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THE DETERMINATION OF THE ANAESTHETIC TENSION OF ETHER VAPOR IN MAN, WITH SOME THEORETICAL DEDUCTIONS THEREFROM, AS TO THE MODE OF ACTION OF THE COMMON VOLATILE ANAESTHETICS[1]

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The perfection and accuracy[2] of the anaesthetometer devised by Dr. Karl Connell (1) of the Roosevelt Hospital, New York, has rendered available a new method applicable to both man and animals, for studying the strength of action of the volatile inhalation anaesthetics.

So far as the apparatus is concerned, the dosage of the anaesthetic can be expressed with equal ease in percentage by weight, percentage by volume, or in millimeters of mercury representing the vapor pressure equivalent (tension). Dr. Connell originally calibrated his apparatus in percentage by weight, and in a recent article on "Ether Percentage" (2), I also adopted this standard. This is now regretted, as it is contrary to the general practice, and leads to confusion. The two other methods of expressing the dosage, namely, by volume and by tension, have the advantage of being readily interchangeable, and of these

[1] Read by invitation to the Society for Pharmacology and Experimental Therapeutics, Philadelphia, December 29, 1913.

[2] The Connell anaesthetometer is accurate to within ± 3 mm. of the true tension. This error can be determined and allowed for if the accuracy of the other factors render it desirable. For a complete discussion of this point, reference may be made to an article by Boothby and Sandiford (3). The apparatus would be improved by making the steps between the possible tensions of less value. This could be done by having three times as many teeth on the ratchet wheel, and near the critical tension small steps between the available tensions.

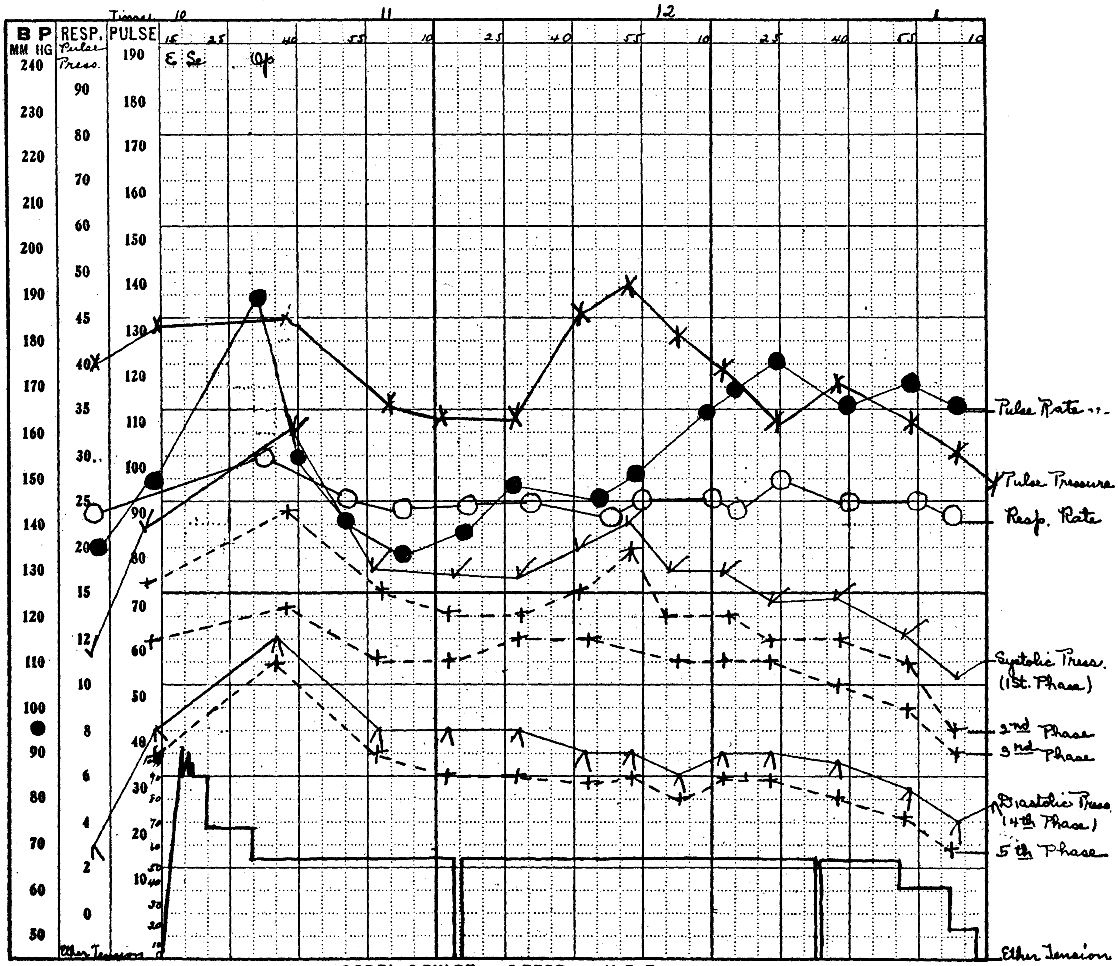
two, though the former is frequently used, the latter is preferable because thereby allowance is made for barometric changes as well as for variations in the partial pressure of ether. This is an essential point in accurate work, because the mass of gas absorbed varies with extreme precision directly as the pressure.

The studies described in this paper were performed for the purpose of determining the lowest partial pressure of ether vapor which, when continuously respired, will maintain an ideal surgical narcosis after it has been once established. The term "anaesthetic tension" has been adopted to express this value.

In order to determine the tension of ether vapor proper to maintain an ideal surgical narcosis, it is necessary to obtain a condition of equilibrium between the tension of ether in the inspired air, alveolar air, blood and tissues. The anaesthetic tension is then equal to the tension of ether as delivered by the apparatus. The details of the precautions taken in the administration of the anaesthetic, to prevent leakage and consequent alteration in the composition of the mixture delivered by the Connell apparatus, need not be considered here.

It is the custom in the Brigham Hospital Surgical Clinic to plot an anaesthesia chart, on which are recorded the vapor tension of ether administered, the pulse and respiration rate, the systolic and diastolic blood pressure determined by the auscultatory method (sometimes with the intermediate phases), and the pulse pressure.

Figure I is a typical chart and represents an ideal ether anaesthesia. In order to produce narcosis, the vapor tension of ether is rapidly, yet gradually, increased to about 100 mm. This can be done without struggling, choking, or any feeling of suffocation on the part of the patient in four to seven minutes; the tension is maintained at this point for two to four minutes, and then gradually lowered, during the following half hour, to a pressure of about 54 mm. By this method, the patient is sufficiently anaesthetized at the end of about ten minutes to allow cleaning the skin and further preparation of the operative field. Complete anaesthesia occurs in about fifteen minutes, at which time the incision can be made without any reflex movements. The dura-



CODE:— ● PULSE O RESP. V. B. P.

FIG. I

Name, C. B.; age, 50; date of operation, September 6, 1913; lungs, negative; heart, apparently normal; urine, negative; arteriosclerosis, none; operator, Dr. Cushing; first assistant, Dr. Bagley; anaesthetic, Squibb's ether, Connell apparatus, Gwathmey mask and towel, cerebellar position; operation, extirpation cerebellar tumor; preliminary drugs, atropin sulphate, 0.5 mgm. S. C. at 9.40; blood pressure, Sys. = 110, Dias. = 70, (Tycos); stimulants, none; practically no bleeding. Tycos correction = − 5 mm. (average).

Remarks: Induction accompanied by slight laryngeal spasm with coughing. It is especially noteworthy that "little ether" was needed for induction; as seen by the ether tension curve the higher tensions were given for only a short time. That is the patient came up to the anaesthetic tension quickly; it was necessary to maintain the ether tension at 54 mm. throughout the operation. Perfect anaesthesia. Anaesthetist, Dr. Boothby.

tion of the period in which the tension of ether administered is above the final tension, varies from twenty to forty minutes in different subjects; as a rule, at the end of thirty minutes, the apparatus can be set at 47 or 54 mm., and thereafter continued at this pressure without change.

Figures II, III, and IV, clearly illustrate how well a surgical anaesthesia can be maintained by the administration and inhalation of a constant mixture of air and ether in which the ether tension is between 47 and 54 mm. At the point marked *a*, spasmodic apnoea occurred as a result of a too high ether tension in an attempt to hurry the preliminary period. This is what frequently happens when using the cone method of administration, and indicates that the respiratory center is suddenly overwhelmed by a tension temporarily in excess of 60 mm.

Figure V is of especial interest. A cystic glioma was extirpated by Dr. Cushing from the cerebellum of a girl eight years old, and, at the point *H*, indicated in the chart, a brisk hemorrhage occurred with resultant drop in blood pressures.

At the point *F*,[3] the ether was interrupted for two or three minutes and, subsequently, an increased tension was necessary to bring about suitable anaesthesia. During the second hour, the pulse pressure dropped alarmingly, but the ether tension could only be lowered from 54 to 49 mm. On account of the continual fall in pulse pressure at point *a*, the administrative tension was reduced to 38 mm., but after an interval of eight minutes, it was necessary to return to 49 mm. At point *b*, the patient was nearly pulseless, yet an attempt to discontinue the anaesthetic during the closure of the wound, resulted in reflex movements, and ether had to be again administered for a brief period. At the conclusion of the operation, the patient was pulseless and the apex beat counted with a stethoscope was 220 to the minute; she was in a comatose condition due to oxygen want from circulatory failure. One hour and twenty minutes after the operation was concluded, a transfusion from the patient's father

[3] *F* in this and the other curves indicate when ether administration had to be interrupted to refill the apparatus.

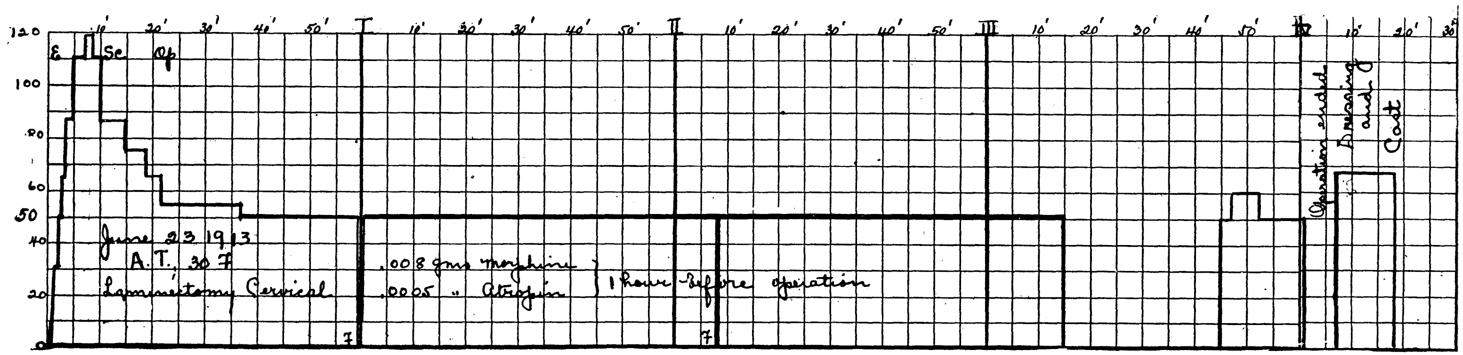


FIG. II

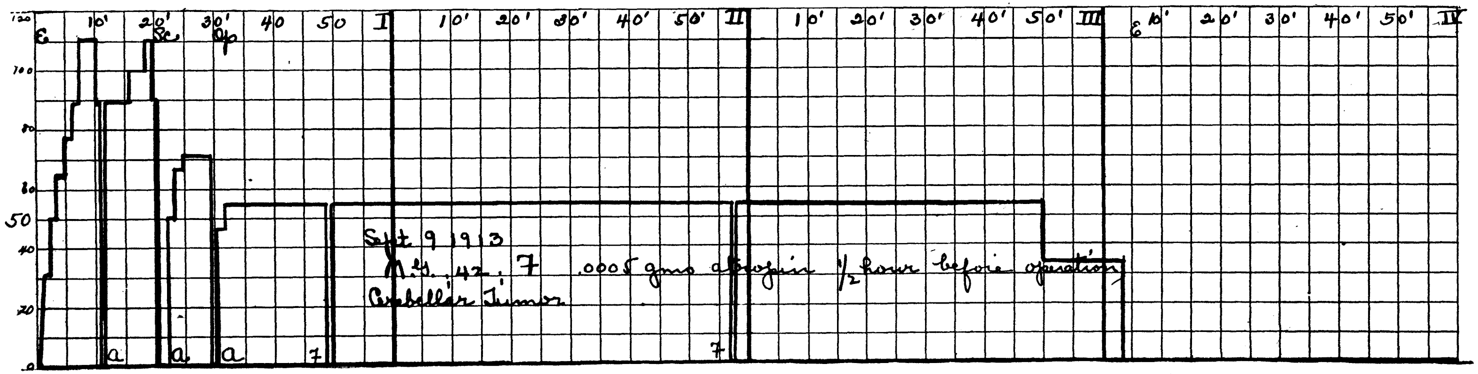


FIG. III

was started, and within forty minutes, the blood pressure had markedly improved as indicated on the chart.

Several similar cases of lowered blood pressure from loss of blood have occurred, but in none was a tension of ether lower than 47 mm. found to produce surgical anaesthesia. However, if the loss of blood exceeds a certain maximum, the patient is rendered comatose and unconscious probably from deprivation of oxygen. In such an extreme condition, no anaesthetic is needed as in the case cited from the time the cerebellar operation was completed till revived by the transfusion. Up to the time at which the loss of blood would have sufficed in itself to produce unconsciousness, it is necessary for surgical anaesthesia to maintain the same anaesthetic tension of ether despite the lowered blood pressure.

Figures VI, VII, and VIII, emphasize the similarity in the ether curve of different patients and further illustrate the conception that for surgical narcosis, the nerve cells [not under the influence of other drugs] must be exposed to an ether tension between 47 and 54 mm., probably about 51 mm. Age, sex, or chronic alcoholism, so far as my experience goes, does not alter the anaesthetic tension of ether. The opportunity has presented itself to test the influence of age on two babies—one nine months, the other eighteen hours old. The fact that new born babies require the same ether tension as adults is not surprising because had an operation taken place on the mother before delivery the foetus would have been saturated—and with safety—by the same anaesthetic tension as the mother. It is very probable that the same tension likewise holds for animals.

Dr. Waller (6) gives "as a preliminary result that full anaesthesia can be produced and maintained by ether and air at approximately 10 per 100." The balance used by him was one in which the chloroform scale 1, 2, and 3, per 100 (by volume) was taken to be practically equivalent to an ether scale, 5, 10, 15, per 100, which makes the ether determination roughly a percentage by weight (3). Ten per cent by weight equals 4.11 per cent by volume, which represents a tension of 31 mm.—evidently too low, but in fairly close agreement with Spenzer's so-called corrected (?) figures.

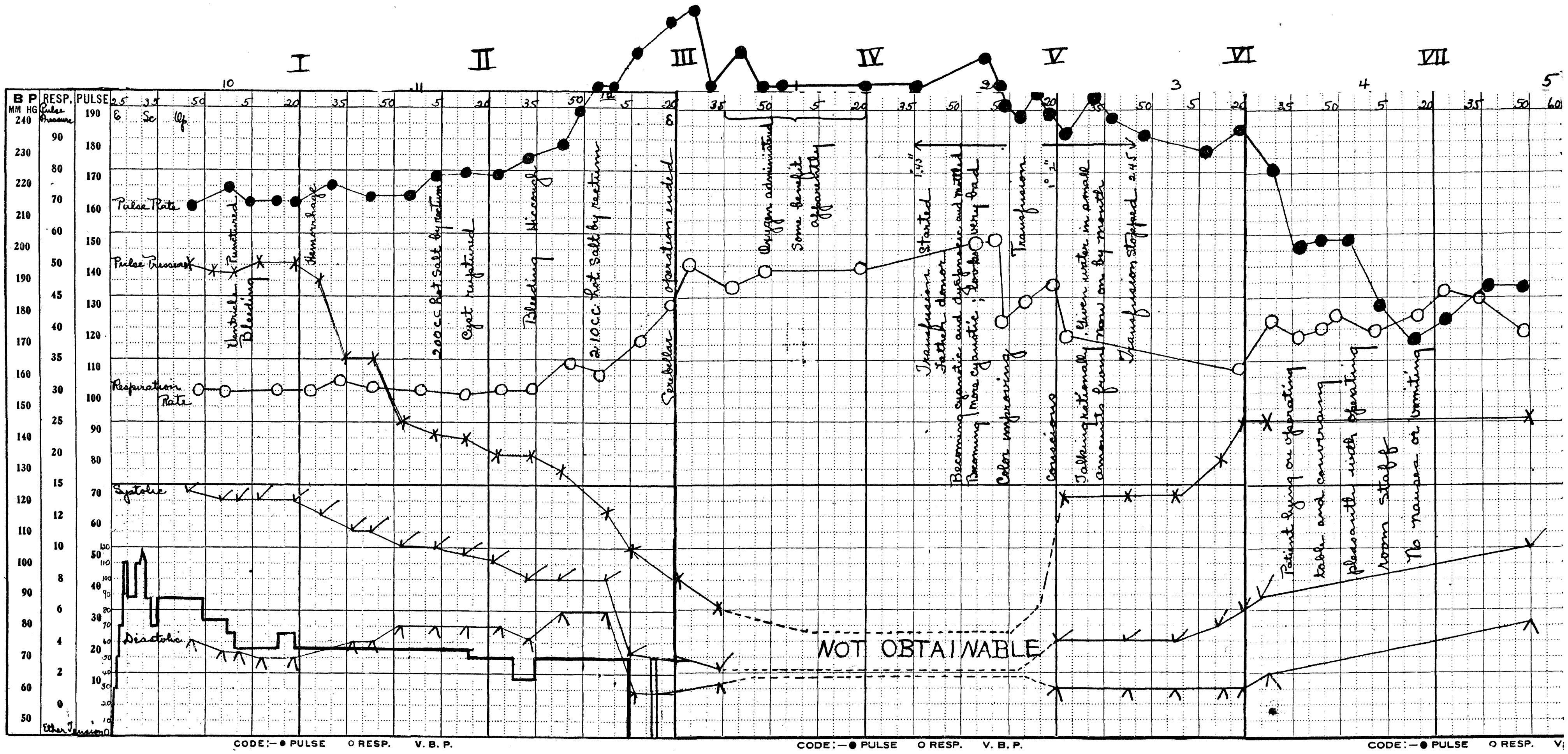


Fig. V

Name, M. E. S.; age, 8; date of operation, June 5, 1913; lungs, normal; heart, normal; urine, negative; arteriosclerosis, none; operator, Dr. Cushing; first assistant, Dr. Bagley; anaesthetic, Squibbs ether, Connell apparatus; operation, extirpation cystic tumor cerebellum; preliminary drugs, atropin sulphate, 0.3 mgm. at 8.30; stimulants, 11.10—200 cc. hot salt by rectum, 12—210 cc. hot salt by rectum, oxygen administered pure from 12.40 till 1.20 with some apparent benefit, patient looked better. Tycos correction = − 2 mm. (average).

Remarks: After 12 noon blood pressure was so low that hand on Tycos barely moved; no sounds audible therefore pressure had to be estimated. Very faint thready pulse palpable in temporal region till 12.15; after that no perceptible pulse till transfusion. Transfusion started with father as donor, at 1.43. Elsberg canular; stream very slow. After ten minutes patient became worse; gradually cyanosis increased in face and body—the latter becoming mottled. At 2 o'clock appeared as though patient would die any moment; then turning point came and in five minutes color was good, respiration less dyspnoeic. By 2.20 patient was conscious and asking rationally for water which was allowed. From 2.40 on till wounds closed in arm conversed with her father. Slight hemolysis apparently occurred at beginning of transfusion. Anaesthetist, Dr. W. Boothby.

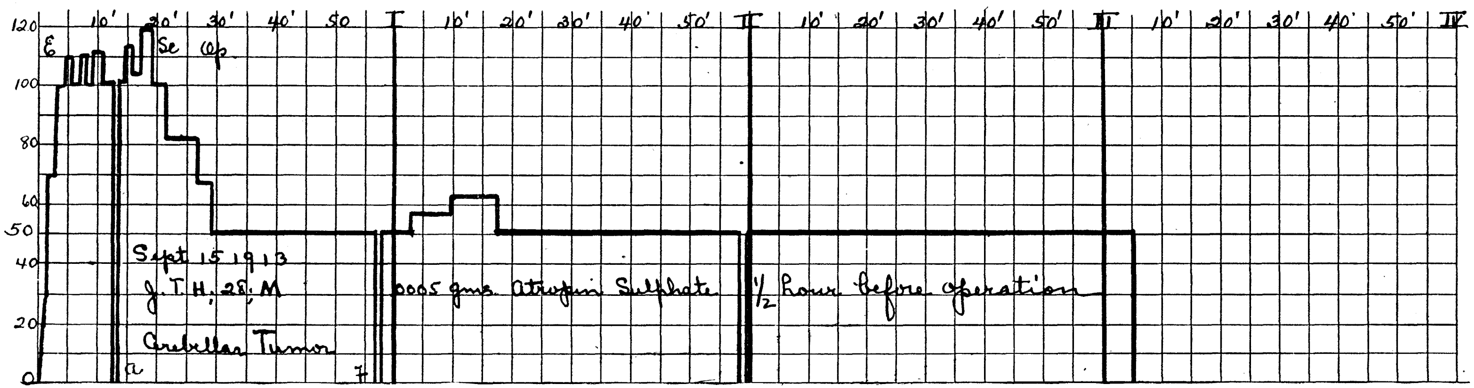

Sept 15 1913
J. T. H., 28, M
Cerebellar Tumor
.0005 gms. Atropin Sulphate
1/2 hour before operation
Se
Op

Fig. IV

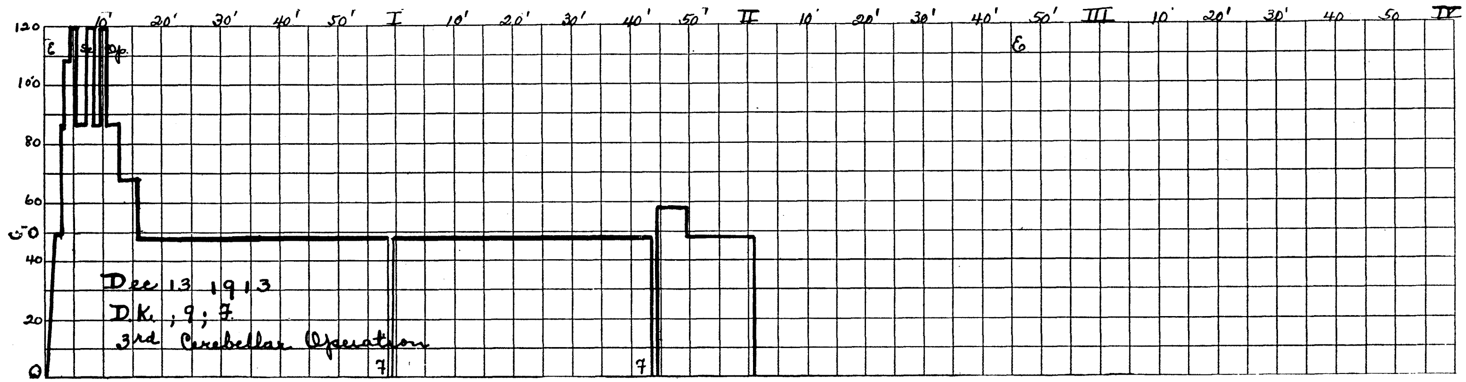

Dec 13 1913
D. K., 9, F
3rd Cerebellar Operation

Fig. VI

Spenzer (7), in 1893, published some very interesting experiments by which he determined the volume per cent of ether that would induce and maintain narcosis in dogs and cats. A mixture of ether and air was carefully made in a spirometer and then analyzed by a combustion method. Spenzer found that an ether and air mixture containing, according to calculation 6.7 per cent by volume, and according to analysis 3.4 per cent by volume, produced complete anaesthesia in twenty-five minutes, and that this mixture could be inspired indefinitely without untoward symptoms. Spenzer's uncorrected figure, 6.7 per cent gives a tension of 49 mm., which is in agreement with our figures. Undoubtedly, Spenzer's method of analysis was at fault. He was probably led to accept the per cent by analysis, because this agreed with the data obtained by Dreser (8) of the volume per cent of ether contained in samples of air taken from within a Julliard mask during narcosis. It is very likely that the same analytical error was made in both Dreser's and Spenzer's experiments.

Boycott, Damant, and Haldane (4) have studied the rapidity of saturation and desaturation of nitrogen up to a pressure of six atmospheres. According to their calculation, the body of a man would be half-saturated with the excess of nitrogen in twenty-three minutes, three-fourths saturated in forty-six minutes, etc., the pressure remaining constant. They also point out that the rate of saturation and desaturation would vary in different individuals according to the relative mass of blood and the rate of circulation. In the same individual, different organs would be more or less quickly saturated and desaturated, according to the proportional volume of their blood-supply. If ether were substituted for nitrogen, it is probable that the rate of saturation would be nearly the same.[4]

Therefore, the time requisite to saturate the body of an average patient up to the anaesthetic tension of 51 mm. is theoretically between one-half and three-quarters of an hour, because

[4] Although the rate of diffusion of gases is inversely according to their densities, it seems probable that the anatomical perfection of the capillary system allows complete equilibrium to occur during the passage of the blood through the capillaries in either case.

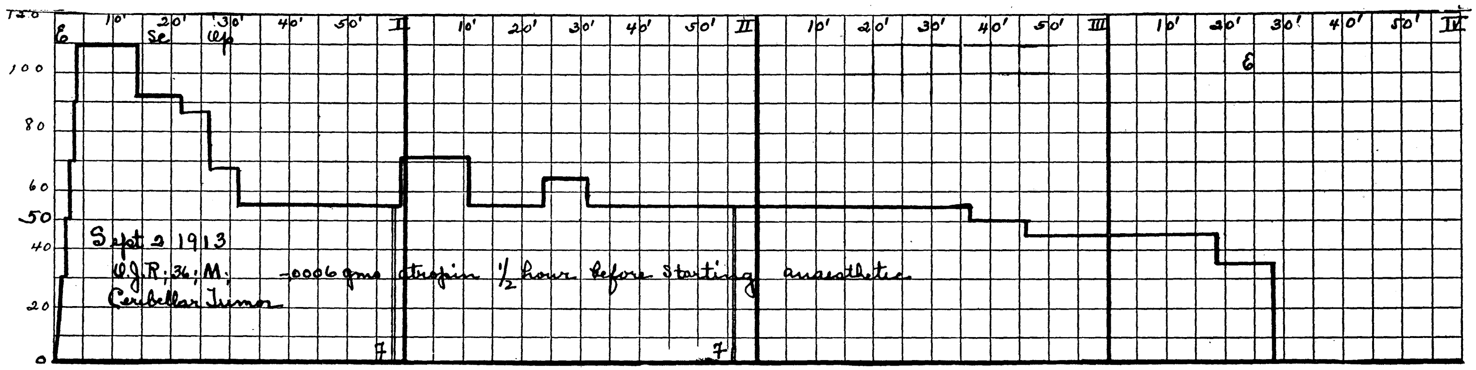


FIG. VII

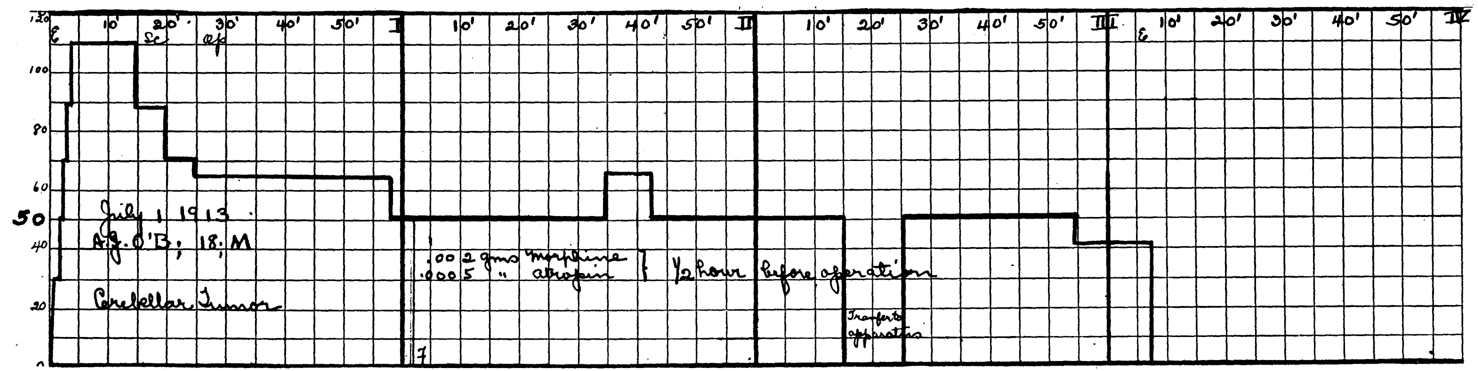


FIG. VIII

during a part of this time, a tension of 100 mm. can be administered, and during the remainder, a tension between 80 and 60 mm. As the point of saturation is approached, the tension of administration must be reduced to 55 mm., so as not to suddenly and dangerously over-shoot the desired tension of 51 mm. My experience indicates that a general body tension of 60 mm. would be dangerous.[5]

The rate of solution saturation and desaturation of ether and nitrogen for the body fluids, in general, is, as stated above, probably very similar. Ether has, however, been shown by Meyer, Overton, and others, to form a "loose (reversible) physico-chemical combination with the lipoids of the cell" (5), thereby producing an inhibition of the cell mechanism resulting in narcosis. The rapidity of action and reaction, and the degree of completeness or percentage saturation of the nerve cell with ether in contrast to the solution saturation of the body fluids, is, therefore, dependent on the chemical inter-relationship and peculiarity of the dissociation curve of the lipoids of the cells and not on the laws of simple solution.

The experimental data given above show that surgical narcosis is produced by a tension of 51 mm.—a higher tension produces a dangerously deep narcosis and a lower tension, an inconveniently light anaesthesia. The percentage saturation of the nerve cell caused by any given tension of ether is not known. However, it can be assumed that the same degree of saturation is always produced by the same tension, and that eventually a correct dissociation curve can be determined as in the thoroughly studied reversible reaction

$$Hb + O_2 \rightleftarrows HbO_2$$

in which the percentage saturation of the haemoglobin with O_2

[5] I feel that a warning should be here given against the danger of an unduly prolonged administration of an ether tension above 55 mm. Dr. Connell's idea of the *safety* of an automatic machine anaesthesia is correct *after* the tension of administration has been *reduced to* 55 mm. An interne forgetting to step down the percentage of administration at the appropriate time, would quickly run his patient into serious danger. True ether poisoning is a rare occurrence with the usual cone method; it may be a frequent occurrence if the use of the Connell apparatus becomes general.

is dependent on the oxygen tension to which the haemoglobin is exposed.

If such be the case, our conception of the theory of production, maintenance, and recovery from anaesthesia can be rendered more concrete by the following hypothetical formula. Let *Mn* represent the molecules in the nerve cell affected by the anaesthetic, and let *An* represent the group of inhalation anaesthetics. Then, substituting in the above haemoglobin-oxygen equation, the reversible reaction

$$Mn + An \rightleftarrows MnAn$$

is seen to take place. In this reaction, the percentage saturation of the *Mn* molecules in the nerve cells, and, therefore, the depth of anaesthesia, is dependent on the tension of the anaesthetic vapor to which these susceptible molecules are exposed. The percentage saturation caused by ether at a pressure of 51 mm., produces that degree of cell inhibition that is necessary for ideal surgical anaesthesia.

The evidence here cited shows that there is little or no variation in the anaesthetic tension of ether in different individuals. Clinical experience has proven that some patients require by the ordinary methods of anaesthesia more ether poured upon the cone than do others. The apparent discrepancy between these two facts can be accounted for by the following three factors.

In the first place, as I explained in an earlier paper (2), there is a wide variation in the amount of air breathed by different patients: therefore, varying amounts of ether must be poured upon the cone to bring the fluctuating amounts of air up to the same tension. When attempting to obtain the higher tensions in the larger amounts of air, the waste of liquid ether is tremendous—just as the amount of fuel necessary to increase the speed of an engine above a certain point is proportionately very great to the result obtained.

Secondly, the volume of blood flowing through the lungs per minute varies greatly, not only in different individuals, but at different times in the same individual; further, the relative amount passing through the various organs will fluctuate from time to time. Accordingly, it is evident that the rate at which the brain, for example, becomes saturated or desaturated—that is, the rate at which the patient becomes anaesthetized or recovers therefrom—depends on the amount of blood flowing between the lungs and the brain (assuming the alveolar ether tension to remain constant). At present, we have no means of estimating changes in the circulation rate, and therefore, cannot calculate the exact value of this factor. That it is of considerable moment, however, can be judged from the experiments previously reported by me, which showed that the rate of elimination of CO_2 was dependent not only on the volume of respiration, but also on the rate of the blood-flow (9).

The third factor is the possibility of a variation in the rate of the chemical reaction due to slight changes in the chemical environment. On account of the well-known influence that environment exerts on the rapidity of chemical reactions, it seems quite possible that even small changes in acidity, viscosity, permeability, or temperature might affect both the rate at which union between the ether and lipoid takes place during the period of saturation and also the rate at which dissociation occurs during desaturation on the reduction of the ether tension.

Dr. A. D. Waller has shown that for chloroform "the maximum value is between 2 and 3 per cent (by volume). The subsequent steady minimal value is about 1.5 per cent" (6). The relationship between the anaesthetic tension of ether and chloroform and their molecular weights is of interest and is shown by the following equations.

$$\frac{\text{Molecular weight } C_4H_{10}O}{\text{Molecular weight } CHCl_3} = \frac{74.1}{119.4} = \frac{1}{1.61}$$

$$\frac{\text{Anaesthetic tension } C_4H_{10}O}{\text{Anaesthetic tension } CHCl_3} = \frac{53}{11} = \frac{1.61 \times 3}{1}$$

SUMMARY

1. The term "anaesthetic tension," is employed to indicate the partial pressure of ether vapor that, after equilibrium is

established, can, for an indefinite period, maintain the subject in the stage of ideal surgical anaesthesia.

2. Curves are given showing that the anaesthetic tension of ether vapor for man is between 47 and 54 mm.—probably 51 mm.

3. A working hypothesis based on the theory of Meyer and Overton is suggested to explain the mode of action of the volatile inhalation anaesthetics which can be summarized in the quantitative reversible equation

$$Mn + An \rightleftarrows MnAn$$

in which the percentage saturation of the susceptible molecules in the nerve cells (Mn), and, therefore, the inhibition of the cell function (the depth of anaesthesia), is dependent on the tension of the anaesthetic vapor (An) to which these susceptible molecules are exposed.

4. To harmonize the fact that large variations occur in the amount of ether required by the usual methods of anaesthesia with the fact that the same ether tension produces the same degree of anaesthesia in all patients, it is pointed out that the apparent variation can be accounted for by (a) changes in volume of respiration; (b) changes in rate of circulation; and (c) by a possible alteration in the rapidity with which the above reversible reaction takes place under a slightly different chemical environment.

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