A STUDY OF PENTOTHAL SODIUM ANESTHESIA AND A CRITICAL INVESTIGATION OF THE USE OF SUCCINATE AS AN ANTIDOTE *†‡

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SINCE we have no real understanding of what takes place during anesthesia (1–6), anything which promises to throw some light on this process must be examined with care (7, 24). The suggestion has been made that anesthesia occurs as the result of diminished oxidation in brain tissue with a consequent loss of the energy normally available for the brain's energy requirements (8, 9). This inhibition of both the glucose and pyruvate metabolism in the brain cells seems to be localized in certain areas owing perhaps to the differential distribution of barbiturates in brain tissue (10). This localized decrease of activity would have little effect on the oxygen consumption of the brain as a whole (11).

A major finding has been that the oxidation of succinic acid, an intermediary step in the metabolic cleavage of sugars, is not greatly affected by the barbiturates (8). It is also well known that other than the barbiturates, certain drugs such as chloretone, urethane, scopolamine and diphenyloxazolidinedione (an experimental drug chemically similar to the barbiturates) are also specific depressants of oxidation in that they will decrease the oxidation of glucose and pyruvate at levels of concentration that do not affect succinate (12).

According to Meyerhof, the energy derived from these oxidative steps in the metabolism of glucose is collected by and into certain phosphate groups which act as "paymasters" for these reactions as well as storehouses (9). Szent-Gyorgyi demonstrated the presence of certain four-carbon acids in oxidation, i.e., succinic, fumaric, malic, and oxalacetic acids (13). To these Krebs added citric, glutaric, and cis-aconitic acids. These are the enzymes through which 70 per cent of

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cellular respiration occurs; the entire system is called the "citric acid cycle" (10, 14).

Each step in the oxidation of glucose involves the passage of electron energy as well as the transfer of two hydrogen atoms to an oxygen acceptor (15). This process has been schematized in figure 1. These steps are facilitated and catalyzed by an important enzyme, diphosphopyridine nucleotide, more commonly known as "DPN" (16). As the two hydrogen atoms leave the "flow line" in their travel to the oxygen acceptor, they are intercepted three or four times by certain chemical

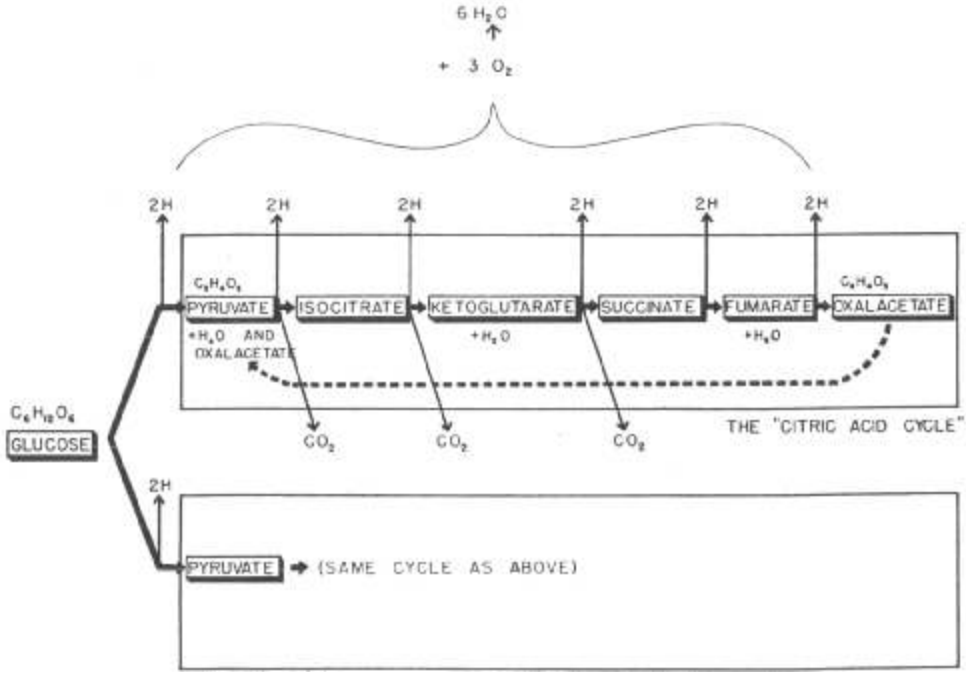

FIG. 1. Stems in glucose catabolism: Dehydrogenation.

devices which, according to Lipmann, transform their electron energy into the phosphate bonds. These devices or "transformers" are at the first levels the pyridines, at the next the flavoproteins and the cytochrome system last (17, 18) (figure 2). It is thought that the greatest inhibiting action of the barbiturates occurs rather specifically at or near the flavoprotein level (19).

Recent work on the effects of oxygen at high tensions on the oxidation of carbohydrates has demonstrated conclusively the vulnerability of the thiolflavoprotein to oxygen when administered under pressures of over one atmosphere (20, 21). Perhaps a parallelism between anesthetic action and oxygen toxicity may be evident (21, 23).

Thus Soskin and Taubenhaus, on finding that succinate alone remains oxidizable both in anesthesia and oxygen poisoning, first sug-

gested, in 1942, that this simple aliphatic drug might be a valuable and physiologic antidote in anesthetic states (24). It was claimed by them that the shortening of recovery time from amytal and nembutal anesthesia was in direct proportion to the amount of succinate used. In their opinion, 100 mg. of succinate could protect the body against 8 mg. of a barbiturate per 100 Gm. of body weight.

Koppanyi has shown that while ammonium chloride increases the excretion of urine and barbiturate in acute poisonings it does not significantly hasten the recovery time (25).

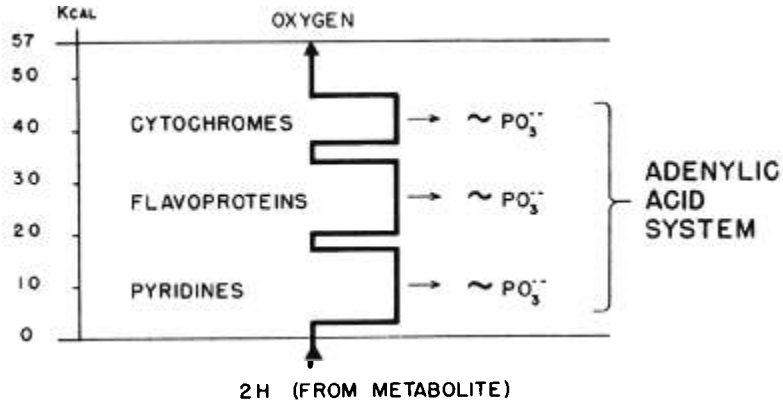

FIG. 2. Path of hydrogen atoms to final oxygen acceptor: Electron potential forms "Energy-Rich" phosphate bonds.

Proger claimed that the A–V oxygen difference is increased greatly through the utilization of more oxygen by the tissues with succinate therapy (26). Lardy and his associates disclaimed the effectiveness of succinate on the basis of their own work (27). Corson et al. recorded the following in their detailed work with succinate: (1) animals treated with succinate recovered in half the time required by the controls, and (2) urine volumes in these animals were markedly greater than those in the controls (28). The first mention of the possible toxic effects of succinate was made by Pinschmidt who found pulmonary edema, hemorrhage, and respiratory failure with doses of 1 Gm. per kilogram of body weight (29).

Because of the scarcity of knowledge of the effects of succinate on man and with the realization that its use might be beneficial on purely theoretical grounds we set out to make an objective study of succinate therapy on barbiturate anesthesia in man.

EXPERIMENTAL DATA

Since the electroencephalogram shows well recognized changes in barbiturate anesthesia, this type of objective test was used in every case studied. Furthermore, since it has been suggested by Hoagland (30)

that the electrical rhythmicity of the cortex is dependent on continuous steady-state chemical events within the cortical cells, such changes in the electroencephalogram might be indicative of interference with the normal procedure of glucose metabolism. If succinate were to prove of value in combating the effects of barbiturate by giving the brain a source of fuel impervious to attack by the drug, the electroencephalogram might by the above hypothesis be expected to indicate this, since some oxidation would be proceeding unchecked.

Electroencephalograms, therefore, were recorded from all subjects studied, the tracings being made by a Grass ink-writing oscillograph and further analyzed by an electronic frequency analyzer of the type designed by Walter. Such an analyzer, a detailed description of which will be found in Walter's original publication (31), enables one to see at a glance the component frequencies present in the original tracing where they may be so intermingled as to confuse the naked eye.

Two groups of subjects were studied during the past three years. One consisted of normal, healthy adult males, the other of patients drawn from the ward population of the Department of Psychiatry at the Massachusetts General Hospital. The latter had been given complete medical, neurologic, and routine laboratory examinations. For all patients in this present series the results of these examinations were within normal limits. Various types of psychoneuroses comprised the clinical diagnoses. All such patients chosen were young, intelligent and cooperative adults, and their subjective impressions seemed to be uniformly accurate and sensitive.

The subjects were prepared in the following manner: breakfast was limited to one cup of coffee and one slice of toast at no later than 8 a.m. Also at this time they were given 50 Gm. of glucose in 3 ounces of water by mouth to avoid the possibility of hypoglycemic reactions affecting the electroencephalogram. No further nourishment or water was allowed until after the experiment, and neither atropine nor other premedication was given. Approximately six hours after breakfast the patient was taken to the electroencephalographic laboratory where the electrodes were applied to the head. The positions were measured in such a way as to place electrodes over each of the frontal, parietal and occipital lobes. The electroencephalogram was then recorded in the usual manner from pairs of electrodes on the scalp.

The general tendency has been to carry over to pentothal anesthesia from work with ether the criteria for the various levels of consciousness. There are, however, important differences. One hundred and twelve experiments on 75 subjects (60 patients and 15 controls) were conducted to obtain an independent measure of the effects of pentothal on the electroencephalogram and on neurologic signs. The characteristics of the successive levels of pentothal anesthesia were quite consistent in the subjects studied. We modified to some extent the criteria described by Himwich and Etsten (32), substantiating most of them.

The criteria may be summarized as follows: Stage of Clouding: *Stage 1.* The first change found as the injection proceeds may be a slight thickening or blurring in speech, and a hesitancy in answering specific questions. The subject sometimes is drowsy, sometimes talkative and euphoric, and occasionally restless (8 per cent). Acute excitement is rare. Eyeball movements are uniformly under voluntary control, as is body musculature. Eyelid tone and corneal reflexes are normal. The pupils are normal in size and react very promptly to light and to pain. The response to peripheral stimulation is slightly hyperactive and, in contrast to the effects of ether, there is no analgesia at this stage. Half of the patients exhibited some evidence of anxiety; but it must be remembered that not only were these psychiatric patients, but also that they had not been given premedication. Pulse rate and respiration remain unchanged. As the injection continues, the speech becomes more blurred as in alcohol intoxication. Attention wanders easily and if the patient has been counting he may repeat the same number over and over, or may stop entirely until commanded to start again. Quite suddenly, contact with the environment is lost and the subject enters the second stage of anesthesia. In 60 per cent of cases a yawn precedes this stage.

Stage of Exaggerated Response: *Stage 2.* The subject is now unconscious. Respiration has suddenly become deeper, more rasping in tone and slightly faster in rate. Peripheral stimulation, such as pinching the skin, at once brings about movement. These movements, however, are purposeful, coordinated and quick, unlike the wild and unrestrained actions often seen under ether anesthesia at this stage. The corneal reflex is absent in 75 per cent of cases. Eyelid tone is normal in half of the cases and only slightly depressed in the other half. The eyeballs show slight rolling motion in 50 per cent of the subjects and are rolled up and divergent in the rest. In 70 per cent of cases pupils are larger than normal, and all react well to light and to pain. Heart rates remain unchanged. As the anesthesia deepens and the third stage is approached the eyeballs remain divergent and tend to roll up in all cases.

Stage of Surgical Anesthesia: *Stage 3: Light.* The subject now makes no spontaneous movements. The corneal reflex is absent in all cases, but eyelid tone is still present to a slight degree in one-third of the cases. Slow oscillations of the eyeballs in a horizontal plane are still present in a few cases; most eyeballs are already fixed. The pupils have become small but still react to pain and to light after a momentary delay. The response to peripheral stimuli is still present though diminished, and reaction time is gradually prolonged by two to four times the normal value. Respiratory activity has settled down after the unevenness of the second stage to a quiet rhythm with a slight increase in rate. Ten per cent of the subjects are snoring. None tolerate an airway at this point. Stimuli to certain sensitive areas or muscle spindles

cause very definite and coordinated responses even while the subject is snoring peacefully and all eye signs are absent. As the deeper plane of the third stage is approached eyeballs in all cases become fixed.

Stage 3: Deep. The pupils are small and pinpoint in all cases. A few may show reaction to light and to pain. Eyelid tone is entirely absent. An incipient relaxation is apparent in the muscles of the extremities and in the abdominal wall in older and more obese subjects. The reaction time to painful stimulation is increased markedly but response is still present in 20 per cent of cases. This, certainly, is in marked contradistinction to the total lack of response to pain found at

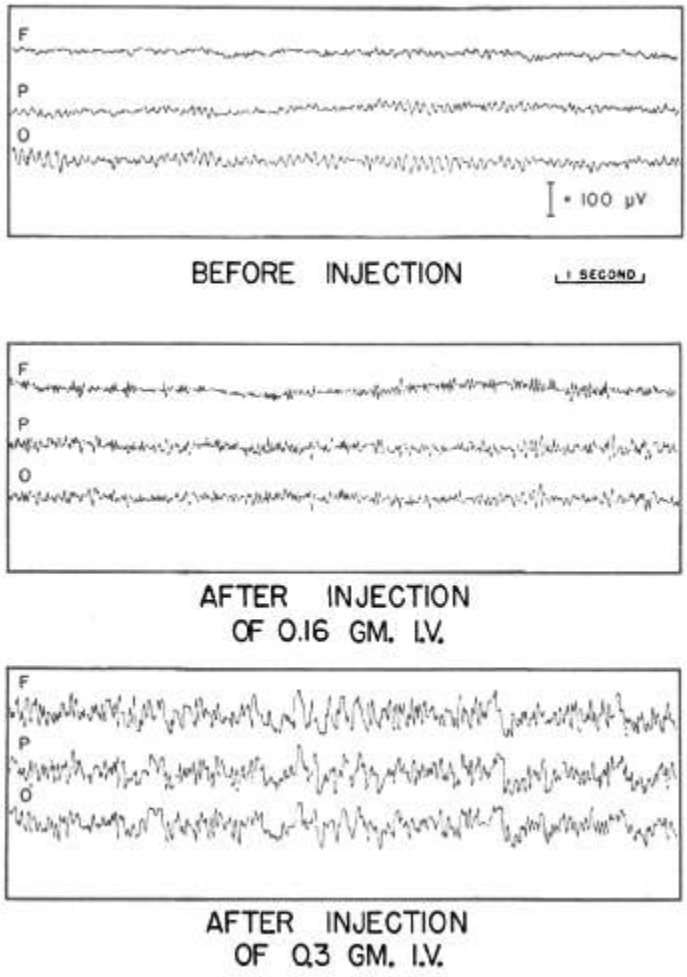

FIG. 3. The effect of intravenous sodium pentothal on the electroencephalogram.

In each of the tracings illustrated, the top recording labelled "F" is from 2 electrodes over the frontal region, the second ("P") from 2 over the parietal region, and the third ("O") from 2 over the occipital region. The amplification and time scale is the same in all records as indicated in the top sample.

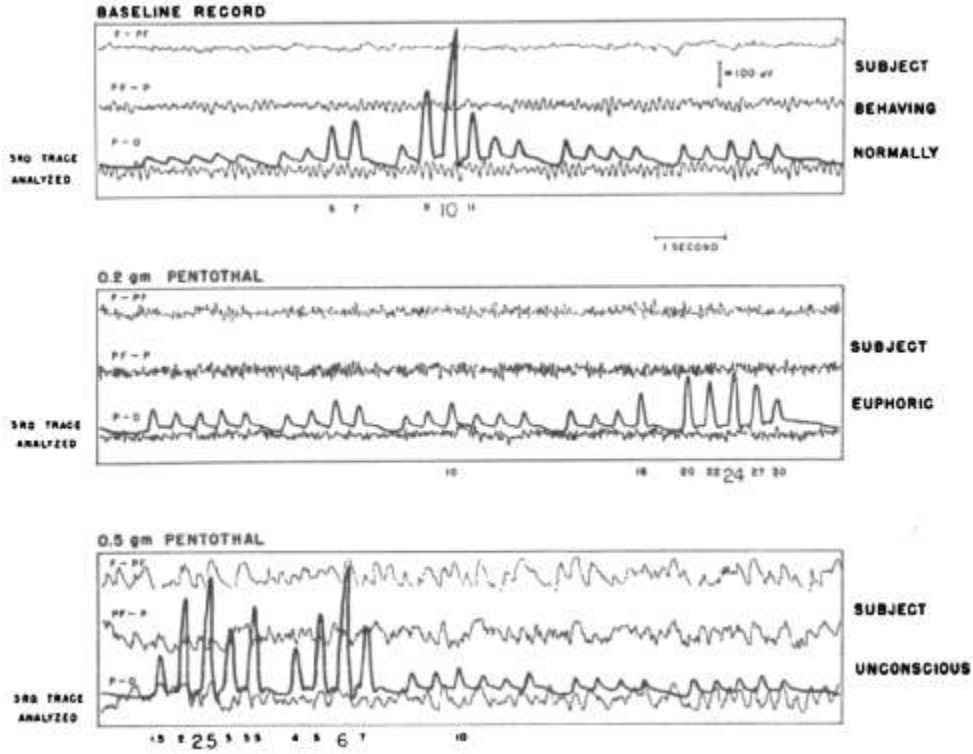

FIG. 4. Effect of pentothal on E.E.G. frequencies.

Bipolar recordings of the E.E.G. with automatic analysis of the third tracing. The upper tracing in each sample is from electrodes on the frontal region, the middle one from the fronto-parietal, and the lower is from the parieto-occipital region. The heavy black trace is the automatic analysis which shows most of the activity in the first record to be in the alpha range with a dominant frequency of 10 per second. In the second record it is in the fast range (20–30 per second) and in the last record it is in the slow range (1.5 to 7 cycles per second).

the corresponding level of ether anesthesia. The pulse rate begins to climb slightly and for the first time a change occurs in the blood pressure which drops almost in proportion to the rise in pulse rate. On no occasion was an alarming reaction observed. At this plane half of the subjects will tolerate an airway and the jaw must be supported in nearly all of them. Strangely enough, in almost 200 experiments of this type insertion of an airway at this time did not serve in itself to produce the slightest sign of a laryngospasm.

This was the deepest level studied on these subjects; they were then allowed to recover from the effects of the drug while observations were made of the steps in the return to consciousness. There seemed no point to be gained in taking the subjects into Stage 4 of pentothal anesthesia with its rather severe attending states of hypoventilation and hypotension.

In a previous study here Brazier and Finesinger (33) had noted that

small doses of the barbiturates produced faster frequencies than normal in the electroencephalogram and that these were followed by slow waves if the anesthesia were deepened. In figure 3 samples are shown of each of these electroencephalographic changes. Figure 4 shows these effects even more clearly and includes the automatic frequency analysis of the waves present at each stage. While the subject is in the first stage, the appearance of this high voltage, fast activity is striking. This is never found when the subject is truly alert but only when some degree of mental clouding or euphoria is present. Further, this tends

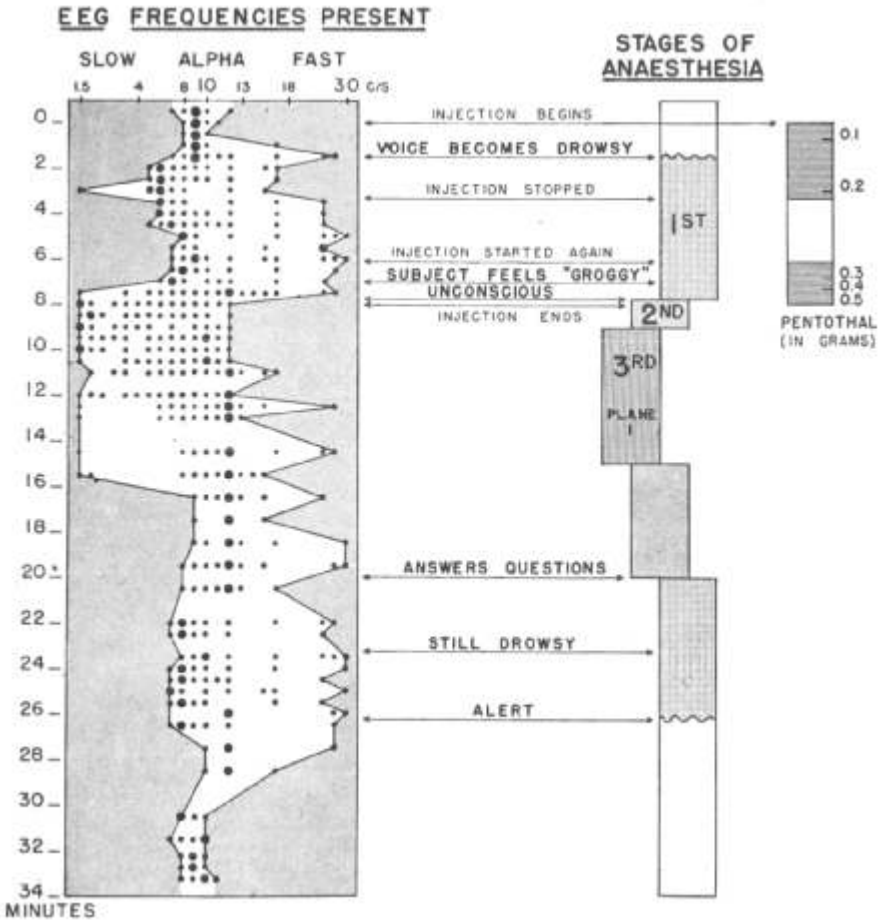

FIG. 5. The E.E.G. in pentothal anesthesia.

Chart showing which frequencies were present in the E.E.G. of an individual throughout a period of anesthesia induced by pentothal. The experiment begins at the top of the chart and proceeds vertically downwards. Each dot indicates a significant peak in the analyzer's trace at the frequency indicated on the abscissa. The heavy dots indicate the dominant frequency of the E.E.G. in each plotted sample. The E.E.G. data are charted at 30-second intervals throughout most of the experiment. The concurrent stages of anesthesia are charted on the right of the diagram and follow the same time scale as the E.E.G. from the top of the chart to the bottom.

to increase in amount as the first stage progresses. To illustrate more clearly the sequence of changes in electroencephalographic frequencies which accompany shifting levels of consciousness in pentothal anesthesia, a different method of charting has been used. This is seen in the analysis given in figure 5. The chart reads from top to bottom, and the width of the white band indicates the spread of frequencies found in the electroencephalogram by automatic analysis, plotted every half minute. The black spots represent the actual frequencies present as indicated on the abscissa and the larger black dot, the dominant frequency of each recorded sample. The column on the right indicates the levels of anesthesia.

The onset of the second stage at the moment of loss of consciousness is coincident with the abrupt appearance of high voltage slow waves. These electroencephalographic changes on induction of anesthesia are strikingly constant (34). During emergence from anesthesia however, the electroencephalographic changes, as well as the clinical signs, are not as clearly cut.

Since, as we have seen, the available evidence would seem to indicate that the blocking of glucose metabolism caused by the barbiturates occurs somewhere in the center of the flow line and, moreover, that the metabolism of succinic acid is invulnerable to the barbiturates, we might expect that the use of succinate intravenously and in large amounts might circumvent this block and thus supply an auxiliary fuel for purposes of brain oxidation. If the brain can utilize succinate in this way, then the electroencephalographic pattern, were it indeed dependent on these oxidative processes, might be expected to revert from one of slow waves characteristic of anesthesia to one more nearly normal. We have conducted over 50 experiments on man to test this hypothesis.

The procedure was as follows: After an adequate preliminary electroencephalographic tracing had been obtained in the resting state the intravenous administration of a 2 per cent solution of sodium pentothal was begun, using either a continuous drip or the fractional method of injection. The rate of injection was adjusted to produce and maintain the particular level of anesthesia desired for study at that time, or in the subjects who were given succinate, to produce the identical pattern of administration which was obtained in the previous experiment with pentothal. When the subject was in the desired plane of anesthesia as shown by clinical observation and by the electroencephalographic pattern the intravenous injection of disodium succinate was begun. We have used the standard 30 per cent solution put up by Brewer, and lately the product called soduxin, from the same company. According to the advice of other workers, we have always used fresh solutions and have stored them in cool, dark places. The amounts of succinate used have ranged from 15 to 36 Gm., and have been given in time periods of from nine to forty-five minutes. The maximum dose at any one time was 35 Gm. in fifteen minutes.

Over half of our subjects have complained of a transient feeling of "mild choking" and thickened voice occurring within the first three to four minutes of the administration of succinate. We have also observed in all cases a confluent flush of the anterior aspect of the neck, chin and face, similar to that produced by moderately large doses of atropine. One-third of the patients showed slight edema or brawniness of the involved skin. Usually, the flush as well as the edema subsides within fifteen minutes. We have, therefore, not recommended the use of succinate in children, tracheotomized patients, or in elderly or debilitated persons with pulmonary disease.

BLOOD SODIUM VALUES IN PENTOTHAL STUDIES

BEFORE INJECTION	141.4	mEq/L
AFTER SODIUM LACTATE (6 GM)	143.4	mEq/L
BEFORE INJECTION	139.2	mEq/L
AFTER SODIUM SUCCINATE (9 GM)	141.3	mEq/L
BEFORE INJECTION	138.8	mEq/L
AFTER SODIUM LACTATE (6 GM)	140.9	mEq/L

FIG. 6

In control experiments, some subjects were given other sodium salts instead of succinate. Both sodium bicarbonate and sodium lactate were used. Sodium determinations to estimate the effect on the system of the rather large amounts of the sodium radical given were found to be well within normal limits whether the subject were given sodium lactate, sodium bicarbonate or sodium succinate. For example, figure 6 shows the results on one subject (O. P.) who was tested on three separate occasions, once with succinate, and twice with sodium lactate, having in each case received 0.5 Gm. of pentothal intravenously. In all other cases similarly tested the range has been within 2 to 3 millequivalents per liter.

In some experiments disodium succinate was injected at times varying in relation to the administration of the pentothal in order to determine its relative effect when given prior to anesthesia, during anes-

thesia, or at the end of anesthesia. It was not possible to demonstrate any definite advantage in the administration of the succinate prior to anesthesia. The results ranged from the most spectacular awakening of the subject in earlier cases to a complete absence of reaction as evidenced both by clinical signs and the electroencephalographic rhythm.

One subject (S. S.) received 50 cc. of a 2 per cent solution of pentothal (1 Gm.) in fifteen minutes and remained in the third stage of anesthesia for nineteen minutes, recovering in approximately forty minutes. When she was given 50 cc. of a 30 per cent solution of succinate (15 Gm.) at the end of fifteen minutes, the third stage lasted twenty-two minutes, and she recovered in about forty-five minutes. No beneficial effect can be claimed here since the time relations of the anesthesia levels were not significantly changed. In a subsequent experiment with the same amount of pentothal, during which she received 95 cc. of succinate (28.5 Gm.), the third stage was reduced to fourteen minutes, but she still required forty-five minutes to recover.

Another person (C. P.) who maintained third plane anesthesia for eight minutes on 800 mg. of pentothal given in ten minutes, did not recover for over an hour. When she was given 50 cc. of succinate (15 Gm.) which was started four minutes before anesthesia, the third stage lasted only seven minutes, but again recovery was not complete for well over an hour. There is no difference of any significance here.

A third subject, however, showed a most spectacular result. This man (O. P.) who received ½ Gm. of pentothal in forty-five seconds developed delta waves in the electroencephalogram in forty seconds. These increased rapidly in number to occupy 50 per cent of his tracing and disappeared entirely after 120 seconds. On 9 Gm. of succinate, a relatively small dose, delta waves did not appear until sixty seconds after the administration of pentothal, rose to occupy only a bare 10 per cent of his record and disappeared completely after 100 seconds. This man never reached the third stage with the succinate although he had done so on pentothal alone. Repeated tests on this man, using lactate and bicarbonate as controls, failed completely to effect the same diminution in delta activity.

In an effort to approximate actual operating room conditions, one subject (D. D.) was given pentothal by the conventional fractional method. Eleven cubic centimeters (220 mg.) was given in three and a half minutes, mostly during the second minute. The subject was then allowed to recover for another two minutes, and was finally "snowed under" with 14 cc. (280 mg.) in the next two minutes. On six separate occasions within the space of twenty-eight days, this man received this exact amount of pentothal (560 mg.) in the same time sequence. The average times for each stage are shown in figure 7. Note especially the percentage variations. On two separate occasions this subject was given 16.5 Gm., and 33 Gm. of succinate respectively, the injection beginning four minutes before the onset of anesthesia and proceeding throughout. With the smaller dose third stage anesthesia was reached

SUBJECT D D : SIX ADMINISTRATIONS
PENTOTHAL DOSAGE 0 5 GRAMS IN A TOTAL OF 75 MINUTES

	AVERAGE TIME IN MINUTES	PERCENT VARIATION
TO ONSET OF LIGHT PLANE	7.8	± 6 %
TO ONSET OF DEEP PLANE	9.4	± 9 %
DURATION OF DEEP PLANE	1.8	± 44 %
TO MOMENT OF COMPLETE RECOVERY	24.0	± 21 %

FIG. 7. Time relations of third stage anesthesia.

in nine and three-fourths minutes, and lasted one and one-fourth minutes. In twenty-five minutes he had recovered completely. With the larger amount of succinate there was no significant difference in his reactions.

In a few of the earlier subjects, large amounts of pentothal were given rapidly; i.e., up to 0.5 Gm. in less than fifty seconds, approximating more closely the overwhelming blood concentration of barbiturates which may occur in suicidal cases. The following are a few of the results. M. C., having received 0.45 Gm. of pentothal in forty-five seconds, went into third stage uncomplicated by anoxia in thirty seconds and maintained this plane for four minutes. With 15 Gm. of succinate started simultaneously with the pentothal, delta waves appeared in twenty seconds and persisted two and a half minutes. Thus, her recovery seemed to be accelerated slightly by the succinate.

Another individual (D. B.) showed a much more profound narcosis, measured both clinically and by the brain-wave pattern, when 10.5 Gm. of succinate was administered with the pentothal than when she had received 0.3 Gm. of pentothal alone. This was also true in the case of G. M., who not only failed to respond to succinate therapy, but actually seemed the worse for it.

Finally, a brief summary is given in table 1 of another case (J. W.) which was very extensively studied. The times are recorded from the beginning of the pentothal injection. In this case succinate was of value in reducing the amount of abnormal electroencephalographic ac-

TABLE 1

	Time of appearance of first delta waves, seconds	Record occupied by delta waves, per cent	Time delta waves lasted, seconds	Time to full recovery, seconds
Pentothal 16 cc in 115 seconds	60	8	180	250
Pentothal + Bicarbonate	40	9	200	250
Pentothal + Succinate (15 Gm.)	70	1.5	120	210

tivity, but neither the onset of anesthesia nor the recovery-time was materially affected.

The remainder of the cases shows the same doubtful or equivocal results. A really critical review of all data obtained reveals questionable advantages in a few of the experiments conducted (35). It may well be that these results are owing to our inability to equilibrate precisely the concentrations of the two drugs in the cerebral cells. Our work on blood concentrations should soon aid in that perplexing question.

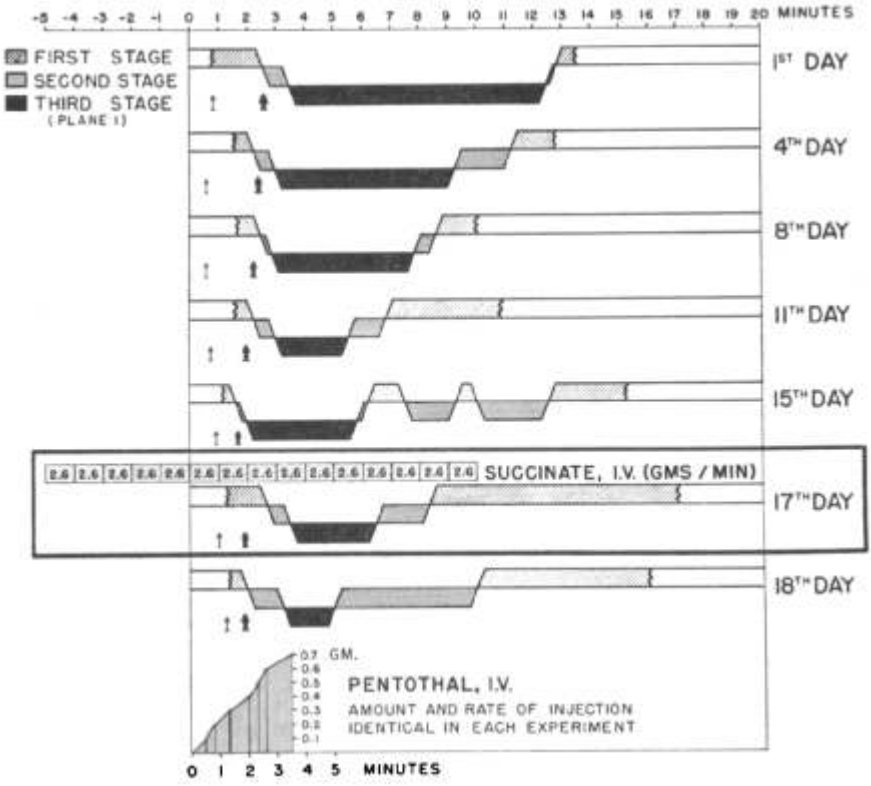

FIG. 8. Pentothal anesthesia effects of repeated doses.

Of interest at this point is the change in response of a subject to repeated injections of the same amount of pentothal sodium given on five or six occasions at intervals of three to four days. Although this observation was made on only a few subjects, it is noteworthy to record that the following occurred. Figure 8, which depicts the duration of each stage in 7 experiments on 7 different days, suggests the possibility that a tolerance to the drug has been developed. With this dosage and rate of injection the period of induction is short and proves to be almost constant, however frequently repeated. On the other hand, the dura-

tion of the subject's unconsciousness is clearly influenced by recent experience of the drug. In spite of identical dosage and rate of injection, there is a tendency for this individual to remain in the third stage for a shorter period on each occasion and seemingly to recover faster with each successive administration of pentothal.

Such an effect as is shown in figures 7 and 8 brings out two points of some importance. One is that acclimatization to sodium pentothal can occur. This may have clinical meaning in surgical procedures by stages requiring repeated anesthesias. The second point grows out of the first; it emphasizes the caution one must exercise in judging the efficacy of antidotes when comparison of anesthetic effect is made between two experiments in which the antidote is given in the second of the pair.

Since this was the case in some of our earliest work, we believe this to account for some of our former observations in which we obtained an apparently beneficial effect with succinate. Our next procedure is to reverse the order of experiments and eliminate the influence of acclimatization. The results will be covered by a later report.

Our purpose in presenting these data now is to emphasize the number of variables involved in the problem of assessing the antidotal value of succinate in pentothal anesthesia. Until the influence of each variable has been determined by carefully controlled experiments, conclusions made on clinical observation alone are premature.

SUMMARY

Some basic biochemical considerations pertinent to the "Oxidation Theory" are mentioned.

Objective neurologic levels of pentothal sodium anesthesia, employing the electroencephalogram, are described.

The rationale, the use and effects of disodium succinate (Sudoxin) are discussed and some typical cases reported.

In spite of extensive experimentation along the lines described in this paper, we believe that a definitive decision as to the value of succinate would be unjustifiable at this time.

Several variables, such as tolerance to pentothal sodium, are suggested as reasons for the need of caution in assessing the antidotal effects of disodium succinate.

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