should have, answers to these highly pertinent questions: What is wrong with the patient? How can it be prevented? The book attempts to answer these questions, as quickly, concisely and clearly as the state of our present knowledge permits".

The first part of the book refers to the different types of epilepsy, arranged with a practical criterion and exposed in a precise way in its clinical and electroencephalographic characteristics, both in vigil and during sleep, showing the benefits derived from this exploration in the investigation of the circunstances and the lesions that can lead to epilepsy, besides following the evolution of each case.

Starting with chapter XVI the different causes of epilepsy are studied, configuring the second part of the book which ends with the chapters on Mental Retardation and Cerebral Palsy, where these states are focused in its relation with epilepsy. As an example of the permanent practical intention of the book, we reproduce the final phrase of the chapter on Cerebral Palsy. "The finding of a normal electroencephalogram in a five-year to a nine-year old child with Cerebral Palsy and no seizures, practically guarantees that seizure will not develop later".

The therapeutical part which follows, refers to the antiepileptic drugs and accessories, the surgical treatment and that of psychiatry the book finishing with a chapter on Counselling and another referring to the Community Aspects of Epilepsy.

With this exposition, the usefulness of the book is evident for all those interested in Neurology, Neurosurgery, Psychiatry, Psychology, Neuroscience and Internal Medicine.

Dr. Víctor Soriano.