MODERN TREATMENT BY HYPNOTICS AND BASAL NARCOSIS

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Of all hypnotics the barbituric acids are the most widespread and various. They are not volatile, and I would like to expound their absorption and detoxication. All the barbituric acids are reabsorbable by the gastro-intestinal tract. Sometimes, indeed, they are rapidly reabsorbed by the stomach. That is, for example, the case with evipan, of which 40 per cent of the minimum narcotic dose is reabsorbed in the guinea-pig when the pylorus is ligatured. By the rectal route and in salt form the barbituric acids are more quickly absorbed. The same is true of avertin. As concerns narcosis one avoids administration by the mouth, not only because of slow absorption but because the absorption depends on the state at the time of the function of the upper digestive passages. The rectum absorbs best and most equally, probably because it is an almost neutral region. Certainty of dosage is thus rendered possible, of which rectidon gives a satisfactory example. Truly exact dosage, however, is impossible unless one suppresses resorption, that is, administers the drug by the intravenous route.

Barbituric acids appear to be combined immediately on their arrival in the blood. Bennhold's researches with cataphoresis show that if not injected too quickly into a vein evipan is very rapidly fixed to the albumens. One must admit it offers a sort of selective transport. If one injects too quickly, so that the blood is charged with evipan, or if the blood is poor in proteins, the excess of the drug circulates as free barbituric acid. With the appearance of the drug in the blood there appears equally the process of elimination, that is, an excretion and a transformation or disintegration. The excretion by the urine of the various barbituric acid derivatives has not been precisely determined after numerous imperfect attempts by Halberkann and his co-workers. Comparison of these ex-
periments with our own shows that each derivative is excreted by the kidneys in its free form and without modification in characteristic proportion. This excretion of the different combinations varies from 1.5 to 71.4 per cent of the dose administered. Veronal is passed as to three-quarters by the urine. Curral and luminal come next with proportions of one-third to one-fourth of the dose given. The other barbituric acid derivatives are found in the urine in only very small proportions. The duration of the excretion varies. One has sought to admit that the important elimination of veronal is simply the consequence of the fact that this drug persists for a long time in the blood and is thus offered continuously to the kidneys. But this is not correct for curral, which is found for almost as long a time in the urine, is only eliminated unchanged in the proportion of one-third. The amount of veronal passed in the urine is the same whether the drug has been given in doses of one gramme a day for 14 days or as 50 grammes a day for 16 days. Each derivative presents a characteristic urinary concentration which is not affected by dose or by quantity of urine, with the exception of veronal for which the excretion of barbituric acid by the kidneys plays no important part from the point of view of elimination.

Since they are never found again in salts nor in their primitive form nor in the form of products of disintegration, these drugs must be eliminated by a chemical process. In only three cases has the chemical confirmation of the existence of the products of transformation been made. After the administration of noctal, Halberkann has been able, by the titre of the unaltered product, to recover nearly 20 per cent of the given dose in the form of an oxidised derivative, isopropylacetonyl-barbituric acid. The disintegration is produced in the shape of an oxidation of the lateral non-saturated bromine chain. It is expressed by the equation:

\[
\begin{align*}
CH_3 & = C - CH_2 - C \quad \text{Br} \\
\text{CH}_3 & = C - CH_2 - C \quad \text{OH}
\end{align*}
\]
By intramolecular displacement and suppression of the double attachment there is produced an acetonyl combination:

\[
\text{CH}^3 - \text{C} - \text{CH}^2 - \text{C} < \\
\| \\
\text{O}
\]

As concerns pernocton, it has been possible to confirm the existence of an homologous combination, butyl-acetonyl-barbituric acid. Dox and Houston have shown that this acetonyl association of mono-alkylised barbituric acid scarcely possesses any narcotic power. In the urine of dogs treated with phanodorm, Halberkann has been able to recover, besides such quantities of the non-modified body its hexeonyl combination. Thus, for this combination, equally disintegration is brought about by nonsaturated substitution which in this case is hydro-aromatic. According to our analyses the hexenyl nucleus must first be oxidised and give a peroxide formation from which follows the ketone. This hexenonylthethyl-barbituric acid is equally shown to be devoid of narcotic properties. Evipan, the homologue of phanodorme, is much more quickly disintegrated.

\[
\text{CO} - \text{N} - \text{CH}^3 \\
\text{C} < \\
\text{CO} \\
\downarrow \\
\downarrow \\
\text{CO} - \text{NH} - \text{CH}_2 \\
\text{H} \\
\text{C} - \text{CH}_3 \\
\text{CO} - \text{NH}_2 \\
\text{CO} - \text{NH} - \text{CO} - \text{NHCO}_3
\]

Unfortunately, it has not been possible up to the present to isolate any of the products of these disintegrations in
crystallized form from the urine. Barbituric acids, with saturated substitutes such as veronal, luminal and amytal stubbornly resist oxidation, and what happens to them is not yet made clear. As to the organs in which disintegration of the barbituric acids is effected one knows only that evipan is destroyed principally in the liver. This knowledge is important from the point of view of narcosis by injection since, in the presence of affections of the liver, one must count on retardation of the disintegrating process. On the other hand, changes in the kidneys have no direct influence on narcosis by the barbiturates. The rapidity of the processes of elimination can be measured by experimental intravenous injections determining the "critical speed." If one injects evipan sodium into the vein of a rabbit at a constant rate, with a dosage of 0.5 mgr. per kilo of animal per minute, one can maintain a light sleep for hours. In such a case administration and elimination are balanced. If before the injection one has put the animal into a state of profound narcosis by the injection of 40-60 mgr. per kilo then the "critical speed" of intravenous injection is raised to 1 mgr. per kilo per minute, a fact which shows that the processes of elimination are not baulked by narcosis. Preliminary treatment by thyrosine or removal of the thyroid has in experimental animals no influence on sensibility or on the rapidity of elimination. Generally speaking, the time of detoxication of barbiturates and the quantity given are in direct proportion.

A word or two on avertin. Tribromethanol is equally absorbable by the stomach and by the rectum. The rectal mucosa, however, absorbs more quickly and uniformly than the stomach and the intestine. But since this drug and the water in which it is dissolved do not enter the circulation with the same rapidity avertin is at first more quickly re-absorbed. The elimination of this substance is carried out along routes quite different from those of the barbiturates. Like camphor, or like chloral hydrate, avertin is detoxicated by glycuronic combination. In this detoxicated form it is practically eliminated entirely by the kidneys. So far as avertin is concerned the processes of disintegration are completely suppressed. While oxidation of barbituric acid takes
place above all in the liver, the formation of glycuronic acid and without doubt also its combination seem to be functions more widespread. Pick and Eichholtz have been able to show that a selective alteration or suppression of the liver, of the spleen, of the kidneys, or of the intestine does not inhibit detoxication of avertin. Variations in the metabolism of sugar are equally without influence on glycuron combination. It has only been established that animals in a state of jaundice suffer retardation of this detoxication. On the other hand, increased basal metabolism brought on by thyroxine hastens detoxication of avertin. One cannot say as yet whether there is acceleration of the combination with glycuronic acid or an increased resistance of the cells to intoxication.

An indirect consequence of an upsetting of the equilibrium between resorption and elimination is represented by accumulation, i.e., by progressive increase in the organism of the active substance. This is considered, generally speaking, as a phenomenon little to be desired and sometimes actually dangerous. The choice of an hypnotic for invalids engaged in professional work is decided by the absence of secondary and cumulative effects. But just as with the glycosites of digitalis there are special indications when a cumulative effect is of service. Indeed, if one wishes to get as persistent an action as possible, as, for example, in the treatment of epilepsy, one can, by having recourse to a drug which has power, the better space the administration of each dose.

Another frequent consequence of the administration of hypnotics is habit. Clinical experience, as well as Boussmann's experimental demonstrations, have established that we should not speak simply of habit, but only of habit as regards an ascertained effect. It is clinically shown in a positive fashion that man and animal accustom themselves more or less rapidly to the hypnotic effects of every narcotic. But a "habit" as regards anti-epileptic activity is not seen in man.

The concentration of a narcotic in the blood is the deciding factor as regards its dispersion in the various organs. If narcotics are given in hypnotic doses by the mouth the concentration increases very slowly and never reaches a
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high value. Consequently the organs which can fix the drug can store only feeble quantities, probably disintegrated or detoxicated locally. It is otherwise when narcotic doses are given by rectum or vein. Then important quantities of the drug pass rapidly into the blood, where a high concentration is reached and the flow of the drug follows a rapidly rising curve. In these conditions the organism is invaded by the narcotic exactly as at the induction of anaesthesia by inhalation. We have studied these phenomena with evipan as soon as we succeeded in improving the method of sublimation to the point of being able to regard it as a quantitative proof. The curves show that with doses which bring profound narcosis when given by the vein evipan is distributed almost equally in the blood, the liver, and the musculature. With almost fatal doses, on the other hand, the brain substance contains appreciably more evipan than the blood. After a few minutes, nevertheless, it appears that the concentrations are balanced at the expense of the brain. It is clear then, that after a complete invasion of the organisms by the narcotic the reflex is necessarily slowed. Organs which play no part in narcosis as such, the muscles, liver, etc., start a slow stream of narcotic which relates to the blood in conformity with the declining degree of concentration. The quantities of barbiturate fixed outside the brain, which are great in comparison with those fixed in the centres, act in increasing the time of elimination.

We are accustomed to refer the qualitative properties of different narcotics, liquid or solid, to their particular mode of distribution in the central nervous system. This was, it was held, alone decisive. So far as non-volatile narcotics were concerned the therapeutic margin had to be considered simply as a consequence of the distribution—the distribution of the narcotic between the ganglion cells, whether of the reflex arc, or of the respiratory centre, for death in narcosis does not follow by intoxication but by narcosis of the respiratory centre, a phenomenon as reversible as the narcosis of even the ganglionic cell.

The above considerations are founded chiefly on the experimental investigations of Pick and Molitor regarding the mechanism of hypnotic action. These authors have shown,
whether by systematic removal of cortex or corpus striatum, or by experiments with puncture of the brain, or finally by acting in selective fashion on the negative centres, that one part of the hypnotic diminishes especially the excitability of the cortex of the hemispheres while others accumulate more in the cerebral peduncles and thus act directly in uniformity by making the effect felt by the regulating centre of sleep. These authors insist, further, that one should never discount accumulation in the hemispheres of the drugs which act on the peduncles. In reality the cortical and subcortical distribution of hypnotics is always made only in relative fashion in the regions indicated. Bromine salts, which may be considered as the typical cortex soothers, can, in strong doses, weaken not only peduncular but also pharyngeal and laryngeal reflexes. Paraldehyde, a hypnotic of the cortex itself, suppresses in strong doses strychnine convulsions. It penetrates the spinal marrow before narcotising the vital centres of the spinal tracts. These pharmacological proofs of the distribution of different narcotics in the central nervous system have been able to be confirmed and extended only in recent years when success has been achieved in the quantitative determination of barbiturates in small fragments of tissues. Keeser's work has been, from this point of view, a true initiation. Vogt analysed the different cerebral regions of dogs subjected to narcosis by veronal and recovered this substance in every part of the central nervous system. At first, it is true, the regions rich in cells were favoured in comparison with those rich in fibres and consequently rich in lipoids. But with the prolongation of the narcosis this difference was wiped out and the narcotic was spread in a completely diffused manner, not only in the central nervous system but also in the blood, in the liver and in the kidneys, as we ourselves found for evipan, independently of Vogt.

This equalizing of distribution is still more rapid with curral and with phenodorm. Only the cerebro-spinal liquid always remains poor in narcotic. A brief washing with saline solution of the animal still living, but bled white, retrieves veronal from the central nervous system with remarkable rapidity. Koppanyi and his fellow-workers arrived at the same result. Vogt has established that the
amount of different barbiturates in the encephalon is universally proportional to their activity for the same stage of narcosis. This means simply that it is not the distribution of each barbiturate in the different regions of the brain which determines the absolute activity of these bodies and their therapeutic margin but the various specific sensibilities of the nervous tissues with regard to the constant concentration. The amount of hypnotic with regard to which the cortex—phylogenetically younger—reacts by narcosis is upheld by the more senior centres of the spinal tracks, almost without reaction. These chemical determinations of the quantity of barbiturates present in the organisms cannot be reconciled with the lipoid theory. From the point of view of the employment of a hypnotic or a narcotic the decisive features are the relationship between absorption and elimination and, on the other hand, the special reaction of various regions of the central nervous system. For each of the substances we can only voluntarily modify them by the rate and the method of administration. So far as adapting different hypnotics to provoke be it drowsiness or be it prolonged sleep, it is, above all, the processes of elimination which decide.

It is more difficult to settle which non-volatile narcotics can be utilized for narcotics. Medical practice has for some time now accepted the convenience of injection or instillation of narcotics. Although not one of these substances is ideal yet these methods of anaesthesia cannot be allowed to disappear. Theoretically, the reproach is constantly made that non-volatile drugs are not controllable. Such reproaches should lead, not to the destruction, but to the development and improvement of the methods we know. Above all, one must remember the principles to which a narcotic of this group must conform. The inconvenience of non-volatile drugs is that they cannot be controlled at will. The safety which being controllable confers on a drug must, in the non-controllable narcotics be compensated for by other factors. According to Eichlotz's animal experiments the therapeutic margin of avertin given per rectum is 1.5; that of ether is, in the same conditions, 1.34. This superiority is too slight to compensate for not being under control. There-
fore in practice complete narcosis by avertin is discarded. However, the therapeutic margin is widened when avertin is used as a basal narcotic. We tried to render innocuous the individual variations occurring in rectal administration which are so difficult to foresee, by giving avertin in doses so weak that they could constitute merely a basis for narcosis without, however, abandoning the advantages of the method. If a basal narcosis has to be deepened or prolonged it will naturally be possible to have recourse, by preference, to the most easily governed anaesthetics, the gaseous anaesthetics. In basal narcosis by intravenous injection of pernocton another means allows one to avoid the variations of individual reaction; slow injection, thanks to which one learns how the patient reacts during the administration, that is to say before the whole dose has been given. In the course of intravenous narcosis by evipan individual dangers are so lessened, as much by a greater therapeutic margin as by the short duration of the effect of the drug, that one can venture to realize with it a complete narcosis of brief duration.

In this exposition of the physiology of sleep and the pharmacology of narcotics I have designedly limited myself to the modifications which can be effected in normal sleep and in the narcosis of healthy animals. Animal experiment shows that in the first instance every reaction is due to the reactivity of the organs and their constituent elements. In the animal series reaction to narcotics is accentuated with the progress of the evolution of the central nervous system. Evidently man, in whom the central nervous system is so elaborately differentiated, will show, in the healthy subject and still more in the invalid, important variations to sensibility. For this reason every patient reacts to narcotics in an individual manner. There will never be one sole hypnotic for sending to sleep, or for prolonged sleep. The doctor based on his pharmacological knowledge and on his experience must choose the appropriate hypnotic and narcotic for every patient and administer it in appropriate doses. The justifiable desire to reduce the number of drugs is not exactly admissible where hypnotics are concerned.