SOME STUDIES ON BLOOD MINERALS IN
PARATHYROIDECTOMISED DOGS

by

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SOME STUDIES ON BLOOD MINERALS IN
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Symptoms Following Removal of the Parathyroids

The symptoms following parathyroidectomy as observed by various investigators have been reviewed by Simpson (1) in his review. Apparently one of the outstanding characteristics is their variability. Although tetany may be the most striking symptom there may be cases in which it is not present at all; and when it is present it may vary from slight muscular tremors to general violent convulsions. Aside from actual tetany, however, the animals suffer other derangements. They are always more or less depressed; do not undertake much activity and do not manifest the usual interest in their surroundings. It seems that these symptoms have received less attention than the more outstanding one of tetany. However that may be, some workers have called attention to the fact that parathyroidectomised animals show other symptoms even though tetany does not develop. Cooke (2) emphasizes the fact that apparently there are two distinct phenomena: first, a metabolic disturbance resulting from the absence of a parathyroid secretion; and second, tetany which follows and is probably caused in some manner by the primary derangement. Just what this metabolic disturbance involves is not made clear in this work, but there is considerable
evidence elsewhere to show that it includes more than changes in the neuromuscular mechanism such as would be necessary in the production of tetany.

Carlson and Jacobson (3) show that gastrointestinal changes are present in parathyroidectomised dogs. These changes are both organic and functional. Anorexia, vomiting, diarrhea (usually), hyperemia, hemorrhages and ulcers of the pyloric and duodenal mucosa are present. These investigators state that hyperexcitability of the peripheral nerves is usually but not always shown. Carlson has produced evidence elsewhere to show that the digestive tract is paralyzed during tetany attacks.

Luckhardt (4) Dragstedt (5) and others working in Carlsons laboratory have brought out evidence showing increased permeability of the intestinal wall after parathyroidectomy.

Blumenstock and Ickstadt (6) have done some preliminary work which suggests that there may be changes in the liver. Their results indicate that the liver probably does not play its supposed role of detoxication. There is a delay and diminution of symptoms following Eck fistual in dogs. Of course this does not in any way prove that the operation has produced this effect. Stoland (7), on the other hand, produces evidence that the liver is probably not directly effected by removal of the parathyroids—at least not so far
secretion is concerned.

The symptom of tetany which indicates involvement of the neuromuscular system is sometimes not present. If present it may vary all the way from mere hyperexcitability of the peripheral nerves—with no actual muscular twitchings showing—to frank tetany. Sometimes this is restricted to localized muscles or muscle groups and sometimes is general and violent in nature. The appearance of these conditions is to well known to need any special description. MacCallum and Vogel (8) indicate that the condition of increased electrical excitability may be present in the muscle, peripheral nerves, cells of the spinal cord and brain. Similar conclusions have been reached by Luckhardt, Sherman and Serbin (9) and by Paton, Findlay and Watson (10). All of these report that clonic twitchings and tremors may be produced independent of the spinal reflex arc. Tonic changes, however, are dependent upon the integrity of the cerebellar arc. All of the tetany symptoms may be increased by decerebration since this removes the inhibiting effect of the cerebral arc.

Perhaps the derangements in the digestive canal are caused by bad function of the autonomic nervous system. The condition of depression and paralysis spoken of by Carlson (11), (12) is attributed by him to depression of the sympathetic system. Keeton (13) also attributes the depression in
quantity and activity of gastric juice to the same effect. Hoskins and Wheelan (14), however, interpret Carsons and Kecton's data differently and present some work of their own to support their contention that there occurs an increased sympathetic irritability after parathyroidectomy. Their findings show an increase vasomotor irritability as demonstrated by the increased reaction to nicotine, epinephrin and pituitrin, in dogs following parathyroid removal.

The literature abundantly testifies to the fact that tetany following parathyroidectomy is only a symptom which may or may not be present, and that the animals are otherwise suffering from severe derangements. It may be that all the symptoms are manifestations of one fundamental derangement. The evidence at present is not sufficient to make a positive statement possible.
5.

Treatment and Recovery

Earlier workers in the field thought that the parathyroids were essential to life. Later workers, however, have been successful, in some animals at least, in removing the bodies without causing death. Simpson (1) gives a very good summary of this work. Aside from this phase it has been shown by several investigators that the animals can be kept in good condition by certain therapeutic measures. This work gives some insight into the cause of the symptoms. It has been testified to by many that it is easier to prevent the symptoms than to cure them once they have started.

Dragstedt (15), (16) and Dragstedt and Peacock (5') have been able to keep dogs alive for quite long periods of time by producing an acid uric flora in the intestine, through dietary control. After about six weeks of such a treatment the regular stock diet has been substituted without producing tetany. In some cases at least these animals appeared to be in a more or less unstable condition for tetany symptoms might be induced by feeding large amounts of meat—especially if somewhat spoiled meat—by occurrence of rut, exercise excessively, excitement or infection. This (18) was interpreted as showing that the parathyroids were not essential to life and that perhaps some other organ takes over their function when they are removed. The liver was thought to be the most probable organ because parathyroid-
ectomised dogs which had been treated may be thrown into
tetany by poisoning with phosphorus. Blumenstock and
Ickstadt (6) recent work, however, throw some doubt on this
conception of liver function. Other suggestions (19) have
been that perhaps small remnants of parathyroid tissue might
hypertrophy or that the tissue might develop a certain im-
munity to any tetany “toxin” which might exist.

Recently Dragstedt (19) has been able to maintain life
in dogs for over two months by the oral administration of
kaolin. This material is thought to check bacterial pro-
teolysis in the intestines and perhaps combine with some of
the toxic products of bacterial growth there.

Maccallum and Vogel (9) and Voegtlin and Maccallum (21)
did some work which shows that perfusion of an isolated limb
or injection into the blood stream of solutions of certain
salts stopped tetany symptoms. Those salts were calcium,
strontium and magnesia salts. All proved effective, but not
equally so. This was true whether bleeding occurred before
injection or not. If bleeding alone occurred, however,
it has been shown to be beneficial in alleviating tetany.
The above authors attribute the beneficial effects of salt
injection to the profuse diuresis occurring, and the conse-
quently washing out of toxic substances. Lackhardt and Rosen-
bloom (20) have also demonstrated this with Ringer’s solution,
both with and without calcium. The removal of toxic sub-
stance has also been claimed as an effect of bleeding. It
might well be, however, that the effects produced are brought about by changing the condition of the nutrition of the nerves or the washing out of phosphate (22).

Carlson and Jacobson (3) discovered that parathyroid symptoms are suppressed, except in extreme cases, by injection of extracts of hypophysis, hypertonic sugar solution, amyl nitrite and by section or section and stimulation of afferent fibres of the vagi. No suggestions were made as to how these might work.

It has been known for some time that the injection into the blood stream or administration by mouth of various calcium salts prevents tetany or will stop it after it has started. MacCallum and his co-workers in the work quoted above were the first to discover and apply this in tetany though the sedative effects of calcium have been known for some time. Since their work however their results have been confirmed by many others. The most effective way of administering the calcium is by intravenous injection. Some salts, of course, are toxic when given in this manner. However, the treatment is just as certain when given by mouth, but is somewhat slower. The salt usually used is calcium lactate. Other salts have been used but have proven less satisfactory. Quite recently Ogle (23) reported the case of parathyroid tetany in a woman after removal of the thyroids. This patient had been under observation for
twenty months after the operation and had received calcium lactate by both intravenous and oral administration with satisfactory results. Dietary control also had been employed, but apparently it had not played as great a part as calcium administration.

It is natural that efforts to control parathyroid tetany by gland transplant should have been made. No great amount of success has followed the work, however, and owing to the difficulty of obtaining fresh glands and of distinguishing them from other tissues as well as the great probability that the transplant will not grow does not make this method a very certain form of treatment. Barker (24) has reviewed the literature on this subject.

MacCallum and Vogel (8) reported that extracts made from parathyroid glands had very little effect on the isolated limbs of an animal or on the entire animal when measured by the decrease in hyperexcitability of the peripheral nerves. They recall the beneficial results on suppression of tetany symptom of injection of such extracts in both men and animals. Recently Collip (25), (26) has been able to prepare an extract of the parathyroid glands which upon subcutaneous injection in appropriate doses will keep parathyroidectomised dogs in excellent condition for long periods of time.
9.

With all the methods of treatment there is apparent a greater or less tendency of the animals to readjust themselves in some way so that they are often able to survive for certain periods of time with either less attention than at first or in some cases with suspension of the treatment entirely. Just what this readjustment is we have not sufficient data to say. Suggestions have been made that perhaps small remnants of parathyroid tissue remain and hypertrophy or that some other organ takes over the function. There are those who claim (27) that if the removal of the parathyroids be complete life is impossible. However it seems that it has been fairly well demonstrated in some species at least that such is not the case.
Theories of Cause of Parathyroid Symptoms

As stated before it has been quite generally conceded that the parathyroids are not essential to life. If these bodies secrete a substance which is used in body activities it is apparently not essential—or if essential may be obtained from other tissues as well. Just what the fundamental derangements are which supervene when the parathyroids are removed is not known definitely at the present time. There are, however, several theories which seek to explain the resulting symptoms. There can be found evidence to support all of these.

It has been shown by MacCallum and Vogel (8) that the electric hyperexcitability of the nerves of an animal in tetany may be alternately raised and lowered by alternately perfusing with blood from tetany and from normal animals respectively. Whether or not the other symptoms are alleviated is not stated. Of course this does not mean that the primary cause is or is not in the blood but it does indicate that something eventually happens to the blood which brings about the characteristic changes.

The Toxin Theory.

One of the earliest explanations offered for the cause of parathyroid symptoms is that there is present in the body some sort of toxin which produces them. This theory is still held by some workers. By some the toxic substance is held
to result from metabolic processes which are normally either not present or if present the results of which are neutralized by the parathyroids or by other organs with the help of the parathyroids. Others, however, consider that the toxins gain entrance to the body, chiefly from the intestinal canal, with greater ease in the absence of the glands—or perhaps are not neutralized in their absence. The toxin theory, to start with, is supported by ordinary observation. The depression and tetany gives the appearance of animals suffering some toxic disturbance. The results of bleeding and of diuresis produced by injecting large amounts of salt solutions referred to before are easily explained as phenomena following the resulting dilution or washing out of toxic substances. When an effort is made to identify or to isolate the offending substance many difficulties appear. To date it is safe to say that no toxic substance has been found which is likely to be responsible for the trouble.

Ammonia is one material which is certainly toxic if present in sufficient concentration and which might account for the symptoms. Carlson and Jacobson (3) find however that the ammonia content of the blood of parathyroidectomised dogs does not exceed that of normal animals. Other workers have since confirmed this report. Moreover these two investigators report that dogs suffering ammonia tetany are not relieved by calcium treatment as easily as those in
parathyroid tetany. They also mention other differences, between the two.

The results of many workers testify that ammonia excretion in the urine is increased after tetany begins \(23\) \(29\) \(30\). This is likely the result of an attempt by the body to counteract the resulting acidosis. On the whole the evidence for ammonia as a toxic substance responsible for conditions in parathyroidectomised dogs is not convincing. Such a view is not generally held at the present time.

The various guanidines are perhaps accepted the most widely as the toxic substances in parathyroid tetany. Koch \(31\) \(32\) seems to have been the first to find these substances in the urine of parathyroidectomised dogs. This author claims that methylguanidine as well as some other toxic bases are much increased after tetany. Since this work Noël Paton and his associates have been the main exponents of this idea. His review \(27\) gives a good summary of the evidence. Their contentions are based mainly on the fact that bleeding and transfusing with calcium free solutions relieves the symptoms and they claim that the only way that this would be possible is by washing out the toxin by diuresis. Loeb \(33\) however, has demonstrated that sodium chloride may act like calcium chloride by changing the permeability of the membranes and thus altering the dif-
fusion of the ions. However, if there is actually an increase in guanidine in the urine following parathyroidectomy that would constitute strong evidence in support of the theory.

Paton and his collaborators claim to have confirmed Koch's original findings. They admit that their methods of estimating guanidine is perhaps faulty. Greenwald (34) criticizes these methods and shows that by using the reagents that are used creatin, which is admittedly increased, is changed into guanidine. Using a procedure which is not open to these criticisms Greenwald was unable to detect any guanidine in normal urine or that from tetany animals, although he was able to detect added guanidine provided the nitrogen constitutes as much as .5 per cent of the total nitrogen. This author also calls attention to an experiment of Burns in which .64 gms. of guanidine hydrochloride was injected into a dog without causing tetany although some 2.2 mg. of methyl guanidine and 3.7 mg. guanidine per kilogram body weight was recovered from the urine within the following twenty-four hours. Ordinarily tetany dogs are said to excrete only .3 to 1.5 mg. guanidine per kilogram body weight. It seems as though this dog excreting three or four times as much should at least have shown tetany symptoms.

It is also interesting to note that those supporting this theory do not agree themselves as to the offending
material. Koch found chiefly methyl guanidine; Burns and Sharpe find chiefly guanidine; while Findley and Sharpe find chiefly dimethyl guanidine. Watanabe (37) states that the calcium phosphorus ratio of the blood is decreased in almost all cases of guanidine tetany although the decrease of calcium in parathyroid tetany is not constant. From this he concludes that the true cause of tetany is increased guanidine content.

In an effort to discover if there is a toxic substance in the blood Greenwald (22) made extracts of large amounts of tetany blood and injected them into dogs which had suffered parathyroidectomy the previous day. In each case the volume of blood used was sufficient to equal about twice the volume in the test animal. Results were negative although the usual tetany developed twelve to thirty-six hours later. The author concludes if there is a toxin in the blood it must be either volatile, insoluble in 80% alcohol or extremely unstable.

Peton claims that the effects of guanidines are cumulative. This might seem to indicate that the result of administration of one large dose of guanidine might be different from the repeated injection of smaller doses. If this is true it is a little difficult to see how symptoms could supervene so quickly after removal of the parathyroids (12 to 24 hours) nor why the injection of guanidine into parathyroidectomised animals which had been kept alive by
treatment for sometime does not produce typical tetany. Eaton's claim that the guanidines produce symptoms very similar to those of parathyroid tetany is not supported by many other observers (36).

There seems to be no doubt that the excretion of nitrogen is increased after parathyroidectomy (28) (29) (30). As to what makes up the total of this increase is not clear. Ammonia appears to be increased after tetany occurs. This is thought to be due to an effort to neutralize the increased formation of acids due to the increased activity of tetany. Ammonia has been found not to be increased in the blood. Creatin excretion is said by some to be very much increased. Eaton considers that the evidence points to an endogenous origin of the toxins although he admits that some precursor may be absorbed from the intestine. The work of Dragstedt, Phillip and Sudan (39) show that conditions which increase metabolism also tend to produce tetany. Shanks (38) thinks that cholin may be the source of the offending guanidines.

Dragstedt, Luckhardt and their collaborators think that the toxins have origin in the intestinal tract through bacterial action. The evidence favoring this conception is that if an aciduric flora of the intestine be produced tetany does not result. If has been shown, however, that in a condition of acidosis tetany is not likely to occur even though the conditions be otherwise favorable, and it seems
probable that a certain degree of acidosis might be induced in this manner.

It does not appear that the resulting changes in metabolism can be of such a nature as to effect the basal metabolic rate. Some results from our laboratory indicate that this does not change after parathyroidectomy except, of course, during actual tetany. Changes which might involve derangements in the utilization of oxygen or production of carbon dioxide are probably not present.

The Calcium and Balanced Salt Theories

As we have seen efforts to demonstrate the existence of a toxic substance in the body responsible for the symptoms following parathyroid removal has not been successful. What other changes occur in the blood which might play a part in these derangements?

Vogtlin and MacCallum (21) show that there is a marked reduction in the calcium content of the blood in tetany. This result has been verified by practically every other investigator. Earlier work by Sabbatani and Quest had shown that the calcium content of the brain affected its activity and that patients dying in tetany showed the brain distinctly low in calcium. Certain other workers have not been able to confirm these findings (37). As a result of his work on elimination of calcium and magnesium after parathyroidectomy Cooke (2) concludes
that tetany is the result of an altered salt equilibrium in the nerve cells and states that the changes in calcium and magnesium precede the onset of tetany. Salvesen (40) states that the blood calcium might be lower than normal and tetany not occur but that when tetany did occur the blood calcium was always reduced to a lower level. This result agrees partly with the findings of Anderson and Graham (41) who claims that in infantile tetany the symptoms may disappear without the blood calcium regaining its normal point, but that tetany never occurs unless the calcium be low. Collip (26) has demonstrated this in parathyroid tetany.

There is some evidence to indicate that the blood calcium may be held in some kind of form that renders it unavailable for body use. This point will be discussed later. A part of it at least seems to be excreted. Voogtlin and MacCallum (21) Cooke (2) and Salvesen (40) all find and increased elimination in some cases in both the urine and feces in parathyroid tetany.

As stated before calcium administration either by mouth or intravenously is one of the certain ways of alleviating the symptoms of parathyroid tetany. This is testified to by every worker in the field. Animals have been kept for long periods of time without showing tetany or the other parathyroid symptoms by administering calcium. They also quickly recover if calcium be injected intra-
venously or subcutaneously during tetany. The blood calcium rises after treatment by calcium but does not remain high long—there being a rather rapid loss (40) making necessary repeated treatments. Calcium salts given by mouth must be administered in larger doses than if given intravenously because of the slow absorption. In fact it may not be absorbed at all—the beneficial consequences being due to the acid radical being absorbed and producing a degree of acidosis.

Results of this kind led MacCallum and Voegtlin to postulate their calcium theory. According to it the removal of the parathyroids in some manner brings about a drop in the blood calcium which renders the nerves hyperexcitable and this produces the symptoms. The results of recent investigation tends to show that the lowered calcium level is not the direct result of the removal of the parathyroid glands but that other conditions supervene which not only play a part in lowering the calcium level but may also contribute in producing the symptoms. It is fairly certain however that the lowered calcium is one of the primary causes, since it is always present. How and to what extent other factors modify the picture is at present not clear.

Sabbatani in his early work observed that substances which precipitated calcium caused convulsions when applied to the brain in sufficient concentration. MacCallum and
Vogel (8) found slow injection of oxalate-like substances caused the excitability of nerves to rise to high levels presumably by removing the calcium. MacCullum, Lambert and Vogel (35) were able to produce extreme hyperexcitability of the nerves by perfusing an isolated extremity with blood that had been dialyzed against a calcium-free solution. If dialyzed against a solution containing calcium equivalent to that found in normal blood no hyperexcitability resulted. They also state that this applies to animals in tetany as well as to isolated extremities.

Collip (25) (26) says that the striking result of the injection of the parathyroid hormone which he extracted is that it raises the level of blood calcium even in dogs not suffering from tetany to extremely high figures.

All the foregoing results are sufficient to show the importance of the calcium level in the body economy. It is certain, however, that other factors play a part.

Work by Loeb (17) (42) (43) and of Mines (44) brings out the important facts that in tissues in general but particularly in muscle and nerve the equilibrium of excitability is controlled not by the presence or absence of certain mineral constituents but by the balance maintained among all of them. Loeb shows that if muscle be immersed in pure isotonic sodium chloride it will begin to twitch rhythmically but if a small amount of calcium chloride be
added these twitches will stop. The poisonous effect of sodium ion may also be counteracted by potassium. What is true regarding antagonism between these salts is also true for various other salts. Solutions of lithium, rubidium and caesium chlorides produce twitchings which are inhibited by small amounts of calcium, magnesium and strontium. The addition of barium makes the twitchings more pronounced.

Garry (45) has discovered that frogs muscle exhibits twitches when immersed in solutions of sodium oxalate, phosphate, carbonate, sulphate, and fluoride as well as when the solutions injected into the circulation. All of these precipitate calcium and the effect of all are counteracted by administration of calcium. They act after destruction of the central nervous system, after section of motor nerves and after injection of curare as well as after nerve fibers and motor end plates have degenerated. In general the same results were obtained on mammalian muscles. Mines, quoted above, has investigated the effect of potassium and calcium chlorides on muscular excitability. He finds that the effect of potassium varies with the concentration causing first an increase in excitability and secondarily its decrease and final abolition. Restoration may be accomplished by use of sodium. Calcium distinctly increased the excitability of muscle if previously
immersed in sodium for only short time— if the time left in sodium is longer calcium generally caused a fall in excitability.

These results all emphasize the statement made by Loeb that the important thing is not the presence or absence of certain constituents but the balance obtained among all of them. In some earlier work (17) he considered that these ions had their effects because of ion protein compounds which they formed with the muscle elements. There is other evidence to indicate that such compounds are formed, however, this is probably not the only effect. Later work by the same author (43) brings forth evidence to show that ions produce also an effect on cell permeability—the concentration of one ion or group of ions changing the permeability of cell membranes for ions which are antagonistic in action. It was shown that the ratio of concentration of sodium, necessary to keep the antagonistic action of the two constant is not the same for the phenomena of permeability as for irritability. Indications are that the ratio concentration of sodium plus potassium concentration of calcium plus magnesium remains very nearly constant. This relation corresponds to Weber's law. The variation of calcium or of calcium and magnesium required to antagonize various concentrations of sodium chloride or of sodium chloride plus potassium chloride in cases of permeability is in direct proportion, while in cases of irritability the concentration of calcium
varied approximately with the square of the concentration of sodium chloride. More recent work by Loeb (33) presents some more evidence of the same character. In this work he shows how sodium chloride may act in the same way as calcium chloride in altering the permeability of the cell wall--his view being that sodium and calcium in certain concentrations cannot diffuse into the cell because each one renders the wall impermeable to the other. This fact may easily explain certain beneficial effects of injection of sodium chloride solution into parathyroidectomised dogs.

When we seek for evidence to support application of conceptions of this kind to parathyroid tetany we find some in a general way but the actual mechanism is not entirely clear. Cooke, as indicated before, thinks since magnesium excretion in the urine is increased as well as that of calcium after parathyroidectomy that a disturbance of inorganic equilibrium is indicated. Some workers, especially Greenwald (46) (47) have noted a retention of phosphates with no retention of sodium or potassium preceding. In one dog the excretion of sodium and potassium was decreased the day of the operation in three others the day following. These facts would indicate a change in the calcium magnesium: sodium potassium ratio spoken of by Loeb. If the phosphates are retained as dibasic phosphates it might explain in part at least the alkalosis spoken of by some. Greenwald says the greater part of the increase is in a fraction not soluble in the usual lipid solvents.
but soluble in a mixture of dilute hydrochloric acid, acetic or picric acids. If the phosphates are dibasic after tetany occurs and the consequent production of acid substances occurs which Cooke (29) and others speak of we would expect to get an increased elimination of phosphorus in the urine. This Greenwald (28) finds to be the case.

Gross and Underhill (49) in some studies on parathyroidectomy dogs carried on in the light of Loeb's work state that if the ratio monovalent ions reaches 40 or above the divalent animals always show convulsive tetany, if the ratio potassium reaches 10 or above tetany accompanies.

There are reasons for believing that the question of acidosis and alkalosis plays a part in producing and alleviating the symptoms of tetany.

Anderson and Graham (41) state that in cases of infantile tetany whenever tetany did not occur with a lowered calcium acidosis was always present. In such cases they were able to bring on tetany by alkali administration but were not able to so produce it in normal patients. Van Slyke's method of determining alkalosis was used. Wilson, Stearns and Murrill (49) and Wilson, Stearns, and Jaminey (30) suggest that this method is not an accurate criterion of the condition of alkalosis. By using other methods they claim an alkalosis can be demonstrated primarily which changes to an acidosis at the onset of tetany.
Cruickshank (50) agrees with this view but does not consider that the final acidosis is due to muscular tremors of tetany.

Perhaps the beneficial results of the injection of calcium lactate or chloride or their administration through the intestinal canal is not entirely the result of raising the calcium level but partly an acidosis caused by the negative ion. In support of this may be mentioned the comparatively large doses required in these cases and the fact that calcium lactate is perhaps not absorbed as such through the intestinal wall. The aciduric flora treatment of Dragstedt may also be explained in this same manner.

MacCallum (35) presents a formula taken from work by Freudenberg and Györzgy may serve to link up some of the facts:

\[
\frac{[\text{Ca}^{2+}] [\text{HCO}_3^-] [\text{HPO}_4^{2-}]}{[\text{H}^+]^2} = K
\]

It can be seen that an increase in the \( \text{H}^+ \) and \( \text{HPO}_4^{2-} \) would result in a decrease in the \( \text{Ca}^{2+} \). This is apparently the changes that are found in the blood of parathyroidectomised animals. MacCallum points out that this conception is "not incompatible with the still more fundamental possibility that it is the relative proportion of sodium, potassium, calcium and magnesium ions which finally affect the excitability of the nerve—even though the change may be exclusively in the calcium."
Of course there may be other factors which also play a part in calcium control. It will be recalled that Leeb suggested that the ions produced their effects by entering into combination with proteins. Salvesen and Linder (51) (52) have noted that in nephritis there is a marked fall in blood calcium and also in blood proteins but no tetany results, while in parathyroid tetany there is a fall in calcium not accompanied by fall in blood proteins. This of course can be explained by saying that the calcium forms a compound with the protein which is partly ionized. In parathyroid cases the lowered calcium effects the ionized portion while in nephritis it effects the un-ionized portion.

Cameron and Macrhouse (53) test this idea further by estimating the calcium in spinal fluid and the blood on the theory that it will be the diffusible calcium which plays the biggest part in prevention of tetany. This will be partly ionized. The diffusible calcium of normal dogs is estimated at 53 per cent of the serum calcium value. These authors postulate, on the basis of their results, an organic calcium compound which slowly and slightly dissociates when all calcium is removed. This constitutes a calcium reservoir which keeps the calcium level constant. Parathyroidectomy is thought to decrease the amount of this compound.

It must be admitted that although the data does not as yet completely establish the balanced ion theory of
tetany causation yet with it there is not the necessity for so many assumptions as with the toxin theory. Of course it is possible that some toxin may initiate the chain of results which follow parathyroid removal. So far it seems that there has been no clean cut demonstration of the existence of such a toxin while the evidence on the other side both direct and indirect is against such a view and in favor of a derangement in the mineral ion equilibrium as the fundamental cause of tetany.
METHODS

Dogs were used in all the experiments. Some of the animals were being used by a member of the department in some metabolism experiments. Those were treated with calcium lactate after parathyroidectomy to prevent death. It was thought advisable to study the blood calcium and phosphorus of those animals and compare them with those who were not treated but allowed to take the natural course after operation. The dogs were all kept indoors in a well ventilated building. Those under calcium treatment received a bread and milk diet while the others received the regular stock diet. Blood was drawn in most cases from the leg vein—in a few cases it was taken directly from the heart.

Some difficulty was experienced in finding a satisfactory method for determination of calcium. After some experimentation the following method, practically like that employed by Clark (54) was used:

The blood was drawn in 10 cc. quantities into a syringe containing a small amount of powdered sodium citrate to prevent coagulation. Five cc. of this citrated blood was placed in a 50 cc. centrifuge tube, marked to show 25 cc., and two 5 cc. portions of warm (65°C) distilled water added and mixed. After standing for at least 20 minutes 5 cc. of 1% ammonium chloride was added
and the volume made up to 25 cc. with distilled water, mixed, covered with rubber dam and centrifuged at high speed for 20 minutes. As large a portion as possible of the clear red supernatant fluid was removed by means of a pipette—care being taken not to stir up the light floculent sediment in the bottom of the tube. This fluid was transferred to another centrifuge tube and 4 cc. of a 3% ammonium oxalate solution added slowly, mixed, and set aside over night. After centrifuging, the clear supernatant fluid was removed by means of a siphon and the precipitate washed once with distilled water, centrifuged and the water removed. About 5 cc. of approximately normal sulphuric acid was next added to dissolve the precipitate. The resulting oxalic acid was titrated with approximately .01 normal standard permanganate. This method is accurate to within about 5%.

The author is indebted to Dr. May Kinney of the Department of Biochemistry for determinations of phosphorus. The method of Bloor was used.

Results,

(1) Symptoms of the animals after operation.

I was able to observe many of the symptoms reported by other workers. In general two types of animals were found. In some no tetany was observed—depression being the principle thing in these cases. This condition was
particularly noted in one group in which several samples of blood were drawn before operation. This result bears out the contention that bleeding relieved the symptoms. However, even though tetany was not present there were evidences of the other symptoms observed. Loss of appetite was almost a constant feature, emaciation was shown and in some cases vomiting and diarrhea was present. The dogs exhibited muscular weakness and became quite inactive. In one animal rapid breathing or panting was observed although no tetany was then present nor did it occur later. The muscles also appeared to be somewhat stiff though this was not marked.

When tetany was present it was of the usual sort consisting partly of fibrillar twitchings with tonic and clonic spasms. Twitching or jerking of the jaw and head muscles was especially noted. Sometimes this was the only evidence of tetany. If the tetany became very marked increased breathing or panting was present but this was not observed in the milder forms.

The same quick and complete relief noted by others investigators when calcium was administered was noted. This was not so rapid when given by stomach tube as when injected intravenously. Relief was evidenced in all the symptoms and not alone in those of tetany. The dogs receiving calcium treatment were lively, had good appetites
and exhibited the usual interest in their surroundings, although some of them occasionally suffered attacks of
tetany. These attacks could be alleviated by administra-
tion of calcium.

(2) Blood Calcium.

Table I. Calcium and Phosphorus in Blood of Dogs receiving
Calcium Treatment.

<table>
<thead>
<tr>
<th>Date</th>
<th>Ca mg. per 100 cc.</th>
<th>P mg. per 100 cc.</th>
<th>P/Ca</th>
</tr>
</thead>
<tbody>
<tr>
<td>1925</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feb. 27</td>
<td>7.47</td>
<td>36.85</td>
<td>4.9</td>
</tr>
<tr>
<td>Mar. 2</td>
<td>5.46</td>
<td>35.71</td>
<td>6.5</td>
</tr>
<tr>
<td>&quot;</td>
<td>5</td>
<td>55.71</td>
<td>5.5</td>
</tr>
<tr>
<td>&quot;</td>
<td>10</td>
<td>35.55</td>
<td>4.11</td>
</tr>
<tr>
<td>&quot;</td>
<td>11</td>
<td>4.55</td>
<td>72.36</td>
</tr>
<tr>
<td>&quot;</td>
<td>17</td>
<td>4.74</td>
<td>67.62</td>
</tr>
<tr>
<td>Apr. 15</td>
<td>5.64</td>
<td>40.76</td>
<td>4.7</td>
</tr>
</tbody>
</table>

Dog #6

Feb. 27    | 6.78              | 27.63             | 4.07 |
Mar. 2     | 4.77              | 39.13             | 8.2  |
"         | 6.50              | 45.50             | 7.9  |
"         | 7.44              | 35.45             | 4.4  |
"         | 7.57              | 94.30             | 12.5 |
"         | 13                | 3.74              | 90.06|
"         | 5.10              | 50.99             | 7.5  |
7:30 P. M. |                   |                   |      |
Mar. 15    | 3.10              | 60.99             | 7.5  |
9:10 P. M. |                   |                   |      |

30 gms. calcium lactate by stomach tube at 7:30 P. M.
and sample of blood drawn.
20 gms. calcium lactate 8:10 P. M.
20 gms. " 8:30 P. M.
Tetany stopped 8:30 P. M.
Sample blood at 9:10 P. M.
In table 1 are shown the calcium levels of dogs 4 and 6. In each of these calcium lactate was administered daily, especially for a time following the operation, by stomach tube. All the calcium values are in general lower than those reported by most other workers. In dog #4 tetany did not occur very often but with dog 6 tetany occurred almost daily toward the latter part of the tests. In this animal depression was not present. After the removal of the parathyroids the calcium seems to fluctuate more but does not seem to be lower, as a general thing, except preceding or during tetany. The lowered calcium occurs before tetany appears. Tetany does not always appear, however, following lowered calcium. In dog 6 it will be noted that calcium levels as a general thing are lower than in dog 4. The former animal developed repeated attacks of rather severe tetany while the latter dog suffered only a few milder attacks. Salvesen's contention, that when calcium drops to 7 mg. per 100 cc. of blood, tetany occurs is not verified by these results. Apparently calcium treatment does not always cause blood calcium to rise although it may be efficient in stopping or preventing tetany symptoms.
Table II shows the calcium levels in dogs receiving no calcium treatment:

**Dog #7**

<table>
<thead>
<tr>
<th>Date</th>
<th>Ca</th>
<th>P</th>
<th>P/ Ca</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1925</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mar. 24</td>
<td>8.43</td>
<td>46.10</td>
<td>5.4</td>
<td>Normal before operation</td>
</tr>
<tr>
<td>&quot; 25</td>
<td>8.32</td>
<td>46.10</td>
<td>5.5</td>
<td></td>
</tr>
<tr>
<td>&quot; 25</td>
<td>8.13</td>
<td>46.76</td>
<td>5.7</td>
<td></td>
</tr>
<tr>
<td>&quot; 27</td>
<td>7.95</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&quot; 30</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&quot; 31</td>
<td>5.51</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apr. 2</td>
<td>7.69</td>
<td></td>
<td></td>
<td>Operation</td>
</tr>
<tr>
<td>&quot; 2</td>
<td>5.59</td>
<td></td>
<td></td>
<td>Showed no tetany but became progressively</td>
</tr>
<tr>
<td>&quot; 5</td>
<td>5.54</td>
<td></td>
<td></td>
<td>weak, refused to eat, showed increased</td>
</tr>
<tr>
<td>&quot; 4</td>
<td>5.62</td>
<td>56.33</td>
<td>11.2</td>
<td>respiration occasionally</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Still depressed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Found dead two days later</td>
</tr>
</tbody>
</table>

**Dog #8**

<table>
<thead>
<tr>
<th>Date</th>
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<th>P/ Ca</th>
<th>Notes</th>
</tr>
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<tbody>
<tr>
<td>1925</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mar. 24</td>
<td>9.26</td>
<td>45.82</td>
<td>4.94</td>
<td>Normal before operation</td>
</tr>
<tr>
<td>&quot; 25</td>
<td>8.92</td>
<td>47.40</td>
<td>5.61</td>
<td></td>
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<tr>
<td>&quot; 26</td>
<td>8.10</td>
<td>46.45</td>
<td>5.6</td>
<td></td>
</tr>
<tr>
<td>&quot; 27</td>
<td>10.05</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&quot; 50</td>
<td></td>
<td></td>
<td></td>
<td>Operation</td>
</tr>
<tr>
<td>&quot; 31</td>
<td>5.54</td>
<td>48.66</td>
<td>8.45</td>
<td>No tetany but depressed</td>
</tr>
<tr>
<td>Apr. 1</td>
<td>5.97</td>
<td></td>
<td></td>
<td>Slight twitching of head muscles.</td>
</tr>
<tr>
<td>&quot; 5</td>
<td>5.65</td>
<td></td>
<td></td>
<td>Found dead next day.</td>
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**Dog #9**

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<td>Apr. 9</td>
<td>9.58</td>
<td></td>
<td></td>
<td>Normal before operation</td>
</tr>
<tr>
<td>&quot; 10</td>
<td>9.11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&quot; 13</td>
<td></td>
<td></td>
<td></td>
<td>Operated</td>
</tr>
<tr>
<td>&quot; 14</td>
<td>6.91</td>
<td></td>
<td></td>
<td>No tetany or fast breathing.</td>
</tr>
<tr>
<td>Dog # 10</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>---------</td>
<td>----------------</td>
<td>----------------</td>
<td>----------------</td>
<td>----------------</td>
</tr>
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<td>Apr. 9</td>
<td>7.15</td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>6.13</td>
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<td>9.83</td>
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<td>Apr. 15</td>
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<td>Apr. 17</td>
<td>5.65</td>
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<td>Apr. 18</td>
<td>5.40</td>
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<td>Apr. 20</td>
<td>5.48</td>
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<tr>
<td>Apr. 21</td>
<td>6.70</td>
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</tbody>
</table>

Normal before operating
" " " "
Operated
No tetany or fast breathing
" " dog normal.
Dog in some tetany -- much
depressed.
Dog in slight tetany -- still
depressed.
Dog depressed no tetany
Dog in some tetany

<table>
<thead>
<tr>
<th>Dog # 11</th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Apr. 9</td>
<td>8.20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apr. 10</td>
<td>6.97</td>
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</tr>
<tr>
<td>Apr. 13</td>
<td>5.87</td>
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</table>

Normal before operating
" " " "
Operated
Rapid breathing some 
tetany
in head muscles.

<table>
<thead>
<tr>
<th>Dog # 12</th>
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</thead>
<tbody>
<tr>
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<td>7.16</td>
<td>42.54</td>
<td>5.9</td>
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</tr>
<tr>
<td>Apr. 21</td>
<td>7.79</td>
<td>42.03</td>
<td>4.7</td>
<td></td>
</tr>
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<td>Apr. 22</td>
<td>5.36</td>
<td>42.66</td>
<td>7.5</td>
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</tr>
<tr>
<td>Apr. 23</td>
<td>4.71</td>
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<td>12.2</td>
<td></td>
</tr>
<tr>
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<td>5.85</td>
<td>42.66</td>
<td>11.0</td>
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</tr>
<tr>
<td>Apr. 23</td>
<td>4.30</td>
<td>49.61</td>
<td>11.5</td>
<td></td>
</tr>
</tbody>
</table>

Normal before operation
" " " "
After tetany
Dog in tetany 9:15 A. M.
" " " " 12:00 A. M.
" " " " 3:35 P. M.

<table>
<thead>
<tr>
<th>Dog # 13</th>
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</thead>
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<tr>
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<td>7.66</td>
<td>42.66</td>
<td>6.3</td>
<td></td>
</tr>
<tr>
<td>Apr. 21</td>
<td>7.86</td>
<td>51.19</td>
<td>6.5</td>
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<tr>
<td>Apr. 22</td>
<td>5.65</td>
<td>37.20</td>
<td>6.6</td>
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</tr>
<tr>
<td>Apr. 23</td>
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<td>49.30</td>
<td>10.4</td>
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</tr>
<tr>
<td>Apr. 23</td>
<td>5.51</td>
<td>49.95</td>
<td>9.4</td>
<td></td>
</tr>
<tr>
<td>Apr. 23</td>
<td>5.49</td>
<td>49.61</td>
<td>12.4</td>
<td></td>
</tr>
<tr>
<td>Apr. 24</td>
<td>7.23</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Normal before operation
" " " "
No tetany
No tetany
Beginning tetany 9:25 A. M.
Tetany 11:45 A. M.
No tetany

The blood calcium level of dogs receiving no calcium
treatment tended to remain lower than normal even in those
animals suffering only depression. During tetany it
dropped still lower. In dogs exhibiting tetany the
calcium in general reached lower values than in those
showing only depression.

In comparing the two groups, Table I and II it seems that the evidence shows that after removal of the parathyroids the body has lost the ability to regulate calcium metabolism. In dogs 7 and 8 before operation it will be noted that the calcium values are fairly constant. This is true for the other animals for the small number of normals which were obtained. After operation the calcium level in the blood fluctuates. Administration of calcium salts causes it to rise but because the body has lost its regulatory ability it rapidly sinks. This may be because it is mostly excreted or perhaps goes into some form which is not available in body metabolism. The conception that it changes into a diffusable form which is more easily excreted would explain the increased excretion of calcium following parathyroidectomy. Perhaps the deranged salt equilibrium has so affected the kidney and intestinal membranes that they are more permeable to the changed form of calcium. The work by Cameron and Moorhouse indicates that a calcium compound which acts as a reservoir has been depleted by parathyroid removal and that consequently all the calcium including that which is injected is diffusible and consequently is rapidly lost. That this is not the only factor is indicated by the work of Blumenstock and Tockstadt who find that removal of the
liver makes smaller doses of calcium efficacious in preventing tetany and also slows up its approach. Perhaps the liver and other organs form compounds with calcium which renders its use by the body impossible. Perhaps again the beneficial results of Eck's fistula results only because of its effect on the volume of the circulation.

(3) Blood phosphorus

The blood phosphorus values in general fluctuate a great deal. In the two animals Table I receiving calcium treatment the values tend to be higher during tetany than normal. This verifies Greenwald's results only partly. However, there is no correlation between the amount of increase and severity of tetany. The P/Ca ratio is always found to be increased during tetany. The increase in phosphorus does not occur at least to any marked extent following removal of the parathyroids except during or perhaps just before tetany. The P/Ca ratio, however, may increase due to the lowering of the calcium level.

In the case of those dogs not receiving calcium treatment the data is not sufficient to be sure, but it seems that the rise of phosphorus was not always apparent though sometimes it did occur. When it did occur there seemed to be a tendency for it not to remain high but to drop; later a second rise might occur. In most cases it
remained down. This is in accord with Greenwald's findings that the rise in phosphorus occurs at first but becomes lower the next day or two. This might be explained by the tendency for an acidosis to develop during tetany. The P/Ca ratio always increased after parathyroidectomy. So far as the results show there is no difference between dogs showing tetany and those showing only depression with respect to blood phosphorus.

Table III Calcium following guanidine injection.

Dog #1

<table>
<thead>
<tr>
<th>Date</th>
<th>Ca</th>
<th>mg. per 100 cc. whole blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mar. 10</td>
<td>3.75</td>
<td>Normal before guanidine injection</td>
</tr>
</tbody>
</table>
| Mar. 11 | 8.64   | " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " 

Mar. 11 | 4.03   | " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " 

" 6 | 7.69   | One hour after injection of ½ grain guanidine carbonate no convulsions. |
| " 8 | 6.37   | Normal before guanidine injection 10:15 A.M. |
| " 8 | 5.52   | One hour and 35 min. after subcutaneous injection of 1 gram of guanidine carbonate |
| " 8 | 7.57   | and 45 min. after injection of ½ gram in vein. |
| " 8 | 9.01   | 2 P.M. 3 hrs. after injection no tetany. |
| " 8 | 9.01   | 6 P.M. clonic contraction. Not typical parathyroid tetany. |

In one animal, that had the parathyroids removed some two or three months previous, guanidine was injected intravenously. The blood calcium is shown in Table III. The symptoms exhibited by this animal were not those of typical parathyroid tetany. It appeared toxic but no convulsions of any kind were observed until rather
enormous quantities of guanidine carbonate had been injected. The respirations were very little if any increased.
SUMMARY

The blood calcium and phosphorus together with the symptoms of parathyroidectomised dogs both with and without calcium treatment have been studied.

The calcium level of parathyroidectomised dogs under calcium treatment fluctuates more than normal. This seems to be due to the loss of the ability of the body to regulate calcium metabolism. The general level does not seem to be lower than normal.

The low calcium level is attained usually before tetany appears but may not be raised to normal when tetany disappears. There may also be low calcium without tetany.

Those dogs showing strong tendency to tetany exhibit lower calcium values than those where tetany has occurred only a few times during treatment. In other words apparently, the harder an animal is to protect from tetany the lower this calcium is likely to be.

In those dogs not receiving treatment the calcium level is lowered and tends to remain so though tetany may or may not be present. If tetany is present the calcium level tends to be lower than if not present. In other respects these dogs are exactly similar to those receiving treatment.

The symptoms following parathyroidectomy vary considerably. Tetany may or may not be present. When tetany is not present general depression is.
The blood phosphorus may or may not be increased during tetany. A greater tendency is shown for it to increase in dogs receiving calcium treatment than in those not receiving it.

The P/Ca ratio is always increased during tetany. Between the attacks, however, it tends to return to the normal value.

The blood calcium changes in one parathyroidectomised dog receiving guanidine injection is shown. This animal did not show true parathyroidectomy symptoms.
BIBLIOGRAPHY