T H E S I S.

"AN INQUIRY AS TO THE CAUSE OF INCREASED ELECTRICAL EXCITABILITY OF THE NEUROMYONE."

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The increased electrical excitability of the neuro-muscular apparatus has been taken as one of the most reliable clinical signs of the presence and severity of idiopathic tetany in children ever since Erb[1] in 1874 ascribed this hyperexcitability of the peripheral nerves to galvanic stimulation. The value of the various therapeutic measures suggested and adopted has been measured by the influence they have on the electrical excitability. That this increased electrical excitability is due to an action upon the peripheral as opposed to the central parts of the neuro-muscular system is clearly shown by the work of MacCallum[2]. This investigator circulated the blood of a parathyreoidectomised dog through the blood-vessels of the amputated leg of a healthy animal and found a marked increase in the electrical excitability of that leg. It has further been shown that this increase persists after the peripheral part has been separated from the central nervous system by section of the nerves.

A knowledge of the ultimate factor or factors of the increase in the electrical excitability of the neuromyone is of great importance in any attempt to prevent the onset of such a pathological condition and when it has developed, in the scientific application of therapeutic measures.

The work detailed in the following thesis was undertaken to/

to determine the cause or causes of increase in electrical excitability of the neuro-myone. Although all the work was done by myself, I should like to thank Prof.D.Noël Paton, F.R.S. for his helpful criticism and advice throughout the course of the research.

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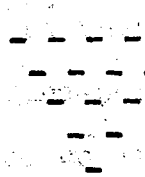
I.

INTRODUCTION.



By the term neuro-myone is meant the peripheral neuro-muscular mechanism. The various elements that go to make up this mechanism are still somewhat in doubt. The axon-fibre, the nerve-ending and muscle are the three constituents which have long been known, and the famous curare experiment of Claude Bernard (3) was taken to mean that the poison acted first on the nerve-endings as being the most susceptible part of the neurone. This view was supported by the statements of Kuhne (4) that there were distinct changes in the nerve-endings in the muscle of lizards after curare-poisoning. Adrenalin was found by Elliott (5) to produce its normal constrictor effect on the frog's sartorius 6 weeks after denervation when all the nerve-endings had disappeared. He concluded that it must therefore act on some substance on the place of entry of the nerve-fibre, which he called the "neuro-myal junction". Langley (6) showed that nicotine produced a marked contraction, if anything greater than normal, when applied to the denervated gastrocnemius muscle of the fowl. Curare, he found, was capable of reducing and, if in sufficient dose, entirely abolishing this nicotine effect on the denervated muscle. These drugs must therefore act on an intermediate substance which must be on the muscle-side of the place of entry of the nerve-fibres. This substance Langley termed the Receptive/

Receptive Substance.

Support for this view was forthcoming in the experiments of Lucas[7] who found that, on stimulating the frog's sartorius muscle with condenser discharges there were two distinct optimal stimuli in one of which the rate is very low, in the other very high. Stimulation with the lower rate is unaffected by curare poisoning whereas the higher optimal rate of incidence of energy showed signs of abolition after moderate doses of curare and had no effect after large doses. The nerve itself Lucas[8] showed had a low optimal rate not differing greatly from the low rate he found in muscle. This work suggests that the higher optimal rate stimulates the "receptive substance" of Langley. The experiments of Noël Paton and Findlay[9] throw further light upon the characters of the receptive substance showing that it generally remains unaltered for some time after the nerve has ceased to act. They suggest that the development of the slow generalised contraction with the increased response to galvanic stimulation which is characteristic of the reaction of degeneration, may be a result of the degeneration of the "receptive substance". After consider-:ing the evidence as to the causal factor of increased electrical excitability of the neuromyone a suggestion will be put forward as to its influence in producing this reaction/

reaction of degeneration.

Meanwhile the neuromyone can be considered as consisting of nerve-fibre, nerve-ending, receptive substance and muscle-substance. In this investigation no endeavour has been made to determine the part played by each component of the neuromyone in the variations of electrical excitability. The evidence, however, leads one to think that the receptive substance is the part, changes in which produce variations in excitability.

As regards the plan adopted in this thesis, the general methods used in the experiments will first be described. Thereafter will be considered some of the views that have been held as to the cause of increased excitability of the neuromyone, following on which will be detailed the evidence on which has been based the view that anoxaemia is the ultimate factor.

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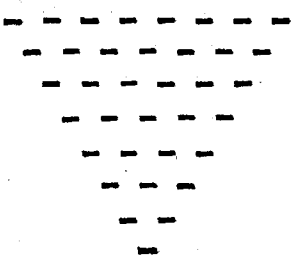
II.

METHODS.



1. Method of Measuring the Strength of Current causing Contraction

A. Apparatus:- As regards the method of testing the electrical excitability, I have followed that described by Noel Paton, Findlay and Watson [10]. The current was taken from the main and passed through a rheostat. A milliamperemeter of the d'Arsonval type was introduced into the circuit as well as a mercury key by which the circuit was made and broken. The electrodes were of copper covered with chamois leather, the smaller or active one having a diameter of 0.5 cm., the larger or neutral electrode measuring 5 cm. in diameter. During their work, Noël Paton, Findlay and Watson found that it was advisable to commence with a weak current, gradually strengthen-:ing it until a definite contraction was induced, and then weakening it until the smallest current that would elicit a contraction was reached. In this way they found that they obtained much more constant results and also that very often the strength of current by which a contraction was ultimately induced, was about one half or one quarter of that originally required, while ascending the scale. These results I have confirmed (Table A.)

TABLE A.

		Ascending.	Descending.
K.C.C.	Cat 7 (1)	0.8	0.3
	" 3 (2)	0.8	0.4
	" 6 (3)	1.3	0.7
	Dog 1 (4)	2.9	2.1
K.O.C.	Cat 7 (1)	2.2	0.8
	" 3 (2)	13.0	9.0
	" 6 (3)	12.0	9.0
	Dog 1 (4)	9.5	5.0

The same investigators state that occasionally they could not elicit a cathodal opening contraction, although 50 milliamperemeters were used. I have found that a current of 20 milliamps. was always more than sufficient to elicit the K.O.C. even when ascending the scale.

B. Nerve Selected. The nerve selected in animals was the posterior tibial, and it was stimulated on the outer aspect of the ankle where it is very superficial, lying as it does in front of the tendo Achillis. The hair of the leg was cut so that the electrode would be placed directly on the skin. The index of a successful stimulation was the flexion of the toes due to contraction of the flexor brevis muscle. Noël Paton, Findlay and Watson investigated the question as to whether direct stimulation of the long flexor played any part in this movement of the toes by cutting the long flexor tendons. They showed that under normal conditions the flexion of the toes is due entirely to stimulation of the flexor brevis. MacCallum,[2] however, believes that there is a transmission of movements from the stimulation of other muscles, and advises that the tendons of all the long muscles be cut. This contraction arising out of the stimulation of other muscles I found to occur only when strong currents were applied, and the movements produced were quite different from those due to contraction of the short muscles; and provided the method detailed in the previous paragraph of gradual ascending and descending currents/

currents is used, I do not think there arises any confusion as to the correct reading. When I was testing the electri-:cal excitability of the neuromyone in children, I used the ulnar nerve and took flexion of the digits as the index of stimulation. This is the nerve commonly used by most workers.

C. Limits of Accuracy. Noël Paton, Findlay and Watson[10] in a duscussion as to the limits of accuracy of the method here detailed, came to the conclusion that while the actual readings in one experiment are not strictly comparable with those of another, as the conditions of conduction in different animals may vary, a series of successive tests on the same animal are strictly comparable. In the following series of experiments the important points to be noted are (1) the presence of any marked change in the electrical excitability, whether in the upward or downward direction: and (2) the relative increase or decrease rather than the actual values. Thus for the purpose of present work the method used is sufficiently accurate.

As the aim of the present research was to discover the cause of variations in the electrical excitability, I have not burdened the work with figures for the anodal contractions. Clinically the cathodal opening contraction is the one used as the index of the electrieal excitability. Experimentally, also, we find that it is subject to the greatest range of variation, so that the value for the cathodal opening contraction has been recorded/

recorded as being the clearest indication of any change in excitability. Normally K.O.C. gives the highest value and K.C.C. the smallest, but ACC. sometimes a higher, sometimes a lower value than AOC. Von Frankl-Hochwart [11] has recorded these variations. Noël Paton, Findlay and Watson [10] taking seventeen experiments at random from their series, show that in the normal state the majority give the smaller values for AOC. than for ACC. (i.e. AOC was induced by a weaker current than was ACC). I have obtained similar results both with animals and with children. (Table B.)

TABLE B.

		KCC.	ACC.	AOC.	KOC.
Cat	2 A	0.5	0.6	0.6	0.8
"	4	1.6	3.5	3.1	11.0
"	5	1.2	2.7	2.1	10.0
"	7	0.5	1.9	2.2	4.8
Dog	2	1.8	3.8	3.8	7.0
Child	A.A. age 8 mths. female.	0.9	2.9	2.4	5*
"	W.L. age 1 11/12 mths. male.	1.1	1.5	4.0	5*
"	M.C. age 16 mths. female.	0.7	1.5	1.5	5*

* 5+ indicates that the K.O.C. was not got with a current of 5 milliamps. Beyond this strength too much pain was caused to allow of any determinations being made.

Thus the cathodal contractions give clearer indications/

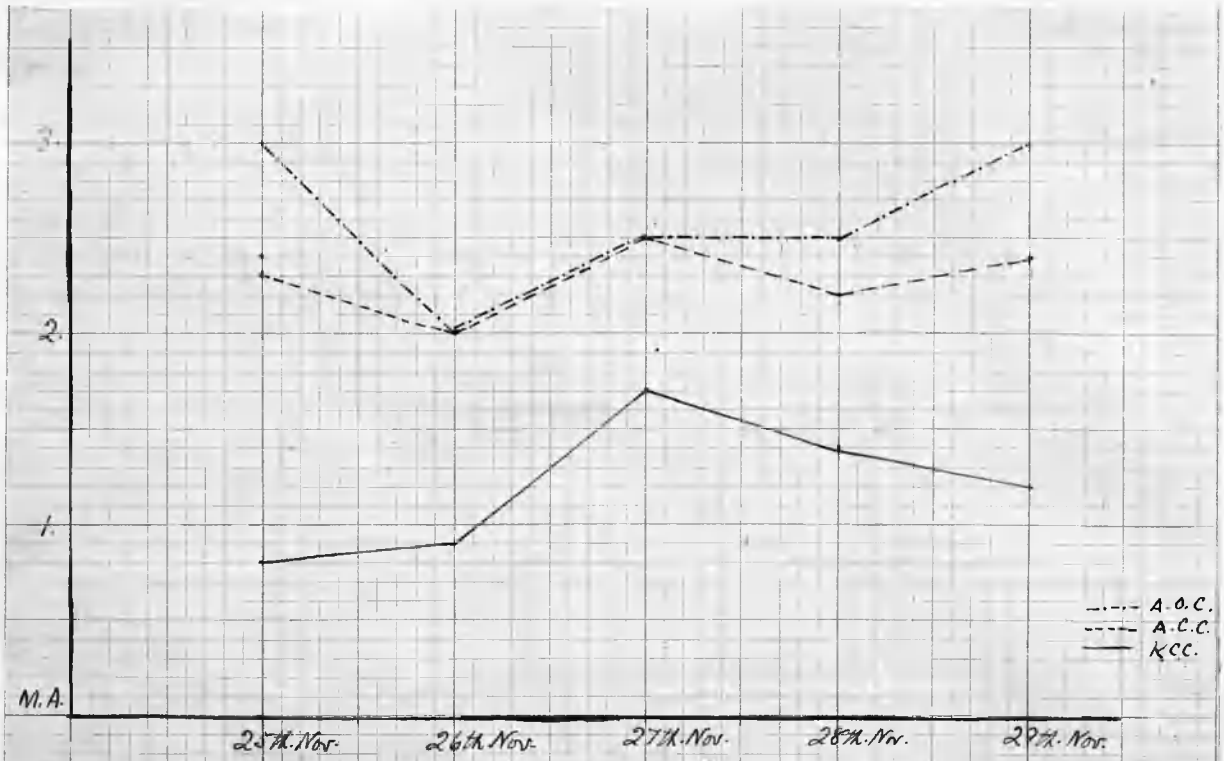


Chart of Electrical Reactions - D.C. - healthy male. age - 8 months.

N.B. Values for K.O.C. are not charted as they were all above 5·0 and it was too painful for the child to have a current of more than 5·0 milliamps. passed.

indications of any change in excitability than do the anodal ones. Falta [12], Von Pirquet[13], and Pineles[14] in their papers on idiopathic tetany, lay great stress on the qualitative change in the electrical reactions, but the records of Hochwart[11] and Noel Paton and Table B. above, all tend to support the view that qualitative changes are not constant and cannot meanwhile be considered of much importance in the diagnosis of the state on which the electrical excitability depends.

D. Variations in the E.E. of normal animals.

Before proceeding to a consideration of the factors modifying the electrical excitability of the neuro-myone, there is to be noted the daily variation in this excitability found in patients and animals apparently quite healthy and normal. Hochwart [11], was the first to point this out and his results have been confirmed by Noël Paton, Findlay and Watson, and a chart (Fig. 1) of the electrical reactions in a normal child over several days shows the variations that may be got.

The reason for these variations has not been determined, and with the insufficient data at our disposal it would be useless to attempt to theorise. As all the experiments on animals to be recorded were completed on the one day this daily variation need not be considered as a disturbing factor. In the case of children, however, although there may be a

marked/

marked variation both in the cathodal and anodal reactions, the cathodal opening reaction never falls to below 5.0 unless there is some condition present causing hyper-excitability of the neuro-myone.

2. Operative Technique.

A. Cats and dogs were the animals used in all the experiments here recorded. Each animal was anaesthetised with chloroform, and when full anaesthesia had been produced ether was used. In order to render the intake of anaesthetic as constant as possible throughout the experiment, tracheotomy was performed and ether administered through a tracheal cannula. The animal could thus be kept under the same depth of anaesthesia throughout the experiment. The common carotid arteries and jugular veins were then exposed and a cannula inserted into the left vein. The venous cannula which previous to insertion was filled with saline free from all air bubbles, was connected by thin rubber tubing to a burette. Into the burette was put the fluid which had to be injected. In this way the rate of administration was constant, being regulated by a screw clamp on the tubing.

The electrical reactions were taken several times before the injection was commenced and it was found that in the majority of cases the excitability varied little, if at all/

all, despite the fact that in some of my earlier experiments the animal was under the effects of the anaesthetic for over an hour before any fluid was injected. Nor had the operat-:ion any effect on the values for the electrical reactions. Noel Paton, Findlay and Watson [10] have shown that anaesthetics have very little actions on the electrical excitability and the results recorded here confirm their findings.

As various estimations had to be made on the blood before and after injection, the arterial blood was withdrawn into a 5 c.c. all-glass syringe rendered air-tight by a thin film of oil. When oxygen determinations were being made blood was also taken from the right external jugular vein. The loss of blood caused by these procedures was never found to produce any alteration in the values for electrical reactions.

B. Blood Pressure. In a few cases tracings of the blood pressure were obtained by means of a three-way cannula inserted into the right carotid and connected with the electric manometer described by McCall.[15]

C. Respirations. Tracings were obtained by a stethograph arra ngement. consisting of a balloon bound by a towel to the chest wall and connected to a tambour with a writing lever by a closed system of rubber-tubing. Every expansion of the chest wall caused an up-stroke of the lever.

D. Movements of Auricle and Ventricle. The chest was opened/

opened and the animal kept alive with artificial respiration from a motor pump. The pericardium was opened and by means of a clip, it was attached to the chest muscles so forming a bed for the heart. Clips were attached to one of the auricles and to the left ventricle. From the clips, threads ran to a straight writing double recorder of the same kind as that used by Cathcart and Clark[16] in their work on the effect of carbon dioxide on the heart movements.

3. Methods of Estimating various changes in the Blood.

A. Alkaline Reserve. The alkaline reserve was determined by the Van Slyke method[17] and by a method communicated by C.J.Martin, as yet unpublished.

The principle of Martin's method is that dilution of a well buffered solution such as plasma does not alter its pH and, if an indicator is used which has a low protein value, the plasma may be titrated with acid. The titrating value indicates the acid-combining power of the plasma. The apparatus used consists of a small wooden stand to hold three non-sol glass test tubes (8 x 0.8 cm.) vertically in a row and close together. The central tube at its upper end runs through the rubber stopper of an inverted non-sol flask (100-150 cc.) The flask is removed from the central tube and 0.5 cc. of plasma or serum and 2 cc. of neutral 0.9% sodium chloride added. The side tubes are almost filled with phosphate buffer mixture of pH7.4. These standard tubes are coloured by the addition of

a/

a drop or two of aqueous solutions of burnt sugar and flavine (1/100,000) till they match the fluid in the central tube. To all of the tubes are then added 2 drops of 0.05% alcoholic solution of neutral red. The optical effect of the turbidity of the plasma may be counteracted by placing a sheet of white tissue paper behind the tubes. The plasma mixture is titrated with N/50 HCl from a 2 cc. burette with fine nose, till its colour matches the standards. This is done by running the plasma into the flask, adding a few drops of acid and rotating gently but steadily for 1 minute, the flask meanwhile being in communication with the air. This readily allows the thin film of plasma to give up the liberated CO_2. The fluid is run back into the tube and compared with the standards. The process is repeated as often as necessary. Rotation for <u>at least</u> one minute is necessary after each addition of acid.

Example of a determination of CO_2 content of a plasma by Martin's method.

Titration value for 0.5 cc. plasma	=	0.4 cc. N/50 HCl.
i.e. Alkaline reserve of 0.5cc. "	=	0.4cc. N/50 $NaHCO_3$
" " 100 cc. "	=	80 cc. " " "
	=	1.6c.c. N/1 " "
	=	1.6 x 22.4 cc. CO_2

i.e. 41.84 volumes per cent of CO_2 are bound as bicarbonate in the plasma.

B. <u>Hydrogen-Ion concentration.</u> This was estimated by the method/

method described by Bayliss[18]. The blood was run direct from the carotid artery through an arterial cannula into a conical centrifuge tube (15 cc.) containing a few grains of chemically pure neutral potassium oxalate and about 4.cc. of internol brand of liquid paraffin so that the blood did not come into contact with the external air. About 10 c.c. of arterial blood was thus collected; the centrifuge tube was then filled with internol. The tube was inverted several times so as to diffuse the oxalate through the blood and then placed in a centrifuge to separate off the plasma. If one plasma was stained red owing to haemolysis, as very often happened after injection of acid, a trace of haemoglobin was added to the tube containing the clear plasma so that it should resemble the other. Three drops of 0.1% neutral red were then added to the upper part of each plasma by means of a fine pipette inserted through the internol. This indicator was mixed with the upper part of the plasma layer by gentle stirring with the pipette. The colour produced was noted and compared with that of a similarly prepared sample taken after the specific treatment of the animal. The pH was estimated in accordance with the table given by Bayliss.

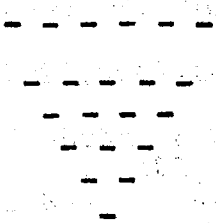
In a few cases, I used the dialysis indicator method described by Levy, Rowntree and Marriott[19] but found it much more cumbersome and got no better results.

C. Oxygen-content of the Blood.

The oxygen content of both arterial and venous bloods was/determined by Barcroft's Differential Method.[20] Results are given in percentage-saturation.

III.

PREVIOUS THEORIES.



Numerous theories have been advanced to explain the increase in the excitability of the neuromyone in the various clinical and experimental conditions in which such an increase has been demonstrated. Of these the principal are the following:-

A. The presence in the blood of excess of sodium.

B. Decrease in the calcium content of the organism.

C. A condition of acidosis.

D. A condition of alkalosis.

E. The presence of a toxic substance.

Of the toxic substances suggested one may mention ammonia, xanthin, B-iminoazolylethylamine, guanidin, and xanthin. This last substance suggested itself as a possible cause to Berkeley and Beebe (21) because of its similarity to convulsant drugs like caffein, and of the possibility of its increased production along with cognate purins in conditions of tetany. These investigators record one experiment where the intravenous injection of xanthin caused generalised convulsions. MacCallum and Voegtlin (22) repeated this work but could not confirm the previous findings as they failed to get any tremors or increase in electrical excitability. One may, therefore, dismiss the possibility of xanthin being the causal factor in the production of increased electrical excitability.

The remaining hypotheses it is necessary to deal with more fully.

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III.A.

EXCESS OF SODIUM.

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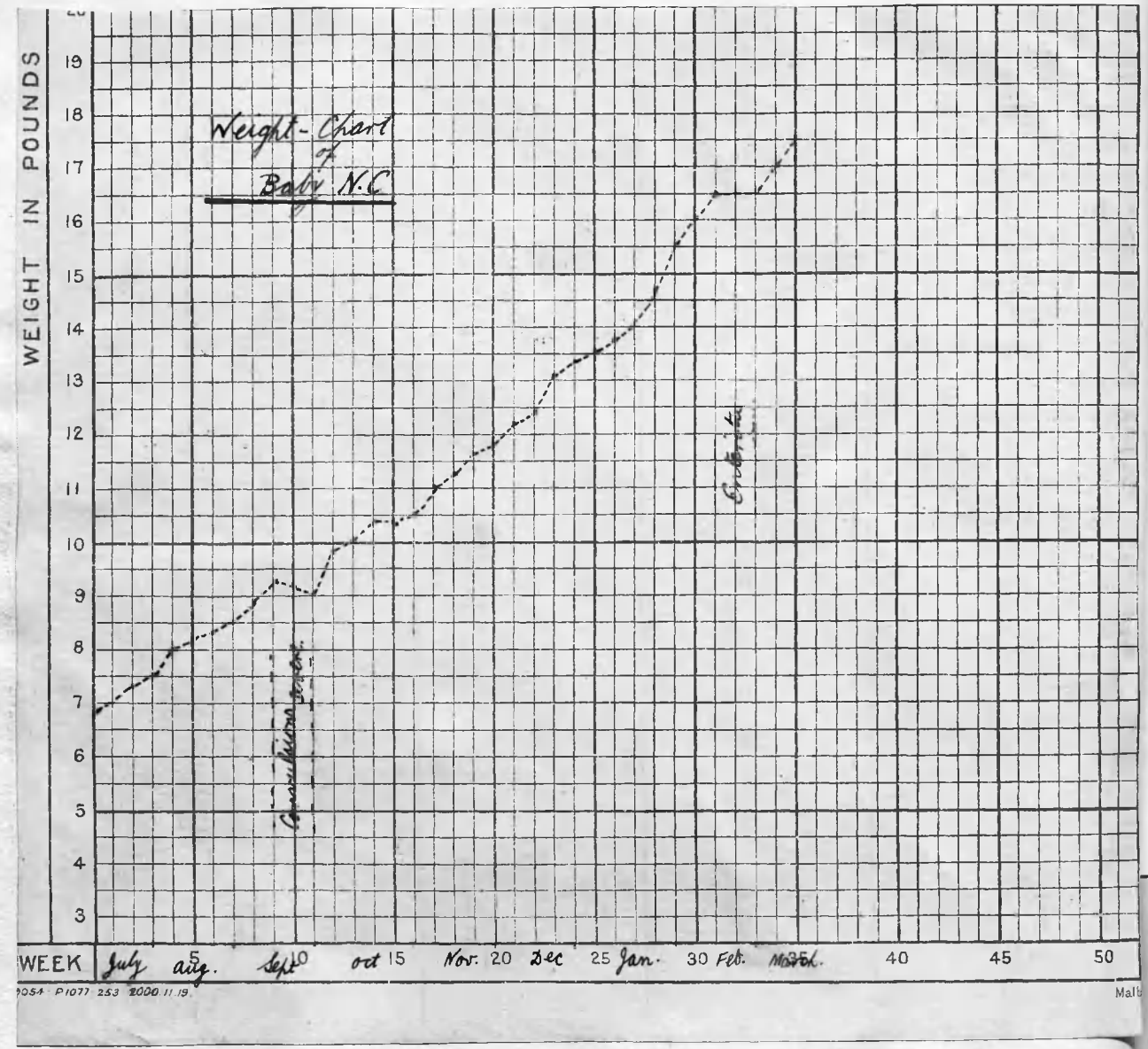
Ringer[23] when experimenting with isolated nerve-muscle preparations, observed an inclination to contracture in muscle that had been kept in pure normal saline solution. Later Carslaw[24] found that on circulating pure sodium chloride solution through the vessels of the posterior end of a frog, spontaneous excitation phenomena (tetanic contractions) appeared very quickly, and lasted for several minutes. The effect was minimal when isotonic solution was used, suggesting that the difference in the molecular strengths of the solutions used might have had something to do with the causation of the increased excitability. Biedermann[25] previously had shown that the excitability produced by pure sodium chloride solution was very evanescent, but when small quantities of sodium carbonate were added to the neutral solution, the immersed muscle sets up rhythmical contractions.

As regards the effect of sodium on mammals Münzer[26] in 1898 stated that he could produce tetany by injection of various sodium salts. Rosenstern[27] maintains that by the administration of common salt (6-8 grms.daily) to "spasmophilic" children recently cured of tetany, a recurrence of all the symptoms was produced. In one experiment which he cites, he gave 100 c.c. of 3% NaCl by the mouth. The A.O.C. changed from 4.6 to 1.8 but the K.O.C. showed little difference (remaining practically at 4.4); there was a rise in temperature from 37.0 to 38.4°C. Nothmann,[28] following up Rosenstern's work/


Weight-Chart
of
Baby N.C
WEIGHT IN POUNDS
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work found that in children disposed to tetany, feeding with salt produced an increased irritability of the nervous system as well as the fever-reaction previously noted. Parhon and Ureche (29) had previously shown that injection of one per cent. sod.chloride into animals suffering from total thyreo-parathyeoidectomy, caused a marked increase of symptoms. In all these cases it is seen that administration of sodium merely precipitated an attack of nervous hyper-excitability in an organism with a spasmophilic diathesis. Chvostek (30) describes a case of a tetany attack following tuberculin injection: he concludes that tuberculin like toxaemia, pregnancy and other causes, is simply an exciting factor in an organism predisposed to tetany. It is quite possible that the cases of tetany attacks described by Rosenstern and Nothmann following administration of salt were precipitated by the disturbance of metabolism caused by the salt, such disturbances being evidenced bythe fever reaction.

More recently tetanoid seizures have been reported by Campbell (31), following a rectal injection of saline. This last case seems rather anomalous as rectal administration of saline is frequently used with advantage in the prevention and inhibition of convulsive attacks. The following are notes of a case occurring in my own practice:-

Baby N.C. Female. Aet 9 weeks. Normal birth. Breast fed. Family history on mother's side showed marked tendency to functional nervous troubles.

14/9/20. Convulsion involving trunk and all the extremities: slight traces of carpopedal spasm: facial sign not present/

present. Examination revealed no abnormality in any of the organs.

15/9/20. Frequent slight convulsions.
K.C.C. 1.4. A.C.C. 2.1. A.0.0. 5.0. K.0.C. + 5.0

18/9/20. Frequent convulsions continuing but all very mild. Now on two feeds of barley water and milk in addition to breast feeds.

29/9/20. Frequent convulsions continued severer in type. Stop breast feeds. Start Allenbury No.1. two feeds in addition to barley water and milk. Injection of normal saline (5. oz.) per rectum twice a day. Also on Hydrarg. ⊖ Cret.gr.½ and Sod.Bic. gr.3.
K.C.C. - 1.6. A.C.C. - 2.0. A.0.C. - 4.5. K.0.C. - + 5.0.

1/10/20. Convulsions although still frequent become very slight.

2/10/20. No convulsions.

3/10/20. A few very slight convulsions.
K.C.C. - 1.6. A.C.C. - 2.5. A.0.C. - 5.0. K.0.C. + 5.0.

4/10/20. No further convulsions.
From now onwards progress favourable.

Further Miss Henderson in the course of some work (unpublished) on the effect of administration of common salt to children found that the electrical reactions were uninfluenced. In order finally to disprove the theory that administration of sodium salts increased the electrical excitability, the following experiments were performed:- 0.9% NaCl was injected.

No.	Cat.	Wt.in Kg.	Amt.of soln. injected c.c.	E.R.before expt. K.C.C.	E.R.before expt. K.0.C.	E.R. after expt. K.C.C.	E.R. after expt. K.0.C.	CO_2 capac. of Plasma in vol.per 100 c.c. Bef.	CO_2 capac. of Plasma in vol.per 100 c.c. After.	Temperature Bef.	Temperature Aft.
3.	Fem.	3.1	250	0.4	9.0	0.6	9.0	34.6	31.3	99.0	103°
11.	Fem.	2.5	220	0.9	4.5	0.9	4.9	48.1	47.5	100.0	101.6
12.	Male	2.7	250	1.1	11.0	1.1	10.0	30.2	28.9	99.5	101.4

It will be seen from the above table that the electrical reactions/

reactions were unchanged by injection of normal saline. The alkaline reserve is also unaltered. There is to be noted, however, a rise in temperature during the administration of the sodium chloride solution. In one case the temperature rose from 99.0°F. to 103.0°F. thus confirming the findings of Nothmann with regard to the rise in temperature.

As regards the onset of tetany after administration of sodium chloride to children with a spasmophilic diathesis, Cushny's observations on the presence of excess of chlorides are of interest. He points out that an excess of chlorides in the body fluids tends to an increased elimination of calcium. The work of Loeb (32) indicates that the irritability of a tissue has some relationship to the relative proportions of sodium and calcium in the body. The disturbance in the sodium-calcium ratio in spasmophilic children may be sufficient to precipitate the onset of a convulsion. The evidence adduced is against the view that excessof sodium salt is of itself the cause of increased electrical excitability. This conclusion is further strengthened by the findings of Hastings, Murray and Murray (33). These investigators found that in dogs with experimental pyloric obstruction there were marked signs of nervous hyperirritability, but an actual decrease in the concentration of sodium in two out of three cases.

It must therefore be concluded that although excess of sodium may be a predisposing factor in the production of an increase in the electrical excitability, it cannot be regarded as the ultimate cause of this increase.

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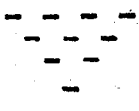
III.B.

DIMINUTION OF CALCIUM.



In his experiments on the effects of various salt solutions on the excitability of frog's muscle Locke[34] showed that the high tetanic contractions caused by immersion in a sodium chloride solution soon disappeared if a 10 per cent. saturated solution of calcium sulphate were added. Loeb[35] when working on the effects of various electrolytes found that injection into the animal body of any salt liable to preipitate calcium produces twitching of the muscles. Bancroft[36] from work done on the isolated sartorius of the frog stated that electrical stimulation of muscle is dependent upon the relative concentration of the calcium ions. He maintained that the effective galvanic stimulation of muscle must either consist in or be associated with a diminution in the ratio of the concentration of the calcium to that of sodium. Previous to this Sabbatant[37] (quoted by MacCallum & Voegtlin) had shown that the electrical excitability of the cortex cerebri was diminished by the application of isotonic solutions of calcium chloride, and raised by a solution such as sodium oxalate which precipitated calcium. Roncoroni[38] confirmed Sabbatani's work and further showed that the same results could be obtained with other salts of calcium such as the iodide, nitrate and acetate.

Quest,[39], on the hypothesis that a calcium-deficiency in the brain tissue might be the cause of tetany, analysed the brains of children who had died of this disease and found a marked reduction in the calcium content. In the following year/

year Weigert[40] analysed the brains of two puppies from the same litter, one of which had suffered from tetany when on cow's milk. In the normal there was 0.1598 per cent. of calcium, in the other 0.152 per cent. Leopold and Reuss[41] estimated the total calcium of rats who were suffering from experimental tetany but could find no diminution. They urge that this cannot be taken as evidence against the calcium deficiency hypothesis as a great part of the calcium might have been rendered inactive. They cite the observations of Erdheim[42] on the remarkable changes in the teeth of rats suffering from tetany, as evidence of the disturbance in the calcium metabolism. Parhon, Dumitresko and Nissipesko[43] produced tetany in cats by total thyreo-parathyreoidectomy and actually found an increase in the calcium content of the brain. Rosenstern[27] criticised their work on the ground that complications were introduced by ablation of the thyreoids. Despite this, it is difficult to understand why a condition of tetany should have been produced in their experiments if a diminution of calcium in the brain was the causal factor. Cohn[44] also had found no decrease in the calcium content of the brain in two out of three infants who had died of tetany. In dogs dying in a condition of experimental tetany Cooke[45] found actually a greater calcium content than normal.

MacCallum and Voegtlen[22] examined the blood in cases of/

of parathyreoidectomy and found the calcium-concentration of the serum markedly lowered.[46] Hastings and Murray working on the same lines found that the calcium content of the serum decreased after a parathyreoidectomy from a normal value of about 11 mg. per 100 c.c. to about 5 mg. per 100 c.c. Howland & Marriott[47] made analyses of the blood in cases of idiopathic tetany in children and got a distinct diminution in the calcium content.

In cases of tetany produced by methods other than that of extirpation of the parathyreoids, there is much divergence in the results. MacCallum, Lintz, Vermilye, Leggitt and Boas[48] describe a case of pyloric obstruction accompanied by tetany in which there was a decrease in the serum calcium content. Hastings, Murray, and Murray[33] produced a pyloric obstruction in dogs and they state that using a better method of calcium analysis than MacCallum and his colleagues they found a slight increase rather than a decrease in the calcium content of the serum.[49] Harrop describes a case of adult tetany caused by injection of sodium bicarbonate, but with no decrease in the calcium content of the blood.[50] Goldman & Grant produced attacks of tetany by hyperpnoea but found that the calcium content actually increased from 12.84 to 13.44 mg. per 100 c.c. We may conclude, therefore, that although a calcium deficiency in the serum may be produced by parathyreoidectomy, it is not/

not necessarily an accompaniment of tetany produced in other ways.

Calcium metabolism in conditions of tetany has received much attention. Cybulski (51) made a study of the calcium metabolism of a seven-months' infant who suffered with tetany and who had no obvious signs of ricketts. The analyses were done at three different periods (1) at the height of the illness when the infant was being fed on two parts of milk and three parts of barley water along with some sugar, (2) shortly after the commencement of breast-feeding when the symptoms of tetany (convulsions, laryngeal spasms, and increased E.E.) were diminishing in intensity and (3) a month after breast-feeding had been started. His results show that in the first period there was a retention of 20.8% of calcium, in the second period 53.7%, and in the third 87.2%. An obvious criticism to be levelled at any conclusion being drawn from this experiment, is that the rise in calcium-retention and the disappearance of the tetany symptoms may be both due to the change in the nature of the feeding and that the relief from tetany may be a result of this change and not of the increased retention of calcium. Cattaneo and Cotta Ramusino (52) made numerous determinations of the calcium metabolism of healthy, sickly and spasmophilic children but did not find any noteworthy differences. Most of his tetany cases, however, were rachitic and this diminishes the value of his experiments. Cooke (45) failed to find any disturbance/

disturbance in the calcium-metabolism after parathyreoidectomy.

Quest tried the effect of calcium-poor diet. He fed four puppies from the same litter, two on normal diet, two on calcium-poor food and after eight weeks got the following results on testing the electrical excitability.

	Normal Diet.		Cal-poor diet.	
	1.	2.	3.	4.
K.O.C.	10.	14.	3.4	4.2

But no confirmation of this experiment has been forthcoming except for an observation of Arons (54) that convulsions developed in a dog fed on calcium-poor food. Stöltzner (55) repeated Quest's experiment but found no difference in the E.E. after six and twelve weeks respectively. He also stated that, despite calcium poor feeding, Voit's experimental animals showed no signs of convulsions even although analyses of the brain revealed a marked diminution of calcium. Stöltzner as a matter of fact put forward the view that tetany is caused by an excess of calcium on the ground that children fed with cow's milk developed tetany-symptoms which disappeared when breast-feeding was resorted to. (The cow's milk, he stated, contained 5 times as much calcium as did the other.) Borgen (56) and von Pirquet (57) could not confirm this although the latter gave 339 gms. of calcium to a child in the course of six months. Rosenstein (27) quotes Risel as having produced a fall in E.E. in eleven out of twenty-four cases by treatment with calcium acetate.

Various attempts have been made to lessen the calcium content of the blood experimentally. Sarvonat and Roubier (58) administered/

administered oxalates bythe mouth with production of such hyperexcitability that it could be measured electrically. MacCallum and Vogel (59) performed perfusion experiments with blood from which the calcium had been dialysed and found that an increase in electrical excitability was produced. There is always the danger that in such experiments anaemia plays an important part. Carlson (60) found that tetany develops very quickly six to twelve hours after removing the parathyreoids in lactating animals and concluded that the early onset was due to the great call for calcium in these animals. Marine (61) cites an old observation by Halsted that pregnancy and lactation induce a relative parathyreoid insufficiency since partial parathyreoidectomy in dogs causes tetany symptoms late in pregnancy. It is questionable how far the calcium metabolism can be blamed for the tetany symptoms. It seems just as probable that the increased demands made on pregnant and lactating animals may reduce the resistance of the animal to the effects of partial parathyreoidectomy.

The therapeutic effects of calcium administration in tetany-like cases has also been closely studied. Rosenstern (27) quotes the experiments of Flamini who found that animals which had received injections of calcium had a greater resistance to convulsion-producing poisons than untreated controlled animals. Langley and Kato (62) quote Loewi's experiment showing that the tonic contractions caused by physostigmine were stopped by injection of calcium chloride. Parhon and

Ureche/

Ureche[29] obtained a diminution in the symptoms of tetany following thyreo-parathyreoidectomy by the injection of 1% calcium chloride. Rosenstern[27] gave 100 c.c. of 3% calcium chloride by the mouth and found a reduction in the E.E. of the K.O.C. from 1.8 to over 6 in one case, and 2.0 to 8.0 in another: the A.O.C. he also found reduced. Arthus and Schaffermann[63] performed total thyreo-parathyreoid-:ectomy in puppies and found that those treated with calcium lived longer than those kept on ordinary diet, also, that if those on intensive calcium therapy survived a month they remained free of tetany symptoms even when on ordinary diet. One would like to be sure, however, in this last series that no accessory parathyreoids had been left.

Marine[61] kept pregnant parathyreoidectomised dogs in a subtetanic state by the administration of calcium salts until the end of pregnancy when an uncontrollable parathyreoid insufficiency developed, ending fatally. Howland and Marriott[47] obtained beneficial results in idiopathic tetany in children by calcium therapy. As cases of tetany very often clear up without any specific treatment it is difficult to know how much the administration of calcium really influenced the recovery. Barach and Murray[64], however, report a case of sprue complicated by typical tetany: there was a reduction of the calcium serum-content to 6.5 mg. (normal 9-11 mg.). No relief was obtained by injection of calcium lactate, not even an increase of the blood/

blood-calcium. They suggest that the condition of the blood colloids was such that the calcium present existed in saturated solution and that any additional calcium was immediately precipitated or claimed by the lime-starved cells. They support this view by showing that the calcium content rose after injection of normal blood.

It would therefore seem from a consideration of the evidence that no definite conclusions can be drawn. As Noël Paton and Findlay (65) remark, "there is no conclusive evidence as regards the relationship of calcium to the condition of tetany."

The following experiments were done to throw some light on the influence of calcium on the electrical excitability. They are divided into two groups:-

(1) To show the effect of calcium administration.

(2) To determine if there were any changes in the calcium content of the serum when the electrical excitability had been altered by some other method.

1. Effect of Calcium Administration.

1.9% calcium chloride was injected into the jugular vein with the following results:-

Cat.	Wt. in Kg.	Amt of Soln.	E.R. before		E.R. after.		Alk. Res.	
			K.C.C.	K.O.C.	K.C.C.	K.O.C.	Bef.	Aft.
18. Male.	3.35	20 c.c.	1.5	1.7	3.8	6.0	.36	.34
53. Fem.	2.40	6 c.c.	.35	2.2	.7	4.5		
		20.5 "	"	"	.7	5.0		
		24.0 "	"	"	.8	5.0		
		43.0 "	"	"	.8	9.0		
20. Fem.	2.70	15.0 "	.60	1.1	1.1	4.0		

In cat 53, methyl alcohol had been injected in order to raise the E.E. Previous to injection of the alcohol the reactions were as follows:- K.C.C. = 0.8. K.O.C. = 10.0.

The results indicate quite clearly that calcium has a sedative effect on the electrical excitability of the neuro-mycne, even when as in cat 53 the E.E. has been previously raised by some other method. This probably explains the beneficial effect of therapeutic administration of calcium salts in cases of tetany. In estimating the curative value of calcium in tetany one must bear in mind the fact that tetany attacks very often terminate quite favourably without any treatment and it is accordingly difficult to know how much credit to apportion to the calcium in the inhibition of the attack.

2. Changes in the calcium content of the serum after increase of Electrical Excitability.

10.c.c. of arterial blood were withdrawn from the carotid artery both before and after the increase in excitability. The calcium was estimated by a method used by Noel Paton, Findlay & Sharpe in a large series of experiments shortly to be published; and I am indebted to Mr.J.Sharpe for the analyses.

No.of Animal.	Wt. in Kg.	Soln.used.	E.R.before. K.C.C.	E.R.before. K.O.C.	E.R.after. KCC.	E.R.after. KOC.	CaO Bef.	CaO Aft.
Cat.49.Fem.	2.9	Alcohol 18cc.	.6	6.0	.5	1.5	.019%	.019
Dog. 4.Fem.	7.4	Na_2CO_3-200cc.	1.2	8.0	1.0	5.5	.017%	.016
Cat.73.Male	2.8.	HCl-25cc.N/20	.5	2.8	.6	6.0	.02%	.02%

It will be seen that the calcium content remains practically unchanged, both when the E.E. is raised and when it is lowered. These results harmonise with those of Givens and Mendel (66) who find that administration of base or acid produces no significant effect upon the calcium balance of the dog.

Conclusions:- We can therefore conclude from the above experiments that calcium deficiency does not enter as a causal factor in the change of electrical excitability. Any change in the calcium concentration of the serum would probably alter the excitability of an animal with the "diathesis spasmophile", a diminution such as may be produced by the administration of chlorides precipitating an attack, an increase in the calcium content having a sedative effect. There is, of course, the possibility mentioned by Grant and Goldman (50) among others that the calcium may be present in normal amounts but in great part inactive, for example, precipitated as very minute particles held in solution by the colloids of the serum.

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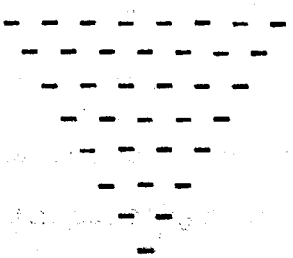
III C.

EFFECT OF AN ACIDOSIS.



following administration of acids, this is not in accord with the experiments of Wilson Stearns and Janney[72] who have shown that some of the symptoms of tetany can be relieved by acid injection.

The following experiments were carried out to determine the effect of acid on the electrical excitability of the neuromyone, HCl (M/7), Lactic Acid (N/100) and Phosphoric Acid (N/10), were used.

TABLE 2.

No. of Animal.	Wt. in Kg.	Soln. inj.	Amt. of Sol. in c.c.	E.R. Before		E.R. After.		CO_2 cap. (V. Slyke) in c.c. per 100cc. of plasma.		CO_2 cap. (Martin)	
				KCC.	KOC.	KCC.	KOC.	Bef.	Aft.	Bef.	Aft.
2. male.	2.8	HCl	170	0.8	2.5	1.0	8.0	32.5	18.9	35.8	22.4
8. male.	2.4	"	250	0.4	2.0	0.7	9.0	35.1	11.2	35.8	44.8
9. Fem.	3.1	"	220	0.5	1.7	0.6	11.0	28.7	8.9	32.3	8.9
33. male.	2.7	"	210	0.9	7.0	1.0	7.0	31.9	16.8	-	-
34. male.	2.8	"	125	0.5	2.8	0.6	6.0	34.7	26.0	-	-
35. male.	2.4	"	150	0.5	2.7	0.7	4.5	32.4	20.6	-	-
13. fem.	2.3	Phos. A	10	0.6	1.1	2.5	4.0	-	-	-	-
14. male.	3.0	Lactic. A.	200	6.7	3.5	0.9	6.5	32.9	21.1	36.7	26.6
15. fem.	2.5	"	250	0.6	2.7	1.0	7.0	30.1	13.1	34.8	13.5
56. fem.	2.9	"	150	0.3	1.1	0.5	3.2	-	-	-	-

TABLE 3. (Showing effect of M/7HCl on pH.)

No. of Cat.	Wt. in Kg.	Previous to any injection.	Value for Ph. 50cc. inj.	100cc. inj.	150cc. inj.
33	2.7	7.4	7.4	7.4-	7.2+
34	2.8	7.4	7.4	7.4	-
35	2.4	7.4	7.4	7.4-	7.2

\+ indicates a value slightly above figure indicated.

\- " " " " below " "

TABLE 4. Effect of HCl.

Cat 2. Wt. 2.8 Kg.

Temperature 100° throughout the experiment.

11.0 a.m. Anaesthetic commenced.
11.15 E.R. taken. K.C.C. = 0.8 K.O.C. = 2.5
11.18 Vessels cut and cannulae inserted. K.C.C.= 0.8 K.O.C= 2.5
11.34 Blood drawn from carotid. K.C.C.= 0.8 K.O.C.= 2.5
11.50 K.C.C. = 0.8 K.O.C. = 2.5
11.53 Injection of M/7 HCl. commenced.
12.25 p.m. 50c.c. of M/7 HCl injected. K.C.C.= 0.9 K.O.C.= 3.3
12.55 100c.c. of HCl injected. K.C.C.= 1.0 K.O.C.= 8.0
1.25 150c.c. of HCl injected. K.C.C.= 1.0 K.O.C.= 8.0
1.47 170c.c. of HCl injected. Animal died.
1.50 (3 minutes after death) K.C.C.= 1.0 K.O.C.= 3.7

TABLE 5. Effect of Na_2CO_3 followed by HCl.

Cat 1. Wt. 3.2 Kg.

11.10 a.m. Anaesthetic commenced.
11.25 E.R. taken. K.C.C.= 1.0 K.O.C.= 7.0
11.40 Vessels cut. Cannulae inserted. K.C.C.= 1.0 K.O.C.=7.0
12.0 Blood withdrawn. K.C.C.=1.0 K.O.C.= 7.0
12.15 p.m. K.C.C.=1.0 K.O.C.= 7.0
12.18 Injection of 1.9% Na_2CO_3 commenced.
12.50 40c.c. Na_2CO_3 injected. K.C.C.= 1.0 K.O.C.= 6.0
1.50 120c.c. Na_2CO_3 injected. K.C.C.= 1.0 K.O.C.= 3.3
2.40 Twitchings of right hind leg.

TABLE 5. Contd.

2.50	200 c.c. NA_2CO_3 injected. K.C.C. = 1.1 K.O.C.= 1.9
3.2	Rhythmic contractions of both hind legs.
3.20	240 c.c. Na_2CO_3 injected. Blood withdrawn. K.C.C.=1.1
3.45	Injection of M/7 HCl commenced. K.O.C.=1.0
4.15	100 c.c. HCl injected. K.C.C.= 1.2 K.O.C.= 1.8
4.45	200 c.c. HCl injected. K.C.C.= 1.4 K.O.C.= 8.5
4.47	Animal killed.
4.52	K.C.C.= 1.0 K.O.C. = 3.5

Electrical Excitability. The electrical excitability is always lowered by the addition of acid unless the excitab-:ility is previously low as in Cat 33. Excitability that has been raised by administration of alkali is also quickly lowered by injection of acid. (Table 5.)

Usually there is a change in the values for the electrical reactions after 50 c.c. of acid have been administered but the extent of the change varies in individual cases.

In no case was there any suggestion of tremors or convulsive movements as are commonly seen in parathyreoidectomised animals or in idiopathic tetany. Even the administration of phosphoric acid which according to Elias is especially potent in producing hyperirritability did not lead to any increase in excitability. While engaged on some work in testing the efficiency of the kidney to acids, I injected intravenously in rabbits on several occasions, acid sodium phosphate but found no signs of increased irritability of the neuromyone system.

(I have no figures for the electrical reactions as these/

these were not taken.)

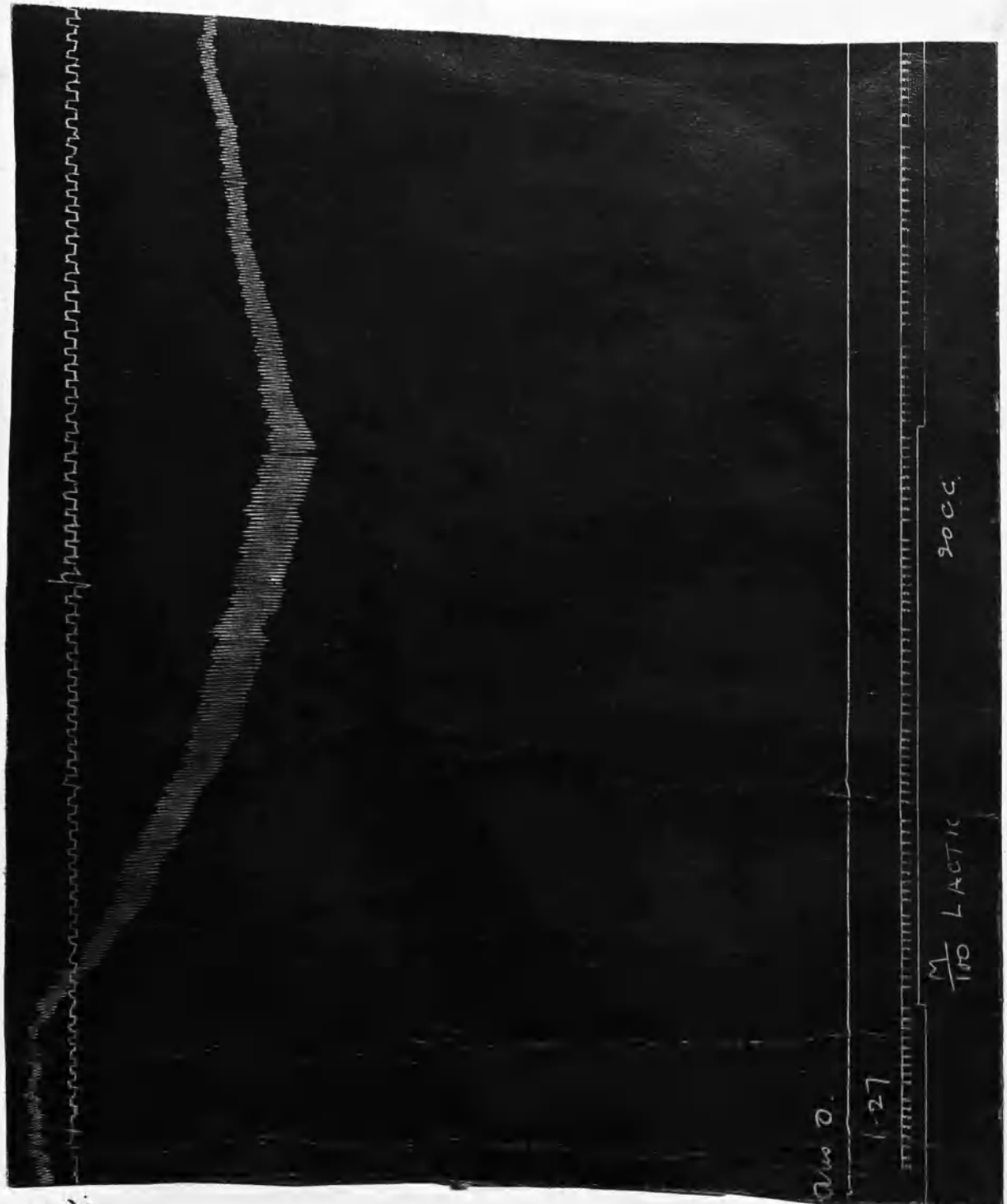
Alkaline Reserve. There is a rapid decrease in the alkaline reserve immediately following the injection of acid, but as with the alkali there is no clear ratio between the change of the CO_2 combining power of the plasma and the amount of acid injected. The changes depend on the sensitiveity of the respiratory centre. Bayliss (18) has pointed out that the reaction of the kidney to acid is not as good as to alkali. The experiments of Dr. J.H. Paul and myself on the efficiency of the kidneys after administration of acid indicate that there is comparatively little excretion by the kidney when acid is injected intravenously.

Hydrogen-ion Concentration in the Blood. Administration of acid is much slower in producing any change of the P_H than is the alkali. In a cat of three kilos weight 100 c.c. of M/7 HCl must be injected before there is the slightest change in the values of the P_H (i.e. 0.17 grm. pure HCl per kilo body-weight). This corresponds to the figure given by Bayliss (18) who has showen that this stability of the P_H is due to the immediate response of the respiratory centre.

Head of Oxygen. As to the effect of acid on the head of oxygen, this has been clearly demonstrated by Barcroft (20) who has shown that blood becomes "meionectic" in presence of acid. Oxyhaemoglobin is more easily dissociated so that the head of oxygen/

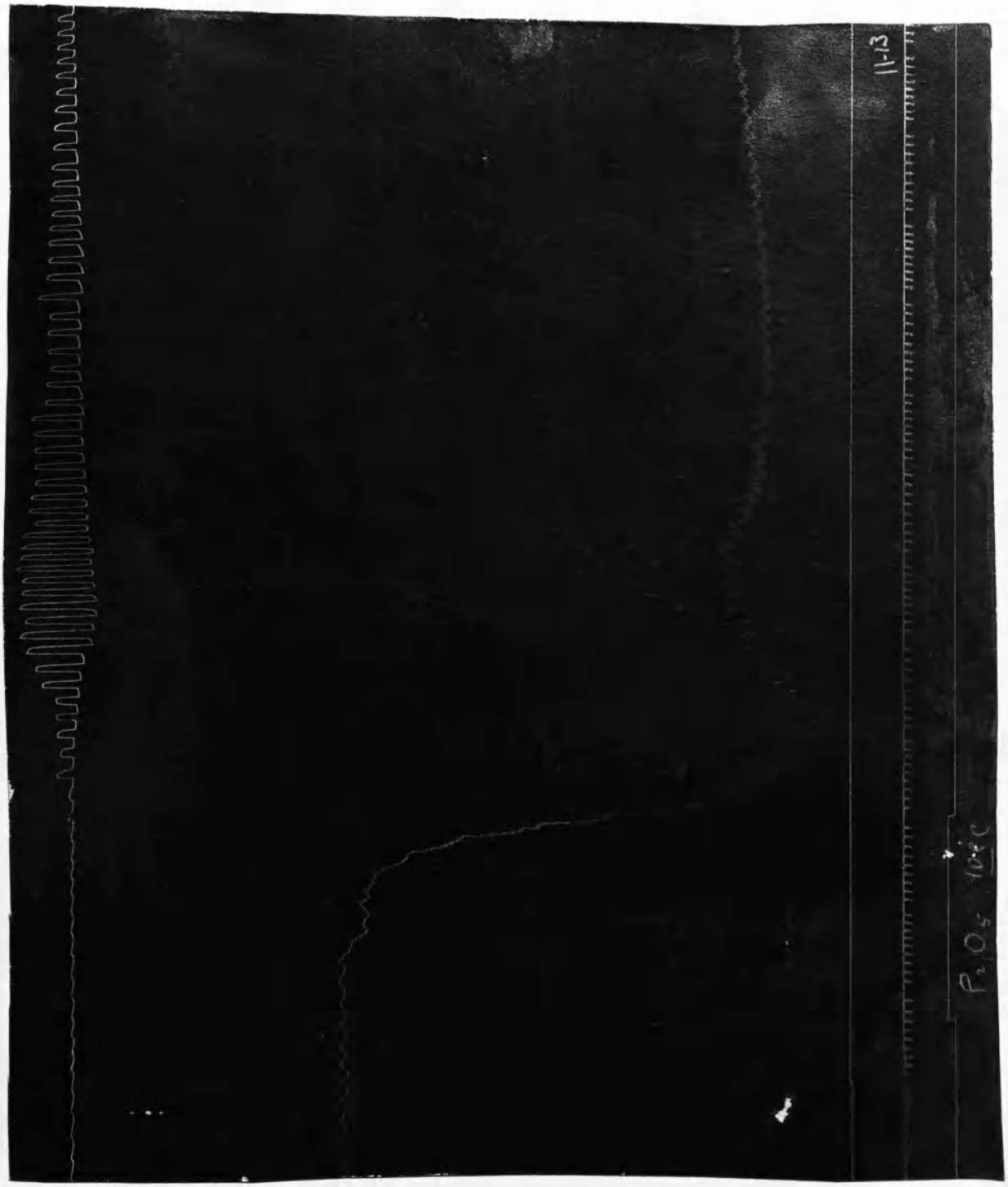
Tracing 1.

Effect of Lactic acid.



Tracing 1.

Showing (i) Slowing of Pulse-rate.
(ii) Rise of Pulse-pressure.
(iii) Slight increase in Frequency of Respirations.



Tracing 2.

Showing (1) Fall of Blood-pressure.

(2) Marked increase in Frequency and amplitude of Respirations.

receive
greater and the tissues a greater supply of

there was always found a fall in blood
the extent of fall depending on the strength of the
and the rate of injection. This is contrary to
of Matheson [1] who found that with injection of
N/8 lactic acid there was a rise of blood pressure.
shows the effect of N/100 lactic acid and tracing 2
N/10 phosphoric acid. Both the rise in pulse
and diminution in pulse pressure is more marked in cases
of acid injection.

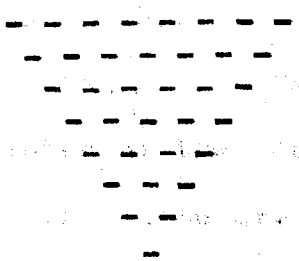
Tracing 2.
Effect of Phosphoric acid

The respirations are increased in frequency
and amplitude. In tracing 3 the respiratory rate after the
injection of acid is 50% of that previous to the

A study of the results of injections of acids
as hydrochloric, phosphoric and lactic acids and acid
sodium salts does not support the view that acid is a cause
of diminished excitability of the neuro-muscular system. Far from
diminished excitability it leads to a marked diminut-
ion of excitability explains the beneficial results obtained
by

III D.

EFFECT OF AN ALKALOSIS.



The effect of alkalis in raising the excitability of the neuro-myone has been noted for quite a considerable time. Biedermann[25] in a description of the effects of various sodium salts on the excitability of the frog's sartorius notes that weak solutions of sodium carbonate and sodium hydrate produce a more striking increase of response to artificial stimuli than do solutions of sodium sulphate.

L. Blum[73] in 1913 reported in a patient suffering with diabetic coma the occurrence of convulsions following the administrations of sod. bicarb. and ceasing when the sod. bicarb. was stopped. Palmer and Van Slyke [74] quote a communication by Tileston of the occurrence of severe convulsions in a case of Weil's disease following the intravenous injection of sod. bicarb. solution which produced a plasma CO_2-combining capacity of eighty volumes per cent. They urge that therapeutic administration of alkalis should be guided by an estimation of the alkaline reserve. Harrop[49] reports a case of tetany following the intravenous injection of sod. bicarb. without any diminution in the calcium concentration of the serum. Howland and Marriott [47] although they support the calcium deficiency hypothesis as the cause of tetany state that it is not unusual to see symptoms of tetany develop in cases of acidosis treated with sod. bicarb. P.S.Henderson [75] however, who investigated

the/

the effect of sod.Bicarb. on children, could not confirm their results, finding that doses as high as 0.92 grm. per kilo body-weight per twenty-four hours had no influence on the electrical excitability of the neuromyone even when the bicarbonate was continued for as long as twenty-three days, nor were any tetany symptoms produced. On the experimental side, Collip and Backus (76) injected large doses of 5% sod. Carb. in distilled water intravenously into dogs, but in two cases only found the least sign of tetany. They did not however test the electrical excitability.

In tetania parathyreopriva, the work of Wilson, Stearns and Janney(72) pointed to the presence of an early alkalosis as demonstrated by the sudden diminution in the urinary excretion of acids and the decrease in the hydrogen-ion concentration of the urine. These same investigators found that injection of acid relieved the symptom of parathy-:reoidectomy. Wilson Stearns and Thurlow (77) followed up this work by showing from a study of the dissociation constant of oxyhaemoglobin and the alveolar CO_2 pressure that there was an increase in the alkalinity of the blood. They found that this alkalosis may be neutralised during tetany periods. The actual increase in the alkaline reserve of the blood as demonstrated by the CO_2 combining capacity of the plasma was soon afterwards demonstrated by McCann(70). Later work, however, by Hastings and Murray (46) who worked on dogs, failed to/

to confirm the work of McCann. In connection with this point it has to be noted that it is often very difficult to take the blood for examination during the period of alkalosis which sometimes lasts for a very short time. This probably explains the great variation in the results published.

McCallum and others [48] have shown that when the pylorus is obstructed and the gastric juice with its hydrochloric acid constantly removed there is produced an increase in the E.E. of nerves with spontaneous twitchings ending in most cases in violent convulsions. Hastings, Murray and Murray [33] performed the operation of pyloric obstruction in dogs and found evidence of nervous hyperirritability but did not test the electrical reactions. They found a marked increase in the CO_2 combining power of the plasma and an insignificant rise in the numerical value of the P_H.

The evidence in favour of the view that an alkalosis is the cause of an increased neuromyal excitability is therefore not conclusive. It was necessary to investigate the full effects of alkalis on the E.E. of the neuromyone. In the first series of experiments 1.9% sod. carb. was used with the results given in the following tables.

TABLEn 6. Showing Effects of injection of Na_2CO_3 1.9%

No.of Animal.	Wt.in Kg.	Amt.of Sol.in c.c.	E.R.Before.		E.R.After.		CO_2 cap. of plasm. (V.Slyke)		CO_2 cap. (Martin)	
			KCC.	KOC.	KCC.	KOC.	Bef.	Aft.	Bef.	Aft.
Cat 1.	3.2	240	1.0	7.0	1.1	1.0	31.0	67.1	-	-
" 4.	2.1	100	1.6	11.0	m1.0	1.4	28.9	61.6	31.0	71.6
" 5.	2.7	200	1.2	10.0	1.0	1.6	31.9	68.3	35.8	75.7
" 6	2.7	150	0.8	6.0	0.7	1.1	33.5	69.9	33.3	75.7
" 7	2.9	250	0.5	4.8	0.3	0.8	30.8	72.5	31.9	80.6
" 12A.	2.3	220	0.5	0.8	m0.5	0.8	31.0	69.4	30.8	74.8
" 30	2.8	150	1.1	9.0	1.0	2.5	-	-	-	-
" 31	1.9	200	0.6	4.5	0.4	0.9	-	-	-	-
" 32	2.4	200	1.0	6.5	0.6	1.2	-	-	-	-
Dog 1	6.8	220	2.1	5.0	1.1	1.0	40.8	76.8	44.8	72.1
" 2	7.0	250	1.8	7.0	1.5	1.5	42.7	78.7	44.8	76.3

TABLE 7. Showing Effects of injection of Na_2CO_3 on Value of PH.

No.of Animal.	Wt.in Kg.	Value for PH.			
		Before inj.	after 50c.c.	After 100cc.	Aft.150
30	2.8	7.4	7.4+	7.7	8.0
31	1.9	7.4	7.7	8.0	9.0-
32	2.4	7.4	7.7-	8.0-	8.0+

- indicates a value slightly below figure indicated.

\+ " " " " above " " .

TABLE 8. Effect of Na_2CO_3.

Cat IV. Wt. 2.1 Kg. Temperature 99.0° throughout the experiment.

2.5 vp.m. Anaesthetic commenced.
2.15 E.R. taken. K.C.C.= 1.6 K.O.C.= 11.0
2.20 Vessels cut and cannulae inserted. K.C.C.= 1.0 K.O.C.= 8.0
2.30 Blood drawn from carotid. K.C.C.= 1.0 K.O.C.= 9.0
2.40 K.C.C.= 1.0 K.O.C.= 9.0
2.42 Injection of Na_2CO_3 commenced.
3.20 50 c.c. of Na_2CO_3 injected. K.C.C.= 1.0 K.O.C.= 7.0
3.41 Clonic movements of both hind limbs.
3.50 100 c.c. of Na_2CO_3 injected K.C.C.= 1.0 K.O.C.= 2.2
4.15 K.C.C.= 1.0 K.O.C.= 1.4
Blood withdrawn.
4.25 Animal killed.
4.30 K.C.C.= 1.0 K.O.C. = 1.4

Electrical Excitability. After all injections of carbonate there was an increase in E.E. unless the excitability was previously high. In the latter case as in cat 12 A, there was no change. The increased excitability was always very marked, but there is not apparent any definite relationship between the amount of alkali injected and this increase of excitability. Occasionally there occurred twitchings resembling those got in parathyreoidectomised animals, but they were not constant phenomena. Thus many cases in which there was produced a markedly increased E.E. by alkali administration might have been put down as being unaffected by the alkali if the electrical reactions had not been taken.

Alkaline Reserve. The CO_2-combining power of the plasma as indicated by the alkaline reserve is increased by the injection of the carbonate. So far as can be seen from the results recorded in Table 6. there is no clear relationship between the change of the CO_2-combining power of the plasma and the amount of alkali injected. The changes depend possibly on two factors, (1) the sensitivity of the respiratory centre which apparently varies in individual animals and (2) in large part on the functional efficiency of the kidney.

In connection with the sensitivity of the respiratory centre the effect of the anaesthetic is of great importance. Scott (78) gives details of two experiments on cats in both of which the animal was made to breathe an atmosphere containing 5% CO_2. In one, anaesthetised with urethane, the tidal air per minute was increased 214% over that when breathing atmospheric air, in the other which was decerebrated 414%. But the sensitivity varies even when the same method is used as shown in the following Table 9. adapted from Scott (78).

TABLE 9.

Cat No.	Wt.	Experimental Number.	Percentile Increase in Minute volume as the inspired CO_2 increased from 1% to 6%					
			1%	2%	3%	4%	5%	6%
20	1.8	1	25	65	140	255	450	600
21	1.3	6	10	30	75	135	210	300
22	2.1	10	32	80	150	240	330	400
26	2.3	15	20	50	95	150	220	300

It may be that the difference in sensitivity of the respiratory centres of various animals account for the differences in the reaction of the neuro-myone to alkali administration, and explain in part at any rate, the varying results got by previous workers. In connection with the electrical excitability however, it has also to be noted that, as I have mentioned, if the reactions are previously very excitable, injection of alkali will not render them more excitable. What the cause of this initial high excitability is, I have not been able to determine.

That the renal efficiancy varies in different animals is shown by a series of experiments done by Dr. J.H. Paul and myself (unpublished). They show that there is an increased excretion of alkaline urine commencing shortly after the injection of alkali but that the increase varies in different animals. (Chart 5.)

Hydrogen-ion Concentration of the Blood.

Injection of alkali raised the value of the P_H, the rise depending on the amount of carbonate injected (Table 7). In no case however did the value of the P_H rise beyond 9 which is well within the limits possible in a living animal.

Haemoglobin. There was a reduction in the percentage of haemoglobin (as determined by the Sahli method), corresponding to the amount of fluid injected, and probably due to dilution of the blood. Similar results for the haemoglobin content were got/

got whatever fluid was injected thus showing that the total amount of Haemoglobin was not markedly influenced by the nature of the solution used.

Head of Oxygen. By this term I mean the difference between the percentage amounts of arterial and venous oxygen, and it indicates the amount of oxygen used by the tissues. Barcroft[20] has shown that the dissociation curve of oxyhaemoglobin depends upon the balance which is maintained between the acid and alkali in the blood. The addition of acids greatly accelerates the reduction of the blood, whereas alkalis retard it.

Wilson Stearns and Thurlow[77] have shown that the value of K (the dissociation constant of oxyhaemoglobin) always rises in tetany parathyreopriva. The following table (10) gives the figures obtained from the oxygen-analysis of the blood.

TABLE 10. Showing effect of Na_2CO_3 on % saturation of oxygen.

No. of Animal.	Wt.	Amt. of Sol. in c.c.	% Satur. of O_2 Before.			% Satur. of O_2 After		
			arter.	Venous.	Diff.	arter.	Venous.	Diff.
30. fem.	2.8	150	94.0	58.6	35.4	88.1	69.8	18.3
31. fem.	1.9	200	94.8	52.0	42.8	80.1	72.6	7.5
32. male.	2.4	200	92.4	47.8	44.6	84.5	70.9	13.6

It will be seen that there is always a reduction in the head of oxygen after injection of alkali, thus indicating a diminished supply of oxygen to the tissues. This is in line with/

Tracing 3.

Showing (1). Slight diminution in Pulse-rate,
(2). Increase in Pulse-pressure.
(3). Diminished frequency of Respirations

...conclusions of Tanfyuli [illegible] ...found that oxidation in the tissues of man was decreased ...destruction of alkali.

...Alkali. ...having demonstrated the effect of ...carbonate in raising the electrical excitability, one ...knew whether its action was a specific one, or ...was common to all alkalis. Accordingly in three ...the sodium hydrate was used but in order to obviate any ...decomposition, the more stable ammonium hydrate was ...

Tracing 3. ...hydrate was injected with the ...

Effect of Sodium Hydrate.

...Tracing 3. Showing effect of NaOH, 0.4%.

	A.E.C.		A.E.C.		60 -Cath. opacity in 120c.c. plasma.	
					Before.	After.
	.6	4.4	.6	1.7	54.9	66.7
	.6	6.6	.4	1.5	59.1	60.5
	1.4	9.0	1.0	2.6	51.1	67.9

...results show that sodium hydrate has an action similar to ...carbonate both on the electrical excitability and the ...coagulation time.

with the conclusions of Taniguti [79] and Jawein [80] who maintained that oxidation in the tissues of man was decreased by administration of alkalis.

Effect of other Alkalis. Having demonstrated the effect of Sodium carbonate in raising the electrical excitability, one had to determine whether its action was a specific one, or whether it was common to all alkalis. Accordingly in three experiments sodium hydrate was used and in order to obviate any effect of the soidum ion, in three others ammonium hydrate was injected.

1. Sodium Hydrate. 2% sodium hydrate was injected with the results detailed in table (11).

TABLE 11. Showing effect of NaOH. 2%.

No. of Cat.	Wt. in Kg.	Amt. of Sol. in c.c.	E.R. Bef.		E.R. Aft.		CO_2 -Comb. capacity in c.c. per 100c.c. plasma.	
			KCC.	KOC.	KCC.	KOC.	Before.	After.
13. fem.	2.9	100	.6	3.0	.5	1.7	34.9	66.9
36. male	1.6	25	.6	6.0	.4	1.5	29.1	60.3
37. male	2.7	150	1.4	9.0	1.0	2.6	31.1	67.9

These results show that sodium hydrate has an action similar to the carbonate both on the electrical excitability and the alkaline reserve.

An examination of tracing (3) showing the effect of NaOH on blood pressure and respirations reveals the following facts.

1. Circulation. There is a fall in the general level of the blood pressure immediately following injection of the sodium hydrate. The diastolic pressure shows a more marked drop than the systolic, leading to the production of an increased pulse pressure. There is also a slowing of the heart rate of 11%. These phenomena of increased pulse pressure and diminished pulse rate I have found as constant accompaniments of all conditions in which the head of oxygen is reduced. There is a very slight rise after the initial fall, the pulse pressure, however, still remaining greater than normal. Thereafter the pressure remains more or less steady until the administration of sodium hydrate is stopped when the pressure slowly rises with concomitant decrease of pulse pressure.

2. Respiration. There is a decrease of 25% in the frequency of the respirations following administration of Sodium Hydrate and also a slight decrease in the amplitude. The respiratory trace is not sufficiently well marked to indicate properly any decrease in amplitude although it clearly shows the lessened frequency.

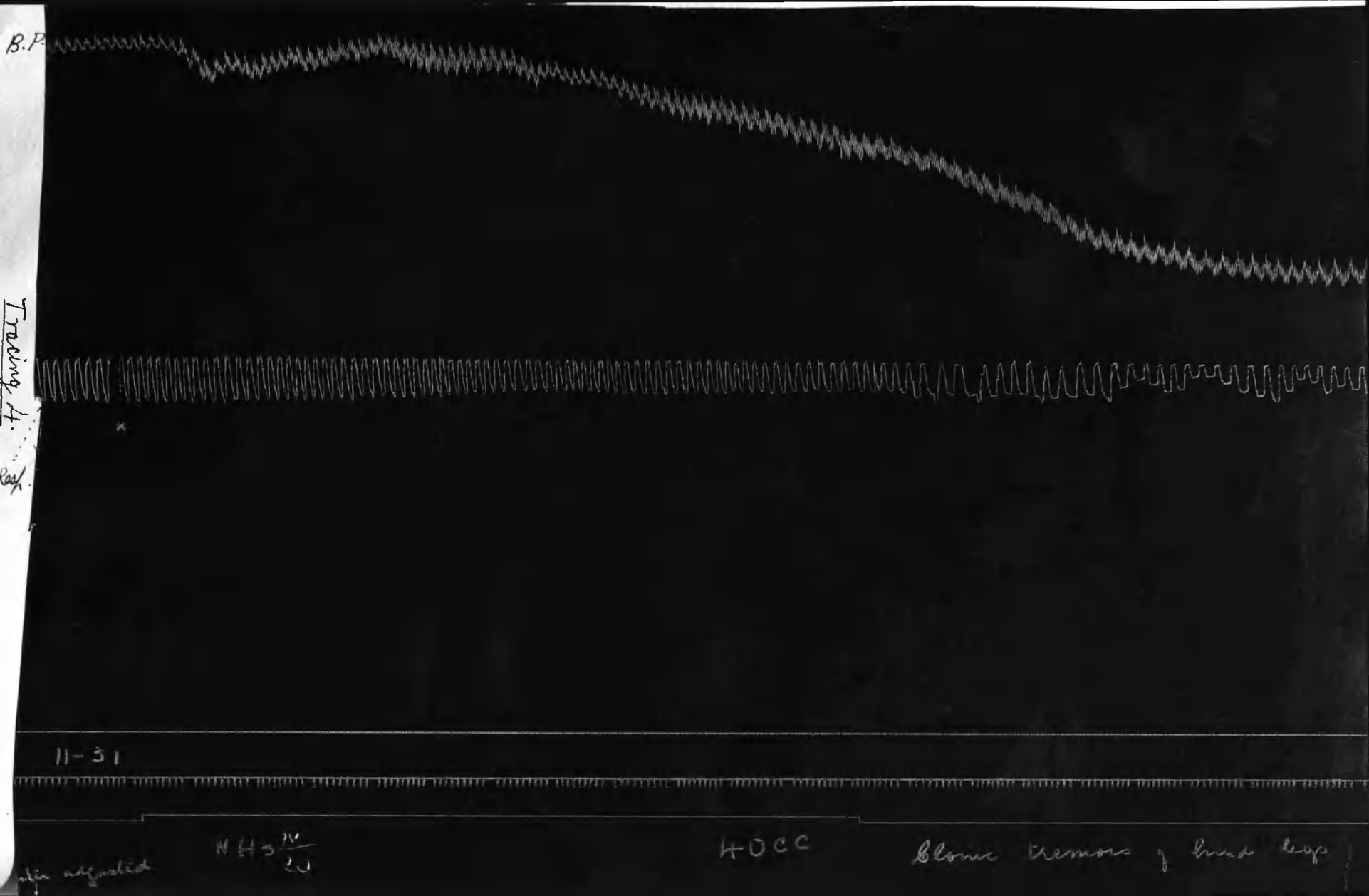
Effect of Ammonia. Berkely and Beebe (21) found that muscular twitchings were produced by intravenous administration of ammonia, Bostock (81) also got tremors and convulsions following on intravenous injections of ammonium carbonate, and persisting even when the animal is under full anaesthesia. Noël Paton, & Findlay (65) in a discussion of the evidence as to the possibility/

possibility of ammonia being the causal factor, in tetany, and quoting the results of Jacobson, Greenwald and Alberçoni and others come to the conclusion that the evidence is quite definite that the symptoms of tetany are not due to an increased production of ammonia. As Noël Paton, Findlay and Watson [10] have, however, pointed out, there is no direct relationship between the severity of the nervous symptoms and the electrical excitability of the neuromyone, and the latter cannot be taken as a measure of the severity of these symptoms. Thus although some increase in the E.E. is a constant accompaniment of tetany the converse is not necessarily true. Ammonia is an alkali and unless the increased excitability got by administration of sodium carbonate or sodium hydrate were due to a specific action of these substances, the intravenous injection of ammonia ought to produce an increased electrical excitability.

The following experiments were done, to determine whether injections of ammonia had any effect on the E.E. of the neuromyone. N/10 NH_4OH was injected.

TABLE 12. Showing effects of NH_4OH. N/10.

No. of Cat.	Wt. in Kg.	Amt. of Sol. used.	E.R. Before.		E.R. After.		CO_2 cap. of plasma. (V. Slyke.)	
			KCC.	KOC.	KCC.	KOC.	Bef.	After.
38	3.1	200	1.3	9.0	.9	3.5	32.5	43.9
39	2.9	190	1.8	1.2	1.7	1.0	-	-
67	2.9	200	1.2	7.5	.4	1.5	31.9	51.1


B.P.
Tracing 4.
Resp.
11-31
HOCC
Blows tremors & hand beg

Tracing 4.

Effect of ammonia

These results indicate that ammonia causes an increase in the E.E. of the neuromyone. The findings of Bostock[81] as to the occurrence of convulsions were confirmed.

Alkaline Reserve. An increase in the alkaline reserve as determined by the Van Slyke circulation and respiration is produced

Tracing 4 shows the effect of injection of ammonia on the blood-pressure and respirations. It will be seen that the results are similar to those got with sodium hydrate vix.,

(1) Circulation.

(1) Blood-pressure. Initial slight fall followed by incomplete rise and subsequent gradual fall.

(2) Pulse pressure markedly increased.

(3) Pulse rate diminished 18%.

(2) Respirations

(1) Frequency of respirations decreased 37.5%.

(2) Amplitude of Respirations markedly diminished.

Conclusions as the Results of Alkali Administration.

(1) Alkalis produce an increase in the electrical excitability of the neuromyone unless that excitability ~~of the neuromyone unless that excitability~~ is previously high.

(2) The alkaline-reserve is increased.

(3) The hydrogen-ion concentration is diminished.

(4) The "head of oxygen" to the tissues is decreased and the tracings of the blood-pressure after treatment of the animal with/

alkalis show phenomena which have been described as occurr-:ing in cases of anoxaemia produced by a low pressure of oxygen.

From a perusal of the effects of alkalis and acids it would seeom on superficial observation as though the alkaline reserve and the hydrogen-ion concentration were the controll-:ing factors of the electrical excitability of the neuromyone, varying directly with the former and inversely with the latter.

M.H.Grant (82) working on the isolated nerve-muscle preparation of the frog showed that the only C_H capable of inducing increased excitability is 10-9 and this is in excess of what is found in the mammalian organism suffering with tetany. She concludes, therefore, that the H-ion concentration is not the chief factor in the production of increased electrical excitability. It is difficult to know how far experiments on isolated organs such as the frog's gastrocnemius are applicable to the organism as a whole. Still, the results of other experiments on the neuromyone in situ tent to support this view. It will be shown later that alcohol, pot. cyanide and other substances have a distinct action in increasing electrical excitability without any action on the C_H. Further it is to be noted that injections of acid produce a marked decrease in electrical excitability before any noticeable change in the C_H is produced.

As for the alkaline-reserve, the following experiments (Table/

(Table 13) will show that there may be an increase in the E.E. despite a fall in the alkaline-reserve.

~~N.B. - Grant and Goldman.~~

TABLE 13.

No. of Cat.	Wt. in Kg.	Subst. inj.	E.R. Before.		E.R. After.		CO_2 combing. cap. in c.c. per 10c.c. plas	
			KCC.	KOC.	KCC.	KOC.	Before.	After.
49. fem.	2.9	Ethyl Alc.	.6	6.0	.5	1.5	34.0	25.8
50. fem.	3.1	" "	.3	2.7	.3	1.6	34.9	24.5
53. male.	3.0	Methyl Alc.	.8	10.0	.35	2.2	38.7	27.8
62. fem.	2.7	Pot. Cyan.	.6	5.5	.6	2.2	33.9	18.4

Collip and Backus[76] showed that one of the effects of hyperpnoea was a cramp-like contraction of the muscles and that thiswas accompanied by a fall in the CO_2 combining power of the plasma, a decreased acidity of the urine and a diuresis. They suggested that this tetany-like muscle contraction was due to the alkalosis produced by the hyperpnoea. Grant and Goldman[50] investigated this point still more fully and by hyperpnoea actually produced some of the symptoms of tetany including an increased electrical excitability of the neuro-myone. The P_H both of the blood and urine during the hyperpnoea indicated a blood-alkalosis, while the plasma CO_2 fell from an average figure of 59.5 vols. per cent. to one of 44.9 per cent. They performed one/

one control experiment where washing out of the CO_2 was prevented by the subject breathing through a tube connected to a 15 litre bottle while the observer at the same time breathed through a second tube connected to the bottom of the bottle. No symptoms of tetany resulted nor were there any signs of an alkalosis. They suggest that alkalosis is the condition at the root of all the various forms of tetany whether idiopathic, toxic, or experimental. Vernon(83) was one of the first to state that a condition of cramp-like spasm was often present while hyperpnoea existed. Hill and Flack(83A) while engaged in observations on the effects of hyperpnoea on the circulation and muscular efficiency, made notes of the spastic conditions of the muscles and in one case twitchings of the facial muscles during the hyperpnoeic state. Their polygraph tracings show that the radial pulse becomes weak and may even disappear with each inspiration, and they conclude that the forced ventilation by its mechanical interference with the circulation lessens the oxygenation. But the most interesting point about Hill and Flack's work is that when forcible breathing of oxygen was tried, the pulse remained strong and none of the twitchings or other uncomfortable signs of hyperpnoea were manifest.

From a consideration of the evidence it must be concluded that neither the C_H nor the alkaline reserve is the primary controlling/

controlling factor of the electrical excitability. Hill and Flack's work is strong presumptive evidence that the oxygen supply to the tissues is of great importance in this connection. Further evidence in favour of this view will be led in the following sections.

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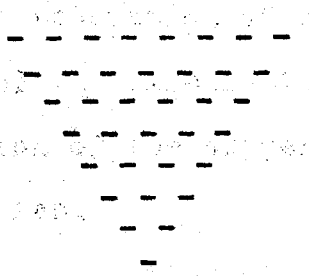
IV. EFFECT OF ANOXAEMIA.



The effects of acids and alkalis on the electrical excitability and the supply of oxygen to the tissues suggest that anoxaemia is the causal factor in production of an increase in the E.E. of the neuromyone. It has long been known that asphyxia raises the excitability of the central nervous system and it seems probable that lack of oxygen might produce a similar result in the peripheral parts of the neuro-muscular system.

Haldane (84) has divided the causes of anoxaemia into:-

(1) Defective saturation of arterial blood with oxygen.

(2) Slowing of the circulation so that an excessive proportion of the oxygen is used up in the systemic capillaries.

(3) Defective proportion of available haemoglobin.

(4) Alteration in the dissociation-curve of oxyhaemoglobin.

In the following work, experiments will be detailed to show the effect on the E.E. of the neuro-myone of each of the above causes of an anoxaemia. Defective saturation of the arterial blood with oxygen was produced by the induction of asphyxia, slowing of the circulation by a diminution in the temperature, a defective proportion of available haemoglobin by the production of an anaemia, and an alteration in the dissociation-curve of oxyhaemoglobin by administration of pot. cyanide. Thereafter the effects of some other substances on the E.E. and oxygen/supply to the tissues will be considered.

IV. ANOXAEMIA.

A. As produced by Asphyxia.

The effects of asphyxia in raising the excitability of the central nervous system has long been known. Bethe[85] in 1906 cut the spinal cord of a dog and found that movements of its hind limbs could be much more easily elicited and were more excitable when the dog respired an atmosphere of hydrogen. Later Sherrington[86] showed that the presence of a certain degree of asphyxia favoured the elicitation of the scratch and other spinal reflexes. Kaya & Starling[87] produced an anoxaemia in the spinal dog with mixtures of nitrogen plus a very little oxygen and found that all the spinal centres were suddenly excited including, of course, the motor centres for the skeletal muscles. Spasm of the whole body and constriction of the vessels immediately occurred, followed quickly by a marked depression. This closely resembled what is got during a convulsion in a parathyreoidectomised animal, for immediately after the convulsion there is a marked lowering of the previously increased E.E. Mathison[67] following up the work of Kaya & Starling showed that the stimulation of the skeletal muscle centres was due to the lack of oxygen and not to the increase of carbon dioxide ordinarily produced by asphyxia. Further proof of the influence of an anoxaemia in exciting nerve centres is got in the note of an experiment by Hooker, Wilson & Connett[88]. These investigators perfused the isolated medulla with blood very poor in oxygen, and

there resulted immediately an increase in the respiratory activity before there was time for any acid metabolic products to be formed.

Noel Paton, Findlay & Watson (10) investigated the effects of asphyxia in the electrical excitability of the neuro-myone, and found that no marked change was produced. An examination of their protocols shows that from the commencement of the induction of asphyxia to the complete re-establishment of breathing there was at most an interval of five minutes. Accordingly only a very mild degree of asphyxia could have been produced. In a series of experiments to determine the changes in the oxygen-content of the blood during the onset of an anoxaemia, Adams & Morris (89) have shown that there is practically no decrease in the head of oxygen until there is a marked degree of asphyxia. This might explain the absence of any change in the electrical excitability in the asphyxia experiments mentioned, for as Haldane & Priestley (90) have pointed out, there is a considerable margin as regards oxygen-supply and the percentage of oxygen in the air breathed can be reduced to about two-thirds of the ordinary amount before any oxygen lack is evident.

The following experiments were undertaken to demonstrate the effect of deep asphyxia on the electrical excitability and determine the concurrent changes in the oxygen-content of arterial and venous blood.

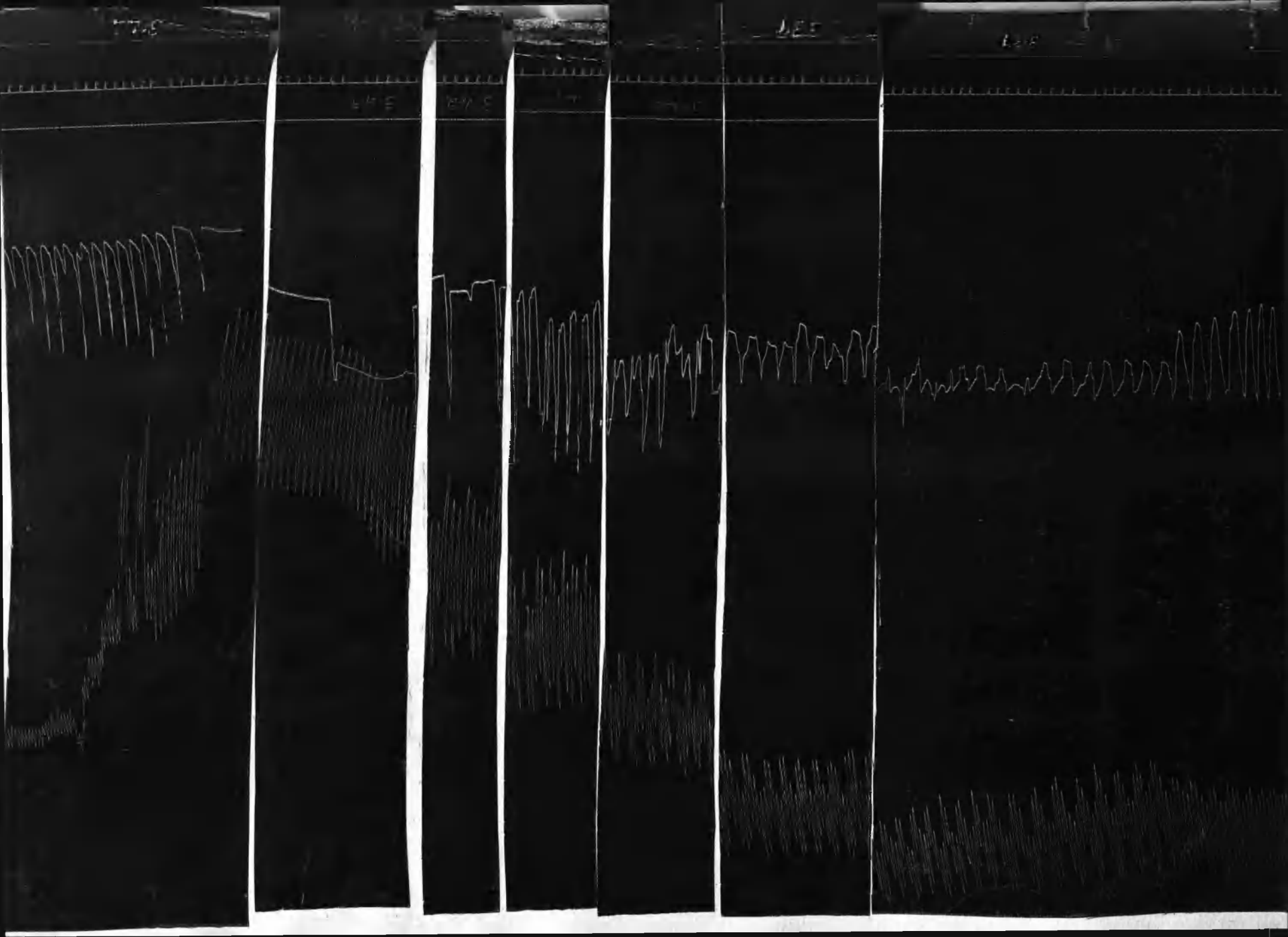
Methods./

Methods. Asphyxia was induced at first by clamping the tube leading from the trachea. This method causes an accumulation of carbon-dioxide in the blood as well as an anoxaemia. In order to obviate this complication of excess of carbon dioxide in the later experiments asphyxia was induced by making the animal breathe in a closed circuit in which there was placed a jar of soda-lime through which the air inspired had to pass. In this way the available oxygen is slowly used up and there is a gradual onset of anoxaemia.

Results:- TABLE 14.

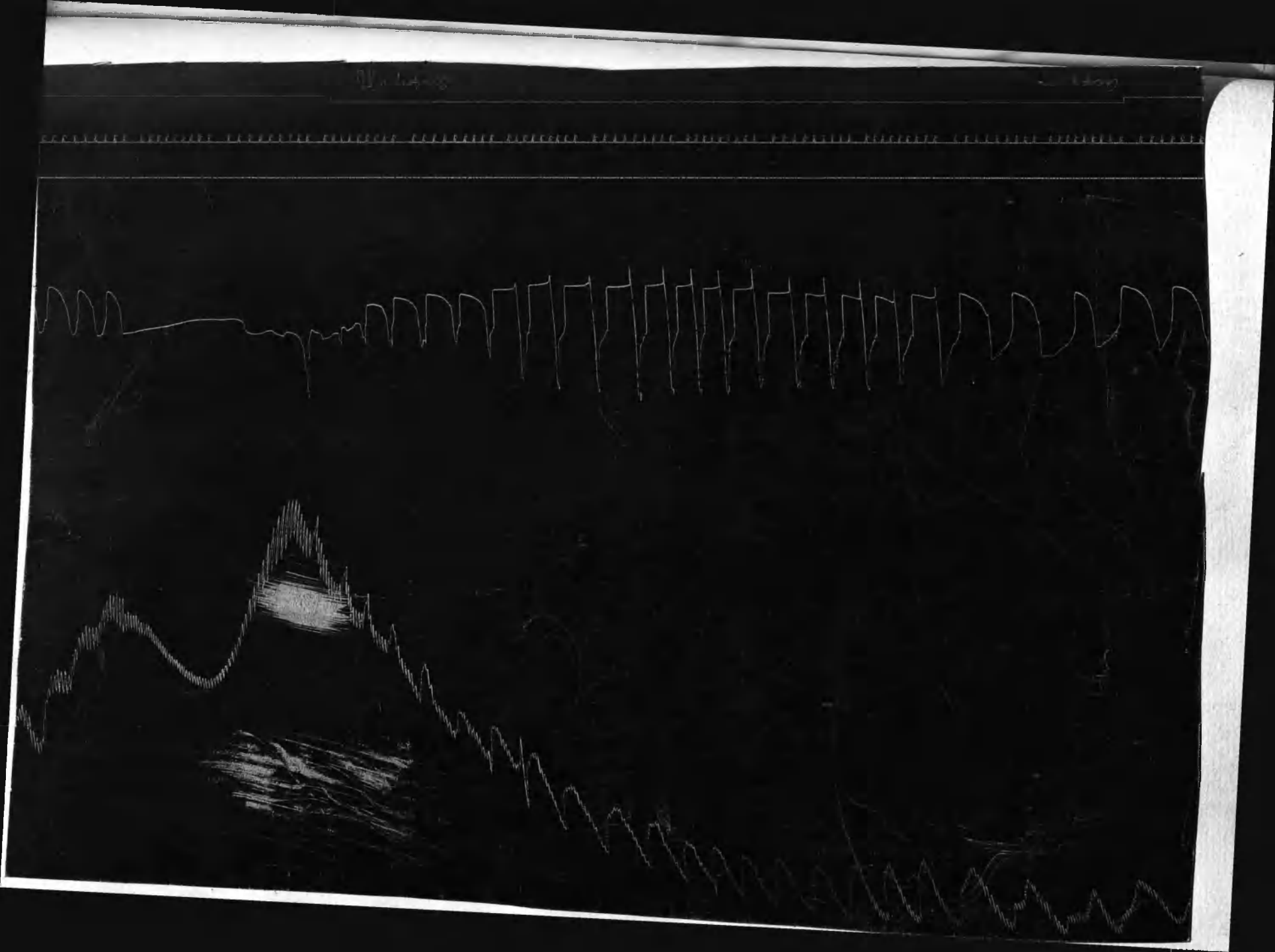
No.of Cat.	Wt. in Kg.	Degree of Asphyxia.	E.R.before.		E.R.after.		O_2% content before.			O_2% content after.		
			K.C.C.	K.O.C.	KCC.	KOC.	Art.	Ven.	Head.	Art.	Ven.	Head.
Fem.	2.6	+	.6	7.0	.6	7.5	95.4	63.7	31.7	74.2	33.8	40.4
Fem.	2.4	++	.6	8.5	.6	9.0	91.0	57.5	33.5	64.2	30.6	33.6
Fem.		+++	.6	7.0	.4	2.4	95.4	63.7	31.7	33.1	21.1	10.0
Fem.	2.4	+++	1.1	7.5	.5	1.7	96.0	58.3	37.7	29.9	17.2	12.7
Male	2.8	+++	.8	10.0	.4	1.7	94.1	51.0	43.1	43.3	20.1	23.2
Fem.	2.4	+++	.6	8.5	.25	1.1	91.0	57.5	33.5	28.0	22.0	6.0

Electrical Excitability. In the most marked stages of asphyxia, there is a distinct increase in the electrical excitability of the neuro-myone associated with an equally marked diminution in the head of oxygen. When the asphyxia is not so complete, the head of oxygen is still/



Tracing 5.

Effect of Slow Induction of Asphyxia.



Tracing 6.

- Effect of Rapid Induction of Asphyxia

than in the systolic, thus leading to an increase in the pulse-pressure. These two features, the fall in blood pressure and the rise in pulse-pressure are so characteristic that it was almost possible to estimate the extent of the anoxaemia by the appearance of the record of the arterial pressure.

IV. EFFECT OF ANOXAEMIA.

B. As produced by Decrease of Temperature.

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Noel Paton, Findlay & Watson (10) investigating the effect of variations of temperature on electrical excitability came to the conclusion that the E.E. of the nerve varies inversely with the temperature. I repeated these experiments with the results as given below:-

Methods. The electrical reactions on both hind legs were taken and in all three cases there was but little difference in the values for the two legs. One leg was then wrapped round with cloths soaked in hot water while the other was covered with small pieces of ice. After ten minutes the electrical reactions were again taken.

The temperature of the legs was then brought back to normal and the femoral veins exposed. Blood was taken from each. The warm and cold applications were again replaced and after ten minutes blood was again withdrawn from each vein. The arterial oxygen content was estimated from blood drawn from the carotid artery.

TABLE 15.

No. of Cat.	Wt. in Kg.	Electr. Reactions.								O_2 Content.			
		Normal.				Hot.		Cold.					
		Rt. leg.		L. Leg.		Rt. leg.		L. Leg.		Arterial.	Venous.		
		KCC.	KOC.	KCC.	KOC.	KCC.	KOC.	KCC.	KOC.		Normal.	Hot.	Cold.
64. Fem.	2.4	.4	7.0	.5	7.5	.5	7.0	.2	2.6	93.6	61.0	69.9	52.3
65. Fem.	2.9	.5	6.0	.4	6.0	.5	5.5	.4	1.5	95.0	65.4	73.7	52.1
68. Male	2.8	.5	2.2	.5	2.8	.5	2.4	.5	1.1	94.4	57.9	66.5	49.2

The electrical excitability is increased by decrease in temperature. The head of oxygen is however apparently increased as the blood taken from the vein on the cold side is more unsaturated than is the blood from the hot side.

The work of Burton Opitz (91) has conclusively proved that the viscosity of the blood reacts very sharply to outside influences of temperature, cold increasing and warmth decreasing the co-efficient of viscosity. The velocity of the blood would thus be markedly decreased by this increase in viscosity as well as by the increased peripheral resistance owing to the contraction of the smaller vessels as a result of the cold. It was noted during the course of these experiments that it was much more difficult to obtain venous blood on the cold than on the warm side but actual measurements of the rate of flow were not made.

There is however some more direct work to show that decrease of temperature leads to a decreased use of oxygen. Vernon (92) when studying the metabolism of the perfused kidney showed that decrease of temperature to freezing point lowers the metabolism to one half or even one third. Scott (93) found later that oxygen-utilisation by fishes could be lowered by reducing the temperature of the water in which they were kept. Hufner (94) however, in calculating the rate of diffusion through lungs of warm blooded animal assumed that the influence of an increased temperature is to diminish the rate of diffusion since diffusion is

proportional to the coefficient of absorption which decreases rapidly with rise of temperature. Krogh (95) criticised this assumption on the ground that the internal friction in water is greatly diminished by increasing the temperature and urged that it was quite conceivable that this decrease of the internal friction might cause an increase in the rate of diffusion of the gas-molecules. In order to test this view Krogh made a series of determinations on the peritoneal membranes got from small dogs and his results led him to the conclusion that the diffusion constant of oxygen through animal tissues increases with increasing temperature, about one per cent. per degree centigrade, taking 20°C. as unity. It would therefore seem that decrease of temperature leads to a lowered utilisation of oxygen by the tissues both through slowing of the circulation and through diminished rate of diffusion of the gas from the blood to the tissues. This view is upheld by an observation of Lovatt Evans (96) on the reduced sensitivity of the heart to adrenalin when the temperature is reduced. This reduced sensitivity bears a strong resemblance to that shown under the influence of oxygen-lack and seems to hint at the possibility of a kindred mechanism in both cases.

Conclusion:- Decrease of temperature produces an increase in the electrical excitability of the neuro-myone. This can probably be explained by the diminished supply of oxygen to the tissues.

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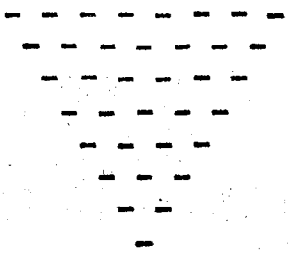
IV.C.

EFFECT OF ANOXAEMIA AS PRODUCED BY ANAEMIA.



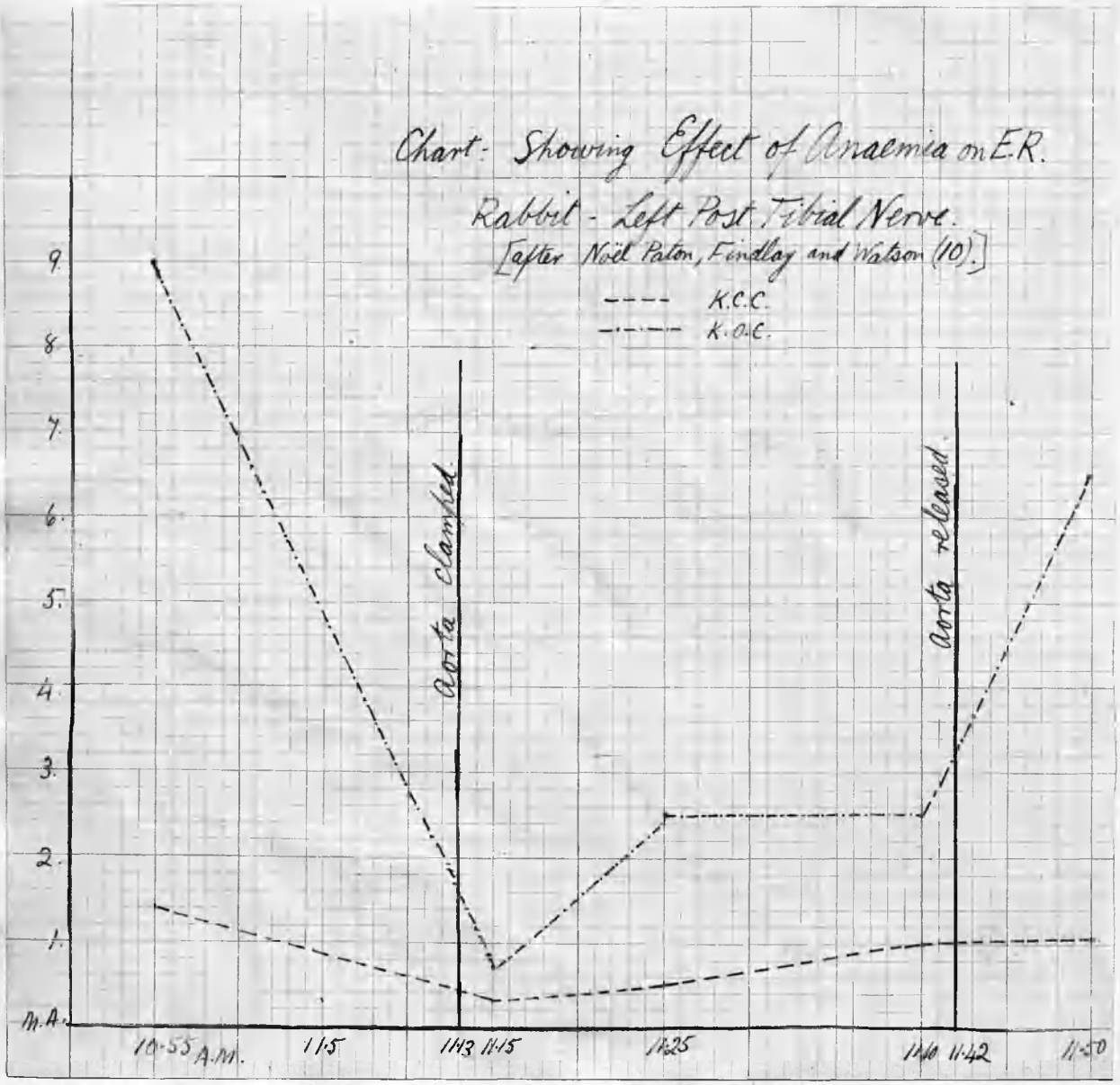


Chart - Showing Effect of Anaemia on E.R.
Rabbit - Left Post. Tibial Nerve.
[after Noël Paton, Findlay and Watson (10).]
K.C.C.
K.O.C.
9.
8.
7.
6.
5.
4.
3.
2.
1.
M.A.
Aorta clamped.
Aorta released.
10-55 A.M.
11-5
11-13
11-15
11-25
11-40
11-42
11-50

Effect of Anaemia. MacCallum (2) showed that ligature of an artery bringing about complete anaemia of the part induces for a time a marked increase in the E.E. of the neuro-myone, but that later the E.E. suddenly disappears probably due to death of the tissues. Noël Paton, Findlay and Watson (10) repeating this work confirmed MacCallum's results. The following chart copied from Noel Paton's paper gives one an idea of the extent to which the E.E. may be increased by a complete anaemia. Compression of a vein on the other hand, MacCallum showed, induced a fall in the E.E. This is probably due to the fact that merely a congestion is produced with consequently a constant supply of oxygen at hand and a moderate but steady increase of the C_H. The phenomenon of anæmic convulsions is also well known indicating an increase of E.E. induced even by partial anaemia. MacCallum, Lambert & Vogel (59) during their perfusion experiments observed the most violent contractions and extreme rigidity during anaemia even when temporary. The following experiments were performed in order to show the effect of anaemia on the electrical excitability. The animal was bled through a cannula in the carotid artery and the electrical reactions taken and the oxygen content of the blood estimated before and half an hour after haemorrhage.

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TABLE 16.

No. of Cat.	Wt. in Kg.	Total Vol. of blood. *	C.C. of blood withdrawn.	E.R. Before.		E.R. After.	
				KCC.	KOC.	KCC.	KOC.
69	2.1	115.5	60	.9	11.0	.4	2.1
70	2.8	154.0	50	1.1	8.5	.4	1.8
71	3.2	176.0	50	1.0	9.0	.8	2.5

TABLE 16. (Contd.)

No. of Cat.	% Sat. of O_2 Before.			% Sat. of O_2 After.			Hb%	
	Arter.	Ven.	Diff.	Arter.	Ven.	Diff.	Bef.	After.
69	92.5	60.1	32.4	51.7	37.9	13.8	100	63
70	96.0	64.6	31.4	69.9	60.6	9.3	100	71
71	94.4	61.4	33.0	74.1	59.1	15.0	100	76

* Estimated on the assumption that the volume of the cat's blood is equivalent to 5.5% of the body-weight.

The electrical excitability is increased by the production of an anaemia. In every case there occurred marked general tremors of greater or less intensity. Of other changes that take place with the onset of anaemia the following are to be noted.

(1) Diminution of the amount of haemoglobin, the carrier of oxygen to the tissues.

(2) Increase in the viscosity of the blood. Saneyoshi [97] states that the viscosity of the blood is high in anaemia. This produces a diminished velocity of the blood-stream thus allowing the tissues to extract as much oxygen as possible/

possible from the diminished amount of oxy-haemoglobin. Burton-Opitz [98], however, has shown that within half an hour of a loss of one quarter of the total blood volume, there is a decrease in viscosity owing to inflow of tissue-lymph, making up the blood volume to its normal amount. The percentage of oxy-haemoglobin is now reduced so that a quicker flow is required to give the tissues their proper supply of oxygen.

(3) Reduction in the alkaline reserve and increase in the C_H. T.H.Milroy [99] using the gas-chain method, demonstrated a dintinct rise in the hydrogen-ion concentration of the blood after harmorrhage of a third of the total volume of the blood. Buell [100], however, using the Van Slyke method, found but a very slight drop in the alkaline reserve of short duration after a total loss of blood amounting to 1.3% of the body-weight (i.e. about one-seventh of the blood volume). The increase in the hydrogen-ion concentration of the blood facilitates the dissociation of the oxy-haemoglobin and this may account for the greater increase in C_H after the larger haemorrhage when it is necessary for the tissues to extract the greatest possible amount of oxygen from the tissues.

Conclusions. Marked anaemia whether local or general leads to an increase in the electrical excitability of the neuromyone. The concomitant changes in viscosity and C_H may be considered as attempts to compensate for the diminution in haemoglobin by making the dissociation of oxy-haemoglobin as thorough as possible.

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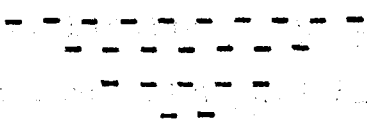
IV. D. EFFECT OF ANOXAEMIA AS PRODUCED BY CYANIDE.



In 1866 Gäthgens [101] showed that administration of sublethal doses of hydrocyanic acid depressed the oxygen usage of the body. Geppert [102] found that oxygen absorbed by mammalian tissues is much lessened by hydrocyanic acid. In moulds the oxidation processes are arrested by cyanides, no oxygen being absorbed and no carbon dioxide given off. (Shroeder [103]). More recently Hyman [104] has shown that potassium cyanide has the same action on the planaria. Rhode and Ugawa [105] observed that the response to adrenalin is greatly lessened both in hearts deprived of oxygen and those perfused with cyanide. Further, Lovatt Evans [106] has shown that soaking in cyanide has almost an identical effect on the frog's sartorius as keeping it in an atmosphere of nitrogen. He concludes that dilute solution of cyanides exert their effects entirely by reason of the oxygen lack they produce, in that they do not affect the contractile process, but the process of recovery. The administration of cyanide is therefore apparently an excellent means of inducing an anoxaemia. Its action is probably in the nature of an inhibition of peroxidase. Cushny [107] mentions the fact that the presence of cyanide prevents the splitting-up of hydrogen peroxide by normal blood as occurs when blood and peroxide are mixed.

Potassium Cyanide made up to M/100 in normal saline was used/

was used. This solution was injected into the jugular vein of cats anaesthetised with ether. If we assume that the blood weighs about 5.5% of the total body-weight (Meek and Gasser)(107A) then the administration of 1c.c. of the above dilution per kilo body-weight means a concentration in the blood of a .00012 m. solution of pot. cyanide. Hyman (108) has found that .00001 m. sodium cyanide causes appreciable reduction in the oxygen intake of sea-urchin eggs and of the marine sponge and planaria. Weizsacker (109) states that a .0005 m. solution depresses the gaseous metabolism of the frog's heart to less than 10% of its normal value, while Allen (110) has got similar results with a .0002 m. pot. cyanide solution on planaria. It will be seen therefore that the concentration of cyanide used in the present work is such as would be expected to cause a definite and marked depression in the amount of tissue oxidation.

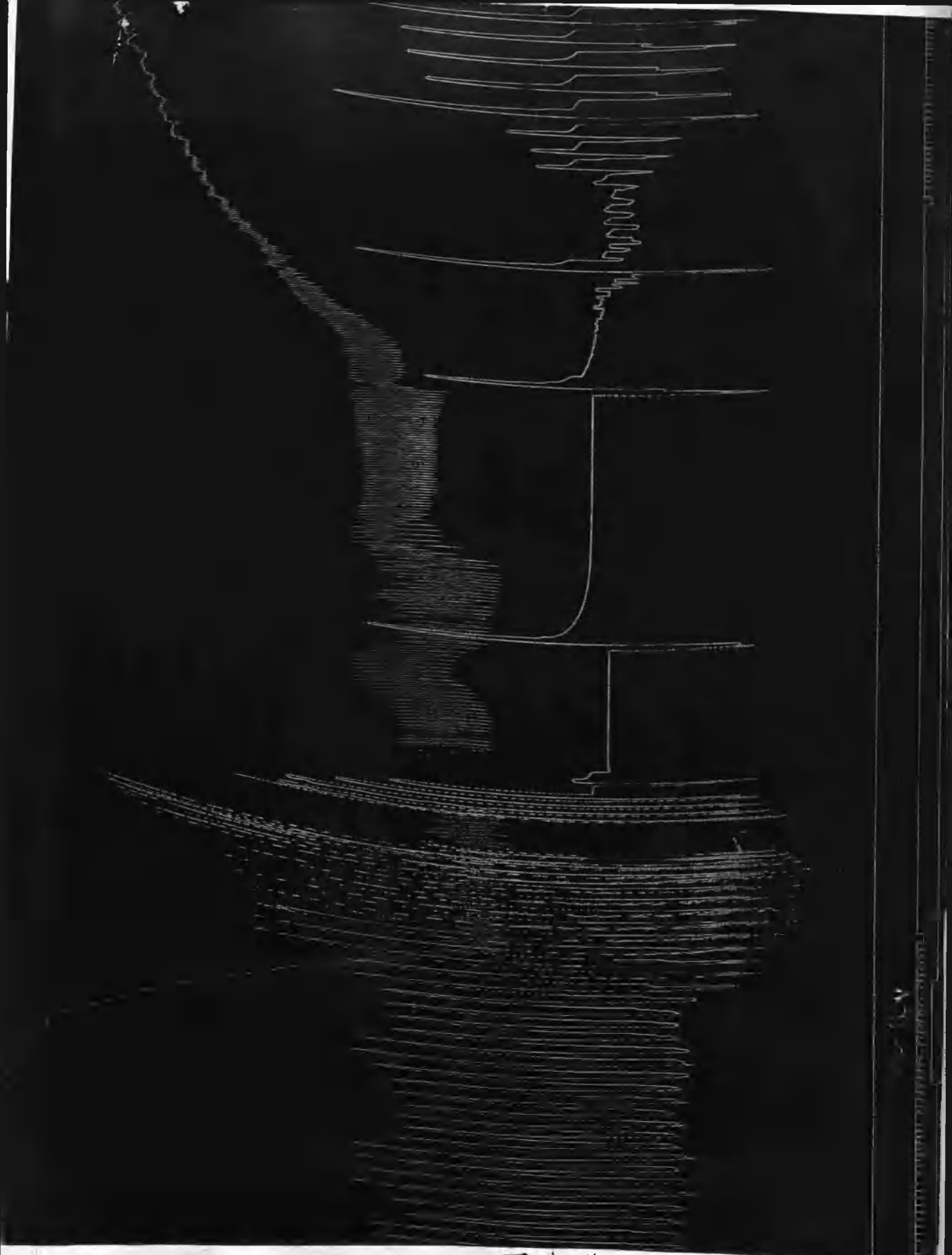
Results.

TABLE 17. Showing effect of Cyanide.

No.of Cat.	Wt. in Kg.	Amt.of Sol.inj.	E.R.Before.		E.R.After.		Comb.CO_2 per 100 c.c. plasma. (V.Slyke.)	
			KCC.	KOC.	KCC.	KOC.	Before.	After.
60	3.1	7c.c.	1.1	9.0	1.0	1.9	-	-
61	3.4	4c.c.	.9	10.0	.6	5.0	30.9	28.4
62	2.9	9c.c.	.6	5.5	.6	2.2	33.9	18.4

(1) Electrical Excitability. These results indicate that, the electrical excitability is markedly increased by the administrat-

:ion/

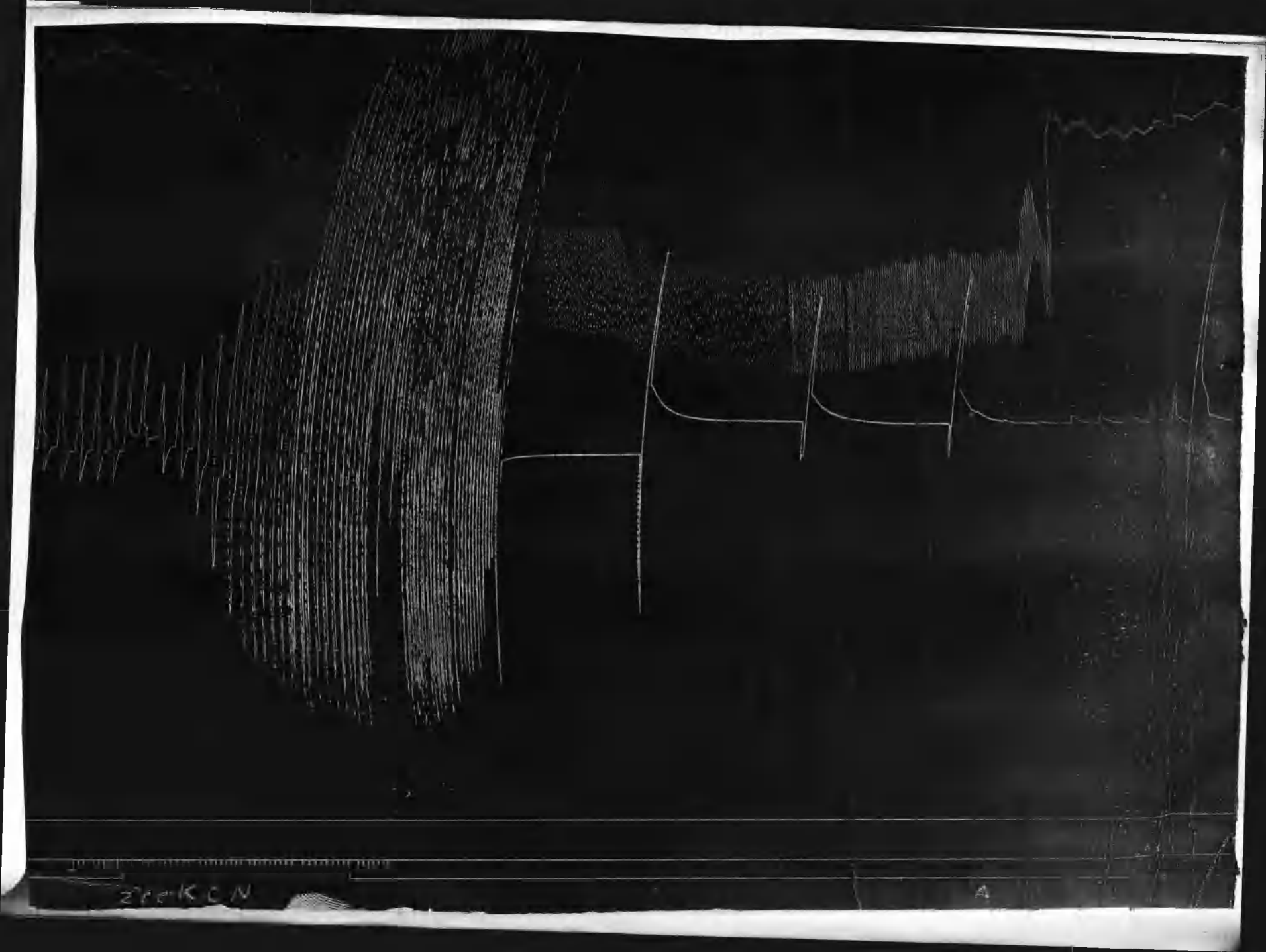


Tracing 4

Showing (1) Fall in Blood-pressure (3) Increase in Amplitude of Respirations
(2) Rise in Pulse-pressure Then Inhibition of Respirations.

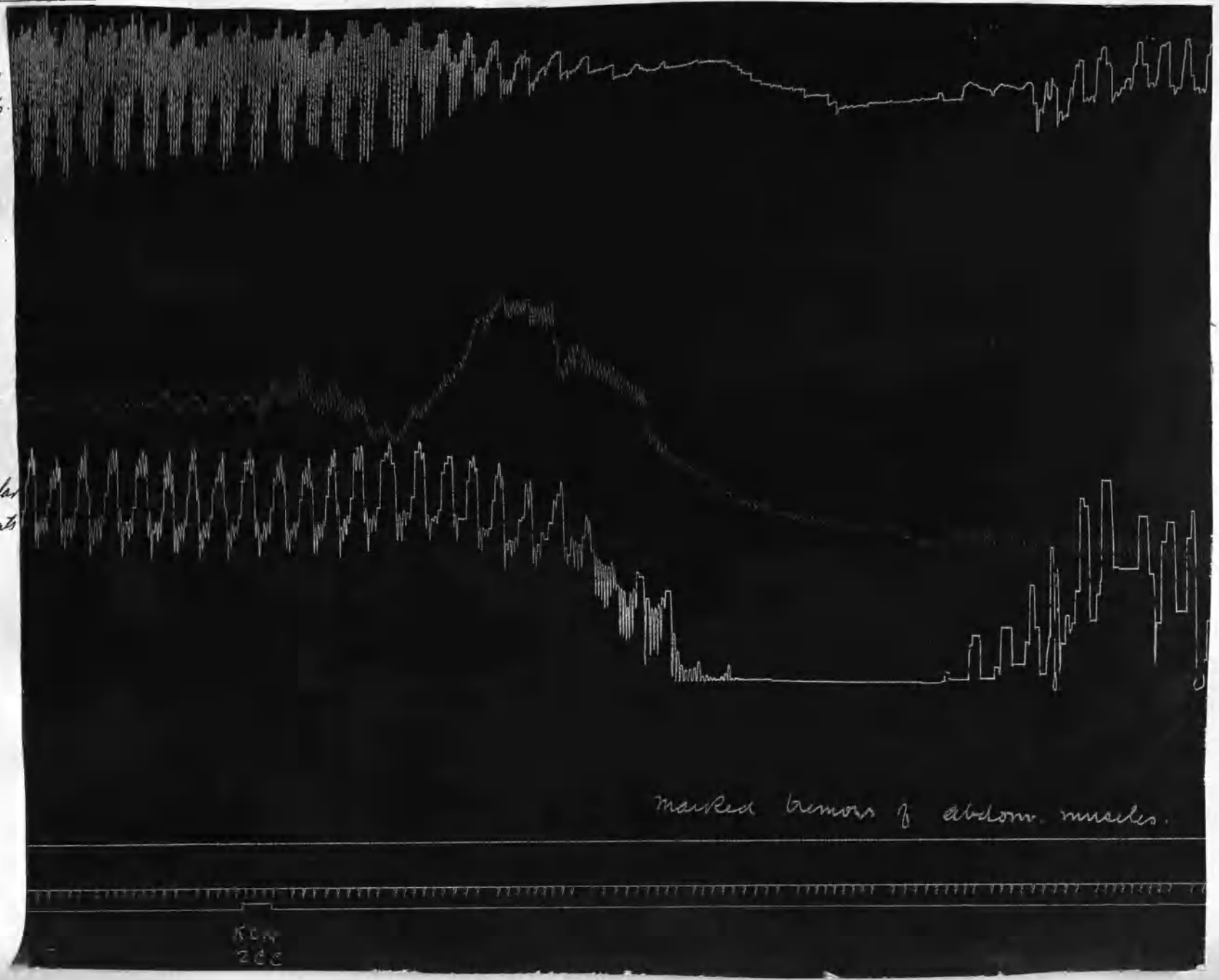
Tracing 7

Effect of Cyanide on Blood-pressure and Respirations.


Zr-KCN
A

Tracing 8.

Effect of Cyanide on Blood-pressure and Respirations.


Auricular Movements
B.P.
Ventricular Movements
marked tremors of abdom. muscles.
Kym
2cc

administration of cyanide. In all three experiments marked general convulsions were produced and in two of the abdominal muscles were particularly noticeable. This is in accord with the work of Dowse,(111) who found that, after injection of potassium cyanide, muscle was still excitable, responding with a slightly contraction than was given by the control in plain saline. Lewandowsky(112) also notes that pot. cyanide increases the tonus of the parasympathetic system.

(8) Alkaline Peptone. There is a fall in the O_2 content of the arterial blood as it shows also an increase and then a sharp suppression, probably as a result of the initial increase in respiration.

Tracing 9.
Effect of Cyanide on Blood-pressure and Auricular and Ventricular Movements.

(9) Diphtheria Toxin. There is a fall in the O_2 content of the blood [illegible] and respiration during the following injection of diphtheria toxin. The fall in blood-pressure is very marked, the diastolic falling more than the systolic as shown by the marked increase of pulse-pressure. The rate of the pulse is greatly diminished, to become again normal as the experiment nears its close. Tracing 9 of the auricular and ventricular contractions indicates that the heart tends to stop in diastole. The heart becomes more and more dilated as the injection proceeds, contraction becomes slower and less powerful and finally the cardiac muscle goes into a state of rest fibrillation which is rapidly followed by complete cessation as the effect of the poison wears off. In tracing 9 it will be seen that the auricle is [illegible]

administration of cyanide. In all three experiments marked general convulsions were produced and in Cat 62 tremors of the abdominal muscles were particularly noticeable. This is in accord with the work of Dontas,[111] who found that, after exposure to cyanide, muscle was still excitable, responding with a bigger contraction than was given by the control in plain saline. E.C.v. Leersum[112] also notes that pot. cyanide increases the tonus of the paraympathetic system.

(2) Alkaline Reserve. There is a fall in the CO_2 content of the plasma just as if there were an acidosis as some (Evans and others) have suggested but more probably as a result of the initial increase in depth and rate of respiration.

(3) Circulation. Tracings 7 and 8 give records of the blood pressures and respiration during and following injections of potassium cyanide. The fall in blood-pressure is very marked, the diastolic falling more than the stystolic as shown by the marked increase of pulse-pressure. The rate of the pulse is greatly diminished, to become again normal as the anoxaemia disappeares. Tracing 9 of the auricular and ventricular contractions indicates that the heart tends to stop in diastole. The heart becomes more and more dilated as the injection proceeds; contraction becomes slower and less powerful and finally the cardiac muscle goes into a state of weak fibrillation which is rapidly followed by complete recovery as the effect of the cyanide wears off. In tracing 9 it will be seen that there is a perliminary rise/

rise of blood pressure immediately following the administration of cyanide.

(4) Respirations. The respirations are at first accelerated and deepened and thereafter the rate is very slow probably due to the over-elimination of the CO_2 from the blood by the preliminary acceleration. Gradually the respirations resume their normal rate. In fact tracing B resembles somewhat one of Cheyne-Stokes' breathing.

Conclusions. The administrations of cyanide induces an increased electrical excitability of the neuromyone as well as other symptoms indicative of a profound anoxaemia. This lends still further support to the view that anoxaemia is the essential factor in the production of an increase in the electrical excitability.

In order to render the evidence for this theory still more secure, there will now be considered some other methods by which the E.E. has been increased. Thereafter will follow a short description of several clinical cases which showed a marked increase in the E.E. of the neuromyone.

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V.

THE INFLUENCE OF ALCOHOL ON ELECTRICAL EXCITABILITY AND THE HEAD OF OXYGEN.

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Alcohol injected intravenously decreases the blood catalase (Burge [113] and thus prevents the tissues from obtaining their normal supply of oxygen. Thus if an anoxaemia is the causal factor in the production of increased electrical excitability, we should find the latter state after administration of the alcohol.

Ethyl alcohol was used diluted with nine times the amount of 1% sodium chloride solution, making a solution of .9% NaCl of which 10c.c. contained 1c.c. absolute alcohol. It was injected into the jugular vein. In one experiment methyl alcohol was substituted and it gave the same results except that convulsions and very marked salivation and sickness were induced. Hunt [114] states that with methyl alcohol the symptoms of gastric irritation are generally more marked than those induced by ethyl alcohol and very often some convulsive movements are observed. Pohl [115] suggests that this is probably due to the action of formaldehyde and formic acid.

Small doses. Schweisheimer [116] found in one case of drunkenness in man that the blood contained .153% of alcohol, and in another instance, when the intoxication was more pronounced .227%. Mellanby [117] found that in a dog when the alcohol of the blood reaches about 354 cm. per 100 grams of blood there appeared signs of intoxication and when the concentration reached 468 cm. per 100 grams, the dog was profoundly intoxicated. In the first four/

four experiments an amount of alcohol was injected to produce a concentration in the blood of 350 to 450 cm. per 100 grammes of blood; i.e. a concentration one would expect to find in a case of fairly marked alcoholic intoxication.

Results:-

TABLE 18.

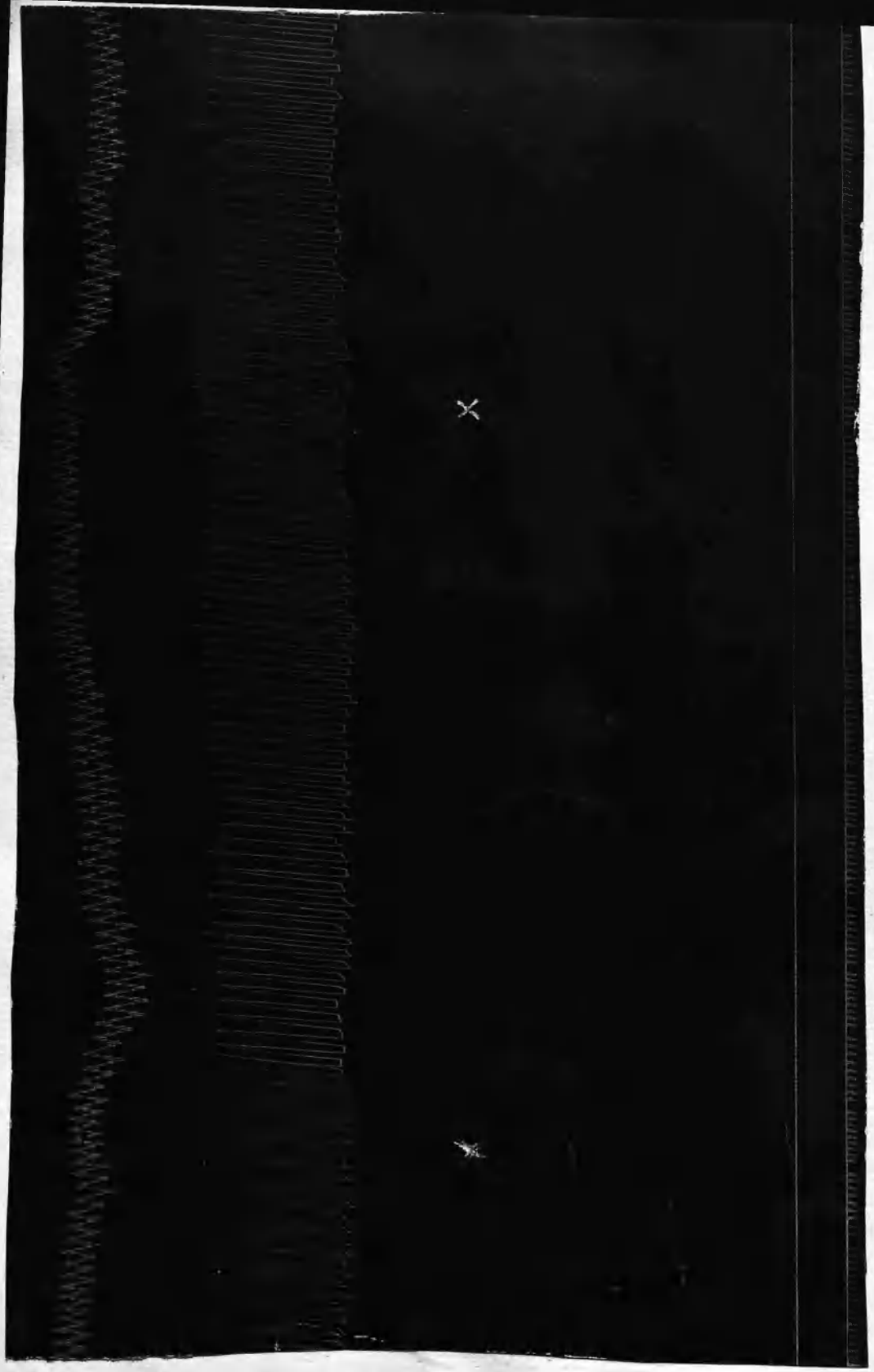
No.of Cat.	Wt.	Amt.of Alco. soln. 10%.	Concentr.of Alc. cm.per 100grms.blood.	E.R.Before.		E.R.After.	
				KCC.	KOC.	KCC.	KOC.
44	3.0	6	363	.4	4.0	.4	3.8
45	2.7	5	403	1.2	8.0	1.0	7.5
46	2.3	5	395	.6	5.5	.6	6.5
47	2.8	7	454	.9	7.0	.7	5.5

TABLE 18. (Contd.)

No.of Cat.	CO_2 Combing.capacity in c.c. per 100 c.c.blood	
	Before	After.
44	34.6	21.9
45	31.8	22.7
46	33.6	22.7
47	35.4	18.8

xx The figures in this column were estimated on the assumption that the blood was 5.5% of the total body-weight.

With such doses there is not produced any marked change in electrical excitability. There is, however, a gradual decrease of the alkaline reserve indicating an increase in the C_H. This increase/



x----- x Administration of Alcohol between the two marks.

Dose = .2 c.c. Abs. Alcohol.

Tracing 10.

Showing Slight increase in Frequency and amplitude of Respirations.

Tracing 10.

Effect of Small Dose of Alcohol.

increase in the C_H of the blood renders it mesonectic and so neutralises the diminished action of the blood catalase. Accordingly the tissues in general and the neuro-myone in particular would receive their normal amounts of oxygen.

Higgins[118] has shown that the alveolar tension of the CO_2 falls with alcoholic administration, indicating that the respiratory centre is more sensitive, probably a result of the increase in C_H. This stimulation of respiration I found to be the case as will be seen in tracing 10. The heart rate was unchanged.

Large doses. When larger doses of alcohol are injected so that the concentration in the blood exceeds 1% there is produced a marked increase in electrical excitability as will be seen from the accompanying table.

TABLE 19. Showing effect of large doses of alcohol.

No.of Cat.	Wt.in Kg.	Amt.of alcohol soln.10% in c.c.	Concentr.of Alc.xx cm.per 100 grm.blood	E.R.Bef. KCC.	E.R.Bef. KOC.	E.R.Aft. KCC.	E.R.Aft. KOC.
48	2.4	10	757	1.4	8.0	1.3	3.5
49	2.9	18	1130	.6	8.0	.5	1.5
50	3.1	12	706	.3	2.7	.3	1.6
51	2.5	10	724	1.0	9.0	.8	2.6
53*	3.0	12	727	.8	10.0	.3	2.2

* Methyl alcohol was injected in this case.

xx The figures in this column were estimated on the assumption that the blood was 5.5% of the total body-weight.

TABLE 19. (Contd.)

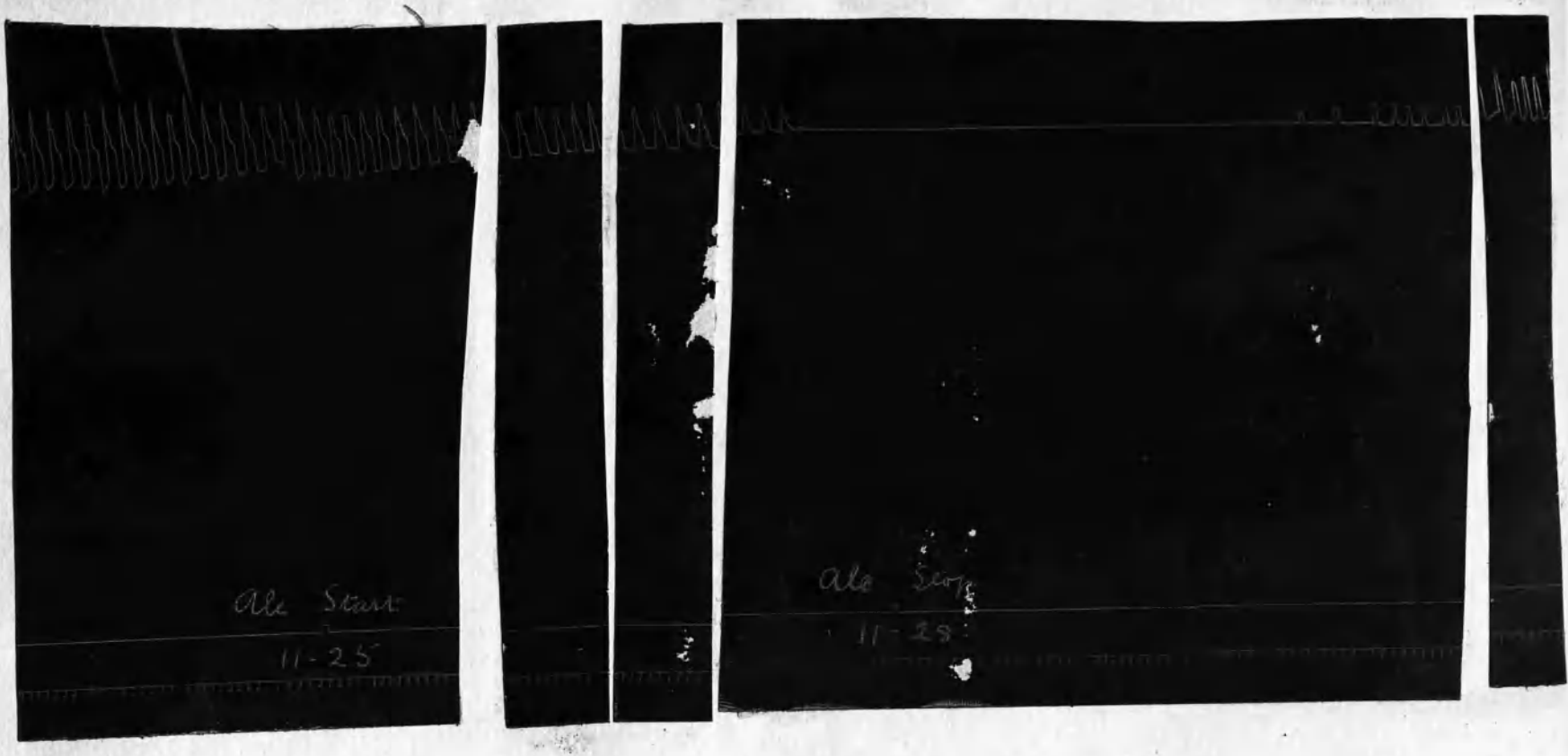
No.of Cat.	CO_2 comb. capacity in c.c per 100c.c. plasma.	
	Before.	After.
48	37.4	20.9
49	34.8	18.2
50	35.3	23.7
51	35.9	26.5
55	38.3	28.9

The alkaline reserve is rather lower than with the smaller doses. The increase of C_H is now no longer able to neutralise the reduced action of the blood catalase as can be seen from a study of the following table, which shows the fall in the head of oxygen after large doses of alcohol.

TABLE 20.

No.of Cat.	Wt.	Amt.of alco. Soln. 10% in c.c.	Conctr.of alco.cm. per 100 grm. blood.	% Saturation of oxygen. Before.			After.		
				Arter.	Ven.	Diff.	Art.	Ven.	Dif.
51	2.5	10	724	89.4	60.7	28.7	80.4	69.8	10.6
76	1.9	10	952	92.1	61.9	30.2	74.3	60.9	7.4
77	2.8	12	779	90.8	50.8	40.0	72.6	60.9	11.7

This fall in the head of oxygen is probably in great part due to the marked slowing and, at times, complete inhibition of respiration. This phenomenon was observed by Hooker (119), and is/

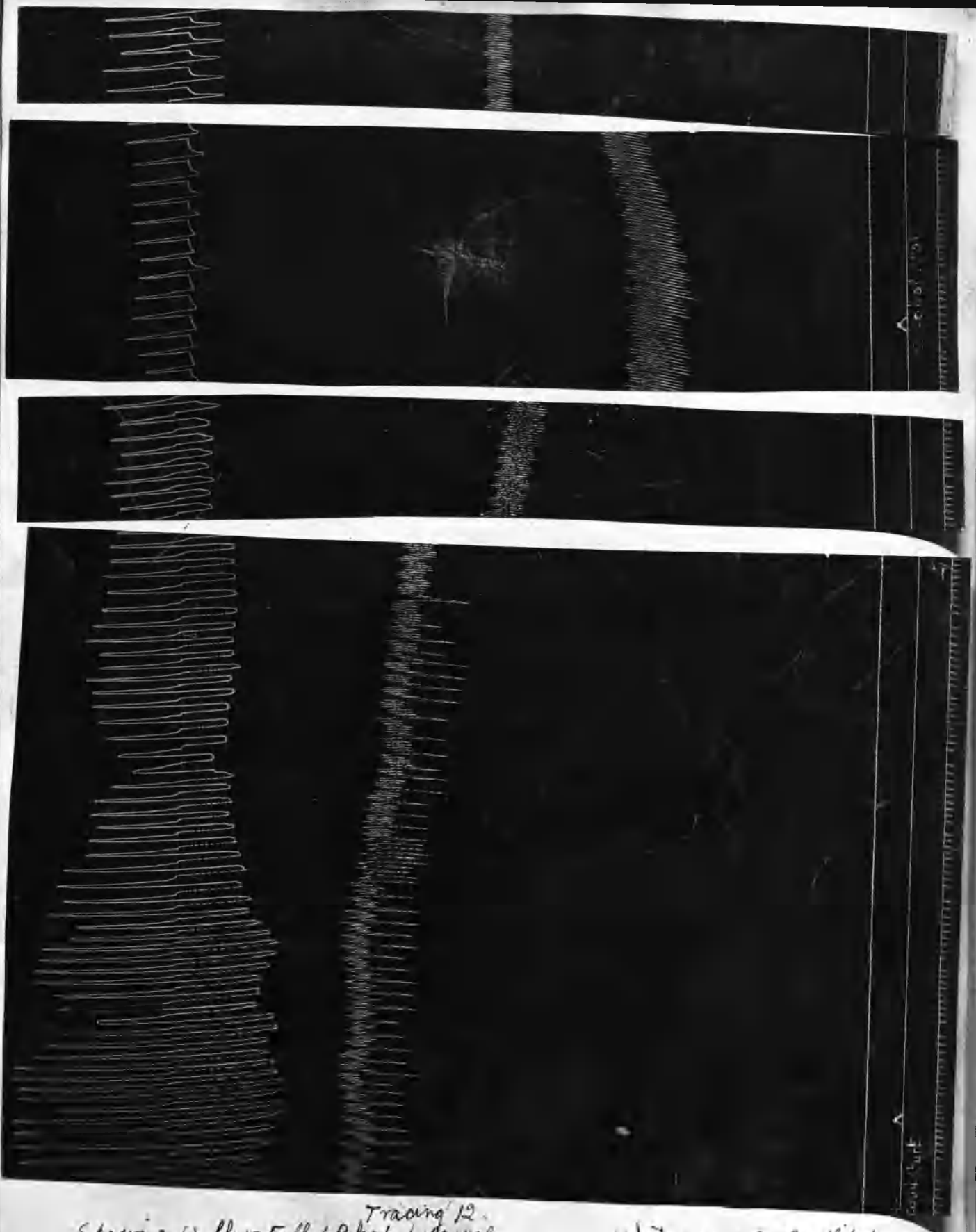


Tracing 11.

Showing Marked Inhibition of Respiration

Tracing 11.

Effect of large dose of alcohol on Respirations.



Tracing 12.

Showing (1) Slow Fall of Blood-pressure.
(2) Marked Increase in Pulse-pressure.
(3) Slowing of Pulse-rate
(4) Decrease in Amplitude and Frequency of Respirations

Tracing 12.

Effect of Large Dose of Alcohol
on Blood-pressure and Respirations.

is well marked in tracing 11.

The blood pressure may show a fall (Tracing 12) which is usually a very slow one. This fall is not a constant phenomenon. The pulse-pressure is markedly increased and the pulse rate diminished, these being constant accompaniments of an excessive dose of alcohol. All these gradually wear off when the administration of alcohol is stopped.

It is probable that alcohol in such excessive doses acts as a protoplasmic poison, lowering the sensitivity of the respiratory centre especially and by this means as well as by its action on the tissue catalase, preventing the utilisation of oxygen by the tissues. This lends support to the view previously put forward that increased electrical excitability is dependent on a deficient supply of oxygen.

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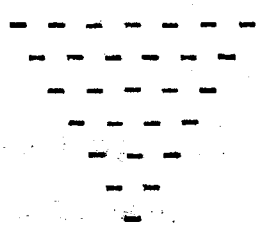
VI. B. THE INFLUENCE OF B-IMINOAZOLYLETHYLAMINE ON ELECTRICAL EXCITABILITY AND THE HEAD OF OXYGEN.



Dale (120) after an exhaustive study of the pharmocology of B-iminoazolylethylamine showed that its main action was on the bronchial musculature and the pulmonary arteries. He found that it had but little effect on the heart itself but that it might produce a fall of the systemic blood-pressure owing to its vaso-dilator effect on the systemic vessels. Its action when applied directly to striped muscle was practically nil. Thus the suggestion of Biedl (121) that tetany is due to the presence of this substance in the blood can not be supported. Noel Paton, Findlay & Watson administered B-I to a few animals but observed none of the symptoms of tetany. They did not test the E.E. of the neuromyone. Biedl however, stated that in a cat he saw, after repeated daily administration of 1 to 2 mg. an increase in the excitability of the peripheral nerves and fibrillar twitching in individual muscles.

Anderes and Cloetta (122) studied the effect of B-I on cats. Their tracings show a marked rise in the pulmonary pressure, and quite a marked fall in the lung volume after administration of 0.5 mg. while the systemic blood-pressure was almost unaffected except for an increase in pulse-pressure. They state that it produces a rapid decrease in oxygen-absopption.

The following experiments were done to determine (1) whether administration of B-I caused a decrease in the head of oxygen and (2) if this was the case, whether the E.E. of the neuromyone was affected. 0.5 mg. dissolved in 1 c.c. of saline was injected into the jugular vein.

In/

In cat 49, as the first dose produced but little effect another 0.5 mg. was given 20 minutes later.

Results:- TABLE 21.

No. of Animal.	Wt. in Kg.	E.R. before. KCC.	E.R. before. KOC.	E.R. after. KCC.	E.R. after. KOC.	O2 Content bef. Art.	O2 Content bef. Ven.	O2 Content bef. Diff.	O2 Content after. Art.	O2 Content after. Ven.	O2 Content after. Diff.
47. Fem.	2.6	1.1	11.0	.4	3.5	94.6	59.3	35.3	77.9	62.7	15.2
48. Male	3.0	.9	7.5	.3	2.8	86.9	51.0	35.9	71.8	49.9	21.9
49. Fem.	2.9	.6	7.0	.5	5.0	93.7	59.9	33.8	81.2	56.7	245
49. (after 2nd dose)	"	"	"	.4	3.0				65.4	50.1	15.3

B.I. produces an increased electrical excitability of the neuromyone as well as a diminution in the head of oxygen. Tremors were not seen in any of the three experiments performed, thus confirming the observations of Noël Paton, Findlay & Watson mentioned above. The result obtained with cat 49 bears out the statement of Dale (120) that the action of B-I on the respiratory system of cats is variable.

Conclusion:- The action of B-iminazolylethylamine on the electrical excitability of the neuromyone and on the head of oxygen lends support to the view that the excitability is dependent on the oxygen supply.

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VII. THE INFLUENCE OF GUANIDIN.

Noël Paton and Findlay were the first to put forward the suggestion that guanidin was the essential cause of the symptoms of tetania parathyreopriva. They produced symptoms very like those caused by removal of the parathyreoids, when they injected guanidin. The electrical excitability of the neuro-myone was increased and this manifestation of guanidin poisoning they showed was mainly if not entirely a result of its action on the nerves or the nerve-endings. Burns and Sharpe (123) found a marked increase in the amount of guanidin and methyl-guanidin in the blood and urine of dogs after removal of the parathyreoids and in the urine of children suffering from idiopathic tetany, and Burns (124) demonstrated a close similarity between the disturbances of protein metabolism produced by parathyreoidectomy and those induced by administration of salts of guanidin. Noël Paton and Findlay after a consideration of the evidence brought forward come to the conclusion that by removal of the parathyreoid glands the metabolism of guanidin is disturbed. They point out, however, that on the administration of guanidin the electrical excitability is often not at once altered, and suggest that there is "an optimum concentration for causing an increase in the reaction of the peripheral mechanism." This probably explains the failure to arrive at any definite results in the work here recorded.

The following experiments (Table 22.) were done to determine whether the administration of guanidin had any effect on the supply of oxygen to the tissues. Guanidin-hydrochloride was the/

the salt used and the amount used was dissolved in 20 c.c. saline and injected into the jugular vein.

TABLE 22.

No. of Expt.	Wt. in Kg.	Dose p. kilo. in gm.	E.R. before. K.C.C.	E.R. before. K.O.C.	E.R. after. KCC.	E.R. after. KOC.	% Sat. of O_2 Before. Arter.	Ven.	Diff.	% Sat. of O_2 After. Arter.	Ven.	Diff.
7	2.7	.074	0.5	2.7	0.4	2.4	89.5	53.9	35.6	83.7	51.1	32.6
8	2.2	.14	0.4	7.0	0.2	6.0	93.1	64.6	28.5	87.7	63.1	24.6
9	3.1	.16	0.9	8.0	0.5	7.5	94.5	69.1	25.4	89.3	56.1	33.2
10	2.3	.21	0.4	5.0	0.6	6.0	90.6	72.2	18.4	94.1	71.9	22.2

As will be seen from the above table guanidin seems to have had very little effect on the "head of oxygen". But in no experiment was there any marked increase in electrical excitability, nor were any tremors observed. Accordingly one cannot come to any conclusions as to whether the action of guanidin in producing an increased electrical excitability is due to a diminished supply of oxygen to the tissues or to some specific action of its own.

In cases of parathyreoidectomy, it has been noted by Wilson, Steams and ~~Janney~~ Thurlow (??) that the dissociation-curve of the blood moved to the left, that is, the blood became pleonectic and the oxyhaemoglobin was split up with difficulty so that the tissues obtained a poorer supply of oxygen. This would suggest that, when guanidin does cause symptoms similar to those of parathyreoidectomy including almost identical disturbances in metabolism, it might also render the blood pleonectic. If guanidin does raise the dissociation-constant of oxyhaemoglobin one/

one would be justified in thinking that it was because of the poorer supply of oxygen to the tissues that the electrical excitability was increased.

Further, a consideration of the asphyxia and cyanide experiments shows that the increase in excitability took place very rapidly after the onset of the experimental condition, certainly too rapidly for any such accumulation of guanidin to take place as has been shown necessary by Noël Paton and Findlay to raise the electrical excitability. There is of course the possibility that conditions such as asphyxia lead to a local accumulation of guanidin in the neighbourhood of the neuromyone, and so might produce an increase in its electrical excitability. This would mean practically a simultaneous local excessof guanidin with a diminution in oxygen-supply. If this hypothesis is correct, then the question as to which is the precursor of the other and which the causa causans of the increased electrical excitability must be left open at present.

Conclusions:- There is no conclusive evidence as to the action of guanidin on the "head of oxygen", but there is reason to believe that when guanidin does increase the electrical excitability it does so because of the diminished supply of oxygen that is induced. The possibility is also suggested of anoxaemia leading to a local concentration of guanidin round the neuromyone.

Whatever the view as to the cause of the guanidin-symptoms there is nothing in this evidence that can be put forward as being/ against the thesis that anoxaemia is the causal factor of increased electrical excitability.

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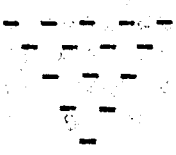
VIII. CLINICAL OBSERVATIONS.



No attempt has been made in this section to deal exhaustively with the clinical conditions in which an increased electrical excitability of the neuro-myone has been found. That it is found in conditions other than clinical tetany seems to be indicated from a preliminary investigation of the electrical reactions ~~made~~, which I am conducting on children who are not suffering with tetany. The following are the notes of a few cases which have come under my observation during the past six months.

CASE I.

C.O. Female. Aet 7 mos. Normal birth.
Breast feeding for first four months. Owing to "mother's milk not satisfying" baby, Glaxo and Sister Laura's food tried. Now on Nestle's Condensed Milk. History of tremors and spasms on and off during past three months.
14/10/20. When first seen, was suffering with convulsions and tremors. Laryngeal spasm + + +. Facial phenomenon + +. Child very emaciated.
E.R.:- K.C.C.0.4 A.C.C. 0.4 A.0.C. 0.4 K.0.C. 1.2
Put on olive-oil a teaspoonful every four hours, and egg-albumen. Phenazone and Hexamine gr.2. of each, every four hours.
21/10/20. Improving. Symptoms much diminished in intensity.
16/1/21. Looks very much better.
E.R: K.C.C.0.6 A.C.C.0.6. A.0.C.0.4 K.0.C. +5.
4/3/21. Mother says she noticed a lump in baby's left upper arm three days ago. No history of injury. Examination revealed a complete fracture of the humerus.
16/3/21. Child doing well on cod liver oil.

This case is undoubtedly one of tetany. The points of interest are (1) the disturbance in the calcium-metabolism as revealed by the spontaneous fracture and (2) the marked improvement obtained by administration of oil. Probably the cod/

cod-liver oil was the more efficient of the two but certainly the child showed a marked improvement when olive-oil feeding was begun.

As regards the disturbance in the metabolism of bone, a recent paper by Hutchison and Patel (125) on the Etiology of Osteomalacia in the City of Bombay, is of interest in showing that there is a large preponderance of osteomalacia among the Mahomedan women who use the purdah system which results in lack of fresh air and exercise. This lack of fresh air, that is, an inadequate supply of oxygen, they regard as the most potent factor in the production of the disease.

CASE II.

Baby McM. Male.aet 19 months. Normal birth.
Marked signs of rickets. Constpiation + +. "
Diet. "porridge, saps and potatoes and 'kitchen'.
12/12/20. Pale pasty-looking child. Has suffered with whooping-cough during past three weeks. At present has marked spasms after cough. No evidence of tetany but examination of chest reveals signs of commencement of broncho-pneumonia.
E.R. K.C.C. .8. A.C.C.1.4. A.O.C.1.4 K.O.C. 3.0.
18/12/20. Died. Cause of death - Broncho-pneumonia.

This case is of interest in that there is present hyperexcitability of the neuromyone associated with the onset of broncho-pneumonia but with no signs of tetany.

CASE III.

R.McG. Male. Aet 15 mos.
2/1/21. Suffering with whooping-cough of three weeks' duration. Diarrhoea and vomiting. Marked rickets.
8/1/21. Improving but still a marked laryngeal "crow".
E.R. K.C.C. .4 A.C.C. .4. A.O.C. .6. K.O.C. 1.8.

One/

Tracing 13.

at point C ↓ the patient was asked to keep her hand steady

Tracing 13.

Showing movements of forefinger
in Case of Paralysis Agitans.

One notes here the association of increased electrical excitability with whopping-cough, another disease interfering with proper oxygenation.

CASE IV.

E.F. Female. Aet 15 mos.
19/1/21. History of diarrhoea and vomiting of two days' duration. One convulsion. Temp.104.2
21/1/21. Signs of broncho-pneumonia.
E.R. K.C.C. 1.2 A.C.C. .8. A.O.C. .8. K.O.C. 3.0.
26/1/21. Marked bronchopneumonia.
27/1/21. Died.

CASE V.

B.H. Female. Aet 13 mos.
18/3/21. History of convulsions during past fortnight. At present shows symptoms of meningitis (retraction of head, Kernig +. etc.)
E.R. K.C.C. 1.2 A.C.C. 2.0. A.O.C. 1.8. K.O.C. 5.0 +.
26/3/21. Died of tubercular meningitis.

CASE VI. The following case is one of marked paralysis agitans and is of interest because of the presence of increased electrical excitability.

Mrs.C. Aet 54 years.
5/12/19. She had enjoyed good health up till ten years ago when she began to suffer from tremors of the hand. Now she presents all the classical symptoms of paralysis agitans. All the back and neck muscles are rigid, so much so that she cannot hold her head erect. Her chest is contracted and she is very liable to bronchial catarrh. During an attack of bronchitis the tremors become very much worse.

E.R. K.C.C. 2.3. A.C.C. 6.0. A.O.C. 2.5. K.O.C. 3.5.

The accompanying trace shows the periodicity of the tremors of the forefinger. At point C. she was asked to try her hardest to keep her hand steady but it will be seen that her attempt was of no avail.

Blood was taken from the median basilic vein and the alkaline/

alkaline reserve estimated by the Van Slyke method. The plasma was found to contain 53.7 vols. per cent. of CO_2 bound as bicarbonate. Unfortunately it was not possible to determine the "head of oxygen".

The view has been put forward that paralysis agitans is due to some lesion in the parathyreoids. The above patient was treated for a few weeks on Parathyreoid Gland 1/10 grain three times a day and it seemed to me that she benefited somewhat from the treatment. Unfortunately a severe "inf:menzal cold" developed, terminating fatally. It is of interest to note that large doses of calcium (30 grains of the lactate daily) were of no avail in lessening the tremors.

The above cases are too few in number to allow of any definite conclusions being drawn therefrom. The association of respiratory disease and increased electrical excitability is, however, very suggestive. Still (126) notes the readiness with which pulmonary collapse occurs as a result of bronchopneumonia and bronchitis in infancy and early childhood. He further remarks on the liability to pulmonary collapse in infancy as a result of such conditions as coryza, and enlargement of tonsils and adenoids. That pulmonary collapse leads to a marked decrease in the oxygen-saturation of the arterial blood has been shown by the work of Adams and Morris. (89) (127)

Bassett-Smith records a case of sprue complicated by definite tetany. Notes of the case show that there was a marked anaemia, the red-cells being reduced to less than one and a half million/

million per cub.centimetre. (The haemoglobin-estimation is not given.) Oxygen was administered by inhalation and ether given per rectum with the result that the tetany symptoms subsided. Bassett-Smith gives the ether the credit but one wonders whether the oxygen was not also of use. Still mentions the administration of oxygen as one of the methods of treatment recommended in tetany attacks but makes no comment on its usefulness. An emergency-treatment in common use by the lay-public is the immersion of the patient in a hot bath up to the neck. Undoubtedly this has in many cases a sedative effect, and it leads one to consider whether its value lies in the stimulation of the circulation and increase of oxygen supply to the tissues that is naturally induced by a hot bath.

The clinical material presented is too meagre to allow of any definite conclusions being based on it. A consideration of the evidence brought forward in this section affords, however, further support to the view that anoxaemia is the essential condition in the production of an increase in electrical excitability of the neuro-myone.

A study of the home-conditions in tetany districts is of great interest in connection with the view that has been advanced on the causation of increased electrical excitability. Miss Ferguson (128) in a recent study of social and economic factors/

factors in the causation of rickets showed quite conclusively (1) that tetany is closely associated with rickets, and (2) that inadequate air and exercise seem to be potent factors in determining the onset of rickets.

I had the opportunity of investigating by means of Leonard Hill's "kafathermometer" the conditions of ventilation in the houses of the east-end of Glasgow, in those districts where tetany and rickets are most prevalent. Hill's work (129) leads him to conclude that for sedentary workers the dry kata cooling power should not be below 6.0, and the wet kata cooling power not below 18.0. On days when in normal houses the readings were well above these figures, I obtained results of less than 5.0 for the "dry" and less than 12.0 for the "wet" readings. In the case of the"semi-concealed bed" so common in Glasgow, the readings were even less. By the kindness of the corpora-:tion sanitary-inspectors I was enabled to visit these same homses, at night, (about 2 a.m.): ventilation was practically non-existent and one felt absolutely exhausted after standing quite still for several moments in such a house. The dry and wet kata readings were usually about 3.5 and 9.5 respectively. When infants are taken into the open-air they are usually well muffled up by a shawl so as to limit the amount of oxygen available. The infant is thus brought up in a state of chronic ocygen-lack, surrounded by an aerial jacket,the one/

one characteristic of which is its low oxygen-content. And it is in these districts, where such a condition of affairs exists, that tetany and its allied disorders are so prevalent.

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IX. A SUGGESTION AS TO THE MECHANISM PRODUCING THE REACTION OF DEGENERATION. GENERAL CONCLUSIONS.

The results of the investigations recorded here lead one to put forward a suggestion as to the mechanism of the reaction of degeneration. Noël Paton and Findlay[9] think that the development of the slow generalised contraction with the increased response to galvanic stimulation, may be a result of the degeneration of the receptive substance. But Langley and Itagaki[130] have found that the oxygen-use of denervated muscle is much greater than that of the normal structure. The result is that there is a relative anoxaemia present round the denervated muscle. This anoxaemia would increase the excitability of the whole neuromyone and so lead to an increased response to galvanic stimulation. Whether or not this is the true explanation of the reaction of degeneration, it appears a plausible hypothesis. It seems also to explain the beneficial effects of gentle massage to denervated muscles while their nerves are in process of repair. The massage would induce a greater flow of blood to the part and consequently a better supply of oxygen to the neuromyone. Thus the irritating effect of an anoxaemia and its resultant increased excitability and generalised contraction would be prevented, and the break-down of the muscle tissue if not prevented, at least inhibited.

A general survey of the evidence brought forward in this/

this thesis is given in the following table:-

Condition.	E.E.	Supply of O_2 to tissues.	Calcium content of serum.
Acidosis.	-	+	0
Alkalosis.	+	-	0
Asphyxia.	+	-	
Cold.	+	-	
Anaemia.	+	-	
Cyanide poisoning.	+	-	
Alcohol poisoning. (excessive dose)	+	-	0
B-Im.	+	-	
Guanidin.	+	?	?

\+ indicates an increase.
\- a decrease.
0 no change.

It will be seen that in practically every case in which there is an increased electrical excitability there is also present a diminished supply of oxygen to the tissues. The evidence as regarding guanidin is certainly not clear and the action of guanidin on the head of oxygen will require further investigation. A consideration of the work previously done on the action of guanidin in the animal body does not, however, oppose the view that anoxaemia is the causal factor. As regards the influence of calcium, the evidence is still far from conclusive. It may be that all the experimental conditions investigated lead to an inactivation of calcium. That there is not necessarily a diminution in the total amount of calcium present/

present in the blood is shown by three results given above. These results, however, do not prove that calcium metabolism is of no importance in conditions where an increased electrical excitability exists. It is quite possible that anoxaemia and diminished amount of "active" calcium are both produced by the toxic or other factors inducing tetany and cognate conditions. Even if this is the case, the view that anoxaemia is the basal cause of increased electrical excitability still holds good, unless it is held that each of the experimental conditions investigated produces the increase by virtue of a specific action of its own. This last hypothesis is so unlikely in view of the evidence brought forward that it might almost be considered untenable.

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