THE IRRITABILITY OF THE VAGUS NERVES OF DOGS, AS SHOWN BY THE RHEOBASE AND CHRONAXIE, IN SOME TYPES OF TETANY; AND THEIR RELIEF BY CALCIUM SALTS.

by

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INTRODUCTION.

The cause or causes of the symptoms present due to deficient activity of the parathyroid glands have been the subject of investigations of many workers from a large number of different angles. Without going into a complete review of the literature, one could briefly summarize the theories as to the causes of the symptoms as follows:

1. Lack of calcium ions.
2. Abnormal phosphorus metabolism.
3. Inorganic ion theory.
4. Alkalosis theory.
5. The accumulation of the compounds of guanidin.
6. An interference of the ammonium metabolism.

In 1918, Burns and Watson (5) observed a modified irritability of the vagus in animals with the parathyroids removed. In these experiments the object has been to compare the relationship between thyroparathyroidectomized dogs to those injected with methyl guanidin sulphate, and to dogs with altered calcium metabolism by observing the irritability of the vagus nerve to the heart by means of the condenser discharge method of Lapicque.

HISTOLOGICAL REVIEW.

The parathyroid glands were first described by Sandström in 1880 (8). It was not until 1891 that Gly (8) and 1895 that Kohn (34), working in separate laboratories showed quite conclusively that a functional independence existed between the thyroids and the parathyroids. They observed the tetany and the acute death resulting from thyroparathyroidectomy were not due to the removal of the thyroid gland, but were caused by the removal of the parathyroid glands.

Observations upon the physiology of the parathyroids have supplied an extensive knowledge of the type of symptoms which appear in animals with deficient parathyroid activity. Described by Paton, Findley, Watson in 1916 (36) and observed many times since then as well as previously, the animals showed muscular tremors, increased salivation, dyspnea, and sometimes vomited; the symptoms increased in severity until co-ordination was difficult and muscular convulsions and tetany occurred; the animals usually died as a result of one of the tetany spasms.

Many theories have been advanced as to the cause of the appearance of these symptoms in parathyroidectomized dogs. Two of the more accepted theories are the symptoms result from: 1st, the decrease in the blood calcium content; and, 2nd, the accumulation of toxins in the body.

The parathyroids do have an important effect upon the blood calcium level. In 1909, MacCollum and Voegtlin (32) found the blood calcium decreased markedly following the removal of the parathyroids. Many workers have since substantiated this observation. Parhon and Ureche in 1907 (35) followed by MacCollum and Voegtlin in 1909 (32), Luckhardt and Goldberg in 1923 (29) and Salvesan in 1923 (39) showed that parathyroidectomized dogs could be kept free from symptoms by frequent administrations of soluble calcium salts either intravenously or in larger quantities orally. Irradiated Ergosterol and other substances rich in vitamin D, have been used successfully in the prevention of the appearance of the symptoms in parathyroidectomized dogs by Brougher, 1928 (6), Greenwald-Gross, 1929 (20), and Demole and Christ, 1929 (10).

Extracts of the parathyroid glands prepared according to the methods outlined by Collip in 1924 (9) and Hansen in 1926(8) are very effective in relieving the symptoms resulting from deficient activity of the parathyroids and raise the blood calcium level very actively. The disappearance of the symptoms occurred as the blood calcium increased.

The investigations of the effect of deficient parathyroid activity upon the blood calcium resulted from the observations of J. Loeb in 1901 (27) and MacCollum in 1905 (31), that the injection of salts that precipitated calcium caused muscular twitches. Bouchaert and Colle (2) observed that tissues placed in diminished

concentration of calcium became more irritable. More recently Lapicque and Lavrier (14), in their observations using the rheobase and the chronaxie as indicators of the irritability of tissues, report that increasing the calcium decreases the irritability that is lengthens the chromaxie.

These observations show that the parathyroids exert an important effect upon calcium metabolism, and that the symptoms which develop following thyroparathyroidectomy may be solely or partly due to the altered calcium metabolism. Much evidence has been presented in support of the theory that the parathyroids play an important role in the prevention of the accumulation of toxins in the body.

The results of Paton, Findley, Watsons, and others, published in 1916 (36) showed that there was a close resemblance between tetania parathyropriva and the tetany caused by guanidin. Previously Koch in 1912-13 (22,23) found an increased amount of guanidin in the urine of dogs following the removal of the parathyroids. Burns and Sharpe (36e) in 1916, and Paton and Sharpe(37) in 1926 report an increase in the guanidin in the blood of parathyroidectomized dogs. Greenwald (19) was unable to find any increase using a different test for guanidin. Luckhardt and Rosenbloom, 1921 (30) were able to reduce or prevent the tetany symptoms in parathyroidectomized dogs by intravenous injections of Ringer's or calcium free Ringer's solutions into dogs fed on a

mixed diet, rich in meat. They concluded the diuresis, resulting from the injection of the Ringer's solution, relieved the animals due to the increased elimination of toxins through the kidney.

Susman, 1926 (42) observed that small repeated injections of guanidin caused a hypertrophy and a hyperplasia of the parathyroid glands, and a decrease of the size and number of fat droplets within the glands.

A diet rich in proteins shortens the length of time until the appearance of the symptoms following the removal of the parathyroids, and the symptoms are more severe. Dragstedt, 1922 (11) reported that parathyroidectomized dogs could be kept alive indefinitely by feeding them a lactose diet. He concluded that parathyroid tetany is due to the absorption of the toxic substances formed in the lower part of the digestive tract by the action of proteolytic bacteria on the proteins or their split products and the decreased ability of the animal to detoxify them. Tsai and Hsu in 1929 (43) report that the removal of the lower part of the digestive tract does not delay the appearance of the symptoms following the removal of the parathyroids.

Secker (40) reported a fall in the amount of glucose and chlorides of the plasma as a result of guanidin administra-

tion. He concluded that guanidin increased the permeability of the tissues. The work of Watamabe in 1918 (44) and that of Frank, Nothman, and Wagner in 1928 (33) substantiated the hypoglycemia following the administration of guanidin compounds.

Whatever causes an increased permeability tends to cause an increased irritiability was shown by Lapicque and co-workers (14). Paton and co-workers (36) have shown that any marked decrease in the amount of parathyroid tissue or the administration of guanidin compounds caused a marked increase in the electrical excitability of peripheral motor nerves, and some increase in the irritability of the peripheral skeletal muscles, but chiefly the efferent neurones. They concluded the symptoms produced by thyroparathyroidectomy and those produced by the administration of the salts of guanidin are identical, and they are not due primarily to any decrease in the constituents of the body, i.e. calcium. These workers maintain the parathyroids regulate the metabolism of guanidin in the body probably by a hormone, and by doing so probably exercise a controling action on the tone of the muscles. Their conclusions of the increase in the electrical excitability of the nerves are based mainly upon the K.C.C. and the K.O.C. using milliamperes as an indicator of the intensity of the stimulus required to elicit a response.

Burns and Watson in 1918 (5) found that a decreased

activity of the vagus nerve occurred following intravenous injections of guanidin salts or after the removal of the parathyroids. The seat of the action seemed to be at the synapsis first and then at the terminal endings. The animals given the guanidin salts showed the more pronounced effects. In 1928 Stoland and Potter (41) observed that when the methyl guanidin sulphate was given subcutaneously the irritability of the vagus was increased as measured by an inductorium. As the effect of the guanidin became more pronounced the irritability would then be decreased as found by Burns and Watson (5).

In these experiments upon the irritability of tissues following the injection of guanidin and after the removal of the parathyroids, only the intensity required to elicit the response was measured and taken as an index of the irritability of the tissue. According to Keith Lucas (28), a stimulus must be of a sufficient time duration as well as be of sufficient intensity to cause a response. Using electrical currents and working on this hypothesis, Lucas (28) developed a method of demonstrating and measuring both of these requirements.

Waller (17) employed condensers for the measurement of the time a tissue must be stimulated to result in a response. Yet it was Lapicque, quoting Fulton (18), who was instrumental in the development of a dependable and accurate method of measuring the time interval by the use of the discharge of condensers.

Lapicque has formulated the words rheobase and chronaxie to designate the strength and time duration of the stimulus necessary to elicit a response. His definition (25) of these terms are: "the rheobase is that intensity of a constant current closed instantaneously which will just excite if it is continued indefinitely, the chronaxie is that time of current flow required to result in an excitation when the intensity of the current is just twice that of the rheobase."

Using apparatus similar to Lapicque's as described by Fulton (17-18), Buchanan and Garven in 1926 (4) report their observations upon the rheobase and chronaxie of the sciatic nerve in tetany resulting from thyroparathyroidectomy and in tetany caused by the administration of guanidin salts. They found that there were variations in the rheobase and the chronaxie from one day to the next, though the rheobase fluctuated more markedly. Methyl guanidin sulphate caused no change in the rheobase and a slight fall in the chronaxie of the sciatic nerve of cats, while following thyroparathyroidectomy the rhebbase diminished and the chronaxie increased. These results differ from those of Paton, Findly, and Watson (36) mentioned above, and lead them to conclude the two types of tetany were not closely related.

In 1925 Bourguignon (3) in his experiments upon man

found that in parathyroid deficient individuals and in cases of artificial tetany caused by hypernea, the onset of tetany was preceded by a lengthening of the chronaxies of the skeletal muscles and their motor nerves, the increase being far more pronounced in the nerves. In one case of tetany from hypernea the increase of the chronaxie was preceded by a decrease. This individual would not breathe deep and rapid enough to induce an attack of tetany.

In 1929 Chauchard, A. and B., and Czarnecki (7) found the irritability of the sympathetic nerves were lessened during the stage of tetany following the removal of the parathyroids.

These results taking the chronaxie as an index of irritability, show a decreased irritability of tissues occurred following the removal of the parathyroids.

The effects of different types of tetany upon the irritability of the vagus nerve in terms of rheobase and chronaxie have been the subject of investigation by the author.

In order to use the rheobase and chronaxie as an accurate index of irritability, many factors must be kept constant while making the determinations.

Adrian (1) and Lucas, according to Fulton (18), found the chronaxie varied with the size of the stimulating electrode; increasing the size of the electrode resulted in an increased chronaxie value. Lucas, Adrian, and Lapicque as stated by Fulton

(18) and Adrian (1) observed that only when the electrodes were separated from each other by less than 20 mm. did the distance separating the electrodes influence the chronaxie. Rushton in 1927 (38) showed that the rheobase varied inversely with the cosine of the angle formed by the electrode and the path of the current through the tissue, the greater this angle was, the larger the rheobase would be. The length of time involved for the establishing of the flow of current effects the intensity necessary for excitation as stated by the DuBois Reymond Law.

Lapicque (26a) showed that increasing the length of time required for the establishing of the current flow resulted in a larger rheobase, if that length of time was less than ten times the chronaxie.

Buchanan and Garven (4) stated that ether anesthesia had a marked effect upon the rheobase and chronaxie of the skeletal motor nerves. They found that the effect was an increase in both the rheobase and chronaxie during the anesthesia. After the withdrawal of the ether, the values returned to normal in 3 to 6 hours and then fell below normal for a few hours, but they had returned to normal always in less than 12 hours after the withdrawal of the ether.

Paton, Findley and Watson (36) found ether caused a transient increase in the electrical excitability of skeletal

motor nerves followed by a progressive decrease.

A review of the literature (14) showed the relationship of the chronaxie value to the irritability of the tissue. The quick acting and quick conducting tissues have small chronaxies, while slow acting tissues such as smooth muscle have large values.

Skeletal muscles and their motor nerves have the same chronaxie values shown by Lapicque (25) in frogs and Bourguignon (3b) in man. The work of Lapicque (25) showed that any condition or drug, which modifies the ratio of 1 to 1 that exists between the neurone and the muscle it innervates, results in a blocking of single stimuli at the synapse, when the effect is sufficient to change the ratio more than 2 to 1 or 1 to 2.

With this means of measuring irritability, much information has been gained concerning the autonomic nervous system, as summarized by Frederick in 1923 (14). He quotes the results of Fredericq, (16a and b), Lapicque and Veil (26), and Field and Brücke (13b), who have shown the chronaxies of tissues innervated by the vagus were decreased when the vagus was faradized. Fredericq (15) has shown that stimulation of the sympathetic lengthened the chronaxies of the tissues innervated. Drugs, excepting quinine, that have the same action as vagus or sympathetic stimulation or blocking, produce the same type of changes in the chronaxies of the tissues as faradization or blocking of these

nerves caused, as summarized by Fredericq (14).

Measuring the chronaxies of the iridodilator and iridoconstrictor nerves in dogs, cats, and rabbits, Kleitman and Chauchard in 1925 (21) found the chronaxie of the postganglionic fibers were shorter than the chronaxies of the preganglionic. The results of others as summarized by Fredericq in 1928 (14), show the chronaxies of the nerves of the autonomic nervous system are very much shorter than those of the organ. A condition of heterochronism exists, which explains why these nerves respond only to repeated stimuli.

DESCRIPTION OF THE APPARATUS.

The apparatus used in these experiments, see diagram 1, is essentially similar to that described by Fulton (18) as used by Lapicque and others. For the earlier experiments the range was 1 to 270 volts in the dondenser circuit; later, by means of a variable transformer with a rectifying tube connected to 110 volts A.C. current, this was increased obtaining an intensity from 1 to 600 volts. In order to provide a steady uniform current, a condenser pack of 6 mfds. capacity was placed on the D.C. side of the tube.

An electric tuning fork was used to supply stimuli at the rate of 82 per second. To the free end of the prong and insulated from the balance of the fork, a copper contact was fastened. This was connected by a flexible wire to the variable condensers.

The prong of the fork in vibrating through its arc of 5. mm. would alternately charge and discharge the condensers, by making, and then breaking, the electrical contact between them and the lead from the E.M.F. source at one end of its stroke, and the lead to the animal at the other end of its stroke. These two leads were L shape; they would then bend somewhat at each contact allowing sufficient time for the charging or the discharging of the condensers.

An electric interrupter of similar construction was used in a few experiments to supply stimuli at the rate of 11 per second.

The length of time that the stimuli were sent to the animal was two seconds, regulated by an adjustable speed, revolving electrical contact wheel, placed in the circuit between the condensers and the constant large external resistances.

DESCRIPTION OF METHOD.

Ether anesthesia was used during these experiments. The trachea was exposed, a cannula inserted into it, and connected to an ether bottle where by means of valves the amount of ether administered could be regulated and then left constant. The left carotid artery was connected to a blood pressure recording apparatus. The vagus was then exposed and the electrodes placed upon it. These were non-polarizing silver chloride coated silver electrodes of 0.3 mm. diameter, placed in a bake-lite

shield, which kept their contact with the nerve constant and always at a right angle. The distance separating the anode and the cathode was always 22 mm. with the latter nearer to the heart. As a precaution against polarization the current was reversed after each series of stimulations, thereby recoating the electrodes with silver chloride.

The irritability of the vagus was determined, taking as an index the fall of the blood pressure. The vagus was blocked centrally by pressure, only during the time that determinations were being made. In the last few animals it was found that a sufficient block was established at the anode by anodal electro-tonus, so the use of pressure was discontinued.

RESULTS.

Ether anæsthesia, according to Buchanan and Garven(4) exerts a marked effect on the rheobase and chronaxie of skeletal motor nerves. The method used minimized and kept constant the influence of the anæsthesia as shown in the results given below.

The dogs used may be classed into five divisions: Group I, called Control Dogs, which were used to check the method and the effect of the ether anæsthesia; Group II, parathyroid deficient dogs; Group III, dogs given methyl guanidin sulphate either subcutaneously or intravenously; Group IV, dogs given

sodium oxalate; and Group V, dogs of the preceding four groups that were given calcium lactate or parathormone.

Group I. Control Dogs.

This group is composed of forty-four dogs. From Table I, it is apparent that light ether anesthesia does not markedly effect the irritability of the vagus nerve to the heart. In the twenty-five adult dogs, with light ether anesthesia, the rheobase readings varied from 30. to 130. volts with an average of 74. volts, see Table 2. The chronaxie values of 23 of the 25 normal adult dogs were between 0.068 and 0.09 sigma; and two were above this range, 0.11 and 0.12 sigma. Therefore under light ether anesthesia, the normal chronaxie value of the vagus nerve to the heart of the dog has been taken to lie between 0.068 and 0.09 sigma, when 82 stimuli are sent to the nerve per second for an interval of two seconds. In a few animals using 11 stimuli per second, the normal value lies between 0.5 and 0.74 sigma.

In two dogs under local anaesthesia (novocain) Table I, the rheobase average 78. volts and the chronaxie 0.077 sigma; and in two decerebrated dogs, Table 1, the readings were 90. volts. and 0.074 sigma, thirty hours after the withdrawal of the ether. The readings under ether anesthesia mentioned above, do not differ markedly from those under local anesthesia or of those decerebrated.

The effect of various degrees of ether anesthesia upon the irritability of the vagi of dogs is shown by the data in table 3. It is very apparent that the rheobase values were markedly increased and the chronaxies were not appreciably changed when the depth of the ether anesthesia was increased. Allowing the animal to become less deeply anesthetized, the rheobase again returned to the former value of light anesthesia.

The effect of the ether on the irritability of the vagus nerve was further investigated by taking readings at various intervals on four dogs over a period of eight hours of continuous ether anesthesia. The results are tabulated in Table 4 and averaged and charted in Group 4 of Figure II. The chronaxies and rheobase decreased in these animals for the first four hours so that at this time the chronaxies were near the value of the lowest chronaxies of the 25 normal dogs. Eight hours after the starting of the ether anesthesia the chronaxies of the vagus nerves of these dogs were as high or higher than at any preceding time during the eight hours, yet they were not above the range of the normal control dogs.

Comparing the data of Table 1 with that of 5, and Groups 1 & 2 in Figure 2, pups are found to have more irritable vagi then adult dogs. Of the five pups under light ether anesthesia, four of them have chronaxie readings below 0.07 sigma, and three of these are less than 0.068 sigma, which was the lowest reading of

the twenty-five adult dogs. The four rat terriors which were litter mates, had unusually high chronaxie values. The vagus nerves of these dogs may have been in a state of hyper-irritability even though the chronaxies were large, due to a partial block ~~existed~~ -- evidence is presented below.

Group II. Parathyroid Deficient Dogs.

This group of animals are of two types: Dogs on which thyroparathyroidectomy was performed, and dogs receiving blood from thyroparathyroidectomized dogs.

The irritability of the vagus was determined upon thirty-two dogs at various time intervals following the removal of the parathyroids until recovery from an attack of tetany had occurred. Of these, seven were given calcium therapy. Three dogs received injections of blood from parathyroidectomized dogs in various stages of parathyroid deficiency.

The early effects of the removal of the parathyroids upon the irritability of the vagus was observed in six dogs. The data is given in Table 6, and their averages are charted in Group 3, Figure 2. Thirty minutes following the removal of the parathyroids under ether anesthesia, three of the six dogs #63, #66, and #60, had chronaxie readings less than the lowest normal control dogs. In one hour all but one gave chronaxie readings of less than 0.068 sigma, the lowest normal value. At this time

the rheobase intensities for a small and a big fall in the blood pressure are very close together. Normally they differ from 30 to 50 or more volts. This shows that the neurones with the higher rheobases were evidently more effected.

After 90 minutes, three of four of the dogs, #60, #61, and #66, showed either a block, or a decreased irritability, possibly a partial block. In the normal control dogs this decreased irritability manifested itself only after eight hours.

In two dogs, Table 7, Dogs #58 and #74, the parathyroids were removed under a local anesthesia, and after six hours ether was given. The chronaxie were 0.06 and 0.1 sigma. Bradycardia developed in the one with the hyper-irritable vagus just shortly before the ether administration was started.

Two pups, #62 and #64, data given in Table 6, developed the stage of hyper-irritability, and then later, the stage of decreased irritability, more rapidly than adult dogs. In pup #64, the hyper-irritability occurred and gave way to a decreased irritability in less than 10 minutes. In pup #62, the vagus was hyper-irritable thirty minutes after the removal of the parathyroids and less irritable than normal one hour after their removal.

As shown by five dogs of Table 13, the blood calcium did not change until after an interval of 1 to 3 days had elapsed since the removal of the parathyroids. Yet in three of the

six dogs reported in Table 6, the irritability of the vagus nerves was markedly increased thirty minutes following the removal of the parathyroids, and the vagus was either partially blocked or hypo-irritable after ninety minutes.

The observations upon the dogs reported in Table 4, showed that ether effected normal animals in the same manner, though the effect was less marked, and developed only after a longer period of etherization. The presence of the parathyroids must retard and decrease this action of ether anesthesia upon the vagus nerve.

In Figure 2, Group 3 and 4, and in Figure 3, Groups 5 and 7, these values of the parathyroidectomized dogs, and of the normal dogs, have been charted. Comparing the above groups of animals, shows very definitely the difference in the time of appearance, and the degree of the changes in the irritability of the vagi of the two types of dogs.

Observations were made upon seventeen dogs following the removal of the parathyroids without the complicating action of long continued ether anesthesia (see Table 7).

The results of dogs #58 and #74, where the parathyroids were removed under a local anesthesia have been given above. Here the period of ether anesthesia is comparable to the period of the twenty-five normal adult dogs. The vagus nerve of one

dog was hyper-irritable six hours after the operation, while the nerve of the other dog was less irritable than the normal.

In the stage where muscular tremors are present, resulting from the removal of the parathyroids, the vagus nerves of all seven dogs were hyper-irritable. As seen in Table 7, the chronaxies of the vagi of the animals in this stage were below 0.068 sigma, the lowest normal value, and the average of the rheobase readings was 30. per cent lower than the average of the values of the normal dogs. In Figure *1*, comparing groups A and C, the marked increase in the irritability of the vagus nerves is very evident. In this stage of parathyroid deficiency, the blood calcium content is decreased quite markedly, usually to 6. or 7. mgm. per cent, according to Esau and Stoland (13a), and previous workers.

Two dogs, #67 and #27, Table 7, in active convulsions at the time of etherization, showed a lessened irritability, the rheobase and chronaxie values both being higher than normal, which suggests a slight block. In dog #27, the apparent low rheobase reading was due to the fact that during the anesthetizing of the animal, a convulsive spasm interfered with respiration sufficiently long to cause the loss of cerebral action, but not of the lower brain centers, so that it was not necessary to give ether to this animal; thereby, eliminating the usual augmenting action of ether upon the rheobase. The blood calcium of dog #67

was 5.7 mgm. per cent.

Six hours following spasms of convulsions, the vagi of two dogs gave chronaxie values very much similar to those of the dogs in convulsions. The rheobase readings were very markedly increased which might indicate a partial block of the vagus nerves due, possibly, to marked heterochronisms. The fall in blood pressure in these animals was delayed, and persisted after the cessation of stimulation. The blood calcium of dog #75 was 5.4 mgm.per cent.

Four dogs recovered following the removal of the parathyroids without, at any time, showing symptoms more severe than mild tremors. After an elapse of 13 days in one dog, a bull dog, 3 months in two dogs, and 100 days in the fourth dog, the animals were sacrificed to determine the irritability of the vagus. The chronaxie of one dog was very much lower than the lowest value of the normal dogs. The readings of the other three dogs and the rheobase values of all four dogs were in the normal range, as shown in Table 7. The blood calcium was not determined on these dogs. In the work of Esau and Stoland (13a), one of their dogs recovered from the removal of the parathyroids and its blood calcium had approximately returned to normal in this length of time, the value was 10.7 mgm. per cent.

Dogs that survived the immediate symptoms of thyroparathyroidectomy, usually, had normal irritability of the vagus nerves

in a few weeks following the removal of the glands. Three dogs, in which the normal irritability of the vagus nerves had been measured, were injected with blood drawn from parathyroidectomized dogs showing various stages of symptoms. The results and conditions of the experiments are given in Table 8.

The chronaxie of Dog #54I, an animal in mild tremors (see Table 7), was 0.061 sigma; when 100 c.c. of its blood was injected into Dog I, the chronaxie of this animal was decreased from 0.07 to 0.059 sigma. The chronaxie of the vagus of Dog 57L, an animal sacrificed six hours after a convulsive spasm (see Table 7), was 0.12 sigma, and the rheobase was 200. volts; when 100. c.c. of its blood was injected into Dog L., the chronaxie of the second animal was decreased from 0.07 to 0.03 sigma. A second injection of 150.c.c. increased the rheobase to 210 volts and the chronaxie to 0.05 sigma. This would indicate the blood contained or was lacking in something that caused the vagus nerve to the heart to be increased irritable irrespective of whether the donor's vagus was hyper or hypo irritable.

The vagus of Dog #48H, whose parathyroids had been removed 90 days preceding, on recovering had a chronaxie value of 0.084 sigma. When 250. c.c. of its blood was injected into Dog H, the chronaxie decreased from 0.1 sigma to the new value of 0.06 sigma and the rheobase also decreased. The irritability of the vagus nerve of Dog #48H was normal, yet its blood when injected into a normal dog caused its vagus to be hyper-irritable. Evi-

dently the parathyroidectomized dog #48H was able to maintain normal irritability of the vagus, in spite of the change resulting from the removal of the parathyroids, due to the length of time of the changed environment of the dog's tissues.

These experiments upon transfusions have not been controlled, and therefore, cannot safely be used to formulate any conclusions.

Vincent and Thompson (43b) described a condition which they call the first crisis that occurs in 2 to 3 hours following thyroparathyroidectomy. This is similar to the time when the vagus became incompletely blocked following its initial hyper-irritability. This occurred in the eight dogs reported in Table 6 in a time range of 10 minutes to 6 hours. The vagi of animals having the three shortest crises, one at 10 minutes and two at 60 minutes, had normal chronaxies of 0.063, 0.068, and 0.07 sigma respectively; all of which are unusually low. Two of these values are below normal and the dogs were pups. The lower the normal chronaxie of the vagus nerve, the more sudden and the sooner the stage of decreased irritability developed. It is in such animals that crises were very apparent.

Group III. Dogs Given Methyl Guanidin Sulphate.

This group of animals consists of dogs given methyl guanidin sulphate in an acute manner either subcutaneously or in-

travenously, and of dogs injected for periods of one or more days and then etherized.

Fourteen dogs, placed under ether anesthesia, were given methyl guanidin sulphate either subcutaneously or intravenously after first determining the irritability of the vagus nerves. The data is given in table 9.

In dogs #3, 5, 2A, 8A, and 11A; intravenous injections of small quantities (6 to 15 mgm. per kilogram body weight) of methyl guanidin sulphate caused a marked increase in the irritability of the vagus. The chronaxie and rheobase values of the vagus nerves of these dogs preceeding the injections were normal. Five minutes after the injections, four of the five animals showed a markedly increased irritability of the nerve, their chronaxies were less than the lowest value of the twenty-five control dogs.

Larger intravenous injections (30 to 210 mgms. per Kilo) resulted in a decreased irritability as shown by dogs #7, 12, 4, 1, 14A and 23A, in Table 9; the rheobase and chronaxie values both were increased. After a short time, the decreased irritability gave way to a condition of hyper-excitability, as shown by dogs #7 and 12, as the effect of the methyl guanidin sulphate become less pronounced.

Subcutaneous injections of 50. to 100. mgms. per Kilo., to dogs #23A, 13, 17, and 15A, produced after 35 to 90 minutes a markedly increased irritability of the vagus nerves, the chronaxies

decreased to a value between 0.05 and 0.06 sigma in the four dogs. After one or two hours in dogs #13 and 17, the vagus became less irritable, the chronaxies were 0.115 and 0.123 sigma. These changes of the irritability of the vagus resemble very closely those observed in parathyroidectomized dogs as shown in Figure 2, Groups 3 and 5, and in Figure 3.

Two dogs (see Table 10, #65 and #88) were injected with methyl guanidin subcutaneously; after 2 and 5 hours in the two cases, the animals developed bradycardia. The blood calcium of the two animals were normal in value. The animals were anesthetized, the vagus nerves of both dogs were very markedly hyper-irritable. The rheobase values were 38. and 70. volts, and the chronaxies were 0.04 and 0.055 sigma.

In the six dogs whose data is given in Table 10, the injections of methyl guanidin sulphate were continued over longer periods of time. The condition was then less acute and served as a comparison to the thyroparathyroidectomized dogs reported in Table 7.

The vagus of dog #71, who had been injected subcutaneously with 400. mgms. (per Kilogram of body weight) of methyl guanidin sulphate during a period of two days, and who displayed tremors, increased salivation, and tachycardia at that time, was very excitable as shown by its rheobase and chronaxie of 40. volts and 0.04 sigma.

Three dogs, #78, 76, and 69 in Table 10, given guanidin for two or three days until they manifested difficult co-ordination and were depressed, showed slightly decreased irritable vagus nerves. The rheobase values were low, but the chronaxies were high, 0.09 to 0.135 sigma.

One dog, #70, was injected till slightly toxic symptoms of guanidin poisoning were apparent, and then the amount of the injections was decreased so that the animal showed no symptoms. The vagus displayed normal irritability.

Dog #9 was injected with 20.mgm. per Kilo. daily for fifty days. Forty days after the cessation of injections, the rheobase was low and the chronaxie was high, yet both values were within the range of the normal animals.

The blood calcium of these dogs showed just a slight increase if any change. This might be caused by the increased activity of the parathyroid glands, which results from the injection of guanidin, as shown by Susman (42). Dog #85, which died in convulsions, showed a higher blood calcium at the time of the convulsions than the remaining dogs in the other stages.

Group IV. Dogs Receiving Sodium Oxalate.

Seven dogs were given sodium Oxalate; of these, three died in convulsions before the irritability of the vagus nerves had been determined. The observations from the remaining four are

given in Table 11, Group D.

Dog #101 was injected during two days with 3. mgms. of sodium oxalate per Kilogram of body weight. The blood calcium was not lowered, and the rheobase and chronaxie of the vagus were normal. Dog #102 with a normal blood calcium of 10.8 mgms. per cent was given 90. mgms of sodium oxalate (per Kilo.) orally and 120 mgms (per Kilo.) intravenously during a period of three days. Three injections were made daily. The animal showed gradually increasing symptoms of oxalate poisoning: restlessness, copious saliva secretion, dyspnea and muscle tremors. The animal's blood calcium was 5.7 mgm per cent and the tremors were very marked. The rheobase of the vagus was 55. volts, and the chronaxie 0.055 sigma. Dog #104 with a normal blood calcium of 10.8 mgms. per cent was injected intravenous with 170. mgms. of sodium oxalate (per Kilo.) in 15 injections during a period of four days. This animal vomited frequently, salivation was increased, and dyspnea and muscle tremors were marked. The vagus nerve of this animal was hyper-irritable; the rheobase equaled 40. volts, and the chronaxie was 0.055 sigma. The blood calcium preceding etherization was 6.7 mgms. per cent and 7.3 at the time the irritability of the vagus was determined.

The vagus nerve of a pup, #81, under ether anesthesia had a chronaxie of 0.074 sigma; the blood calcium of this animal was 12.6 mgm. per cent. The injection of 30. mgm. of sodium oxalate

(per Kilo) reduced the blood calcium to 8.3 mgm. per cent, and the chronaxie of the vagus became 0.1156 sigma, which evidently corresponded to the stage of depressed vagus excitability following the initial hyper-irritability, as an injection of 100. mgms. of calcium lactate intravenously raised the blood calcium so that after 30 minutes it was 16.5 mgm. per cent, and yet the chronaxie was decreased to 0.06 sigma. A second injection of calcium lactate increased the blood calcium to 21. mgm. per cent and the chronaxie to 0.074 sigma.

The vagus nerves of these dogs given sodium oxalate, which precipitates the calcium, manifested the various changes in its irritability as were observed in thyroparathyroidectomized dogs and in dogs given methyl guanidin sulphate.

Group V. Dogs Receiving Calcium Lactate or Parathormone.

Twenty-two of the various types of dogs were given calcium lactate in various quantities and two dogs were given parathormone. The effect upon the irritability of the vagus nerve of increasing the blood calcium content above normal either by the injection of calcium lactate or by parathormone was determined in five dogs, see Table 11.

Two pups, litter mates, were used to observe the effect of parathormone. By the injection of parathormone, the blood calcium of Dog #94 was increased from 11.5 to 16.5 mgms. per cent dur-

ing an interval of 12 hours. The rheobase was 70. volts and the chronaxie was 0.07 sigma, when the irritability of the vagus was measured. The vagus of the normal control litter mate gave a rheobase of 110 volts and a chronaxie of the same value, 0.07 sigma.

The blood calcium of the adult dog #91 was increased from 10.5 to 14.3 mgms. per cent sixteen hours following the administration of parathormone. The values found for the vagus nerve of this animal were: rheobase, 115 volts; chronaxie, 0.08 sigma. This chronaxie value corresponds with those of the normal control dogs.

The elevation of the blood calcium in normal dogs by the administration of parathormone does not modify appreciably the chronaxie values of the vagus nerves.

Two dogs, #80 and #92, were given calcium lactate over a period of two days till their blood calcium levels were 18.5 mgms. per cent. The vagus nerves of the animals displayed normal irritability.

One of these animals was then injected intravenously with 100. mgms. of calcium lactate per Kilo. After thirty minutes the rheobase increased from 60 to 110. volts and the chronaxie decreased from 0.09 to 0.074 sigma.

Dog #93, whose values for its vagus were 110. volts and 0.07 sigma, was injected intravenously with 200. mgms. of cal-

cium lactate (per Kilogram of body weight). After thirty minutes an opposite effect was present to that found in dog #92. The vagus showed a decrease in the rheobase and an increase in the chronaxie.

These animals showed that the increasing of the blood calcium slowly did not appreciably effect the irritability of the vagus in a normal animal.

The irritability of the vagus nerves of five animals was determined when the blood calcium content was decreased by the administration of sodium oxalate. Of these animals two were then given calcium lactate. The results are given in Table 12.

A decrease in the blood calcium of Dogs #104 and 102, produced an increased irritability of the vagus nerves. In these dogs, 100. mgms. of sodium oxalate was given orally the first day in #102 and for two days in #104. The administrations were then made intravenously in four injections daily of 8 to 10 mgms. per Kilo.

Only 6. mgms. of sodium oxalate was given to dog #101 per kilogram of body weight during an interval of $2\frac{1}{2}$ days. This was too small of a quantity to effect the blood calcium to any extent, so consequently the irritability of the vagus was normal.

Two dogs, #81 and 99, were given sodium oxalate intravenously after first measuring the irritability of the vagus.

In both the chronaxie values increased. The vagus nerves of both animals had passed through thehyper-irritable stage and showed the depressed irritability stage as shown by the values a short time later.

As the effect of the sodium oxalate was buffered and decreased in severity in dog #99, the vagus nerve became hyper-irritable so that thirty minutes following the administration of the oxalate the chronaxie value was 0.061 sigma. This animal was then in the early stage of oxalate poisoning as observed in dog #102 and 104.

In dog #81, the effect of the sodium oxalate was decreased by the injection of 100 mgms. of calcium lactate, which after an interval of thirty minutes, maintained the blood calcium level at 16.5 mgms. per cent. The vagus of this animal became hyper-irritable, the rheobase was 50. volts and the chronaxie 0.06 sigma, due to this animal reaching the stage of slight oxalate poisoning following the more severe effect that was first produced.

Nine thyroparathyroidectomized dogs were given calcium lactate. The observations upon these animals are given in Table 13. Of these dogs, seven were given calcium therapy when their blood calcium started to decrease as a result of the removal of the parathyroids. The two others in the same table were given an injection of calcium lactate after the irritability of the vagus had been measured following the removal of the parathyroids.

The blood calcium of dog #86 and #96 were approximately normal due to calcium therapy five days after the removal of the parathyroids. The irritability of their vagi was normal.

The blood calcium of four dogs, #95, 84, 105, and 83, were slightly below normal even though calcium therapy had been given. The vagus nerves of the latter three of these animals were hyper-irritable, and the vagus of one dog was normal. The blood calcium of the dogs, whose vagi were hyper-irritable, had been allowed to reach a low level before the calcium therapy was started. These results are in agreement with the conclusion of Esau and Stoland (13a) that the rapidity of the decrease of the blood calcium is a factor in the severity of the symptoms. Luckhardt and Goldberg (29) have shown that if the symptoms are allowed to appear, it requires larger amounts of calcium to keep the animals symptom free. Joseph Dye in 1927 (12) showed that functional activity and tetany spasms increased the severity of the nerve cell lesions that occurred following the removal of the parathyroids.

In four thyroparathyroidectomized dogs, the irritability of the vagus nerves was measured less than thirty minutes following the injection of calcium lactate. The effect of the calcium administration varied somewhat in the different animals.

The chronaxie of the vagus of dog #63, two hours after the removal of the parathyroids had decreased from its former of 0.09 sigma to 0.05 sigma. When 20. mgms. of calcium lactate (per

Kilo.) were injected the chronaxie increased to 0.09 sigma, its original value.

During the thirteen days following the removal of the parathyroids, dog #22 had shown only the symptoms of slight tremors during the period between the fourth and eighth days. On the thirteenth day, the irritability of the vagus was: rheobase = 80. volts, chronaxie = 0.07 sigma. When 7.mgms. of calcium lactate (per Kilo.) were injected, these values became 90. volts and 0.09 sigma.

Three dogs, #84, 106 and 83, that had been given calcium therapy beginning when the symptoms caused by the removal of the parathyroids were very marked, were injected with calcium lactate after first determining the blood calcium content and the irritability of the vagus. In dog #84, the blood calcium was increased from 9.5 to 12.5 mgms. per cent after thirty minutes, and the rheobase increased from its former value of 50. volts to 70. volts, while the chronaxie decreased from 0.067 to 0.04 sigma. In dog #106, after increasing the blood calcium from 7.4 to 10.7 mgms. per cent, the vagus was blocked; when the blood calcium was increased to 15.mgms. per cent, the vagus was hyper-irritable in thirty minutes; and when it was further increased to 23, mgms. per cent the chronaxie was increased to 0.115 sigma. In dog #83, the calcium lactate injection increased the blood calcium from 9.5 to 15. mgms. per cent, and caused the vagus to become even

more irritable than its former value. The chronaxie was decreased from 0.04 to 0.03 sigma.

The acute administration of calcium lactate relieved the hyper-irritable condition of the vagus nerves in three of the five dogs.

Calcium lactate was given to five dogs following the administration of guanidin (see Table 14). When the guanidin administration was acute, (dogs #15A and 65), the injection of calcium lactate caused an immediate return to normal irritability. Where the guanidin was administered over a period of several days, an injection of calcium lactate increased the chronaxie, yet the irritability of the vagus did not appear to be normal.

DISCUSSION OF RESULTS.

As given in Table 4 and Figure, 2, Group 4, long continued ether administration effected the irritability of the vagus nerves to the heart. First there was a gradual decrease of the chronaxie reaching a minimum after the average interval of four hours; then after remaining hyper-irritable for an interval between two and three hours, there appeared rather quickly a decreased irritability until the chronaxie readings were higher than normal.

Ether anesthesia produced changes in the irritability of the vagus nerve similar to those caused by thyroparathyroid-

ectomy and guanidin compounds. The parathyroids delayed the appearance of these changes and the removal of these glands allowed the changes to occur sooner and to be more pronounced. These changes appeared sooner and more suddenly in dogs that were given methyl guanidin sulphate during the period of ether administration as seen in Figure 1, Group 4 and in Figure 2, Group 5; and in thyroparathyroidectomized dogs kept under ether anesthesia, Figure 2, Group 3. In Figure 3, a comparison of these shows the differences in the length of time very clearly.

The irritability of the vagus nerves of pups was effected quicker and more pronounced by deficient parathyroid activity, and ether anesthesia. Young individuals are more susceptible to toxins, to lack of calcium, to parathyro-priva, and to ether anesthesia. In Figure 3, the time required for the removal of the parathyroids to effect the irritability of the vagus is shown.

When the vagus nerves were changing from a hyper-irritable state to a condition of a partial block may have been the period called the crisis by Vincent and Thompson in 1928 (43b). If this change was sudden the crisis was more apparent. In pups, the crises were usually more apparent and the changes in the irritability were quicker.

In the stage of decreased irritability, observations indicate this was a partial block caused by a heterochronism resulting from the hyper-irritability. In some animals the fall of

blood pressure lagged the vagus stimulation at this time. The injection of calcium eliminated this and caused the vagus to be hyper-irritable. When a large quantity of methyl guanidin sulphate was given intravenously, Figure 1, Group 5, the vagus nerve was blocked. As the effect of the guanidin became less pronounced the vagus nerves of these dogs became hyper-irritable and then gradually returned towards normal. As seen in Dog #81, Table 12, oxalate in an acute administration caused the vagus to be decreased irritable, and then was caused to be hyper-irritable by the administration of calcium. A second injection of calcium resulted in the vagus being in a normal state of excitability. These results indicate the stage of depressed excitability is a stage of partial block.

The blood calcium was not decreased by the injection of methyl guanidin sulphate. Rather from the results in Table 10, it appears the level was slightly increased. This may be the result of the increased activity of the parathyroid glands. Susman (42) as reported above observed that small repeated injections of guanidin compounds caused a hypertrophy and hyperplasia of the parathyroid glands.

The results, reported above in Table 8, of animals receiving blood from thyroparathyroidectomized dogs, indicate the removal of these glands results in the appearance of some material

in the blood to which a tolerance can be developed. Injections of 100. to 200. c.c. of this blood caused the animals to show as pronounced changes in the irritability of the vagus nerves as were present in the animals with the parathyroids removed. Evidently, the latter animals had developed a resistance or a tolerance to this substance; otherwise, the effect of the injections of just small portions of these animals' blood would not have caused just as large a change in the animals receiving the blood as had occurred in the donors.

Dog #48 had recovered from the effects of the removal of the parathyroids, its vagus possessed normal irritability; yet the injection of 250. c.c. of its blood into dog # H resulted in the chronaxie of the vagus nerve decreasing from 0.1 to 0.06 sigma. This would explain why the animals of Esau and Stolands (13b) showed more pronounced symptoms when the blood calcium decreased quickly, and why Luckhardt and Goldberg (29) were able to slowly decrease the amount of calcium salts administered to thyroparathyroidectomized dogs.

In the animals in these experiments the chronaxie changes of the vagus to the heart were very similar to each other in the three types of tetany investigated. The apparent discrepancies of some of the previous workers may be due; to the lack of the use of the chronaxie method to measure the irritability of

the tissues, to the different effects of different sizes of doses, to whether the administration was acute or slow, and to whether the animal was anesthetized for a period of time before the observations were taken.

The results of Buchanan and Garven published in 1928 (4) lead them to the conclusion that there is no relationship between guanidin compounds and parathyroid tetany in their effect upon the electrical excitability of somatic nerves.

They conclude that guanidin has no effect upon either the rheobase or the chronaxie. In their discussion they state they find a slight decrease in the chronaxie following subcutaneous administrations, but that large injections do not effect the chronaxie. A closer study of their results in Tables 3 and 4, and Figures 7, and 8 of their paper show that small doses of guanidin did effect the irritability of the somatic nerves in very much the same manner as it effects the vagus nerves. In small doses it diminished the chronaxie, and in larger doses the hyper-irritability gives way to a state where the values are fairly normal.

Their tables 3 and 4 are included in this paper as Table 15, and the evident condition of their animals has been stated by the author. In Figure 3 of their paper the normal chronaxie values of the nerve to the semitendinosus muscle ranged from 0.06

to 0.27 sigma. In Figure 7, this nerve in the same animal following the administration of guanidin salts had the chronaxie range of 0.03 to 0.14 sigma with five of the ten readings below 0.06 sigma.

These chronaxie values following guanidin administrations were approximately one half of those in the normal state. According to Lapicque a further decrease would establish sufficient heterochronism to cause a block of individual stimuli. Possibly this may be a more accurate interpretation of their observations with guanidin compounds.

Their results upon the somatic nerves of parathyroidectomized cats do not agree with the results reported in this paper, yet this may be due to a difference in the animals or in the types of nerves measured. Their first observations were made 24 hours following the removal of the parathyroids, and there may have been an initial hyper-excitability during this interval since they used ether as an anesthetic in removing the parathyroids.

Their results of the parathyroidectomized animals agreed with the observations of Bourguignon (3a) upon the somatic system in tetany conditions. In Bourguignon's observations one individual, in which the tetany was being induced by hypernea, showed an initial decrease of the chronaxie before the increase. This individual hesitated in producing marked hypernea and in this way the

probable initial action of the hypernea became apparent. Of course the somatic system and the autonomic system may be effected differently. Yet further research may disclose both systems are effected similarly.

CONCLUSIONS.

A. The Effect of Ether Upon the Irritability of the Vagus Nerve.

1. Light ether anesthesia augments the rheobase to some extent, and has very little, if any, effect upon the chronaxie of the vagus nerve to the heart. To cause a marked fall in the blood pressure, the readings of normal animals under light ether anesthesia are: rheobase = 45 to 80 volts; chronaxie 0.068 to 0.09 sigma, using a frequency of 82 stimuli per second for two seconds, and chronaxie = 0.55 to 0.94 sigma with a frequency of 11 stimuli per second for 5 seconds.
2. When the depth of etherization is greater, the rheobase is markedly higher and the chronaxie changes very little.
3. Long continued etherization causes the vagus nerve to the heart to have an increased excitability during the period, usually beginning in less than an hour and continuing till after the fourth hour. Later a period of approximately normal irritability developes. The values throughout both periods are within the normal range of the chronaxie values.

B. The Effect of Parathyroidectomy Upon the Irritability of the Vagus Nerve.

1. The irritability of the vagus is initially increased fol-

lowing the removal of the parathyroids; the rheobase and the chronaxie are both decreased. Soon after the chronaxie reaches a value in the vicinity of 0.04 to .06 sigma, the vagus goes into a condition of decreased irritability; the rheobase rises, the chronaxie remains low for a short time, but rises to the higher value, 0.09 to 0.123 sigma very suddenly. Calcium lactate given intravenously causes the vagus to be hyper-irritable again, and then in larger amounts restores the vagus to normal irritability.

2. When the dogs are kept etherized only during the time required to remove the parathyroids, the vagus nerve becomes hyper-irritable in approximately 6 hours, and continues to be hyper-excitable during the stage of tremors until the animals are in tetany convulsions. At this time the vagus is decreased irritable.

3. When the dogs are kept under ether anesthesia following the removal of the parathyroids, the increased irritability of the vagus is marked in 30 to 60 minutes, the chronaxie is less than 0.06 sigma. The chronaxie of the vagus nerves of all the animals in this group, except one, became larger very suddenly between 1 and 1½ hours. The value of the chronaxies varied between 0.09 and 0.123 sigma.

C. The Effect of Injections of Methyl Guanidin Sulphate Upon the Irritability of the Vagus Nerve.

1. Dogs given 50. mgms. of methyl guanidin sulphate subcutaneously would display bradycardia in 2 to 5 hours. When etherized, the vagi were hyper-irritable, the chronaxies were between 0.04 and 0.055 sigma. As the muscle tremors became fairly marked and the animals somewhat depressed as the result of repeated subcutaneous injections of methyl guanidin sulphate, the chronaxies of the vagus nerves were between 0.09 and 0.135 sigma.

2. The vagus of animals receiving 10 to 15 mgms. of methyl guanidin sulphate per Kilo. intravenously became hyper-irritable immediately. Their chronaxies were between 0.055 and 0.066 sigma, while before the injections they were between 0.07 and 0.11 sigma. When 50. mgms. were injected per Kilo. subcutaneously to etherized animals, the chronaxies of the vagus nerves were below 0.06 sigma in 35 to 90 minutes, and the stage of decreased irritability appeared in 80 minutes to 2 hours, the chronaxies were between 0.1 and 0.123 sigma. The injection of calcium lactate resulted in the return of the irritability of the vagus to normal.

3. The injection of 50. to 150. mgms. of methyl guanidin sulphate per Kilo of body wt., intravenously, caused the

vagus nerves to be blocked for a short time. In 5 to 20 minutes, depending on the dosage injected, the vagus would be hyper-irritable. The chronaxies were less than 0.06 sigma.

D. The Effect of the Administration of Sodium Oxalate upon the Irritability of the Vagus Nerves.

1. The chronaxies of the Vagus Nerves in dogs, receiving small, frequently repeated, intravenous injections of sodium oxalate, were 0.055 sigma, when the animal displayed mild tremors.
2. The injection of 30. to 40. mgms. of sodium oxalate intravenously per Kilo. caused the chronaxies of the Vagus Nerves to be increased from the value of 0.074 sigma to values between 0.09 and 0.115 sigma. After 30 minutes the chronaxie of the vagus was 0.06 sigma. The vagus became hyper-irritable very quickly if calcium lactate was injected, the chronaxie was 0.06 sigma. A second injection of calcium lactate restored the vagus to normal irritability.

E. The Irritability of the Vagus Nerves of Pups.

1. The chronaxies of the vagus nerves of pups were lower than adult dogs. They were between 0.065 and 0.07 sigma.
2. The vagus nerves of pups were more susceptible to the effects of the removal of the parathyroids.

F. The Relationship of Various Types of Conditions That Caused Tetany in Their Effect Upon the Irritability of the Vagus Nerve.

1. The removal of the parathyroids, the injection of methyl guanidin sulphate, and the administration of sodium oxalate caused an initial increase in the irritability of the vagus nerve to the heart, followed by a decreased irritability when the effect was more pronounced or very sudden.
2. This decreased irritability appears to be a condition of partial block resulting from a marked heterochronism established as the hyper-irritability of a part of the vagus mechanism became more marked.
3. The vagus nerves of etherized animals were very much more susceptible to the removal of the parathyroids, to guanidin, and to sodium oxalate.
4. As the conditions caused the vagus to become increasingly hyper-irritable, the animals were in a state where the crisis of Vincent and Thompson (43b) might occur. The more sudden the rate of the development of the hyper- irritability, the more apparent the crisis.

G. The Effect of Increasing the Blood Calcium Level.

1. The increasing of the blood calcium levels of normal dogs by injections of calcium lactate or parathormone did not effect the irritability of the vagus nerve to the heart.
2. The increasing of the blood calcium levels of thyropara-

thyroidectomized dogs, of dogs given methyl guanidin sulphate, and of dogs given sodium oxalate caused the irritability of the vagus to return towards its normal value.

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Table 1.

NORMAL ADULT DOGS.

No. of Dogs.	The Condition of the Animals.	Rheobase in volts	Chronaxie in sigma.	B.P. Fall in mm. of Hg.
2	Decerebrated, 11 hrs.	90.	0.074	10.
2	Novocaine Anesthesia	78.	0.077	7.
2	Chloroform Anesthesia	54.	0.087	6.
1	Barbital Anesthesia	80.	0.068	10.
4	Amytal Anesthesia	70.	0.08	10.
25	Light Ether Anesthesia.	74.	0.082	10.

Table 2.

NORMAL ADULT DOGS UNDER ETHER ANESTHESIA .

No. of Dogs	Rheobase in volts	Chronaxie in sigma.
12	100.	0.068
B-7	60.	0.068
60.0	150.	0.068
1	30.	0.07-
14.A	50.	0.07
5	120.	0.074
99	50.	0.074
42	80.	0.08-
4	150.	0.08
15	45.	0.08
17	75.	0.08
79	68.	0.08
61	80.	0.084
66	35.	0.084
66.B	50.	0.084
98	68.	0.084
60	90.	0.09-
62	80.	0.09-
3	55.	0.09
41	100.	0.09
63	60.	0.09
23.A	65.	0.094
2.A	55.	0.112
15.A	70.	0.123
68	80.	0.084
Average =	74.	0.082

TABLE 3

EFFECT OF VARIOUS DEPTHS OF ETHER ANESTHESIA

Dog's No.	No. of Dogs in Group.	The Condition of the Animals.	Rheobase in volts	Chronaxie in sigma.	B.P. fall in mm.
	25	Under light ether	74.	0.082	10.
	9	" light "	60.	0.083	10.
		" medium "	108.	0.074	10.
		" deep "	240.	0.078	6.
		" light "	80.	0.08	10.
53		Durbital Anesthesia, 20 min.	138.	0.068	60.
		After 50 minutes	140.	0.069	55.
		" 55 " plus a small amt. of ether	152.	0.07	50
		" 70 " plus usual amt. of ether	165.	0.074	60
		" 110 " plus a large amt. of ether	256.	0.084	24
		" 170 " ether was withdrawn	170.	0.074	45
10.M		Chloroform anesthesia	45.	0.09	6
		plus a large amt. of ether	260.	0.09	6

TABLE 5

NORMAL PUPS

No. of Dogs	The Condition of the Animals.	Rheobase in volts	Chronaxie in sigma.	B.P. fall in mm.
2	Amytal Anesthesia	60.	0.068	8
5	Light Ether Anesthesia	84.	0.066	20.
4 Rat terriers from 1 litter,	Light Ether Anes.	65.	0.16	8

TABLE 4

EFFECT OF LONG CONTINUED ETHER ANESTHESIA

Dog #	Normal Values		After 1 Hr.		After 2 Hrs.		After 4 Hrs.		After 8 Hrs.	
	Rheobase in Volts	Chronaxie in Sigma	Rheobase in Volts	Chronaxie in Sigma	Rheobase in Volts	Chronaxie in Sigma	Rheobase in Volts	Chronaxie in Sigma	Rheo. Volts	Chron. Sigma
23A	60.	0.094	58.	0.07	55.	0.07	30.	0.066		
77	75.	0.08	65.	0.074	68.	0.07	52.	0.07	70.	0.08
46	55.	0.079	62.	0.068	63.	0.074	40.	0.07	65.	0.08
42	110.	0.074	80.	0.078	100.	0.074	80.	0.07	80.	0.084
Av.	73.	0.082	67.	0.072	72.	0.072	50.	0.069	72.	0.082

TABLE 6

IMMEDIATE EFFECTS FOLLOWING THYROPARATHYROIDECTOMY IN DOGS

Dog No.	Normal Values		Stage of Hyperirritability			Stage of Lessened Irritability		
	Rheobase in Volts	Chronaxie in Sigma	Time since T. P.	Rheobase in Volts	Chronaxie in Sigma	Time since T. P.	Rheobase in Volts	Chronaxie in Sigma
41	108.	0.09	240.	75.	0.068	360.	blocked	
60	130.	0.07	30.	110.	0.06	60.	135.	0.09
61	110.	0.09	60.	60.	0.07	90.	blocked	
63	60.	0.09	60.	60.	0.055			
72-A			120.	65.	0.051			
66	30.	0.084	30.	26.	0.05	90.	22.	0.12
Pups								
62	130.	0.068	30.	110.	0.06	60.	130.	0.1
64	83.	0.063				10..	83.	0.123

T. P. Thyroparathyroidectomy

TABLE 7.

THYROPARATHYROIDECTOMIZED DOGS .

Dog No.	Time Since T. P.	The Condition of the Dogs .	Bl. Ca.	Rheobase in Volts	Chronaxie in Sigma.
		Twenty five normal dogs	11.2	74.	0.082
58	7 hours	Bradycardia	11.	60.	0.06
74	5 hours	no symptons	10.8	70.	0.1
49	1 day	In muscle tremors		75.	0.066
D-3	1 day	" "		65.	0.06
21	1 day	" "		74.	0.055
68	2 days	" "	6.9	40.	0.05-
23	2 days	" "		43.	0.061
54I	4 days	" "		60.	0.061
24	4 days	" "		35.	0.068
		Group C. Average ----------		56.	0.06
67b		Tetany Convulsions	5.7	95.	0.1
27	5 days	Tetany convulsions *		35.	0.1
		Group D. Average ----------			0.1
75	3 days	6 hrs. following an attack	5.4	170.	0.09
57L	2 days	6 hrs. " " "		200.	0.12
		Group E. Average ----------		185.	0.105
56K	3 Months	Recovered, no active tetany		60.	0.055
48H	3 Months	" " " "		80.	0.084
22	13 days	" " " "		85.	0.07
55J	3 Months,10 d.	" " " "		60.	0.084
		Group G. Average ----------		71.	0.073

T. P. Thyroparathyroidectomy
* no ether was given this dog.

Interpretation of Groups in all of the Tables and Figures .

A. Normal Animals .
B. Dogs showing slight symptons .
C. Dogs in the stage of slight tremors .
D. Dogs in the stage of tetany convulsions .
E. Dogs shortly following an attack of tetany convulsions .
F. Dogs with acute marked symptons .
G. Dogs that recovered from the symptons .

TABLE 8.

DOGS RECEIVING BLOOD FROM THYROPARATHYROIDECTOMIZED DOGS.

	Normal Values.		Injections from		After 100. c.c.		After 250. c.c.	
	Rheobase in volts	Chronaxie in sigma.	Donor	Group	Rheobase in volts	Chronaxie in sigma.	Rheobase in volts	Chronaxie in sigma.
I.	170.	0.07	54 I	B	173.	0.059		
L.	100.	0.07	57 L	E	120.	0.03	210.	0.05
H.	105.	0.1	48 H	G	80.	0.084	70.	0.06

Table 9.

ETHERIZED DOGS GIVEN METHYL GUANIDIN SULPHATE.

Dog's No.	Normal Values of the Vagus Nerves		Mgms. M.G.S. per Kilogm. body weight.		The Effect upon the Vagus.		
	Rheobase	Chronaxie			Time in Minutes	Rheobase in volts	Chronaxie in sigma.
3	55.	0.09	12.	intraven.	5	30.	0.068
5	120.	0.07	6.	"	5	70.	0.08
2A	62.	0.123	6.	"	5	65.	0.06
8A	60.	0.074	15.	"	5	40.	0.066
			30.	"	10	50.	0.055
11A	28.	0.112	6.	"	5	28.	0.055
7	110.	0.068	150.	"	5	over 170.	
					20	109.	0.06
12	108.	0.07	100.	"	5	over 170.	
					20.	110.	0.055
4	130.	0.082	100.	"	5	over 270.	
1	40.	0.07	50.	"	15	37.	0.08
14A	50.	0.07	100.	"	10	130.	0.09
23A	43.	0.09	50.	subcut.	60	25.	0.056
			210.	intraven.	20	300.	0.084
13	90.	0.074	50.	subcut.	35	52.	0.06
					80	80.	0.115
17	75.	0.08	50.	"	60	50.	0.05
					120	45.	0.123
15A	70.	0.123	100.	"	90.	60.	0.058

TABLE 10

DOGS GIVEN METHYL GUANIDIN SULPHATE
FOR VARIOUS PERIODS OF TIME

Dog No.	Normal Bl.Ca.	Mgms.M.G.S. per K. injected subcut.	The Condition of the Animals.	Group	Blood Ca.	Rheobase in volts	Chronaxie in sigma
65	11.3	50.	2 hrs. = bradycardia				
			Etherised	B	11.8	58.	0.04
88	11.	90.	5 hrs. = bradycardia		11.3		
			Etherised	B	12.	70.	0.055
71	11.2	100. on 1st day					
		300. on 2nd day	Tremors, salivation		12.		
			Etherised	C	14.	40.	0.04
78	10.9	50. on 1st day			11.		
		200. on 2nd day	Tremors, difficult coordination		11.4		
			Etherised	D	11.9	58.	0.133
76	10.6	50. for two days	2nd day = bradycardia		10.6		
		250. on 3rd day	Animal was very depressed		12.		
			Etherised	D	14.	42.	0.155
69	11.	250. during two days	Tremors, dyspnoea		10.9		
		100. on 3rd day	Depressed				
			Etherised	D		60.	0.09
85	10.6	100. on 1st day			10.9		
		500. during 3 days	Tremors		11.8		
		200. on 5th day	Convulsions		12.		
			Marked Convulsion, died		14.		
70	11.4	400. during 4 days	Salivation, bradycardia				
		50. on 5th day	Slight bradycardia		11.		
		50. on 6th day	Inactive, but no symptoms		11.2		
			Etherised	C	11.7	58.	0.064
9		20. for 50 days					
		None for 40 days	Appears normal				
			Etherised	C		38.	0.113

TABLE 11.

NORMAL DOGS RECEIVING
PARATHORMONE OR CALCIUM LACTATE

Dog No.	Normal Bl.Ca.	The Condition of the Animals	Time since 1st inject.	Blood Ca.	Rheobase in volts	Chronaxie in sigma.
93		Normal Pup,(litter mate to 94,95)		11.8	110.	0.07
94	11.5	6 units,Parathormone	12. hrs.	16.5	70.	0.07
		Twenty five Normals		11.2	74.	0.082
91	10.5	8 units,Parathormone	16. Hrs.	14.3	115.	0.08
80	11.3	Given Calcium Lactate	2. days	18.3	75.	0.07
92	10.	" " "	2. days	18.7	60.	0.09
		100. mgms. intraven.	30 minutes		110.	0.074
93		Normal			110.	0.07
		200. mgms. intraven.	30 minutes		70.	0.084

TABLE 12.

DOGS GIVEN SODIUM OXALATE
INTRAVENOUSLY

Dog No.	Normal Bl. Ca	The Condition of the Animals-Mgms.injected	Blood Ca. 1 d.	Blood Ca. 2 d.	After ether *	Rheobase in volts	Chronaxie in sigma.
101	10.3	6. Na.Ox. during 40 hrs	10.6	10.2	12.5	40.	0.078
		33. Ca.Lact. intravena			15.2	83.	0.115
						95.	0.07
104	10.8	170. Na.Ox.during 3 days	9.3				
		Dog is sick - vomited		6.7	7.3	40.	0.055
		Calcium Lact.intraven.			11.	80..	0.074
102	10.8	120 Na. Ox. with meals	9.2				
		100 Na. Ox.inj. intraven.		8.			
		Salivation, Convulsion.			5.7	55.	0.055
81	12.6	Pup.				68.	0.074
		30. Na. Ox.			8.3	80.	0.115
		100. Ca. Lactate			16.5	50.	0.06
		80. Ca. Lactate			21.	56.	0.074
99		----------				50.	0.074
		40. Na. Ox. ----------				40.	0.09
		thirty minutes later ----------				92.	0.061

* This column of blood calciums were determined on the dogs, when the animals were anesthetized .

TABLE 13.

THYROPARATHYROIDECTOMIZED DOGS
RECEIVING CALCIUM LACTATE.

Dog No.	Normal Bl.Ca.	Blood Calciums at Intervals after the Removal of Paras. 1hr.	3hrs	6hrs	½day	1day	2nd.	3rd.	4th.	5th	6th	7th	8th.	Values under Ether. Bl.Ca.	Rheobase	Chronaxie
86	12.	-	13.7	-	-	9. *	7.9	9.	9.7	9.2				12.7	40.	0.086
														# 14.5	48.	0.084
96	13.	-	-	-	-	-	11.4 *	8.6	11.5					11.5	70.	0.09
95	11.8	-	-	-	-	-	8.5 *	10.	-	-	7.6	8.	7.5	7.5	60.	0.09-
														✚ 5.5	120.	0.08
84	10.5	11.	11.4	10.8	11.6	10.6	7.9	5.4 *	8.	9.2	9.	8.	8.3	9.5	50.	0.067
														# 12.5	70.	0.04
105	12.	-	11.1	11.3	-	6.8 *	7.5	7.8	9.					8.2	40.	0.059
83	12.1	11.3	11.	12.8	-	11.	8.5	6. *	5.3	-				9.5	70.	0.04
														# 15.	65.	0.03
106	11.	11.9	10.8	9.4	-	7.8	6.7 *	6.6	7.8	-	-	7.4		# 10.7	over 300.	
														# 15.	160.	0.04
														# 23.	115.	0.115
22	---------- 13 days after thyroparathyroidectomy ----------														80.	0.07
	7. mgms. Calcium Lactate per K. intravenously -													#	90.	0.09
63	---------- Normal ----------														60.	0.09
	2. hours after thyroparathyroidectomy ----------														60.	0.05
	20. mgms. Calcium Lactate per K. intravenously													#	40.	0.09

* Calcium Therapy Started .
\# Calcium Lactate Injected 15 to 30 minutes previous to Readings .
✚ Sodium Oxalate injected intravenously .

TABLE 14.

THE EFFECT OF CALCIUM LACTATE
ON DOGS GIVEN METHYL GUANIDIN SULPHATE.

Time	Mgms. injected per Kilogm. body Wt.	Time	Mgms. El. Ca.	Rheobase in volts	Chronaxie in sigma.
Dog # 15A. Hound, Male, Wt. 16 K., Group B.					
		0:00	10.8		
0:00	Etherized	0:50	12.2	70.	0.123
0:55	100. M.G.S. Subcut.	3:10	12.	60.	0.058
3:20	75. Ca. Lact. intraven.	3:50	22.2	70.	0.09
4:10	15. M.G.S. Intraven.	4:30	17.2	80.	0.06
		6:00	16.	100.	0.06
6:10	250. Ca. Lact. Intraven.	6:40	36.	120.	0.07
# 65. Collie, Female, Wt. 9. K., Group B.					
0:00	50. M.G.S. Subcut.				
1:30	Etherized	2:00	11.8	38.	0.04
2:20	25. Ca. Lact. Intraven.			45.	0.055
		2:30		43.	0.064
		2:40	14.2	50.	0.084
3:00	50. Ca. Lact. intraven.	3:15		33.	0.085
		3:40		40.	0.084
# 71. Male Dog, Wt. 14 K., Group C.					
		0:00	11.2		
2 Days	410. M.G.S. Subcut.				
0:00	Etherized	0:10	14.	40.	0.04
0:15	57. Ca. Lact. intraven.	0:30		40.	0.05-
0:35	57. " " "	0:55		40.	0.06-
*0:65	15. M.G.S. intraven.	1:25		30.	0.04
1:40	100. Ca. Lact. "	1:55		37.	0.07
2:00 } 4:00 }	470. " " "	4:10		30.	0.07
# 78. Small Spitz, Female, Wt. 5. K. Group D.					
		0:00	10.9		
2 Days	290. M.G.S. Subcut.				
0:00	Etherized	0:10	11.9	38.	0.123
0:15	30. Ca. Lact. intraven.	0:25		35.	0.123
0:30	30. " " "	0:35		28.	0.115
0:40	250. " " "	1:20		40.	0.14
*1:30					

Table continued on next page .

TABLE 14.

Continued.

Time	Mgms. injected per Kilogm. body wt.	Time	Mgms. Bl. Ca	Rheobase Chronaxie in volts in sigma.	
# 76. Spitz, Male, Wt. 11.3 K., Group D.				10.6	
3 days	350. M.G.S. subcut.				
0:00	Etherized	0:10	14.	42.	0.155
0:20	90. Ca. Lact. intraven.	0:30		55.	0.266
0:40	50. " " "	0:50		65.	0.185
0:55	180. " " "	1:00		60.	0.266
1:05	180. " " "	1:10		87.	0.185
1:20	300. " " "	1:40		90.	0.09

* Marked bradycardia occurred at these times .

TABLE 15.

THE RESULTS OF BUCHANAN AND GARVEN (4), INTERPRETED.

Dates	Interpreted Condition of somatic nerves.	Rheobase in volts	Chronaxie in sigma.	Injections gms. per K.
	Cat # 12 Deep Flexors.			
	The Normal Average		0.24	
3/ 2/25	Preceding the Injections	14.	0.22	.05 di-m.g.cl.
3/ 3/25	Slightly inc. irritable	18.	0.15	.5 di-m.g.cl.
	Marked inc. irritability	15.	0.11	
	Difficult conduction(blocked incompletely)	30.	0.26	
	Returning hyper irritability	14.	0.19	
3/ 4/25	Increased irritability	23.	0.14	(average)
	Cat # 8 Deep Flexors.			
	The normal average		0.17	
2/ 5/25		50.	0.13	.06 guan. cl.
2/ 6/25	Recovered	50.	0.26	.1 " "
	Gradual increase of irrit.	36.	0.22	
2/7/25	" " " "	55.	0.15	
2/ 9/25		31.	0.07	.1 " "
	Dec. irrit. developing	39.	0.15	
2/10/25		40.	0.26	.2 " "
		30.	0.28	(average)
	Returning hyper irrit.	30.	0.15	

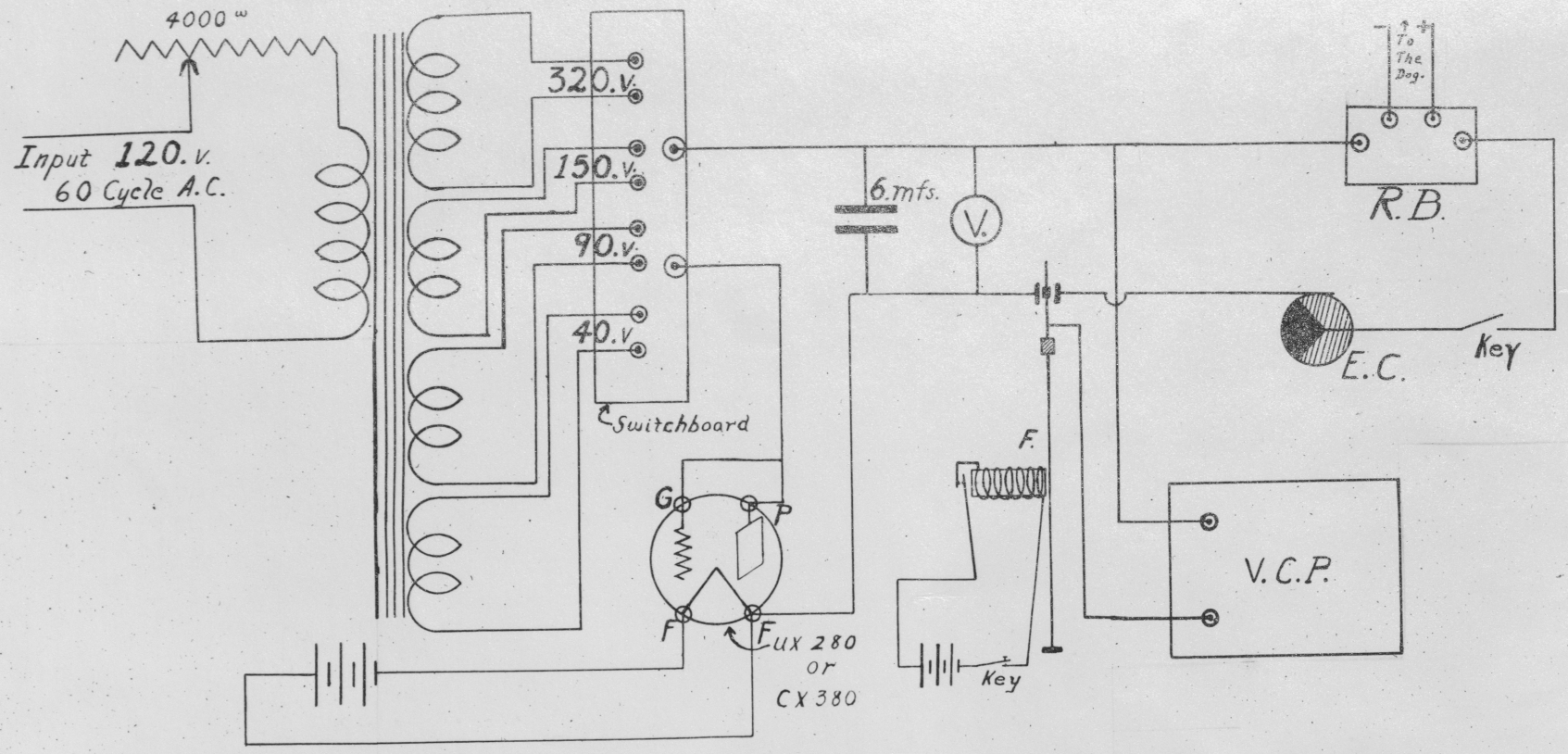


DIAGRAM I. Diagram of the circuit of the apparatus.

F - Vibrating Fork. R. B. - Resistance Box (Lapicque)

V. C. B. - Variable Condenser Jack

E. C. - Electrical Contact Clock

Code of Figure 1.

Groups.

1.A. Twenty five normal adult dogs .

1. Seventeen thyroparathyroidectomized adult dogs .
   B. Two dogs showing the immediate effect .
   C. Seven dogs in the stage of muscle tremors .
   D. Two dogs in the stage of tetany convulsions .
   E. Two dogs in the stage six hours following a convulsion .
   G. Four dogs in which convulsions did not occur .

2. Three dogs injected intravenously with 6. to 170. mgms. per K. of sodium oxalate for 2 to 3 days.
   B. One dog with the effect of a small quanity .
   C. Two dogs in the stage of muscle tremors .

3. Eight adult dogs injected subcutaneously with 50. to 800. mgms. per K. of methyl guanidin sulphate during 1 to 4 days .
   C. Three dogs in the stage of muscle tremors .
   D. Five dogs in the stage of tetany convulsions .
   G. One dog in which convulsions did not occur .

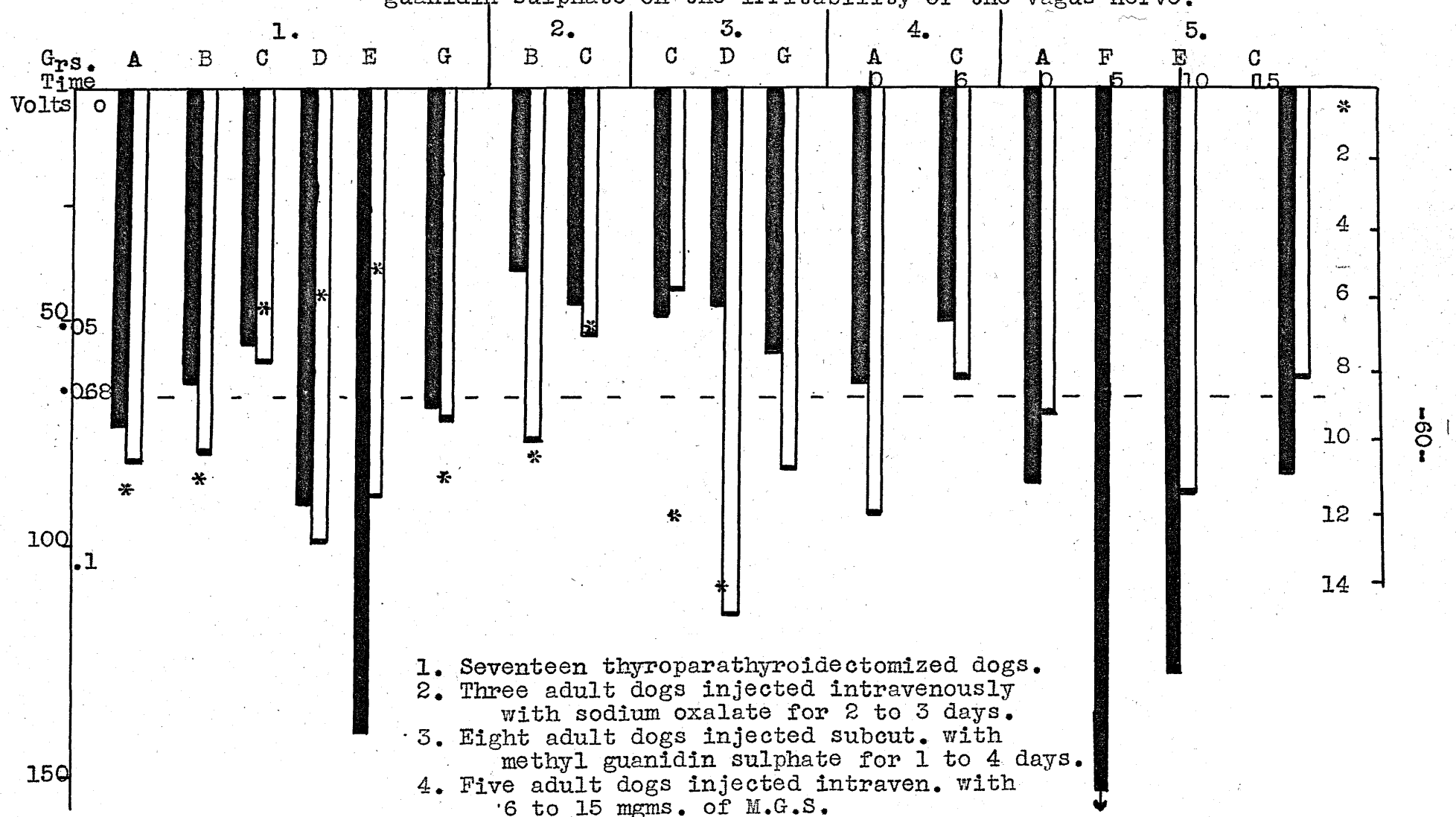
4. Five adult dogs injected intravenously with 6. to 15. mgms. per K. of M. G. S. during anesthesia.
   A. Five normal adult dogs.
   C. Five dogs in the stage of muscle tremors .

5. Five adult dogs injected intravenously with 50. to 150. mgms. per K. of M. G. S. during the anestesia .
   A. The normal values of these five dogs.
   F. Following the acute administration of a large amount of methyl guanidin sulphate.
   E. The same animals 5 minutes later.
   C. The same animals after an additional 5 minutes .

Ordinates ; dark columns = rheobase in volts .
light columns = chronaxie in sigma .
* = blood calcium in mgms. per cent .

Abscissa ; Animals in groups .
Time in minutes .

Figure 1. The influence of parathyroidectomy and methyl guanidin sulphate on the irritability of the vagus nerve.

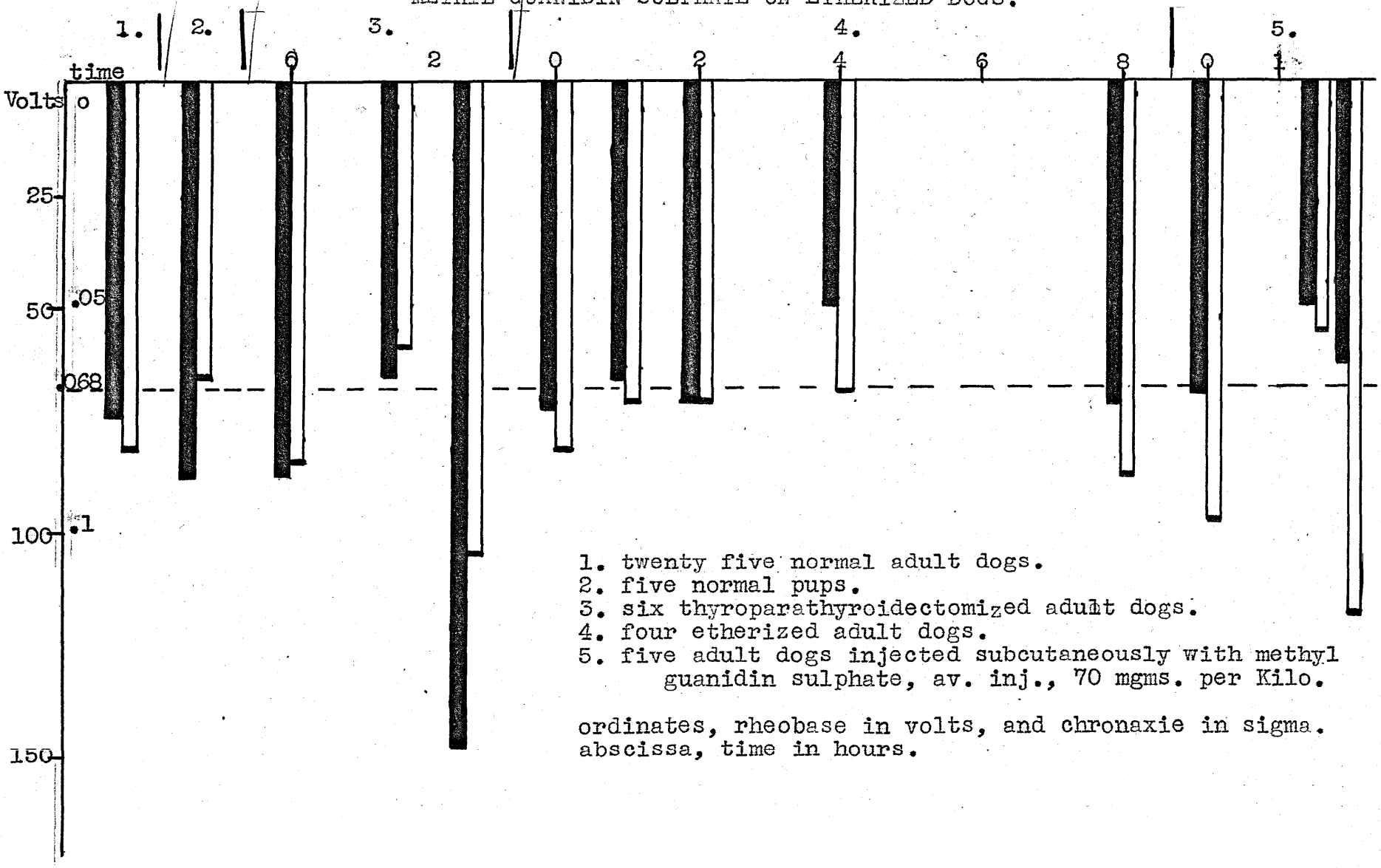


1. Seventeen thyroparathyroidectomized dogs.
2. Three adult dogs injected intravenously with sodium oxalate for 2 to 3 days.
3. Eight adult dogs injected subcut. with methyl guanidin sulphate for 1 to 4 days.
4. Five adult dogs injected intraven. with 6 to 15 mgms. of M.G.S.
5. Five adult dogs injected intravenously with 50 to 150 mgms. of M.G.S.

Code - see page 59.

FIGURE 2

THE EFFECT OF PARATHYROIDECTOMY AND METHYL GUANIDIN SULPHATE ON ETHERIZED DOGS.



1. twenty five normal adult dogs.
2. five normal pups.
3. six thyroparathyroidectomized adult dogs.
4. four etherized adult dogs.
5. five adult dogs injected subcutaneously with methyl guanidin sulphate, av. inj., 70 mgms. per Kilo.

ordinates, rheobase in volts, and chronaxie in sigma.
abscissa, time in hours.

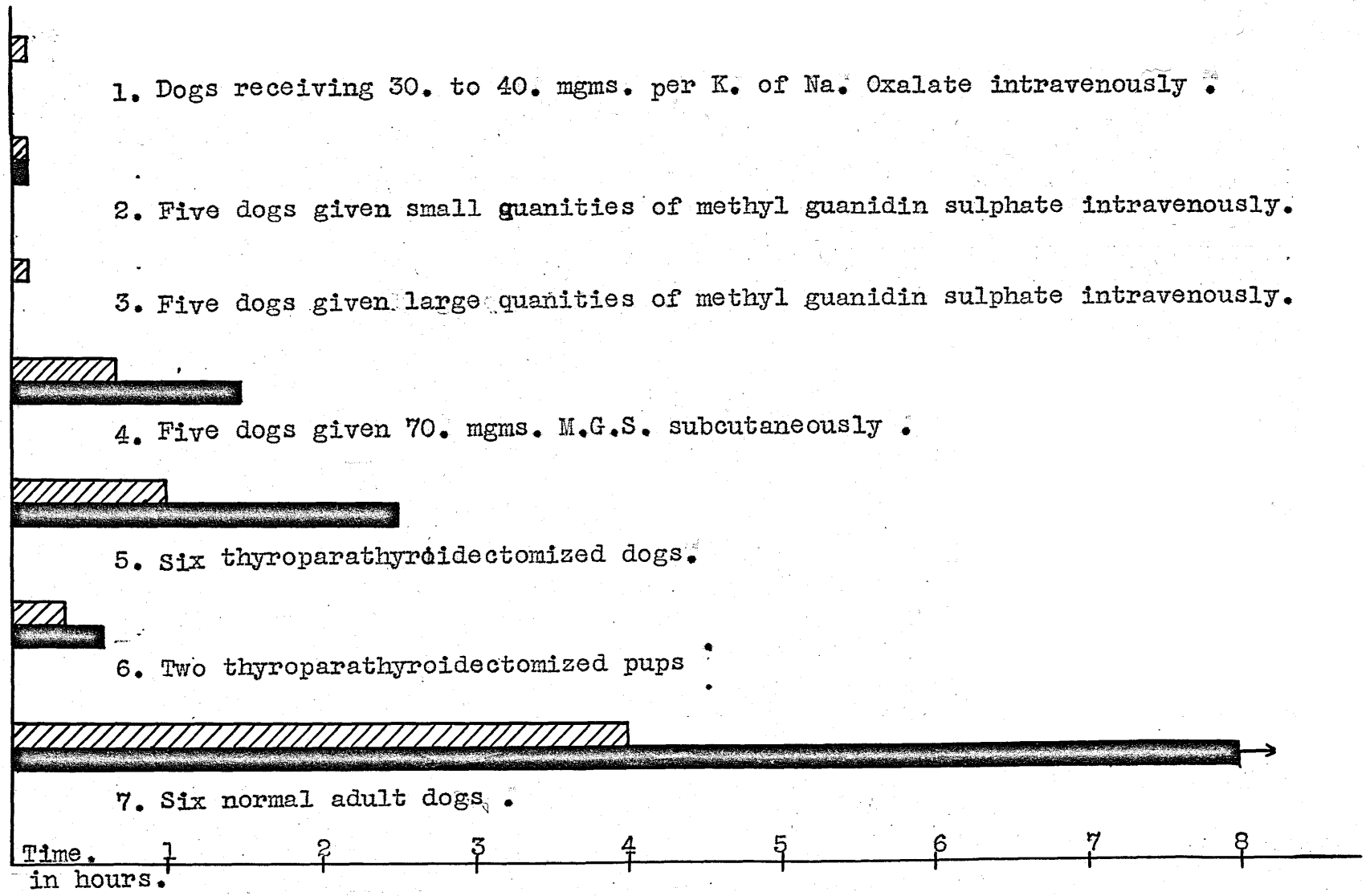


Figure 3. The effects of sodium oxalate, methyl guanidin sulphate, and the removal of the parathyroids on the irritability of the vagus nerves in etherized dogs.

Shaded columns = the time in which hyper-irritability developed.
Solid columns, the time in which decreased irritability developed.

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