THE INORGANIC AND TOTAL ACID SOLUBLE PHOSPHORUS IN THE WHOLE BLOOD OF DOGS SUFFERING FROM VARIOUS CONDITIONS OF PARATHYROID DEFICIENCY.

by

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TABLE OF CONTENTS.

I. Review of Literature: p.

1. Kinds of P compounds in the blood. 1.
2. Relative distribution of P compounds in the blood. 2.
3. Physiological and pathological variations of P in the blood. 4.
4. Blood P in parathyroid deficiency. 16.
5. Ca/P ratios in the blood of parathyroid deficient animals. 13.
6. Other ionic relationships in parathyroid deficiency. 13.
7. Blood P in parathormone over-dosage. 18.
8. Parathyroid glands.
   a. Embryology and anatomy. 20.
   b. Pathological disturbances. 24.
   c. Discovery of parathyroids. 25.
   d. Historical. 26.
   e. Clinical symptoms of parathyroid deficiency. 28.

II. Procedure for Blood Analysis. 31.

III. General Method of Experimentation. 34.

IV. Concentration of P Compounds in Blood of

1. Normal dogs. 35.
2. Thyroparathyroidectomized dogs.
   a. When symptoms of parathyroid deficiency appear. 43.

b. At the time of death without treatment. 56
c. At time of recovery without treatment. 59
d. Treated with liver extract. (Heparmone.) 68
e. Treated with calcium lactate. 99
f. Treated with strontium lactate. 117
g. Treated with magnesium lactate. 124
h. Treated with morphine sulphate. 137
i. Treated with ammonium chloride. 146
j. Treated with uranium nitrate. 160
k. Treated with parathormone. 179

V. General Summary. 212
VI. General Discussion. 236
VII. Conclusions. 243
VIII Bibliography. 246

TABLES AND PROTOCOLS.

I. Normal P of Blood. 36 to 40
II. Summary of Table I. 41
III. P of Blood in Parathyroid Deficiency. 45 to 48
IV. Summary of Table III. 48a
V. P of Blood at Time of Death Due to Parathyroid Deficiency. 57a
VI. Protocols for Untreated Dogs. 64

VII. Protocols for Dogs Treated with

1. Liver extract (Heparmone). 86-98.
2. Calcium lactate. 109-116.
3. Strontium lactate. 122,123.
4. Magnesium lactate. 135,136.
5. Morphine sulphate. 143-145.
6. Ammonium chloride. 156-159.
7. Uranium nitrate. 172-178.
8. Parathormone. 201-211.

GRAPHS.

I. Composite graph of tables III, IV, and V. 48 b

II. Dog 69. Recovering without treatment. 60 & 61

III to VII. Dogs treated with Heparmone. 73, 74, & 78 to 80.

VIII. Dog 88. Treated with calcium lactate. 105 & 106.

IX. Dog 113. Treated with strontium lactate. 120.

X. Dog 111. Treated with magnesium lactate. 133.

XI. Dog 105. Treated with morphine sulphate. 140-141.

XII. Dog 107. Treated with ammonium chloride. 151.

XIII. Dog 95. Treated with uranium nitrate. 164.

XIV. Dog 102. Treated with uranium nitrate. 166.

XV. Dog 97. Treated with uranium nitrate. 167.

XVI. Dog 110. Treated with uranium nitrate. 169.

XVII. Dog 121. Treated with Parathormone. 189.

XVIII. Dog 125. Treated with Parathormone. 190.

XIX. Dog 120. Treated with Parathormone. 194.

XX. Dog 129. Treated with Parathormone. 195.

XXI. Dog 131. Treated with Parathormone. 197.

THE INORGANIC AND TOTAL ACID SOLUBLE PHOSPHORUS IN THE WHOLE BLOOD OF DOGS SUFFERING FROM VARIOUS CONDITIONS OF PARATHYROID DEFICIENCY.

A variety of researches by many different investigators have brought out the importance of the phosphorus compounds in the body and body fluids as a disturbing factor in many experimental, physiological, and pathological conditions. In fact in any condition where a disturbance in calcium metabolism is involved, it has become universal to question and investigate the phosphorus compounds of the structures affected by the former. Failure to discover a clear cut physiological relationship between the two, as one might suppose from their simple chemical and biological properties, has led even farther, so that their relationship to other ions in the body such as $Na^{'}$, $K^{'}$, $Mg^{''}$, $Cl^{'}$, $CO_3^{''}$, $SO_4^{''}$ and $NH_4^{'}$ and perhaps other organic ions are being considered. It is thus eminent that the question of Parathyroid deficiency may be approached by a study of any or all of these ions. In this paper, chiefly the inorganic and acid soluble phosphates of the whole blood will be considered.

The phosphoric acid compounds of the blood may be divided into three groups: proteins, lipoid and acid soluble (98, 99, 108, 16, 67). The acid soluble H_3PO_4 includes those compounds that are not precipitated with the proteins and lipoids when treated with the usual

acid protein precipitants (108). That portion found as H_3PO_4 in the acid protein-free filtrate is known as the inorganic phosphate. The portion liberated in the same filtrate only after prolonged boiling with H_2SO_4 and HNO_3 is known as the organic acid soluble phosphate. The two together are known as the total acid soluble phosphoric acid and represent the total Phosphorus of the blood not in lipoid or protein combination.

These same authors and others give indication that even this organic acid soluble P is divided into at least two different portions: (1) an easy acid hydrolizable portion which is liberated by hemolysis and broken up by the esterases of the blood; (2) a portion which is quite acid stable, not attacked by blood esterases. Thus due to portion (1) standing and hemolysis of red cells will increase the inorgorganic P of the serum and plasma. Hence also the differences in amounts of inorganic and acid soluble P compounds according to whether the method of analysis involved hemolysis of red cells or prolonged weak acid extraction of serum or plasma.

The older literature as to the relative distribution between the plasma or serum and cells of the blood of these various compounds is found in the works of Abderhalden (1), Rona and Takahashi (210), Liebermeister (158), Bürker (23), and Deetjen (49). The

work of these men and the errors that they pointed out in the older methods has led to our present conception of the relative distribution of these various phosphorus compounds in the blood. Nevertheless, there seems to be some difference of opinion on the question. Buell (22) found no inorganic P in the blood corpuscles and no organic P in the plasma. Barrenscheen, Doleschall and Popper (5) report all but a negligible percent of organic P in the corpuscles, 37.4% of inorganic P in corpuscles and 62.6% in the plasma or serum. Roller (209) states that most if not all of the organic H_3PO_4 found in serum is in the form of Lecithin or phosphoprotein. Meigs, Blatherwick and Cray (182) show conclusively that the portion of the plasma H_3PO_4 in organic combination (better than 50%) that is not lipoid is negligible. The small amount of nucleoprotein H_3PO_4 found in serum is due to breaking up of the platelets (49). In the plasma therefore the acid soluble P seems to consist almost entirely of inorganic H_3PO_4(Greenwald (99), (100), (102), (108); Bloor (16); Meigs, Blatherwick and Cray (182); Bell and Doisy (7); Roller (209); Barrenscheen, Doleschall and Popper (5); Macheboeul (17)), variations therefrom being due to errors in the methods of analysis employed as pointed out by Bloor (16) and confirmed by Feigl (67), Bell and Doisy (7), Zucker and Gutman (262), Kay and Robison (145). However, later Martland and Robison (178)

by a specialized technique believe to have shown definitely as much as .1 mg. of organic acid soluble P per 100 cc of serum or plasma.

For the nature of these compounds composing the organic acid soluble H_3PO_4 of the blood see the papers of Greenwald (108), Roller (209), Feigl (67), Martland and Robison (178), and Macheboeuf (171). Suffice it to say that this portion is thought to consist largely of acid soluble esterlike H_3PO_4 combination, chief of which is Di phospho-1-glyeric acid.

According to Greenwald (99) by his older method of P determination, large variations occur in the acid soluble P of the serum of the same individuals (1.97-6.80 mg per 100 cc serum.). This portion according to the newer methods used is principally the inorganic Phosphoric acid. Grassheim and Lucas (95) finally resorting to a method similar to that used by Greenwald (99) found a variation in the serum of inorganic P (2-3.5 mg per cent) and serum organic acid soluble P (7-9 mg per cent). They pointed out the seasonal variations depending upon the length of exposure of the patient to the sun light and the angle at which these rays struck the earth during exposure. They thus affirmed previous findings (82), (123). These same results have just recently

been shown to be true for the whole blood inorganic acid soluble P by Tisdall and Brown (239). The literature on raising the blood inorganic P by vitamin D and irradiation Rickets is voluminous.

That the blood inorganic P rises during sleep has been shown by Havard and Reay (123). Considerable variation even from day to day in the blood inorganic and organic acid soluble P have been reported in man (209). These same variatiations in blood inorganic P from day to day, seasonal, and rise on caging of rabbits have been observed by Brown (20 and Grant and Gates (93), while Cuthberton (48) has reported an increase in blood inorganic and total acid soluble P and a decrease in organic acid soluble P in exercise and fatigue and Havard and Reay (124) showed variations in exercise with an increase on performing work that the organism was unaccustomed to. The latter is in accord with the earlier findings of Engelman (64), Keng and Olsavsky (146), Paton, et al (198), Greenwald (97) and Cooke (45). Riabouschinsky (207) states that inorganic phosphate increases after work but not proportional with the duration of the work. In the rest period after work the inorganic phosphate falls and the harder the work the greater the fall below the resting level. Irving and Bastedo (137) have undoubtedly shown that there is no

increase in the inorganic P of the venous blood from the muscles being exercised. They show that even during and following venous stasis in a ligated leg there is no increase in inorganic P of the venous blood. Therefore if there is an increase in inorganic P of the blood during exercise it is not of muscular origin.

Kay and Byrom (144) and others have shown a fall in blood inorganic P following a meal. Variation in blood inorganic P have been linked up with carbohydrate metabolism by MacCleod (170). Fiske (73) first showed a diminution in blood inorganic and urinary P followed by a compensatory rise after ingestion of sugar. In diabetes and alimentary hyperglycemia, injection of phosphates reduces the blood sugar (170). On the other hand the injection of sugar causes only a fall of blood P in diabetes and not a compensatory rise as in the normals (Barrenschein, Doleschall and Popper (5); and Markowitz et al (176).

Various endocrine disturbances have been found to cause a variation in the blood inorganic P. The findings in pancreatic and adrenal disturbances seem to be parallel in blood and urine and are related to sugar metabolism. Insulin decreases the blood inorganic P (Wigglesworth et al (254); Blatherwick et al (15); Perlzweig et al (203); Harrop and Benedict (120)), but is followed by a compensatory rise after about

2 to 3 hours which precedes the rise in blood sugar. Thatthis was not followed by urinary increased P until the P had reached a high level in the blood has been shown to take place (Eadie, MacCleod, and Noble (58); Chaikoff et al (26). Contrary to these findings Barrenschein et al (5) states that in normal healthy individuals insulin does not change the inorganic nor the total acid soluble P. Again Simola (226) showed that blood inorganic P always fell after insulin increase and Häusler and Heesch (122a) showed that this was always accompanied by a K decrease but neither PO_4 nor K increased on addition of insulin to blood in vitro. Vollmer (243) and Peterson and Hughes (202) also showed this diaphasic variation in the blood inorganic P on adrenalin injection, the changes in phosphate paralleling the changes in K and rate of metabolism and being opposite to the changes in blood Ca, H ion and sugar and acid excretion. To support the above Yonkman (259) showed a marked increase in serum inorganic P paralleling the symptoms of adrenalectomy. There are many other investigations that may be quoted in support of the blood P variations caused by these and other hormones, but let this suffice to show that the sugar metabolism and variation in hormonal function will produce variations in the P picture of the blood.

There are many other factors that vary the blood inorganic and acid Soluble Phosphorus concentrations

which are not within the scope of this paper and have been adequately reviewed by others, such as: increasing age, pregnancy, lactation, change in rations, diet content in vitamin, phosphate ion in relation to other ions in the digestive tract, effects of acids and alkalies in varying excretion of phosphates by kidney or large intestine and thus affecting blood P. Considerations of these will be found by Zucker (261) and with full bibliographies by Fiske and Stokhey (74); Chaney and Blunt (27); Meigs et al (182); and Stewart and Percival (232).

Meigs (182) work is of expecial importance since it affirms Greenwalds (99) findings showing that normally plasma inorganic PO_4 is chiefly influenced by changes in ration and that the blood derives its phosphate from the digestive tract only in the form of inorganic phosphate. They indicated in addition that phospharized proteins are not carried from one part of the body to another in the plasma, pointing to the conclusion that these compounds are always manufactured within the cells in which they are formed. They advanced the opinion that many of the tissues of the body, notably the mammary gland and skeletal muscle, can receive their fat and phosphorus from the blood only in the form of phosphatides. I have not been able to find anything at variance with this viewpoint if the energy metabolism for muscular work is excluded.

Even in the light of all these variations, it seems that Kay and Byrom (144) by determining the P index (= Vol. of cells/P in whole blood = Ester P) have shown that at least the P in ester combination (organic acid soluble) is fairly constant in health and many diseases. It is thus another affirmation of the facts that the acid soluble P is found chiefly if not all together in the red cells and that it varies with the cell content of the blood. Therefore too, that we are to look for changes principally in the inorganic P of the blood and that this (inorganic P) is the only acid soluble P found in the plasma as is shown in the beginning of this paper.

However, before we leave this subject of P variation in the blood, we should consider a more or less pathological factor which may cause considerable variation in our experimental work since it has been many times shown that in the measures used to counteract tetany in parathyroid deficiency, renal function is more or less involved. Recently, Salvesen (219) has worked with and reviewed the serum electrolytes in renal insufficiency. He states that in renal insufficiency phosphate retension is very common and that there is no case of acidosis in which this factor is entirely absent. He found it rather difficult to evaluate this factor, however, since phosphates may be retained as the neutral or acid salts.

Grassheim and Lucas (95) in their work on Renal

disease conclude that there is usually a serum acid soluble P rise paralleling the degree of functional disturbance in the Kidney and that this may be due to (1) a rise in both the inorganic and organic portion; (2) rise in the organic P with a normal inorganic P; or (3) rise in inorganic P with a normal content of organic P. This work is hard to evaluate because of the older method of phosphorus determination used.

Thus from the foregoing considerations it must be clear from the onset that in the consideration of our present problem of the acid-soluble phosphorus compounds in various conditions of parathyroid deficiency, any number of factors more or less obscure or uncontrolable, may play a part in hiding the true relationship of the parathyroid function to the phosphorus compound in the blood. It will also be evident that in such a complex problem, the greater the number of angles of approach the greater will be the possibility to a final solution. This, and the constant reference in the literature of the possible involvement of the phosphorus compound in the function of the parathyroids led Dr. O. O. Stoland to outline the present method of approach and to give constant help and encouragement to the completion of this work.

In the literature on parathyroid deficiency, the Phosphorus of the blood has not been determined except in the course of parathyroidectomy followed by no treatment or only treatment with parathormone or calcium. Even these results are few and consist very largely of determinations of the inorganic P of the blood. Under all conditions of treatment the attention in the blood chemistry has been primarily directed to its calcium content and secondarily to certain other properties.

We shall therefore devote ourselves primarily to the blood acid soluble phosphorus and reference will be made to other constituents only as it bears directly on the current problem. The reviews of Stewart and Percival (232) on calcium metabolism, and the general reviews by Paton and Findley (199); Morel (188); Hertz (126); Sachs (214); Boothby (19); Biedl (12); Simpson (224); Carlson (25); Jacobson (167); MacCallum (167); Collip (41); Dragstedt (57); deal adequately with the older literature and what is presently known about the Parathyroids.

Greenwald (97) in 1911 when making a series of analysis of the blood of parathyroidectomized dogs for all the important known constituents was the first to note a marked change in the P metabolism. He noted a

P retention, as low as 2% of the normal being excreted after parathyroidectomy up to the time of tetany when the excretion was markedly increased, similar to that found in excessive P exertion when an animal labors with some unaccustomed task (Engelman (64); King and Olsavsky (146); Paton et al (198). With Greenwald's work there also appeared an article by Cooke (46) which was in complete accord with the work of Greenwald. Since then Greenwald (98), (99), (100), (101), (103),(107), and Greenwald and Gross (109) in a series of articles concluded that there are two and only two well authenticated findings following parathyroidectomy: a serum calcium fall and a P retention followed by a decreased excretion in Na and K. They have shown in the course of their experiments that following parathyroidectomy in dogs, (contrary to the findings of Salvesen, Hastings and McIntosh (220)) there is no increase in Ca excretion; (affirmed by author's work in M. A. thesis); that the phosphorus retention following a drop in the serum calcium is primary, followed by a retention in K and Na and terminating in anuria; that the phosphorus retained is largely if not entirely precipitated with Ca in the tissues; and that whatever increase in inorganic P is found in the blood is due to the break down of excess lipoid and protein phosphates. Total phosphorus retention and a rise in blood inorganic phosphorus after parathyroidectomy

have been substantiated by most investigators. Elias et al (61), (63); Hastings and Murray (122); Salvesen (216); and others (118), (135), (76).

Collip (42) states that the calcium falls immediately and inorganic P rises later and is found much increased in tetany. Howland (131), (133), and Freudenberg and György (84) found a normal or increased inorganic P in tetany. Salvesen (217) found a slight rise in the acid soluble P of the plasma. Gross, and Underhill (196) show an increased total acid soluble P in seven dogs that developed tetany.

Hammet (118a) found an increase in the P/Ca ratio following parathyroidectomy and ascribed tetany to a disturbance in this ratio, whereas Reed, Lackey and Payte (206) at first announced a definite mathematical relationship between the concentration of Ca and inorganic P which was progressively reduced until it was 1 at the time of tetany, Reed (205) found after further experimentation no such definite relationship. He found that only when tetany occurs in the early postoperative period does this Ca/P ratio of 1 or less seem to hold but that at a later stage these low ratios occurred not being accompanied by tetany.

The original and subsequent work of Greenwald (97), (99), on the P of the blood and excretions led him and others independently (Binger (14), Jeppson and Klercker (140)

Tisdall (238); Elias et al (59), (60), (62); Adlersburg and Rogers (2): Collip (41)) to investigate the action of phosphates by the injection of various phosphate salts into the blood. The fact that various cations were used with the PO_4''', HPO_4'', H_2PO_4' anions brought various other cation and anion relationships as well as the acid base balance into question, not only in parathyroid tetany but in all other forms of tetany. This question with all the literature has been most excellently reviewed by MacCallum (167). To this may be added the later reviews of Stewart and Percival (232) and the earlier papers of Greenwald (103), (103), (104). Full consideration of the subject is out of the scope of this paper.

However, a consideration of the work of Howland and Kramer (133); Ross and Howland (213); Rona and Takahashi (210), (211); Freudenburg and György (79 to 85) would be of prime importance on the question of the blood phosphates in producing tetany. It has been pointed out by Howland and Kramer that $Ca_3(PO_4)_2$ is but slightly soluble in the serum. Holt, La Mer and Chown (129) have shown that serum is 200% supersaturated with calcium in the presence of CO_3 and PO_4. The former give the following formula when the $Ca_3(PO_4)_2$ is exposed to carbonic acid as is found in the blood stream:

$$Ca_3(PO_4)_2 + 2H_2CO_3 \rightleftharpoons 2CaHPO_4 + Ca(HCO_3)_2 \rightleftharpoons$$
$$2Ca^{++} + 2HPO_4^{--} + Ca^{++} + 2HCO_3^-$$

establishing an equilibrium between dicalcium phosphate and calcium bicarbonate and between these and $Ca''HPO_4''$ and HCO_3'. Thus by reducing the CO_2 tension of the solution $Ca_3(PO_4)_2$ will increase, and HCO_3' will increase in relation to CO_2 which amounts to increased alkalinity. Ross and Howland, as many others, refer in this respect to the formula of Rona and Takahashi:

$$\frac{(Ca^{++})\ (HCO_3')}{(H^{+})} = K$$

It is clear that the above formula of Rona and Takahshi would not satisfy Howland's equation and the ionization of Ca'' would be a simple function of the H ion concentration.

The conception therefore of Freudenberg and György is much more useful, and though more complete, evidence is accumulating that even their formula cannot be the whole story. Their formula is as follows:

$$\frac{(Ca'')\ (HCO_3')\ (HPO_4'')}{(H')} = K$$

This equation, of course, still excludes other ionic relationships but with a thorough understanding of the important factors that maintain in the blood a constant acid-base balance and osmotic pressure as brought out by Marriott and Hartman (175) and Salvesen (219) the effects of other ions on this formula may be estimated.

It will be seen, however from this equation that when acid or alkaline phosphates are injected the primary effects will be modified by the change in pH and its effect on Ca'' and only secondarily after the acid-base balance is fully established will the phosphate ion show its effect if it is then still in excess. The above is not in the least incompatible with the more fundamental possibility that it is the relative ionic proportion of Na', K', Ca'' and Mg'' as well as certain anions which finally affect the excitability of a nerve or tissue--even though the change may be only in the calcium.

Indeed such disturbances have been recorded in parathyroid deficiency causing increased K and decreased Ca--this being attributed as an etiological or a contributory factor. (Gross and Underhill (96); Frank, Notham and Guttman (77)). One may be erroneously led to conclude that this cannot be a primary factor in increasing excitability when the parathyroids are intact as is shown by the administration of K salts (Wetzel (252)) and by the fact that the administration of narcotics (Cloetta and Thamann (31), (32)) (alcohol, ether, barbituric acid compounds) produce a Ca fall and a K rise paralleling the depth of narcosis. Tetrahydronaphthylamine, a psychic excitant producing hallucinations, has the opposite effect on the plasma Ca and K. In all of these

the sodium content is never affected, which is also true of morphine. Arousal from sleep reestablishes the normal ratio. This work has been affirmed by Glasser (87) (88).

But morphine (32) is irregular in its effect on both Ca and K which in its contrast to the hypnotics is contributed to a more complex relationship of the same ions due to the drug's variation in causing various degrees of central, visceral and peripheral actions in different individuals. However, Rosemann (212) has shown experimentally that increase or decrease of calcium in blood of normal individuals always brings about a remarkable retention or elimination of K so that the quotient K/Ca remains constant. That disturbance of this ratio should bring about abnormalities agrees with the results of Kylin and Myhrman (154) who found that in 14 cases of hypertonia the K/Ca ratio of the blood was from 2.08 to 2.97 whereas in normals it was 1.70 to 2.15. These authors (Cleotta and Thamann (31), (32)) also showed that by the injection of phosphates and oxalates the narcosis could be shortened by 8 to 3 hours in which the former was by far the more effective, showing that the PO_4 ion in addition to precipitating Ca'' may have a stimulating effect. But since experimental lowering of the Ca brought about the opposite results they concluded that the lower Ca and higher K content in the plasma during sleep and narcosis was due to these ions changing in concentration

in the brain. That such an increase of Ca by direct injection (.2 to 1 mg in 1/20 to 1/40 cc) in the region of the infundibular gray matter brings about an extreme feeling of well being resulting in sleep which can be carried to deep narcosis, whereas a corresponding increase of K in the same region brings about the extreme opposite, including epileptiform crisis have been shown by Demole (50). Variations of these ions in many other regions of the brain were shown to alter and modify the syndrome. NaCl injections caused no noticeable effects. Moreover, it was later shown by Fischer (72) that if the narcotics were introduced into decerebrated and decorticated animals, the plasma changes in K and Ca still took place but were absent when administered to animals which had their brain stems also removed. All of these men thus concluded that there was in the brain and especially in the region of the sleep center (Gray matter of the Infundibulum) a profound antagonism between these two ions. They established in addition that the action of the K could be abolished by the Ca but not vice versa. To this may be added the antagonism between Ca and K afforded by the classical experiments on the isolated heart and intestine.

On the other hand, parathormone overdosage both in normal and parathyroidectomized animals bring about a

marked rise in inorganic P which is secondary to a marked calcium rise to above the normal value. (Fisher and Larson (70), (71); Collip (41), (43)).

Salvesen (218) observed in parathyroidectomized dogs and cats a decrease in inorganic P (6 or 7 to 4 mg per 100 cc) with a terminal rise as in the normals. Collip (41) found in parathyroidectomized rabbits that with the Ca almost normal, the injection of parathormone may bring about a rapid high inorganic P accompanying fatal tatany. They found increased excretion of Ca and P in the urine. These results on Parathormone were affirmed by Greenwald and Gross (110), (111); and Grollmann (92).

It can thus be concluded that given a low Ca level, the effect of parathormone on the blood inorganic P is opposite to that caused by parathyroidectomy. Thus with the view of possibly obtaining more insight into the mechanism of parathyroid function the present work was undertaken. The points investigated were, the inorganic phosphorus and the total acid soluble phosphorus of the blood in normal and thyroparathyroidectomized dogs, and these same animals treated variously to prevent or abolish tetany. The serum calcium was determined in every case for comparison to the blood phosphates. Substances used to prevent or abolish tetany were: (1) Liver extract (Heparmone); (2) calcium lactate; (3) strontium lactate;

(4) Magnesium lactate; (5) morphine sulphate; (6) ammonium chloride; (7) uranium nitrate; (8) Parathormone.

But before we go further to our experimental work let us consider a few things in particular concerning the Parathyroid glands.

THE PARATHYROID GLANDS.

ANATOMY OF THE PARATHYROIDS: According to Dragstedt (57) the parathyroid glands appear first as definite structures in the amphibia and are present and, so far as is known, exert an analogous function in reptiles, birds and mammals. They are not present in fishes Cowdry (47). Embryologically, each dorsal diverticulum of the third and fourth pharyngeal pouches gives rise to a small mass of epithelial cells termed a parathyroid gland. (Arey (4)). Two pairs of these bodies are thus formed, and, with the atrophy of the ducts of the pharyngeal pouches, they are set free and migrate caudalward until the pair from the third pouches come to lie at the caudal border and the pair from the fourth pouches at the cranial border of the thyroid gland. Since the ventral outgrowths of these same structures give rise to the thymus, the parathyroids are often associated with this organ, and its embedment, usually

beneath the capsule of the thyroid gives rise to its association with the latter organ. Thus, usually at least two pairs of parathyroids are recognized; one pair associated with each lobe of the thyroids. In addition nodules of accessory parathyroid tissue are recognized in and about the thyroid and thymus (Pepere (207); Hammar (117); Pappenheimer (196); Nicholas and Swingle (195)) or in the connective tissue in the anterior mediastinum, along the trachea, arch of the aorta, or pulmonary artery (Biedl (12)). The four glands weigh less than .5 gm in man (Welsh (246)). The form, size and color of each parathyroid gland is not uniform. Histologically, these glands are variously described (Dragstedt (57); Collip (41); Williamson and Pearse (255); Tomaszewski (240)). By far the best detailed description of the parathyroids from their appearance until old age and in various physiological and pathological conditions is made by Kurokawa (153), in which he reports the histology on 815 parathyroids of 240 necropsies. According to his findings each parathyroid is composed of parenchymal and interstitial tissues, well encapsulated, and at least in man never found in the substance of the thyroid gland, but just underneath its capsule. (It contains no more iodine than is found in organs such as the ovary, pituitary, or thymus (Chenu and Morel (28); Estes and Cecil (65); Hjort et al (128))).

The parenchyma consists of the following structures: (1) Oxyphile cells, usually appear in masss (presenting the picture of hyperplasia); they are large with sharp and angular margins, having a relatively small nucleus and finely and deeply staining chromatin; (2) Chief cells compose the larger portion of the parathyroids throughout life; they are polygonal in shape and smaller with a relatively larger deep stained eccentrically placed nucleus containing many distinct nucleoli, having a clear (clear chief cells) cytoplasm or a highly granular cytoplasm (dark chief cells) which, when it resembles the cytoplasm of the oxyphil cells is classified as the rosarot cell; may be a transitional cell but numbered with the chief cells; (Both oxyphile and chief cells may show syncitial forms) (3) Follicles, not limited to but appearing near the edge of the gland and encapsulated by chief cells; (4) Colloidal formations found in the chief cells of the follicles and often intercellularly between both chief cells and oxyphile cells (Chief cells form follicles and colloidal substance but it is doubtful whether oxyphile cells do either.); (5) Fatty substances, contained in large amounts in the dark chief cells but only traces are found in the clear chief cells, rosarot cells and oxyphile cells bearing distinct oxyphile granules; (No marantic pigment granules can be found in the parenchyma.)

(6) Glycogen is very abundant in the clear chief and follicular cells and is totally absent in the oxyphile cells. The author thinks that glycogen in the parathyroid glands has a different significance than the presence of glycogen in other organs. It appears that glycogen constitutes a specific element of the glands and has an important bearing on the function of the cells.

The interstitial tissue consists of connective and fatty tissues; the former is hardly perceptible in the fetus and newborn, is distinct in children and does not increase in and after adult age, except in certain diseases, whereas the latter is totally absent in the fetus and up to the time of infancy, is slightly increased in the adult with no tendency of increase in old age, but a very marked increase in such wasting diseases as tuberculosis and malignant tumors.

A further consideration of Kurokawa's findings may at least in part explain the varied findings reported on the histology of the parathyroid glands. He found that they became larger with advance of age, but there was no physiological atrophy. Its development is most marked at the period of adolescense when the most marked metabolic fluctations also occur. In fetal life the gland is entirely composed of clear chief cells which predominate up to the time of adolescence when upon the

appearance of the dark chief cells the former decrease whereas the latter increase to predominance in adult life. Since the glycogen and fat content of these cells is inverse in quantity it is obvious that the gland will be rich in glycogen when the clear predominate and rich in fat when the dark cells predominate, etc. The oxyphile cells contain only traces of fat or glycogen. They, together with the follicles and colloidal formations, do not make their appearance until the period of adolescence and increase with advance of age, but the increase has nothing to do with senility.

This histological change may express itself physiologically in the increased severity of tetany and the acute termination of young parathyroidectomized animals when compared with the delayed mild tetany and depression symptoms of older animals. Indeed there is no reason why the symptoms and course manifested by a young animal and an old animal when parathyroidectomized should not be different. We all subscribe to this phenomenon or principle in infant and adult thyroid deficiency, (cretinism and myxedema) pituitary deficiency and gonadectomy.

Kurokawa's pathological studies of the parathyroids in almost every known disease revealed the following: That in status lymphaticus there were lipomatosis and

atrophy of the parenchyma with marked increase of the oxyphile cells; that in chronic tuberculosis and syphilis there was in addition to lipomatosis marked interstitial and replacement fibrosis; that malignant tumors showed in addition to the interstitial lipomatosis a marked increase in oxyphile cells; that only the latter increased in pregnancy; that there were marked follicular formations in sarcomas of bones; that the clear chief cells are hypertrophic and in adult beri-beri they are markedly increased. Numerous other pathological findings have been reported by others.

DISCOVERY OF THE PARATHYROIDS. Sandström (215) in 1880 was the first to describe the parathyroids, their position and structure in the dog, cat, rabbit, ox and horse. This contribution was lost until eleven years later when the superior pair were rediscovered by Gley (89) in 1891. In 1895 Kohn (145) discovered the inferior or internal pair. He recognized at least two pairs in every animal; one pair in the substance of the gland and one pair at some distance from the thyroid in herbivera and on the surface or just under the thyroid capsule in the carnivora. He also gave proof that the thyroids and parathyroids were anatomically and functionally distinct.

HISTORICAL. The first physiological experiments were made by Raynard in 1835 (204). He found that several dogs died in a few days on removal of the thyroids. Schiff (1859) (221) in a similar experiment on rabbits, rats, dogs, guinea pigs and fowls found that some survived, others died in a few days. He showed in 1884 that rats and rabbits did not die but cats and dogs almost invariably died. These results were easily explainable by Gleys discovery (1891) showing the external pair of parathyroid outside of the thyroid in herbivera. Close in Gley's footsteps followed Vasalle and Generali (1900) (241) who affirmed and proved conclusively that the rapid course leading to fatality after thyroidectomy was due to the removal of the parathyroids. They characteristically described the symptoms following parathyroidectomy, and held that the parathyroids exerted an antitoxic function in the body whose removal produced death by poisoning. This gave rise to the toxin theory various phases and modifications of which have been supported by many different investigators. (MacCallum 1909 (169); Berkley and Beebe 1909 (10); Joseph and Meltzer 1911 (11), (142); Biedl 1913 (13); Koch 1912 (and 1913) (148); Findlay and Sharpe 1920 (69); Nattrass and Sharpe 1921 (191); Paton 1924 (197); Frank Stern and Notthmann 1921 (78); György and Vollmer 1922 (113); Palladin and Griliche 1924 (195); Dragstedt et al 1923 (53); Luckhardt

and Compere 1924 (162); and many others.)

However soon after the discovery of Vasalle and Generali, J. Loeb (1901) (160) reported that Calcium precipitating salts produced muscular twitches when injected in animals. Parhon and Ureche (1907) (200) followed by MacCallum and Voegtlin (1909) (169) made the next contribution in showing the relief of tetany by administration of Calcium salts. They then announced that the parathyroids regulated the Calcium exchange in the body and that the symptoms observed in parathyroid-ectomized animals were due to Ca deficiency. This theory has been supported by the investigations of MacCallum (1912) (165) and MacCallum et al (1914) (166); Luckhardt (1923) (161); Salvesen (1923) (216); Collip (1926) (41) to mention only a few.

Since these two chief theories have been advanced and variously supported many other miscellaneous observations bearing upon the Physiology of the Parathyroid glands have been recorded, notably, the acid-base equilibrium (Wilson et al 1915 (256), (257); Collip and Backus 1920 (33); Grant and Goldman 1920 (94); Greenwald 1922 (104); Cameron and Carmichael 1925 (24); and others), the inorganic ion ratios (Cooke 1910 (45); Gross and Underhill 1922 (96); Collip 1920 (34);), the phosphorus factor (reviewed above), and numerous other findings.

PARATHYROID DEFICIENT SYMPTOMS, CLINICALLY. The symptomatolgy following complete removal of the parathyroid glands have been recorded by many authors. They have been aptly and adequately reviewed and summarized by Dragstedt (57). His report has been verified in almost every detail in dogs.

When the parathyroid glands of the dog are completely removed at one operation, there results in over 90% of cases a characteristic symptom complex, parathyroid tetany or tetania parathyropriva, which has its counterpart in most other species. The recovery from the operation is complete and for a varying period of from 12 hours to 3 or 4 or rarely 5 to 6 days the animal may appear entirely normal. In most cases the earliest sign of any disturbance is an apparent loss of appetite, the refusal of food and water, and an increasing restlessness. At this time if food be introduced into the stomach by a tube it will usually be promptly vomited. Upon examination the peripheral motor nerves will be found hyper-excitable to electrical but not to mechanical stimulation. Respiration is increased. Often the animal thrusts its hot dry nose between the steel bars of its cage or scratches it frantically. Paroxysms of sneezing are a common feature in some dogs and in these and in most exhibiting laryngismus stridulus breathing may become difficult. A diarrhea, often bloody and

very offensive, is a frequent symptom. Soon fine fibrillary contractions of the temporal muscles can be felt and as these become pronounced, other muscles about the head and jaws are involved, and finally the legs. These are succeeded by more coarse irregular contractions and a gradually developing spasticity. If the stomach tube is now introduced, the esophagus and in particular the cardia will be found tonically contracted. There is a slight enophthalmos, the nictating membrane is drawn partly over the eye, and the spasm of the orbicularis oculi produces a definite trichiasis. The heart beat is slow and forcible and the temperature very high (106 to 107° F.). A profuse salivation now occurs, and this together with an increasing hyperpnea and clonic contractions of the leg muscles, initiates the spasm. The animal falls on its side, salivating and panting sterterously, its spastic legs stretched out and showing intermittent clonic contractions which become more frequent and severe until finally all the muscles contract in a tonic spasm, respiration stops, urine and feces are expelled, and death may occur. Usually however recovery, often surprisingly complete, takes place only to be succeeded by other and more severe attacks at progressively shorter intervals. Death is commonly produced by the asphyxia resulting from the long continued spastic contraction of the larynx and the muscles of respiration. A small number of animals die apparently

from exhaustion between attacks.

There are many variations in this general picture in dogs and marked differences in other animals. Often cats and occasionally dogs are depressed from the start and the condition progresses through an apathy, somnolence, rapid cachexia, paresis, to death within two weeks (Carlson (25); Paton and Findlay (199)). In the monkey the symptom complex is much milder, acute convulsions may not occur at all, the animal passing into a state of chronic tetany with progressive cachexia (Paton and Findlay (199)).

PROCEDURE FOR BLOOD ANALYSIS.

In order to involve the least possible amount of error, bleeding from the left ventricle with a fairly large needle was resorted to. In using a sharp needle and bleeding from the apex of the heart, I have bled dogs as many as 2 to 7 times a day and over a period of 12 to 30 days. Never was it necessary to tie the dog down and never was it necessary for any one to assist me in the performance. I found that after the first few bleedings, there was less objection on the part of the animal in this mode of bleeding than from the leg. The needles and the surface area need only be steralized in 95% alcohol. 15 cc were drawn in this manner and immediately transferred to a 15 cc centrifuge tube. From here on, the method as described by Subbarow and Fiske (234) was followed. With a delivery pipette, 4 cc of whole blood were at once transfered to a 50 cc Erlenmeyer flask containing 16 cc of 10% trichloracetic acid. (Slowly rotate the flask in this process.) The flask is at once stoppered with a clean and dry rubber stopper and shaken vigorously for a few moments. This may be filtered immediately through a small ashless filter. 5 cc of this protein free filtrate is used for the inorganic phosphorus determination and 5 cc for the total acid soluble phosphorus.

In determining the inorganic phosphorus, to the 5 cc of filtrate in a 10 cc graduated centrifuge tube or volumetric flask are added 1 cc of a 2.5% ammonium molybdate solution, made up in 5 N sulphuric acid. To this is added .4 cc of a 1,2,4-aminonaptholsulfonic acid (a coloring reagent solution prepared as directed from an Eastman Kodak Co product), made up to volume with distilled water and compared colorimetrically after 5 min. to a standard made at the same time which has in it per 100 cc, .4 mgm P, 10 cc of 2.5% ammonium molybdate in 5 N sulphuric acid and 4 cc of the color reagent.

The total acid soluble phosphorus is determined by adding to the 5 cc of filtrate in a large pyrex test tube containing some quartz crystals, 2.5 cc of 10 N sulphuric acid. This is placed above a micro-burner so that the bottom is 2 cm from the tip of the burner. In order to prevent spattering and produce accurate results, the flame should never reach the level of the fluid in the tube. When blackening appears in solution or fumes in the tube, the flame is turned low and ashing continued until no more blackening appears. One drop of concentrated nitric acid should turn the contents colorless immediately after which boiling is continued for 30 sec. The tube is then cooled to room

room temperature under the tap and the contents brought up to 35 cc by phosphorus free water, 5 cc of 2.5% ammonium molybdate in water are added, followed by 2 cc of the color reagent, made up to the 50 cc mark and then compared to the standard as described above.

The remaining 10 cc of the blood left in the centrifuge tube, was allowed to clot in the ice-chest or room temperature and the serum calcium determined according to the method of Kramer and Tisdall (152) as modified by Clark and Collip (30).

The serum was usually obtained by centrifuging the blood. To 2 cc of clear serum in a graduated centrifuge tube an equal volume of distilled water is added followed by 1 cc of 4% $(NH_4)_2C_2O_4$ solution. This was allowed to stand at room temperature for an hour in order to completely precipitate the calcium as the oxalate. This precipitate was then packed in the bottom of the tube by centrifuging at a high rate of speed for 5 minutes. The supernatant liquid was then decanted and the tube inverted and allowed to drain on filter-paper for 5 minutes. The mouth of the test tube was dried with a clean cloth, the precipitate stirred up by 3 cc of 2% (2 cc NH_4OH in 100 cc distilled H_2O) NH_3 water and the whole process of sedimentation repeated.

To this precipitate was added 2 cc of normal H_2SO_4,

boiled in a water bath for 1 minute and then removed to a water bath kept at 76° C where it was titrated with a N/100 $KMnO_4$ solution to a slight pink. This color should last at least 1 minute after titration. The $KMnO_4$ must be standardized from an approximately N/10 $KMnO_4$ solution each day for which a N/100 sodium oxalate solution may be used

GENERAL METHOD OF EXPERIMENTATION.

Normal concentrations of serum calcium and blood inorganic and total acid soluble phosphorus were determined. Dogs were used exclusively. A complete thyroparathyroidectomy was performed followed by treatment either before or after the symptoms of parathyroid-deficiency appeared. Blood analysis was continued usually from one to several times daily throughout the experimental period. The treatment consisted of well known measures taken for prevention and cure of toxemias or tetany viz: I. Heparmone; II. Calcium lactate; III. Strontium lactate; IV. Magnesium lactate; V. Morphine sulphate; VI. Ammonium chloride; VII. Uranium nitrate; and VIII. Parathormone. In the tables throughout this work the serum calcium is always reported as mg per cent (mg calcium per 100 cc of serum) and inorganic P and total acid soluble phosphorus (T.A.S.P.) are always reported as mg per cent (mg of P per 100 cc of whole blood).

NORMAL CONCENTRATIONS OF WHOLE BLOOD INORGANIC AND TOTAL ACID SOLUBLE PHOSPHORUS, SERUM CALCIUM AND THEIR RATIOS.

The serum calcium values found everywhere in the literature (Review by Stewart and Percival (232)) for normal and parathyroidectomized dogs were confirmed. The values of inorganic and total acid soluble phosphorus are within the range reported in the Literature (96), (239), (41). However, since the number of animals and determinations reported in this paper is by far larger than any others found in the literature, the following 2 tables have been constructed.

Table I was constructed with the object of giving the reader an idea of the individual and experimental variations in these blood constituents. It gives, therefore in the first column the number of each individual dog; in the second, the number of determinations made on that dog under normal conditions; and then in the following 9 columns have been listed, respectively, the highest, the lowest and the average of all normal determinations of serum calcium, inorganic and total acid soluble phosphorus for each given dog, followed in the last 2 colums by the normal average Inorg $\frac{P}{Ca}$ and T.A.S.P/Ca ratios. The table represents a total of 261 determinations made on 71 dogs.

TABLE I.

Table Showing the Highest, Lowest and Average of all Normal Determination of the Calcium, Inorganic and Total Acid Soluble Phosphorous and Average P/Ca Ratios.

Dog No.	No. of Determinations.	Serum Ca (mg)			Inorg P. (mg)			T.A.S.P.			Average. Inorg P/Ca	Average. TASP./Ca
		High	Low	Average	High	Low	Average	High	Low	Average		
52	6	12.79	12.28	12.55	4.61	3.64	4.08	28.37	27.00	27.66	.33	2.20
53	12	12.96	12.14	12.42	4.47	3.27	4.24	27.90	24.97	26.82	.35	2.15
54	6	10.86	10.04	10.57	4.41	3.85	4.11	30.36	29.06	29.81	.38	2.82
55	7	10.46	8.73	9.43	4.83	4.21	4.56	26.16	24.10	25.77	.48	2.73
56	4	10.77	9.60	10.16	4.61	4.20	4.45	27.68	25.48	27.00	.44	2.65
57	3	8.65	8.42	8.54	4.41	4.20	4.28	29.95	29.00	29.43	.50	3.44
58	3	9.45	9.30	9.35	4.13	3.69	3.84	27.39	25.05	26.09	.41	2.79
59	3	11.02	8.52	9.70	4.90	4.18	4.46	28.41	26.97	27.75	.46	2.86
60	4	12.62	10.82	11.98	7.11	4.54	5.46	26.89	24.75	26.43	.45	2.21
61	5	11.96	11.15	11.62	5.41	4.56	4.77	27.58	25.68	26.94	.41	2.32
62	5	11.76	11.18	11.52	5.91	5.37	5.55	30.97	27.88	28.93	.48	2.51

Dog No.	No. of determinations.	Serum Ca (mg)			Inorg P. (mg)			T.A.S.P.			Average. Inorg P/Ca	Average. T.A.S.P./Ca
		High	Low	Average	High	Low	Average	High	Low	Average		
63	5	10.62	10.00	10.29	5.33	3.41	4.63	29.59	27.38	28.20	.45	2.74
64	5	10.86	10.05	10.55	4.66	2.99	3.94	27.74	24.63	25.62	.37	2.42
65	6	10.83	10.52	10.60	4.16	3.55	3.95	26.91	23.65	25.00	.37	2.35
66	5	11.80	10.98	11.42	4.91	3.70	4.18	25.47	23.68	24.52	.37	2.14
67	8	12.41	11.30	11.88	4.81	3.63	4.20	23.26	21.05	22.23	.35	1.87
68	5	12.08	11.56	11.70	5.36	4.61	5.03	25.69	24.08	25.30	.43	2.16
69	5	11.71	19.59	11.48	4.69	4.39	4.55	25.30	24.18	24.66	.40	2.15
70	5	11.03	10.68	10.80	5.09	4.50	4.78	29.75	28.75	29.31	.44	2.71
71	4	11.64	11.46	11.53	5.49	5.08	5.33	29.65	27.70	28.60	.46	2.48
72	7	11.50	10.60	10.95	4.25	3.74	4.11	27.44	22.74	24.40	.37	2.24
73	4	11.53	10.90	11.13	4.85	4.38	4.58	34.80	29.12	32.20	.41	2.89
78	3	10.23	9.78	10.07	4.91	2.36	3.63	24.81	20.47	22.35	.36	2.21
79	4	11.50	10.70	11.12	6.09	3.58	4.40	26.64	24.34	25.10	.39	2.25
80	4	11.78	10.62	11.25	6.90	5.83	6.30	34.50	25.85	30.00	.56	2.66
81	2	10.94	10.93	10.94	4.09	3.02	3.60	33.30	33.17	33.23	.33	3.03

Dog No.	No. of determinations.	Serum Ca (mg)			Inorg P. (mg)			T.A.S.P.			Average. Inorg P/Ca	Average. TASP/Ca
		High	Low	Average	High	Low	Average	High	Low	Average		
82	2	12.03	11.46	11.75	6.04	5.58	5.81	29.66	29.39	29.52	.49	2.51
83	3	13.31	12.43	11.93	6.03	4.45	5.45	31.67	27.60	30.20	.44	2.42
84	3	10.70	10.52	10.71	5.08	4.44	4.68	27.49	24.32	25.40	.44	2.37
85	3	11.48	10.62	10.90	5.48	4.02	4.55	30.96	26.35	28.10	.42	2.57
86	3	10.46	10.05	10.20	3.84	3.68	3.74	23.78	22.54	23.18	.37	2.27
87	3.	10.75	10.63	10.70	5.80	4.70	5.12	26.20	23.10	25.35	.53	2.36
88	3	10.86	10.72	10.77	4.87	4.37	4.65	26.84	24.02	25.12	.43	2.33
89	2	10.48	10.38	10.43	3.63	3.60	3.62	19.48	18.75	19.12	.35	1.83
90	2	10.46	10.42	10.44	3.49	3.37	3.43	23.47	22.85	23.16	.33	2.21
91	2	10.48	10.35	10.41	4.73	4.48	4.50	23.48	23.47	23.48	.43	2.25
92	4	11.76	10.62	11.04	5.16	3.94	4.51	31.31	23.51	25.40	.41	2.30
93	4	12.82	11.38	11.90	5.33	4.37	4.93	24.85	20.42	22.62	.41	1.90
94	3	11.21	10.42	10.70	4.00	3.48	3.66	26.77	25.51	26.27	.34	2.45
95	2	10.62	10.43	10.49	3.61	3.53	3.56	28.19	27.92	28.05	.34	2.72
96	2	10.43	10.05	10.24	4.86	4.63	4.75	25.88	25.87	25.87	.46	2.52
97	2	11.41	11.40	11.40	4.44	3.68	4.15	25.79	25.67	25.73	.36	2.25

Dog No.	No. of Determinations.	Serum Ca (mg)			Inorg P. (mg)			T.A.S.P.			Average.	
		High	Low	Average	High	Low	Average	High	Low	Average	Inorg P/Ca	TASP./Ca.
98	2	10.40	10.00	10.20	2.97	2.95	2.96	25.41	23.25	24.33	.29	2.38
99	2	10.18	10.15	10.16	4.42	4.06	4.24	28.84	27.60	28.22	.42	2.66
100	2	11.20	10.03	10.61	4.18	3.73	3.95	26.72	26.30	26.50	.39	2.62
101	2	10.24	10.00	10.12	3.74	3.35	3.54	22.85	22.82	22.84	.35	2.25
102	2	10.52	10.52	10.52	3.26	3.14	3.20	25.73	24.53	25.13	.30	2.38
103	2	10.91	10.46	10.68	4.39	4.26	4.32	25.43	24.55	25.02	.40	2.34
104	2	10.53	10.52	10.53	3.26	3.11	3.18	24.08	22.73	23.40	.30	2.22
105	2	11.05	10.71	10.88	4.16	3.73	3.95	28.19	26.50	27.35	.36	2.51
106	2	11.10	10.88	11.00	4.99	4.95	4.97	25.72	24.70	25.21	.45	2.29
107	2	11.33	11.32	11.33	5.03	4.99	5.01	27.40	26.655	27.02	.44	2.38
108	2	10.82	10.21	10.52	3.24	2.77	3.00	30.42	29.74	30.08	.29	2.85
109	2	11.40	11.25	11.32	4.29	3.92	4.10	28.23	27.40	27.81	.36	2.45
111	2	11.10	10.95	11.02	4.61	3.96	4.28	26.84	21.90	24.37	.39	2.21
112	2	10.94	10.20	10.57	6.76	3.42	5.09	27.88	24.84	25.36	.48	2.39
113	2	10.20	10.10	10.15	6.96	4.10	5.53	28.15	24.62	26.38	.54	2.59
114	2	10.95	10.70	10.82	5.02	4.08	5.50	25.18	23.08	24.13	.51	2.23

Dog No.	No. of Determinations.	Serum Ca (mg)			Inorg P. (mg)			T.A.S.P.			Average. Inorg P/Ca	Average. TASP./Ca
		High	Low	Average	High	Low	Average	High	Low	Average		
115	3	11.80	11.54	11.68	5.19	5.02	5.11	24.85	22.52	23.62	.44	2.02
116	2	12.10	11.53	11.81	4.26	3.88	4.07	25.45	23.80	24.60	.34	2.08
118	2	11.20	11.08	11.14	3.75	3.70	3.72	23.50	23.50	23.50	.33	2.10
120	2	11.20	11.02	11.11	4.00	3.96	3.98	25.66	25.16	25.40	.36	2.28
121	16	12.10	10.62	11.32	5.91	4.34	4.93	31.00	25.91	29.20	.43	2.57
122	2	12.08	11.35	11.70	6.00	5.40	5.70	28.55	26.30	27.42	.49	2.34
123	16	12.96	11.30	11.87	6.43	5.48	5.90	28.32	26.10	27.08	.49	2.28
124	5	11.32	10.53	10.85	3.64	3.49	3.54	24.85	22.27	23.32	.33	2.14
125*	5	11.05	10.10	10.68	4.56	3.15	3.82	29.77	18.95	23.90	.36	2.23
128	2	10.62	10.20	10.41	6.15	5.21	5.68	26.38	25.98	26.58	.54	2.55
129	2	10.71	10.51	10.61	6.06	6.01	6.04	31.25	29.90	30.52	.57	2.28
130	2	10.88	10.61	10.74	4.34	4.14	4.24	26.92	26.26	26.59	.39	2.47
131	2	10.91	10.68	10.80	3.58	3.53	3.55	28.31	28.15	28.23	.33	2.61
Average for 71 dogs and 261 determinations:												
		11.03	10.60	10.84	4.82	4.08	4.44	27.38	24.85	26.25	.41	2.42

* Dog had extreme diarrhea. Otherwise well.

TABLE II

The Table is a summary of Table I. Maximal variations and average concentrations of whole blood inorganic and total acid soluble phosphorus and serum Ca and their ratios in normal dogs.

Average normal readings	Ca (mg)	Inorg. P	T.A.S.P. (mg)	Inorg P / Ca	T.A.S.P. / Ca	T.A.S.P. / Inorg P	No of Dogs	No of Determinations.
A. Dog No.	(52)	(80)	(81)	(129)	(57)			
Highest ave. value found	12.55	6.30	33.23	.57	3.44			
B. Dog No.	(57)	(98)	(89)	(108)	(89)			
Lowest ave. value found	8.54	2.96	19.12	.29	1.83			
C. Highest Readings on all Dogs	11.03	4.82	27.38	.44	2.48	5.7	71	71
D. Lowest Readings on all Dogs	10.60	4.08	24.85	.39	2.35	6.0	71	71
E. Average of all normal readings	10.84	4.44	26.65	.41	2.42	5.9	71	261

Table II is a brief Summary of Table I, showing (1) in A and B, respectively, the highest and lowest values found in any given dog; (2) in C and D, respectively, the average of all the highest and lowest readings of all the dogs; (3) in E the average of all normal readings (261) on all the dogs (71).

It would seem from Table II (A and B) that the serum Ca and whole blood inorganic and Total Acid Soluble Phosphorus content may even normally vary widely from an accepted average as given in E of the same table. But on closer examination of Table I we find that the data listed in Table II (A and B) are rather the maximal and minimal exceptions to the rule.

In serum calcium content there were only 6 dogs (3 above and 3 below) that varied markedly more than ±.3 mg per cent from the average (10.84). In whole-blood inorganic P content there were 18 dogs (7 above and 11 below) that varied markedly more than ±.5 mg per cent from the average (4.44). In the total acid soluble P content there were 20 dogs (10 above and 10 below) that varied markedly more than ± 2 mg per cent from the normal (2.42). It will be noted that in this large series the total acid soluble P/Inorganic P ratio is nearly 6. However there is a wide individual variation --5 or 7

are not uncqmmon. Even within the individual this ratio may vary ± 50-100% normally from time to time.

We find therefore that the serum calcium is quite constant in a dog from day to day and as one proceeds from dog to dog; that both the inorganic and total acid soluble phosphorus of the whole blood may vary widely from day to day and dog to dog, whereas the phosphorus calcium ratio, particularly the total acid soluble phosphorus/Ca ratio tends to be fairly constant from day to day but not from dog to dog.

THE WHOLE BLOOD TOTAL ACID SOLUBLE AND INORGANIC PHOSPHORUS, SERUM CALCIUM, AND THEIR RATIOS WHEN PARATHYROID DEFICIENT SYMPTOMS APPEAR IN UNTREATED DOGS.

Of the 71 dogs reported above 41 were not treated until parathyroid deficient symptoms appeared. The results on these 41 dogs are shown in the form of tables (III and IV) and Graphs (I-A, B, C and D). These tables and graphs are divided into 3 parts representing 3 groups of dogs classified according to the type of symptoms shown and the severity of their onset. Group I includes 11 dogs that developed sudden and severe tetany (Table III and IV, Part I; Graph I, A). Group II

includes 23 dogs that developed mild tetany (Tables III and IV, Part II; Graph I, B). Group III includes 8 dogs showing profound depression (Tables III and IV, Part III; Graph I, C). Graph I D is a summary of A, B, C, obtained by averaging the data of each dog in Table I.

Since it appeared that the blood chemistry did not only vary with the type of symptoms and the severity of their onset but also with the time of onset after the operation, the data in the tables and graphs have been further arranged according to the post-operative days when symptoms became manifested. Thus, for example in Graph I A numbers as abscissae indicate the days when symptoms appeared, whereas the numbers at the top of the graph indicate the number of dogs showing symptoms on each respective day and whose data has been averaged to compose that portion of the graph. For further comparison of these 3 groups as a whole, the last lines of Parts I, II and III of Table IV show the average values for P, Ca and P/Ca ratios for its respective part of the table and this data is shown separately in Graph I D. This data for Graph I D and the last lines of each part of Table IV was obtained by averaging the data of the individual dogs of each part or group as listed in Table III and not by averaging the values of each part of Table IV. Table IV and Graph I A, B, C, and D thus completely summarize Table III.

TABLE III.

Table Showing the Concentrations of Serum Ca. Inorganic and Total Acid Soluble Phosphorous and the P/Ca Ratios of Dogs when Normal and when Symptoms Appear: Part I--Dogs Showing Sudden and Severe Tetany; Part II--Dogs Showing Mild Tetany; Part III--Dogs Showing Depression. (Arranged in order of Days when Symptoms appeared.)

Dog	Day of	Serum Ca (mg)		Inorg P (mg)		T.A.S.P. (mg)		Inorg P/Ca		T.A.S.P./Ca	
	symptoms	Nor-mal	Sympt-oms	Nor-mal	Sympt-oms	Nor-mal	Sympt-oms	Nor-mal	Sympt-oms	Nor-mal	Sympt-oms
		PART I--DOGS SHOWING SUDDEN AND SEVERE TETANY.									
53	2	12.42	7.44	4.24	4.75	26.82	31.87	.35	.64	2.15	4.28
54	2	10.57	4.23	4.11	5.07	28.81	27.50	.38	1.20	2.82	6.50
71	2	11.533	6.36	5.33	5.48	28.60	29.55	.46	.86	2.48	4.64
81	2	10.94	5.35	3.60	5.33	33.23	34.59	.33	1.00	2.54	6.46
99	2	10.16	6.40	4.24	6.29	28.22	33.05	.42	.98	2.66	5.16
106	2	11.00	6.04	4.97	5.51	25.21	27.56	.45	.91	2.29	4.56
109	2	11.32	6.71	4.10	5.76	27.81	29.00	.36	.86	2.45	4.32
125	2	10.68	5.16	3.82	6.25	22.45	26.50	.49	1.21	2.34	5.13

Part I (con)

Dog	Day of symptoms	Serum Ca (mg)		Inorg P (mg)		T.A.S.P. (mg)		Inorg P/Ca		T.A.S.P./Ca	
		Normal	Symptoms	Normal	Symptoms	Normal	Symptoms	Normal	Symptoms	Normal	Symptoms
104	3	10.53	4.81	3.18	3.92	23.40	24.67	.30	.81	2.22	5.12
102	4	10.52	6.62	3.20	4.73	25.13	33.18	.30	.71	2.38	5.01
101	5	10.12	5.13	3.54	5.98	22.84	27.40	.35	1.15	2.25	5.34
		PART II--DOGS SHOWING MILD TETANY.									
655	1	10.60	7.85	3.95	5.91	25.00	25.52	.37	.75	2.35	3.25
108	1	10.52	7.50	3.00	5.10	30.08	31.67	.29	.68	2.85	4.22
61	2	11.62	7.93	4.77	6.57	26.95	28.68	.41	.83	2.32	3.61
63	2	10.29	6.02	4.63	5.93	28.20	27.44	.45	.99	2.74	4.55
64	2	10.55	6.02	3.94	5.29	25.62	25.95	.37	.88	2.42	4.31
78	2	10.07	5.06	3.63	6.27	22.35	25.22	.36	1.24	2.21	4.98
79	2	11.12	7.23	4.40	5.16	25.10	23.20	.39	.71	2.25	3.52
80	2	11.25	6.40	6.30	6.55	30.00	26.02	.56	1.02	2.66	4.06
82	2	11.75	6.51	5.81	6.05	29.52	28.55	.49	.93	2.56	4.38
83	2	12.43	7.12	5.39	6.66	30.20	25.22	.44	.94	2.42	3.54

TABLE III

Part II (con)

Dog	Day of	Serum Ca (mg)		Inorg P (mg)		T.A.S.P. (mg)		Inorg P/Ca		T.A.S.P./Ca	
	symptoms	Normal	Symptoms	Normal	Symptoms	Normal	Symptoms	Normal	Symptoms	Normal	Symptoms
88	2	10.77	6.40	4.65	5.45	25.12	27.70	.43	.85	2.33	4.32
94	2	10.70	6.65	3.66	6.20	26.27	27.40	.34	.45	2.45	4.12
95	2	10.49	5.73	3.56	4.00	28.05	29.45	.34	.70	2.72	5.13
96	2	10.24	6.82	4.75	5.06	25.87	31.00	.46	.74	2.52	4.54
97	2	11.40	6.18	4.15	5.44	25.73	27.20	.36	.88	2.25	4.40
107	2	11.33	6.13	5.01	7.00	27.02	29.82	.44	1.14	2.38	4.86
121	2	11.23	6.23	4.93	6.66	27.87	27.76	.43	1.07	2.57	4.45
56	3	10.61	5.12	4.45	6.64	27.00	28.00	.44	1.30	2.65	5.46
84	3	10.71	5.83	4.68	6.31	25.40	26.14	.44	1.08	2.27	4.48
85	3	10.90	6.73	4.55	5.29	28.10	23.24	.42	0.77	2.57	3.47
105	3	10.88	6.24	3.95	3.48	27.35	23.37	.36	.56	2.51	3.74
103	4	10.68	5.88	4.32	4.00	25.02	24.17	.40	.68	2.34	4.11
100	5	10.11	5.41	3.95	5.61	26.50	25.53	.39	1.04	2.62	4.71

TABLE III (con).

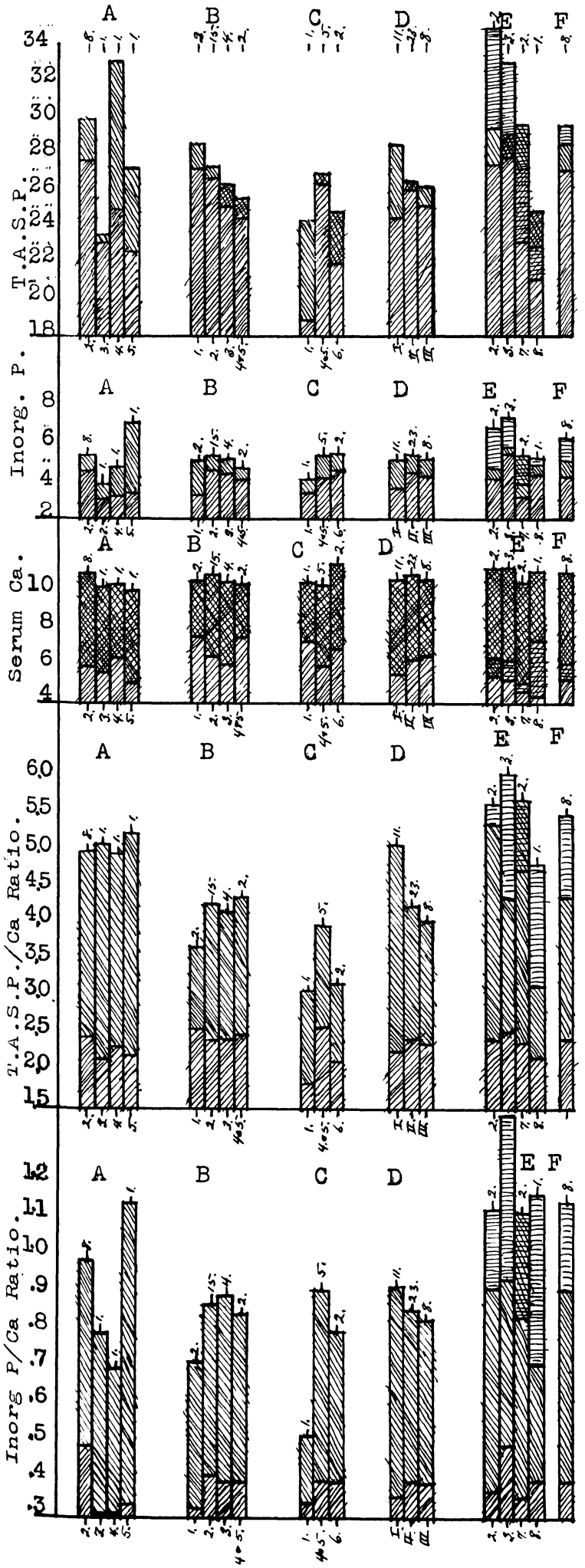
PART III----DOGS SHOWING DEPRESSION.

Dog	Day of	Serum Ca (mg)		Inorg P (mg)		T.A.S.P. (mg)		Inorg P/Ca		T.A.S.P./Ca	
	symptoms	Normal	Symptoms	Normal	Symptoms	Normal	Symptoms	Normal	Symptoms	Normal	Symptoms
89	1	10.43	7.84	3.62	4.14	19.12	24.37	.35	.53	1.83	3.10
58	4	9.35	5.88	3.84	4.61	26.09	25.00	.41	1.27	2.79	4.25
59	4	9.70	4.55	4.46	6.78	27.75	24.54	.46	1.49	2.86	6.04
52	5	12.55	7.33	4.08	5.38	27.66	27.81	.33	.73	2.20	3.79
57	55	8.54	5.84	4.28	4.46	29.43	29.63	.50	1.07	3.44	5.07
66	5	11.42	6.50	4.18	5.40	24.52	22.83	.37	.83	2.14	3.51
60	6	11.98	7.88	4.60	5.21	25.43	19.46	.45	.66	2.21	2.46
69	6	11.48	6.03	4.555	5.87	24.66	24.87	.40	.97	2.15	4.10
Average for all:											
	41	10.84	6.32	4.28	5.47	26.46	27.29	.40	.91	2.44	4.32

TABLE IV.

Summary of Table III: Parts I, II and III averaged according to the Day when symptoms appeared, with total average in last line of each part.

Remarks	No. of dogs	Day of Symptoms	Serum Ca (mg)		Inorg P (mg)		T.A.S.P. (mg)		INORG P/Ca		T.A.S.P./Ca	
			Normal.	Symptoms.	Normal.	Symptoms.	Normal.	Symptoms.	Normal.	Symptoms.	Normal.	Symptoms.
			Part I. Dogs showing sudden and severe tetany.									
Severe	8	2	11.20	5.99	4.60	5.56	27.76	29.95	.41	.99	2.45	5.00
Tetany	1	3	10.53	4.81	3.18	3.92	23.40	23.67	.30	.81	2.22	5.12
Dogs	1	4	10.52	6.62	3.20	4.73	25.13	33.18	.30	.71	2.38	5.01
	1	5	10.12	5.13	3.54	7.27	22.84	27.40	.35	1.15	2.25	5.34
Average	11		10.59	5.66	3.84	5.34	24.78	28.55	.24	.92	2.33	5.12
			Part II. Dogs showing mild tetany.									
Mild	2	1	10.56	7.68	3.48	5.51	27.54	28.59	.33	.72	2.61	3.72
Tetany	15	2	11.01	6.43	4.64	5.67	26.92	27.52	.42	.88	2.45	4.28
Dogs	4	3	10.67	5.98	4.41	5.41	26.46	25.23	.41	.90	2.48	4.22
	2	4 & 5	10.39	5.64	4.13	4.81	25.76	24.85	.40	.85	2.48	4.41
Average	23		10.90	6.35	4.48	5.60	26.67	26.55	.39	.86	2.45	4.25
			Part III. Dogs showing depression.									
Depres-	1	1	10.43	7.84	3.62	4.14	19.12	24.37	.35	.53	1.83	3.10
sion	5	4 & 5	10.31	6.02	4.17	5.53	27.09	26.55	.40	.92	2.63	4.41
Dogs	2	6	11.73	6.95	4.58	5.54	25.05	22.21	.39	.80	2.14	3.20
Average	8		10.68	6.48	4.20	5.35	25.58	26.42	.39	.83	2.40	4.08



Graph I. Showing the concentration of Total Acid soluble and Inorganic P per 100 cc of whole blood and the Ca per 100 cc of serum and the P/Ca ratios when Parathyroid deficient symptoms appeared in untreated dogs: A. Dogs showing sudden and severe tetany; B. Dogs showing mild tetany; C. Dogs showing depression; D. (I, II, & III), respectively, showing the average of A, B, & C; E. shows in addition the concentration and ratios of 8 untreated dogs at time of death.

Numerals as abscissae in A, B, & C indicate the day when symptoms appeared and in E when dogs died, whereas numerals at the top of each graph indicate the number of dogs included in each respective day of the graph. (In E and F all 8 dogs showed symptoms on the second postoperative day.) F shows the average of E.

Normal Concentration and Ratios.

Difference in Concentration between Normal and when Symptoms appeared.

Difference in Concentration between Symptomatic and time of Death.

It will be noted that the Tables and Graphs referred to above only present calcium and phosphorus concentration and the P/Ca ratios at the time of operation (average of all normal determinations) and at the time when symptoms appeared. The post-operative presymptomatic determination are entirely excluded from these tables and graphs. These readings may be obtained from the protocols of the individual dogs, for the serial number of each dog is given in Table III column 1. Determinations were usually made daily postoperatively up to the time when symptoms appeared. The results were too variable to be included in the table.

Whereas the calcium fell progressively from the time of operation until symptoms appeared there was no such constancy for the inorg and total acid soluble phosphorus. The P/Ca ratios always tended upward from the time of operation. Both inorganic and total acid soluble phosphorus varied widely during this presymptomatic period. A dog may show a high inorganic and total acid soluble phosphorus within 24 hours of the operation and then a progressive fall until symptoms appear (Dog 60 and 69) or he may show just the reverse (Dog 61). All gradations between these variations are recorded in the protocols.

The inorganic and total acid soluble phosphorus did

by no means always vary in the same direction. Again, it is also evident from the individual protocols that though there is a rapid rise in the P/Ca ratios post-operatively, symptoms do not always occur when the disturbance in either or both the inorg P/Ca and T.A.S.P./Ca ratios are at a maximum. This is especially the case when symptoms develop several days after the operation. However, as a rule these ratios are in the neighborhood of the maximum disturbance when symptoms first appear. But dogs surviving a few attacks of tetany show no direct constant relationship in symptomatology to these ratios (Dog 69).

TOTAL ACID SOLUBLE PHOSPHORUS WHEN SYMPTOMS APPEARED: The total acid soluble phosphorus finds its widest variation and greatest rise in the severe tetany dogs (Group I; Tables III and IV, Part I; Graph I, A). With one exception (Dog 54) every dog in this group showed a higher than normal total acid soluble phosphorus when symptoms appeared, no matter whether tetany occurred on the second or 5th post-operative day. The rise was from 1 to 8 mg per cent. The severity of tetany was not identical and proportional to the change of phosphorus content. The change in phosphorus content precedes, accompanies or follows the appearance of symptoms.

The dogs in group II (Table III and IV, Part II; Graph I, B) differ from the first group in that the

phosphorus variations were not so extensive and in that the symptomatic values were below the normals in the later days. Only in one dog (Dog 96) was there a rise of 6 mg per cent of total acid soluble phosphorus. The remaining mild tetany dogs showed only a slight rise (1 to 2 mg per cent) or an actual decrease in blood total acid soluble phosphorus (2 to 6 mg per cent). In this group the phosphorus is actually the same or below the normal when symptoms appear on the third, fourth and fifth days and when in some on the second day. The depression dogs (Group III, Tables III and IV, Part III; Graph I, C) show about the same phosphorus variations as group II.

Comparing these three groups as a whole (Graph I D) it is significant that only the tetany dogs (D I) show a marked average increase of total acid soluble phosphorus above the normal at the time that symptoms appeared whereas the mild tetany (D II) and depression dogs (D III) showed very little change.

These considerations would lead us to conclude that in a large series of dogs the total acid soluble phosphorus tends to vary directly with the severity of the symptoms manifested and inversely with the time of their post-operative onset. The exceptions to this have been discussed above. Obviously, there is no symptomatic value for the total phosphorus, symptoms appearing at levels as low as 19.5 mg per cent (Dog 60) and 34.6 mg per cent (Dog 81).

INORGANIC PHOSPHORUS WHEN SYMPTOMS APPEARED: The inorganic phosphorus of the whole blood for these 3 groups of dogs are represented in the same respective portion of the tables and graphs.that have been discussed for the T.A.S.P. About all that can be said of the inorganic phosphorus is that without exception the concentration is always higher than normal when symptoms appear. It does not tend to exhibit the relationship to the severity of the symptoms and the time of their onset that the total acid soluble phosphorus does. The symptomatic values of inorg P are from .25 to 2.5 mg per cent above the normal concentration.

SERUM CALCIUM WHEN SYMPTOMS APPEARED: From the tables and graphs it is very evident that with five exceptions the calcium is constantly in the neighborhood of 5 to 7 mg per cent when symptoms appear in untreated dogs. Our data is of interest in that the average values for the 3 groups at the time that symptoms appeared are within .85 mg per cent of each other:

Group I 4.23 to 7.44; average 5.66

Group II 5.06 to 7.93; average 6.35

Group III 4.55 to 7.84; average 6.48

However, the calcium range at which symptoms (no matter how mild or severe) may appear is just as great for one group of dogs as it is for another and has little respect

of the post-operative time when symptoms appear. It seems that the calcium tends to fall progressively from the time of operation and that it is the rate of change that determines the symptomatology. That is to say a dog showing a slow decrease in serum calcium in the course of several days, as in the case of dog 69, can withstand a much lower calcium than a dog that shows the same decrease in the first day or two, as in the case of dog 54 or dog 106. However the rate of calcium change does not determine the type or severity of symptoms that may appear. Thus dog 53 showed the same severe tetany on the second post-operative day at 7.44 mg per cent Ca or dog 54 at 4.23 mg per cent Ca as did dog 101 on the fifth day at 5.13 mg per cent Ca. Similar comparisons may be made for the mild tetany dogs (Dog 65 and Dog 100) and the depression dogs (Dog 89 and Dog 60).

Although this progressive lowering of serum calcium is the rule, the mild tetany and depression dogs showing symptoms beginning with the fourth to the sixth post-operative day have a slightly higher calcium than a day or two previous to the time that symptoms appear. (Graph I, B and C.).

TOTAL ACID SOLUBLE PHOSPHORUS/Ca RATIO WHEN SYMPTOMS APPEARED: (Tables III and IV and Graph I A, B, C and D) This ratio is highest for group I (4.28 to 6.50; average

5.12); next comes group II (3.25 to 5.46; average 4.25), followed closely by group III (2.46 to 6.04; average 4.08). This is just what one would expect since the total acid soluble phosphorus tends to vary directly with the severity of the symptoms manifested and inversely with the time of their post-operative onset. Again since the rate of calcium change is related to the post-operative time when symptoms appear but not to their severity, it follows that the calcium with few exceptions falls progressively until symptoms appear.

Hence, within any of these respective groups the high total acid soluble phosphorus in early and severe symptoms when the serum Ca is still relatively high will tend to equalize the ratio to that found in dogs showing symptoms several days later when the total acid soluble phosphorus has already fallen below the normal, but the calcium is relatively lower because of its progressive fall from day to day. But since the progressive fall of calcium is relatively greater than the later decrease of total acid soluble phosphorus in all three groups of dogs, the total acid soluble phosphorus/Ca ratio remains the same or shows a slightly higher ratio in dogs showing symptoms in later days. This is shown in graph I A, B, C and D. These graphs show that the ratio is highest for the severest tetany dogs and progressively lower for the mild tetany and

depression dogs (D). A, B, and C show that the increase in ratio above the normal is the same or progressively higher as one goes from day to day when symptoms were manifested.

INORGANIC P/Ca RATIO WHEN SYMPTOMS APPEAR: From the tables (III and IV) and graphs (I A, B, C and D) it is obvious that the inorganic P/Ca ratio tends to parallel the total acid soluble phosphorus/Ca ratio; however the extent of change for the inorganic P/Ca ratio is not as constant as that of the total acid soluble P/Ca ratio.

CONCLUSIONS.

1. The total acid soluble phosphorus (whole blood content relative to its normal concentration) of parathyroidectomized dogs when parathyroid deficient symptoms appear tends to vary directly with the severity of the symptoms manifested and inversely with the time of their post-operative onset. Exceptions to this are found in the very severe tetany dogs.

2. Under the same conditions the inorganic phosphorus is always above normal when symptoms appear but the exception to paralleling the total acid soluble P changes are numerous.

3. The rate of serum calcium fall and not so much the absolute content determines the onset of parathyroid

deficient symptoms but bears no relationship to the type and severity of symptoms manifested.

4. The total acid soluble P/Ca ratio tend to vary directly with the severity of the symptoms manifested and the time of their post-operative onset.

5. The inorganic P/Ca ratio tends to parallel the T.A.S.P./Ca ratio exhibiting less constancy in its extent of change.

WHOLE BLOOD TOTAL ACID SOLUBLE AND INORGANIC PHOSPHORUS, SERUM CALCIUM AND THEIR RATIOS IN PARATHYROIDECTOMIZED DOGS AT OF (1) DEATH OR (2) RECOVERY.

Of the untreated parathyroidectomized dogs that showed symptoms, there were ten. Eight of these died; 2 on the second, 3 on the third, 2 on the seventh and 1 on the eight post-operative day. All of these dogs showed more or less severe symptoms from the second post-operative day. The two dogs (Dogs 53 and 54) dying shortly after precipitation of tetany on the second post-operative day do not strictly belong to this group. They received some liver extract immediately upon showing symptoms. However, comparison with other dogs treated with liver extract shows that the dose these animals received was prabably ineffective and for that reason they

are included in this series. The other 2 dogs both showed mild tetany and severe depression symptoms but not until the seventh day. Recovery occured on the 18th (Dog 69) and 34th (Dog 115) days, respectively. One of these dogs, a female, was later injected with parathormone, developing parathyroid deficient symptoms subsequent to discontinued treatment, from which she died; the other, a male is still in excellent condition now, 14 months after operation and more than 13 months after complete recovery.

Ca AND P VALUES AT TIME OF DEATH: The results from these dogs are shown in Table V and in Graph I, E and F. It is evident from these results without much further discussion that the conclusion drawn above for the changes taking place until symptoms appear apply equally well to the changes taking place in the blood from the time that symptoms appear until death.

Thus the total acid soluble phosphorus on the dogs that died about 2 hours after sudden precipitation of severe tetany on the second post-operative day indicate a rise of 2 mg per cent to the time that symptoms appear and an additional 5 mg per cent just preceeding death; those dying on the third day, a fall of 1.5 mg per cent at the time of symptoms and then a rise of 6 mg per cent above the symptomatic value; those dying on the seventh day, a 2 mg per cent rise at the time of symptoms and a

TABLE V.

Table showing eight dogs that died of parathyroid deficiency without treatment. All dogs showed symptoms on second post-operative day. Table is arranged according to day of post-operative death--showing concentration of serum Ca, whole blood Inorg. and total acid soluble phosphorus and the P/Ca ratios when normal, when symptoms appeared and at time of death.

No. of Days	Day of Death	Serum Ca (mg)			Inorg P (mg)			T.A.S.P. (mg)			Inorg P/Ca			T.A.S.P./Ca		
		Normal	Symptoms.	Death	Normal.	Symptoms.	Death	Normal.	Symptoms.	Death	Normal.	Symptoms.	Death	Normal.	Symptoms.	Death
2	2	11.50	5.84	6.52	4.18	4.92	7.00	27.81	29.68	34.94	.37	.92	1.13	2.45	5.37	5.68
3	3	11.51	6.23	5.46	5.81	6.02	7.56	29.40	28.03	33.16	.50	.94	1.41	2.57	4.38	6.09
2	7	10.50	5.20	4.77	3.62	5.75	4.00	27.79	29.91	23.50	.35	1.12	.84	2.38	5.72	4.95
1	8	11.12	7.23	4.42	4.40	5.16	5.20	25.10	23.20	21.55	.39	.71	1.17	2.25	3.20	4.87
8	Average	11.15	6.07	5.46	4.50	5.58	6.26	27.53	28.60	29.74	.40	.92	1.15	2.41	4.67	5.51

fall of 6 mg per cent at the time of death; whereas the dog on the eighth day showed a 2 mg per cent fall to the time that symptoms appeared and an additional fall of 1.7 mg per cent at the time of death.

The inorganic P shows a similar change bo that of the total acid soluble phosphorus but is never below its normal concentration at the time of death, although in one instance it is below the symptomatic concentration at the time of death.

The serum calcium falls more or less progressively from day to day until death, although it may be lower between convulsions at times than at the time of severe tetanic seizures (Dog 81). The dogs that died with the first sudden and acute attack and one dying on the seventh day showed a rise in serum calcium just preceeding death, amounting to 1 mg per cent (Dogs 53, 54 and 81).

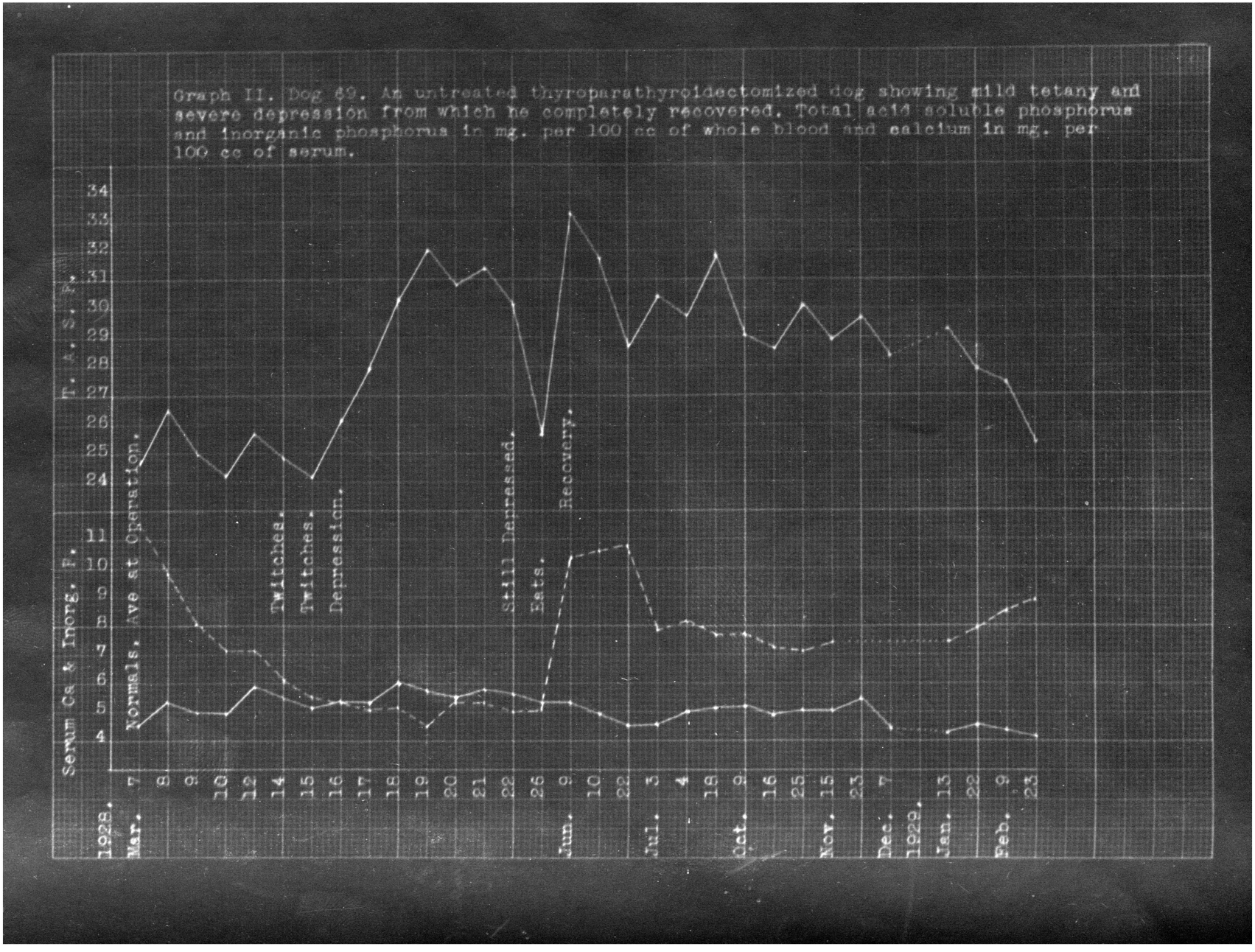
Both total acid soluble and inorganic P/Ca ratios were higher at the time of death than at the time when symptoms appeared except in one dog dying on the seventh day (Dog 81). His ratio fell so markedly on the day of death due to a clacium rise (4.05 to 5.17) that on the graph (Graph I, E and Table IV) it would seem that both dogs dying on the seventh day had lower ratios at the time of death than at the time when symptoms appeared.

Obviously, however, there is no constant relationship between the time of post-operative death and the maximum disturbance of these ratios. For instance in Dog 81 these ratios varied between 5.62 and 6.40 (T.A.S.P./Ca) and .75 and 1.20 (Inorg. P/Ca) from the time of tetany on the second day until death on the seventh day, with death finally occurring at the respective ratios of 4.73 and .82. On the other hand dog 69 did not die and his respective ratios rose as high as 7.01 and 1.26.

Ca AND P VALUES DURING AND AFTER RECOVERY: Dog 69 Graph II now living 14 months after operation and in good condition showed severe depression and mild tetany and was fed daily during this period (by stomach tube) the regular maintenance diet, consisting of powdered dried beef heart, ground cracker meal, kaolin and corn oil and a definite amount of water. Thus this dog even with a balanced protein diet without milk and no treatment was able to withstand a calcium as low as 4.56 and an inorganic P and T.A.S.P., respectively, of 6.00 and 31.97 with ratios of 1.26 (Inorg P/Ca) and 7.01 (T.A.S.P./Ca). Even after 10 such days when convalescence began the respective values in the order named above were 5.16; 5.26; 25.67; 1.02; and 4.97.

A month later the animal was returned to the regular stock diet of bread, hamburger and some milk and has never

Graph II. Dog 69. T.A.S.P/Ca and Inorg.P/Ca ratios of dog from opposite page.


Graph II. Dog 69. An untreated thyroparathyroidectomized dog showing mild tetany and severe depression from which he completely recovered. Total acid soluble phosphorus and inorganic phosphorus in mg. per 100 cc of whole blood and calcium in mg. per 100 cc of serum.
F. A. S. P.
Serum Ca & Inorg. P.
Normals. Ave at Operation.
Twitches.
Twitches.
Depression.
Still Depressed.
Eats.
Recovery.
1928. Mar. Jun. Jul. Oct. Nov. Dec. 1929. Jan. Feb.

since shown marked symptoms. In the period (See Graph II) from Jan. 9, 1928 to Feb. 23, 1929, his calcium varied from 7.13 to 10.72 mg per cent; his inorg P from 4.08 to 5.44 mg per cent; his T.A.S.P. from 33.25 to 25.30 mg per cent; his inorg P/Ca ratio from .42 to .71; and his T.A.S.P./Ca ratio from 4.22 to 2.84. There is a marked tendency to reestablish the normal ratios, either by lowering the P content or raising the calcium or both. This latter fact is also seen in Dog 115 where in recovery the Ca rose from 5.33 to 8.20 mg per cent; the inorg P and T.A.S.P. fell, respectively, from 7.02 to 5.16 and 27.20 and 19.80 mg per cent while the ratios were reduced from 1.32 to .62 (Inorg P/Ca) and 5.14 to 2.41 (T.A.S.P./Ca)

From this alone it would seem that there must be more to the question of parathyroid deficiency than a mere low blood calcium being the cause of the symptoms and death. Here were 2 dogs that received absolutely no treatment at all, were both fed a balanced protein diet, had a low serum calcium, high acid soluble phosphorus compounds accompanied by depression, mild tetany and laryngismus stridulus--in fact they had all the indications of a parathyroid deficiency that ordinarily leads to fatality--and still the animals recovered.

It is thus difficult to conclude just what role any of the factors discussed may play in the symptomatology

and events leading to death in a parathyroid deficient animal. It seems that in the events leading to early death the rate of Ca and phosphorus change may play a part, whereas in animals dying or recovering after several days of symptoms it becomes a question of maintenance of life at a progressively lower absolute calcium content until the body is able to compensate more fully for the parathyroid deficiency. A low blood inorganic and particularly total acid soluble phosphorus content is highly favorable in bringing about this compensation or readjustment.

Our findings on the blood inorganic phosphorus in dogs suffering from parathyroid deficiency agree with those reported by other investigators, namely that it increases, however inconstantly and varies considerably in amount (Greenwald (98), (105), (106), (107); Salvesen (216), (217); Gross and underhill (96)). It is possible in some cases that the changes observed in both total acid soluble and inorganic P may have been due to kidney injury or even to ether anaesthesia (especially in those where a marked increase in both was observed only the first post-operative day) since this has been found to increase the inorganic phosphate of the blood in normal rabbits (Martland and Robson (177)) and also in dogs (Stehle and Bourne (230)).

DOGS THAT RECEIVED NO TREATMENT.

(Protocols.)

Ca in mg per 100 cc of serum. Inorganic and total acid soluble P in mg per 100 cc whole blood.

Date	Time	Remarks	Serum Ca	Inorg P	T.A.S.P.	Inorg / Ca	T.A.S.P. / Ca
Dog 69. Male. 10 Kilo.							
1928							
Feb.							
27	3:00 PM		10.59	4.39	24.54	.44	2.32
28	4:00 PM		11.07	4.52	24.85	.41	2.24
March							
1	6:00 PM		11.42	4.54	24.47	.40	2.14
2	5:20 PM		11.52	4.61	24.18	.40	2.10
6	5:00 PM		11.71	4.69	25.30	.40	2.11
7	4:40 PM	Thyroparathyroidectomy					
8	3:00 PM		9.81	5.35	26.44	.54	2.69
9	2:00 PM		8.03	4.97	24.97	.62	3.11
10	10:00 AM	No symptoms	7.08	4.88	24.28	.69	3.43
11		Not fed					
12	2:00 PM	No symptoms of tetany	7.06	5.87	25.66	.83	3.63
13		Did not eat					
14	3:00 PM	Twitches. Meal by St. tube Vomites 1/3	6.03	5.47	24.78	.91	4.11
15	9:00 AM	Twitches. Meal by St. tube Vomites 1/2	5.52	5.13	24.13	.93	4.37
16	1:40 PM	No twitches Meal by St. tube Depressed	5.31	5.34	26.14	1.01	4.92
17	11:50 AM	No twitches Depressed Meal by St. tube Vomites 1/2	5.11	5.33	27.95	1.02	5.47
18	1:00PM	No twitches Depressed Meal by St. tube	5.16	6.00	30.30	1.16	5.87

Date	Time	Remarks	Serum Ca	Inorg P	T.A.S.P..	Inorg / Ca	T.A.S.P. / Ca
March							
19	3:30 PM	No twitches.Depressed. Meall by St. tube.	4.56	5.72	31.97	1.26	7.01
20	3:45 PM		5.32	5.52	30.80	1.04	5.79
21	3:30 PM		5.29	5.79	31.37	1.09	5.93
22	3:35 PM		5.00	5.63	30.12	1.13	6.02
26	4:00 PM	Eats own meal.	5.16	5.26	25.67	1.02	4.97
June							
9		Growing fatter	10.44	5.34	33.25	.51	3.19
10		Weight 13.4 Kilo.	10.62	4.94	31.67	.47	2.98
22			10.72	4.52	28.68	.42	2.68
July							
3	3:15 PM	Excellent condition	7.85	4.57	30.44	.58	3.88
4	10:15 AM	Quite well	8.15	4.98	29.73	.61	3.65
18	10:00 AM	Excellent condition	7.67	5.10	31.90	.66	4.16
Oct.							
9	10:30 AM	Dog in excellent shape Wt 29½ lb.	7.62	5.19	29.00	.68	3.81
16	11:00 AM	Dog in excellent shape	7.22	4.91	28.55	.68	3.95
25	11:00 AM	" " " "	7.13	5.03	30.06	.71	4.22
Nov.							
15	12:00 M	" " " "	7.43	5.05	28.92	.68	3.89
23	2:00 PM	" " " "	---	5.44	29.65		
Dec.							
7	10:30 AM	Excellent shape	---	4.44	28.35		
1929							
Jan							
13	2:00 AM	" "	7.62	4.30	29.20	.56	3.83
22	2:30 PM	" "	7.93	4.56	27.87	.58	3.51
Feb							
9	3:00 PM	" "	8.45	4.37	27.40	.52	3.24
23	1:00 PM	" "	8.92	4.08	25.30	.46	2.84

DOGS THAT RECEIVED NO TREATMENT.

(Protocols)

Ca in mg per 100 cc of serum. Inorganic and total acid soluble P in mg per 100 cc whole blood.

Date	Time	Remarks	Ca	Inorg P	T.A.S.P.
Dog 78. Male. 8.4 K					
1928 June					
9			9.98	4.91	24.81
10			10.00	2.36	20.47
11	11:00 AM	Thyroparathyroidectomy 2:10-3:00 PM	10.23	3.45	21.22
12	8:30	Normal	7.73	4.78	23.87
13	8:30	Past severe tetany Very weak	5.06	6.27	25.22
	4:45 PM	Only labored breathing and intervals of convulsions	4.96	5.12	23.95
14	9:10 Am	No symptoms	4.84	4.31	22.98
	5:10 PM	Has been in occasional convulsions. Twitches	4.72	4.32	22.94
15	9:40 AM	Twitches. Depressed	4.19	4.80	23.00
16	10:10 AM	Same. Eye symptoms	4.42	4.21	22.85
17	7:35 AM	" " "	4.48	4.61	23.13
18		Died during night.			
Dog 79. Male. 7 K.					
June					
9			11.50	6.09	26.64
10			11.28	4.04	24.34
11			11.04	3.58	24.83
12			10.70	3.82	24.63
14	1:50 to 2:30	Thyroparathyroidect.			
15		Normal	8.78	5.16	24.18
16	10:15AM	Some slight tremors	7.23	5.16	23.18
	9:15PM	Severe tetany	5.92	5.36	25.52
17	8:00AM	Recovering from tetany	6.12	6.46	25.45
18	10:20AM	Anorexia.	6.02	5.19	22.79
19	9:40AM	"	5.41	5.97	26.02
20	9:40AM	"	5.43	7.09	26.02
	4:15PM	Severe tetany.	5.22	6.84	25.65
	6:40PM	Very severe tetany	5.17	6.39	24.00
21	9:35AM	Anorexia. No Tetany	5.03	4.98	24.04
22	10:10AM	" " "	4.42	5.33	21.55
	9:30PM	Dead. Still warm.			

Date	Time	Remarks	Ca	Inorg P	T.A.S.P.
Dog 81. Female. (9 K.)					
June					
10			10.94	3.86	33.30
11	3:00PM	Thyroparathyroidectomy	10.93	3.02	33.17
12			7.09	4.09	29.78
13	8:40AM	Severe tetany (2 hrs.) Respiration rapid	5.35	5.33	34.59
	2:00PM	Severe Tetany.Rapid Respiration.	5.11	5.33	31.57
	4:50PM	Severe tetany. Subsiding respiration.	4.96	5.36	31.75
14	9:20AM	No symptoms	4.92	5.91	26.98
	3:20PM	Resting	4.84	5.16	26.96
15	10:00AM	Tetany for sometime. Respiration rapid.	4.51	4.14	27.80
16	10:20AM	Resting	4.18	3.15	23.50
17	8:05AM	Tetany. Respiration rapid	4.05	3.26	23.72
18	2:25PM	Death. Sample just before heart stopped	5.17	4.29	24.49
Dog 82. Female. 7 K.					
June					
10			12.03	6.04	29.67
11	4:05	Thyroparathyroidectomy	11.46	5.58	29.39
12			7.83	6.18	30.86
13	8:50	No tetany	6.51	5.92	28.67
	4:50	Has been in beginning tetany for 2 hours.	5.76	6.05	28.55
14	9:20	Twitches on handling	5.50	5.91	27.32
	9:33	Died in convulsions. Death not caused by bleeding from heart.	5.50	5.93	29.45
Dog 92. Female. 12.5 K.					
June					
20			11.76	3.94	23.52
21			10.62	4.23	24.51
22			10.80	5.16	31.31
23			10.98	4.60	24.38
26	2:10PM	Thyroparathyroidectomy	----	---	---
27	10:30		8.60	5.62	30.43
28	11:00		7.27	5.48	25.87
	1:30PM	Dead for some time. Due to hemmorage into the pericardium.			
Dog 93. Male. 16 K.					
June					
20			12.82	4.37	20.42
21			11.78	4.70	22.67
22			11.64	5.33	24.85
23			11.38	5.26	22.58

Date	Time	Remarks	Ca	Inorg P	T.A.S.P.
June					
26	2:55PM	Thyroparathyroidectomy	----	----	----
27	10:30		9.48	5.47	25.71
28	11:00		7.68	5.83	25.57
29		Spry all day.			
30		" " "			
July					
1	9:00AM	Had died during night in tetany.			

Dog 116. Male. 12.8 K

July					
31		Started on diet			
Aug.					
2	4:15		12:10	4.26	23.80
3	4:00		11.53	3.88	25.45
7	12:30PM	Thyroparathyroidectomy	-----	-----	----
11			7.95	3.90	22.32
15 to 21		Showed some slight attacks of tetany			
Oct					
9		Severe condition due to skin eruptions and deep ulcers and abscesses of joints. Dog is depressed. Weight 11 K	7.25	3.25	15.10
11		Killed because of severe skin lesions.			

Note: For dog 115 see protocols under dogs treated by Parathormone.

THE INFLUENCE OF LIVER EXTRACT UPON DOGS SUFFERING FROM PARATHYROID DEFICIENCY.

During the last few years a number of articles have appeared setting forth the action of certain liver extracts which produce a lowering of blood pressure (172). This depressor action is said to be most pronounced in patients suffering from hypertension or in cases of experimental hypertension produced by intravenous injections

of guanidine or methyl guanidine salts (173). Quite recently Miller and Martinez (187) have successfully treated toxemias of pregnancy with liver extract (Heparmone).

If the liver extract has the ability to neutralize toxic substances produced under abnormal conditions and especially if it neutralizes the action of such substances as guanidine and methyl guanidine it seemed to us possible that it might counteract the toxemia produced in parathyroid deficiency. We grant that the theory that guanidine is responsible for tetany in animals suffering from removal of the parathyroids has met with considerable amount of opposition, nevertheless the possibility remains that toxemia may be an important factor in producing the symptoms following parathyroid removal.

In order to determine whether the parathyroid tetany could be counteracted by the liver extract a series of experiments were undertaken in which thryoparathyroidectomized dogs were treated with varying doses of the liver extract upon the development of tetany. The clinical symptoms were followed in these animals and the blood calcium, inorganic phosphorus, and acid soluble phosphorus determined.

METHOD.

After an adequate control period during which the serum calcium and the whole blood inorganic and total

acid soluble phosphorus were determined, dogs were thyroparathyroidectomized after which determination were continued during various stages of intravenous administration of liver extract (Heparmone). The dogs were fed daily a maintenance diet consisting of dried beef heart, cracker meal, corn oil and kaolin. No attempt was made to prolong the life of the animals treated with liver extract by calcium therapy.

RESULTS.

This work includes the data on 27 dogs, of which all but 4 were treated with liver extract, 3 serving as controls and the other, a bull-dog (119) strain, never developing any symptoms at all. Of the 3 dogs used as controls, one developed violent tetany which lasted for 2 days, (Graph I B Dog 71); a second developed a marked depression with moderate tetany now and then lasting for 2 days (Graph III B Dog 57) and the third dog was of the depression type which finally recovered, (Graph II). Of the remaining 23 dogs treated, no phosphorus determinations were made on 5.

These 23 dogs may be divided into two groups: 1.) 17 dogs that were not injected with liver extract until symptoms developed, and(2). 6 dogs that were treated presymptomatically.

Seven of the dogs in group 1 were injected in small doses of 5 to 15 cc of liver extract at intervals of 10 to 30 minutes, the total dose rarely exceeding 40 cc a day. Ten received large massive doses varying from 40 to 110 cc a day. Dogs were all from 9.5 to 11 Kilo body weight. Four of the dogs died with the first attack of tetany regardless of the amount and division of dosage of liver extract injected, though seemingly out of the tetany at the time of death. These are the acute dogs not benefitted by the liver extract treatment (Graph III A). Nine developed tetany and recovery was brought about from time to time by liver extract administration. Graph III C shows examples of these where blood analysis during tetany was followed by injections of heparmone and Graph IV B shows a dog on successive days, while Graph VII shows a dog throughout the post-operative period of heparmone treatment. The remaining four in this group went into a state of depression after operation and though the liver extract brought about marked aleviation, never was a dog completely restored to his normal reactiveness. Graph IV A although representing a depression dog treated right after operation also represents the average picture found in this group.

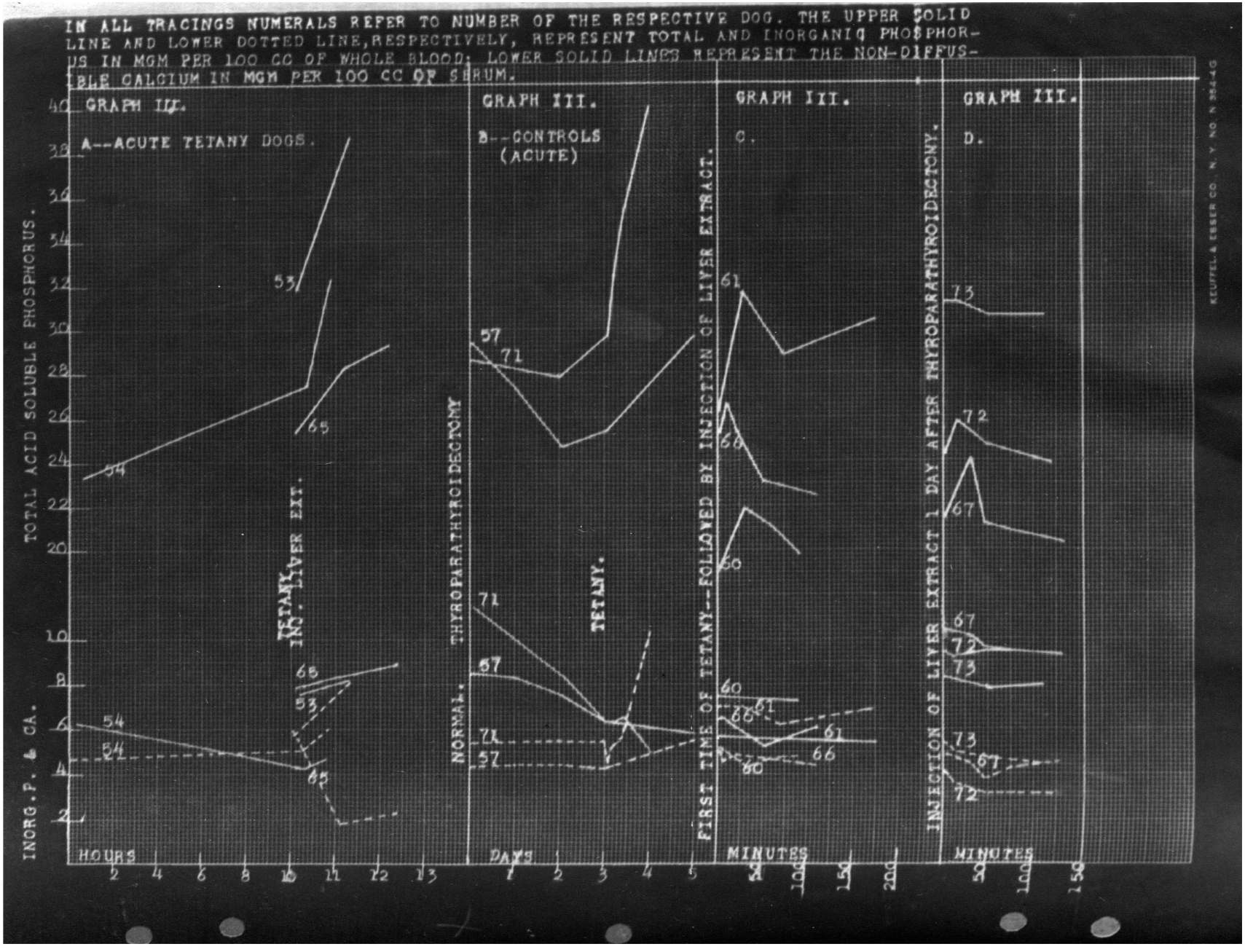
The six dogs in group 2 were treated with heparmone before any symptoms appeared; one dog on the eighth day

after operation which never developed any symptoms whatsoever and was subsequently used in another experiment; another from the third day until death, and the other four, daily, following thyroparathyroidectomy. Of these last five only one survived and was finally used in an experiment to determine the effect on the blood pressure of such a massive dose as 75 cc of liver extract. The other four died apparently free from tetany although one or two of these had shown some signs of tetany preceding some previous period of injection. Graph III D represents these dogs on the first day of injection and Graph IV A a dog in this group on successive days of treatment during tetany, while Graph VI shows two of these dogs from the time of thyroparathyroidectomy until death, never showing tetany.

It so happens that of the three dogs injected preoperatively as indicated in Graph V that Dog 54 was not benefitted by post-operative treatment and died with the first attack as shown in Graph III A; Dog 56 developed acute tetany post-operatively but was always brought to recovery by liver extract treatment, and that Dog 60 proved to be a depression dog and was benefited by the liver extract.

CLINICAL SYMPTOMS.

The clinical symptoms ensuing thyroparathyroidectomy


IN ALL TRACINGS NUMERALS REFER TO NUMBER OF THE RESPECTIVE DOG. THE UPPER SOLID LINE AND LOWER DOTTED LINE, RESPECTIVELY, REPRESENT TOTAL AND INORGANIC PHOSPHORUS IN MGM PER 100 CC OF WHOLE BLOOD; LOWER SOLID LINES REPRESENT THE NON-DIFFUSIBLE CALCIUM IN MGM PER 100 CC OF SERUM.
GRAPH III.
A--ACUTE TETANY DOGS.
GRAPH III.
B--CONTROLS (ACUTE)
GRAPH III.
C.
GRAPH III.
D.
TOTAL ACID SOLUBLE PHOSPHORUS.
INORG. P. & CA.
TETANY. INJ. LIVER EXT.
NORMAL. THYROPARATHYROIDECTOMY
TETANY.
FIRST TIME OF TETANY--FOLLOWED BY INJECTION OF LIVER EXTRACT.
INJECTION OF LIVER EXTRACT 1 DAY AFTER THYROPARATHYROIDECTOMY.
HOURS
DAYS
MINUTES
MINUTES
KEUFFEL & ESSER CO., N.Y. NO. N 3544G

GRAPH IV A.

DOG 72.

UPPER SOLID AND LOWER DOTTED LINES, RESPECTIVELY, REPRESENT TOTAL ACID SOLUBLE AND INORGANIC PHOSPHORUS IN MGM PER 100 CC WHOLE BLOOD; LOWER SOLID LINE IS NON-DIFFUSIBLE CALCIUM IN MGM PER 100 CC SERUM.

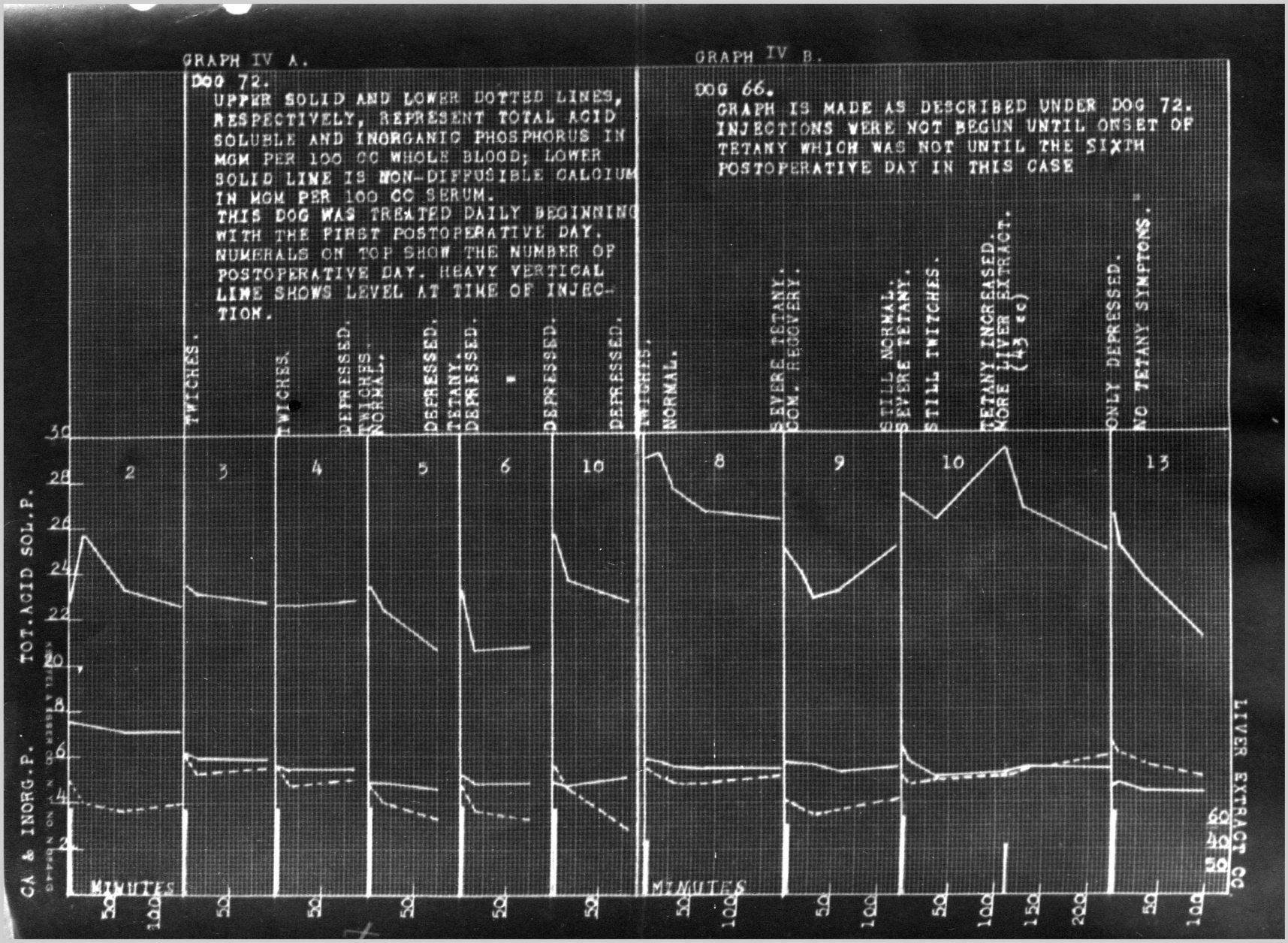
THIS DOG WAS TREATED DAILY BEGINNING WITH THE FIRST POSTOPERATIVE DAY.

NUMERALS ON TOP SHOW THE NUMBER OF POSTOPERATIVE DAY. HEAVY VERTICAL LINE SHOWS LEVEL AT TIME OF INJECTION.

GRAPH IV B.

DOG 66.

GRAPH IS MADE AS DESCRIBED UNDER DOG 72. INJECTIONS WERE NOT BEGUN UNTIL ONSET OF TETANY WHICH WAS NOT UNTIL THE SIXTH POSTOPERATIVE DAY IN THIS CASE



as described by Dragstedt (57) and others were amply confirmed in our observations. The clinical symptoms following post-operative injection of liver extract may be divided into immediate, referring to those of the first 5 to 10 minutes, and the more remote, a period varying in length during which complete recovery or death took place. The immediate symptoms vary within certain limits; according to the dose injected (25 to 40 cc in a 10 K. dog), the condition of the animal and the individual animal. In general it may be said that whatever symptoms prevail, such as depression, tetany, etc., are markedly increased during the first 2 to 5 minutes after the injection. Tetany may even be brought on by injection of 40 cc postoperatively, when the dog is near the tetany stage. This is accompanied by marked salivation, borborigmus, passing of flatus, forced micturition and violent intestinal movements resulting in defecation. Usually vomiting movements take place, the respiration becomes deeper and slower and the heart beat becomes so faint at times that it can hardly be felt. In 15 minutes or sooner the heart beat becomes very pronounced. Due to this primary faint heart beat it is very dangerous to bleed the dog from the heart during the first 5 to 10 minutes. After these symptoms have subsided the dog usually comes out of the tetany in from 15 minutes to 2 hours, although as short as

2 minutes and as long as 6 hours have been noted before the respiration came back to normal. If the dog is in a very violent tetany before the injections are begun, these immediate visceral symptoms mentioned above are not noticable; if the tetany and respiration gradually subside following the injection, the dog returns to normal, but if he becomes very weak so that he cannot stand he invariably dies within an hour or two and no amount of liver extract or calcium injection can save him. (See the dogs on Graph III A). Another thing of importance is that those animals which are improved by liver extract administration show the immediate symptoms in a more aleviated and delayed form with each succeeding period of injection and may be entirely absent by the sixth period, even when as much as 75 cc are injected in a 12 Kilo. dog. (Graph IV).

CALCIUM LEVELS.

Preoperative injection of liver extract produced a fall from 10 to 7 mg per 100 cc of serum calcium in a dog that later took an acute course (Dog 54, Graphs V and III A) and another that was improved by post-operative treatment of liver extract (Dog 5 6, Graph V), while the dog that post-operatively went into depression showed only a 1 to 2 mg fall (Dog 56, Graph V).

In Group 1 the acute cases treated with liver extract (Graph III A) the rise in calcium following injection till death was from .5 to 2 mg and with one exception these dogs went into tetany at a high calcium level, the exception being dog 54 injected preoperatively (Graphs V and III A). In both the tetany and depression dogs that were improved by the liver extract treatment (Graphs III C, IV B and VII) the calcium with two exceptions always fell where determinations were made within 1 to 3 hours after injection and no exceptions if made in 5 to 30 minutes after injection. During the third hour and thereafter (following the injection) the calcium usually rises and may exceed the pre-injection level by .1 to 1 mg per cent by the next day. The two exceptional initial increases were slight enough to be contributed to experimental or personal error and in both of these cases the animal was if anything worse than before injection.

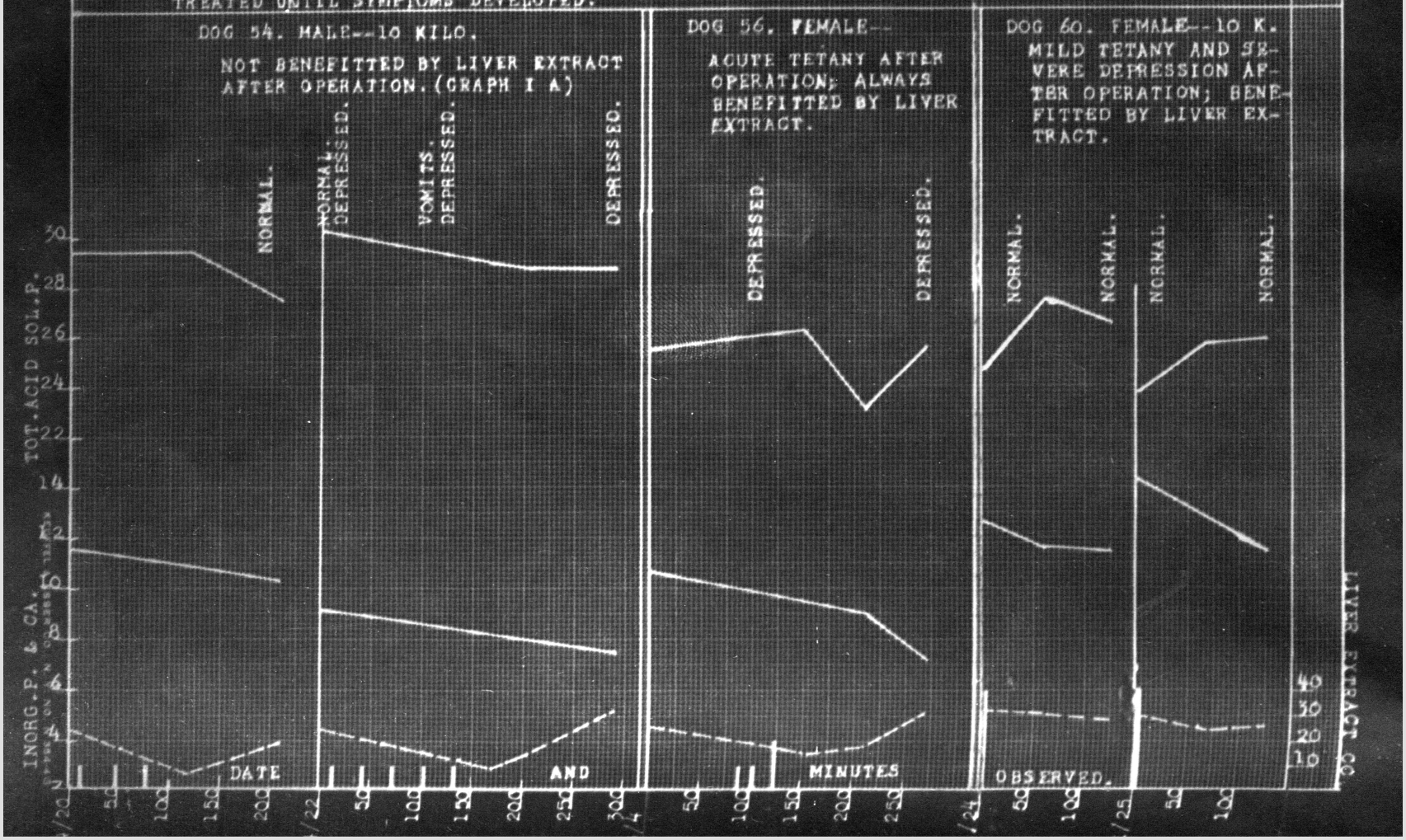
Without exception in group II the calcium was progressively decreased initially and from day to day during the injection periods. (Graphs III D, IV A, and VI). The bull-dog showed no marked variation from the normal whatsoever. Both, the acute controls (Graph III B) and the depression control (Graph II) showed a progressive decrease in calcium.

GRAPH V.

THREE DOGS TREATED WITH LIVER EXTRACT BEFORE THYROPARATHYROIDECTOMY. UPPER SOLID AND LOWER BROKEN LINES, RESPECTIVELY, REPRESENT TOTAL ACID SOLUBLE AND INORGANIC PHOSPHORUS IN MGM PER 100 CC WHOLE BLOOD; LOWER SOLID LINES SHOW CALCIUM IN MGM PER 100 CC SERUM. ALL WERE LATER OPERATED AND NOT TREATED UNTIL SYMPTOMS DEVELOPED.

DOG 54. MALE--10 KILO.

NOT BENEFITTED BY LIVER EXTRACT AFTER OPERATION. (GRAPH I A)



DOG 56. FEMALE--

ACUTE TETANY AFTER OPERATION; ALWAYS BENEFITTED BY LIVER EXTRACT.

DOG 60. FEMALE--10 K.

MILD TETANY AND SEVERE DEPRESSION AFTER OPERATION; BENEFITTED BY LIVER EXTRACT.

GRAPH VI.

DOGS WITH ACUTE COURSE, DYING APPARENTLY WITHOUT TETANY SYMPTOMS AFTER DAILY INJECTION OF LIVER EXTRACT FOLLOWING THYROPARATHYROIDECTOMY. UPPER SOLID AND LOWER BROKEN LINES, RESPECTIVELY, REPRESENT TOTAL & INORGANIC P. IN MGM PER 100 CC WHOLE BLOOD, WHILE LOWER SOLID LINE IS THE CA. IN MGM PER 100 CC SERUM.

INORG.P.& CA. TOT.ACID SOL.P.

4 6 8 10 22 24 26 28

2/21
2/22
2/23
50
100
150
200
250
300
350
400
450
500
2/24
2/25
50
100
2/26
2/27
50
100
150
200
250
300
350
2/28

DATES

MINUTES OF OBSERVATION

FIVE DAY AVERAGE AT THYROPARATHYROIDECTOMY.

TETANY.

TETANY

NO SYMPTOMS

TREMORS

TREMORS
NORMAL.
TREMORS
TWITCHES
RECOVERED.

TETANY WITH RECOVERY IN 3 MIN.
X.

DEPRESSED.

NORMAL.

X.

X.
X.X.

NORMAL.
X.X.--DEATH.

GRAPH VII.

DOG 64. FEMALE--11 KILO.
DOG DEVELOPING SEVERE AGUTE TETANY BUT BENEFITED BY INJECTION OF LIVER EXTRACT ON APPEARANCE OF SYMPTOMS. UPPER SOLID AND LOWER BROKEN LINES ARE RESPECTIVELY, TOTAL P. AND INORGANIC P_i. LOWER SOLID LINE IS SERUM CA. ALL IN MGM PER 100 CC OF WHOLE BLOOD AND SERUM, RESPECTIVELY. DOTTED LINES REPRESENT ASSUMED LEVELS OR CONNECTING DAYS WHEREIN ONLY ONE DETERMINATION WAS MADE. X-INDICATES WHERE DOG WENT INTO AN ASPHYXIATION SPELL. SHE WOULD WALK, FALL AND GO INTO A SEVERE TETANIC EXTENSOR RIGOR IN THE INSPIRATORY PHASE OF RESPIRATION, FOLLOWED BY RAPID RUNNING MOVEMENTS DURING WHICH CONTROL OF BREATHING RETURNED, BECAME VERY FAST FOR 2 TO 3 MIN. THEN RAPIDLY AND COMPLETELY SUBSIDED.

LIVER EXTRACT. CC

2 5 8

INORGANIC AND TOTAL ACID SOLUBLE PHOSPHORUS LEVELS.

Since no characteristic line of symptoms can be attached to the inorganic phosphorus, the blood content of this element being so variable under various conditions, no particular significance is attached to it by us in these investigations. It may be said that the liver extract has a tendency initially to decrease it, sometimes to $\frac{1}{2}$ its normal level, and then follows in 2 to 5 hours a compensatory rise which may be up to twice the normal. A dog in tetany may die with an inorganic phosphorus level as low as 1.85 mg per cent or as high as 10.0 mg per cent of whole blood (Graph III B) and in one case the inorganic phosphorus was 19.4 mg per cent immediately after death, having been more than twice the calcium concentration during the entire day and death occurring with the increase in total acid soluble phosphorus.

The total acid soluble phosphorus of the acute dogs in group 1 (Graph III A) rose progressively till death ensued and the liver extract seemingly only had the effect of raising it without later decreasing it as it did in the acute dogs that recovered (Graph III C). The rise may be from 25 to 32 or 40 mg per 100 cc of whole blood. Pre-operative injection in all three dogs (Graph V) showed an initial increase of 1 to 3 mg according to the time of determination after the injection of heparmone.

The tetany and depression dogs of group 1 (Graphs III C, IV B, and VII) and all of group 2 (Graphs III D, IV A, and VI) showed an initial increase of 1 to 6 mg per cent in the total acid soluble phosphorus whenever determinations were made 5 and 15 minutes after the injections after which a progressive fall set in, at times exceeding 5 mg per cent below the pre-injection level. If at any time during successive days of treatment the compensatory fall did not take place the animal soon died. After two to six periods of injection when the clinical symptoms were very faint or no longer evident the total acid soluble phosphorus decreased progressively from the time of injection. (Graphs IV and VII). The acute controls that died in tetany without treatment (Graph III B) showed a progressive rise till the point of death. The untreated depression control (Graph II) showed a maintenance of the phosphorus as the calcium fell until symptoms appeared. After this the severity of symptoms follows the total phosphorus concentration. This dog has completely recovered and still lives 14 months after the operation.

BLOOD PRESSURE AND COAGULATION TIME.

To determine the possible relationship of the symptomatology to the fall in blood pressure upon in-

jection of liver extract one dog out of this series (Dog 73, Graph IV A) having not been treated for the last days was anaesthetized and the blood pressure determined on injection of 75 cc of the liver extract. Three more dogs were likewise thyroparathyroidectomized and upon development of tetany were treated as dog 72, only the dose of liver extract varied from 40 to 60 cc. In all of these dogs the blood pressure fell rapidly 53 to 88% in 1 to 2 minutes and returned to the pre-injection level in 6 to 10 minutes. The coagulation time was in these incidences decreased to $\frac{1}{2}$ or less but returned to the pre-injection state within 10 minutes. It will thus be seen that the long periods of recovery cannot be attributed to the hypotension produced, although it may play a part in the production and recovery from the immediate symptoms described above.

DISCUSSION AND CONCLUSIONS.

The data and graphs here presented are always taken to be representative of the average results in our investigations. It will be seen from these graphs that there may be much evidence to support the views of Reed, (206) Lackey and Payte, namely, that tetany occurs at varying levels of serum calcium content and at a P/Ca ratio of approximately 1; and that this is inconstant for dogs not showing early and severe attacks of tetany as Reed

announced later (205). As a rule our results in inorganic phosphorus determinations correspond with theirs, but there are such evident discrepancies when compared to the normal variations, the clinical symptoms, the blood content in severe tetany and the pre-mortum stage compared to the constancy of the calcium lowering and total acid phosphorus rise that its primary importance becomes doubtful. Our results would correspond with Greenwalds work in which it seems that with a low calcium the total phosphorus rise to normal or above is coincident with the symptomatology.

It is of importance to note that liver extract produces an initial fall of the calcium wherever the animal is benefitted and a rise where it is not benefitted. Also that in this latter case the total phosphorus rises till death sets in and the initial symptoms of the liver extract are not evident above the increased momentary tetany due to the injection, whereas the total phosphorus rapidly rises in the dogs that are benefitted and then falls rapidly to below the pre-injection level, and that with successive injections this initial rise in the total acid soluble phosphorus finally disappears, as do also the immediate clinical symptoms. However, we have always noted that the clinical symptoms subsided before

the fall in total phosphorus after the initial rise took place which would tend to show that the increased phosphorus was the result and not the cause of the disorder. The latter and the fact that the total acid soluble phosphorus may be high at times when the calcium is low suggest that there are other factors involved, possibly a toxic substance. Be it though fully understood that even if the dog may not always show an increase in symptoms with an increase in total phosphorus, the total phosphorus is always increased when symptoms become more severe and death ensues.

The initial rise in total phosphorus may explain the slow drop in serum calcium following the injection of liver extract. Salvesen, Hastings and McIntosch (220) have found this to be true when they raised the phosphorus by injection of mono- and di-sodium orthophosphates. However, this does not explain the more marked calcium rise in the acute treated tetany dogs that are not benefitted (Graph III A) when the total phosphorus keeps on going up, nor would it explain the same fall of serum calcium in the successive days of treatment (Graph IV) when no more initial rise of total phosphorus takes place.

No attempt at preserving the life of the animal, and no other known methods of preventing or aleviating tetany were employed. The dogs all died or were used in other experiments except Dog 69 (Graph II) who is still living.

DOGS TREATED WITH LIVER EXTRACT.

Protocols of Dogs found in M.A. Thesis are omitted here.

Date	Time	Serum Ca	Inorg P	T.A.S.P.	
Dog 60. 10 K. Female. Black short hair with white neck color. Fed daily since Jan. 12: 30 gm heart, 43 gm cracker meal, 42 cc mazol and 22 gm kaolin.					
19		12.05	7.11	26.89	
20		10.82	4.54	26.73	
21		12.49	4.70	26.36	
24	11:20	12.62	5.23	24.75	Inj. 40 cc L.E. No effect clinically
	12:20	11.65	5.07	27.44	
	1:25	11.56	4.87	26.55	
25	9:25	11.22	5.02	23.79	Inj. 40 cc L.E. No clinical symptoms
	10:30		4.45	25.74	
	11:30	11.57	4.58	25.91	
Feb.					
2		14.40	4.64	24.48	
3		13.62	4.82	24.22	
4	2:00				Thyroparathyroidectomy. No meal. 550 cc water--150 cc
5					No symptoms
6	2:20PM	11.86	4.45	25.64	No symptoms
7	2:20PM	11.18	4.79	24.42	No symptoms
8					" "
9	2:20PM	10.32	4.72	23.57	" "
10	1:30	9.77	5.20	23.60	" "
11	7:00AM	8.07	4.76	20.39	" "
	12:30PM	7.88	4.78	19.46	Somewhat depressed.Meal at 12:50.Vomited about ½ at 3:15.Fed its equivalent at 3:40
	11:30PM	7.42	5.21	19.04	Some twitches at 11:00 Faster resp. Inj. of 22½ L.E. at PM 11:40, 11:40 & 11:50. Each time immediate increas in symptoms, causing also borborigmus, Flatus & retching.
	12:00PM		4.37	22.81	Had front ext. rigor which ceased at 12:10
	12:30AM		4.65	21.11	Normal
	1:00AM	7.37	4.78	19.92	"
12					Normal. Would not dring water. No meal.

Date	Time	Serum Ca	Inorg P	T.A.S.P.	
Feb.					
13	2:00	7.73	5.98	21.25	Normal. Meal at 10:30. Had vomited greater part. Refed after bleeding.
14	3:00PM		6.21	24.10	No symptoms. Fed about 2/3 ration at 10:30 AM. Vomited about ½. Fed again with other 1/3 at 3:30. Vomited again. Refed at 5:00 PM
15	2:00PM		8.15	27.91	Fed 2/3 meal at 11:00AM
	5:30PM	5.70	6.87	28.81	Beginning tetany at 4:00PM. Inj of L.E as follows: 22 cc at 5:30 & 5:50; 45 cc at 6:40, and 22 cc at 7:15. Symptoms were not aleviated completely until
	7:00	5.60	5.73	21.62	10:00 PM. With each Inj of L.E. the immediate sympt-
	8:15	5.61	5.61	spatt'g	oms as recorded the first day of post-operative Inj
	9:00	5.60	8.89	21.65	appeared, but in a progressively milder form.
16	2:00	5.60	7.02	27.90	No symptoms. Fed 2/3 meal at 11:00AM. In stage of beginning tetany at 8:00PM.
17	2:00	6.11	4.82	21.98	Fed 1/2 meal at 1:30PM. No symptoms except usual depression.
18	10:10AM	4.92	4.75	26.49	Dog is in extensor position but no rigor. Has persistent muscular tremor & twitches on effort.
	11:45		2.91	18.02	Inj of L. E. were as follows: 24 cc at 10:10 and 46 cc at 10:45 with immediate symptoms occuring (as recorded previously) in a still milder form. These symptoms were initiated by the second Inj.
	1:25PM	4.89	3.62	18.36	Dog was free after 11:30AM. [illegible] of t
19					Fed 1/4 meal. No symptoms of tetany.
20	2:30PM	4.64	6.80	25.72	Tetany and extensor rigor. Resp. not so marked. Inj L. E. as follows: 28 cc at 2:30 and 27 cc at 3:00PM with some symptoms noted above in a more aleviated form.
	4:30PM	4.47	3.86	18.45	Dog was entirely tetanus free, but had marked muscular incoordination on effort. All handling was painful to him.
21					No tetany symptoms. Fed 1/3 meal at 4:30PM
22	9:00AM	4.43	5.93	22.73	" " " " " " " "
	10:45	4.39	6.59	22.87	" " " . Was restless at 5:30PM

Date	Time	Serum Ca	Inorg P	T.A.S.P.	
Feb 23	3:00PM	4.12	5.63	22.09	Has very marked symptoms of depression. Will occasionally yelp and lose control of breathing and then come back again and be over symptoms. Fed about 2/3 of meal at 9:00PM. At 12:00PM vomited about ¼ of meal.
24	3:00 PM	3.80	4.81	21.97	Same as previous day. Had considerable difficulty in bleeding and blood was much thinner than normal. At 3:30 dog was very low but no tetany symptoms. 3:40 death. 7:00PM Necropsy showed a freshly formed pericardial clot filling the entire pericardial sac. Intravascularly the blood was imperfectly clotted. Otherwise no pathological condition could be noted grossly.
Dog 61. 9 Kilo. Female. Long black and white hair. (small head.)					
Feb.					
2		11.86	5.41	27.49	
3		11.74	4.61	27.02	
4		11.95	4.59	27.58	
6		11.15	4.56	25.68	
7		11.54	4.70	26.94	
8	2:00PM				Thyroparathyroidectomy. No meal. 500 cc water
9	2:20PM	8.78	5.96	26.82	No symptoms
10	1:35PM	7.93	6.57	28.68	Ate only liquid part of meal--By stomach tube. 8:00 PM--muscle tremors & respiration fast. Less at 9:30.
11	7:00AM	7.43	6.72	28.37	Somewhat depressed.
	12:30PM	7.18	6.22	27.72	" "
	9:35PM	6.42	6.19	31.89	Rather severe tetanic symptoms. Difficulty in standing. Inj of 45 cc L.E. followed by increased symptoms, borborygimus & vomiting movements. Normal at 9:40
	9:45		5.77	28.17	Normal.
	9:55		5.78	28.12	"
	10:30		5.89	24.18	Few twitches on effort. Some labored breathing.
	12:00	6.02	6.03	25.30	11:10 rapid resp. No tetany. Inj 22 cc L.E.--Increased symptoms as above. 11:13 normal in every way
12					Normal. Drank about 200 cc water. No meal.

Date	Time	Serum Ca	Inorg P	T.A.S.P.	
Feb					
13	2:05PM	5.69	7.02	26.07	Fed at 10:30. Had vomited about 15 gm at 2:00. Inj of 22 cc L.E. at 2:05, 2:10, 2:20 & 3:50. Followed by symptoms as on 2/11 with each Inj.
	2:30	5.66	7.01	31.66	Still some twitches at 2:20. Only depressed. 2:42 --some marked twitching.
	3:15		6.21	28.82	Still some twitches. At 3:50 tetanic twitches.
	5:00	5.52	6.87	30.28	No symptoms except a twitch now and then.
	6:25	Dog went into a violent rigor which was that of asphyxiation. When heart beat was very faint I began artificial respiration and within 5 minutes breathing was established. In 10 min. dog walked normally.			
14	6:30AM				Dog was without tetanic symptoms. Resting.
	10:00AM				Found dead.

Dog 63. Male. 10 Kilo. Dirty white, black and yellow spotted. Short hair.

Feb.					
15		10.00	4.72	29.59	
16		10.32	5.33	27.94	
17		10.11	4.71	27.92	
18		10.62	3.42	28.81	
20		10.23	4.57	27.38	
21	1:45PM				Thyroparathyroidectomy. No meal
22	9:00AM	9.68	5.37	30.64	Normal. Fed by stomach tube at 5:00 PM
23	2:45PM	6.02	5.92	27.44	Neck swollen due to hemorrhage. Has front leg muscular tremors.
	5:45	5.83	5.41	27.80	Very rapid resp. Extensive twitches but not a violent tetany. Inj of 28 cc L.E.--Immediate increase in symptoms. Retching. At 6:10 Inj 27 cc L. E. with same results.
	8:35	6.32	4.15	24.69	Resp. still rapid. No twitches.
	9:30				Death. Due to feeding while resp. was still rapid. He threw up and drew food into lungs.
	9:40				Necropsy revealed food in all the air passages. The hemorrhage from the neck had penetrated to the auricles.

Date	Time	Serum Ca	Inorg P	T.A.S.P.	
Dog 64. Female. 11 Kilo. Short hair. Yellow with white neck collar. Very fat.					
Feb 15		10.56	3.67	27.74	
16		10.05	4.33	27.58	
17		10.58	2.99	24.66	
18		10.79	3.08	23.63	
20		10.86	4.66	27.40	
21	3:10PM				Thyroparathyroidectomy. No meal. Had eaten very little on 2/20
22	9:00AM	8.15	4.25	28.41	Normal. Meal by stomach tube at 5:30 PM
23	3:25PM	6.02	5.29	25.95	Has labored breathing and extensive musuular twitches on effort. Inj 28 cc L.E. Immediate increase symptoms. 3:30 no twitches. 4:10 tremor and twitches. Inj 26 cc. Same immediate symptom in aleviated form. Recovery in 2 min.
	5:30PM	5.56	4.08	27.85	No symptoms.
	8:40	5.53	6.29	27.95	Tremors. Groaning. Fed full meal at 9:30. 10:45 yelping. Rapid resp. and twitches as at 3:25. Same at 11:50. Inj 45 cc L.E. Symptoms as above including retching.
	12:15AM	4.92	4.82	22.98	Had lain quietly on table for 20 min. Resp normal 12:35 twitches on handling. Slight tremors. 2:00AM some twitches. Resp slightly above normal.
24	3:00PM	5.24	4.69	26.84	Tremors but no evident twitches. Meal at 6:30
	8:00				Had vomited a very small part of meal. Resp faster few twitches on effort.
25	12:40PM	5.32	3.56	26.66	Some vomiting during night. Tremors and frequent twitches. Depressed. Inj. L.E? 22 cc. Deep breathing and then relaxation followed by some temporal twitches, borborigimus. Flatism. Rests quietly in a few minutes but has tremors on being disturbed.
	1:10		2.71	26.30	1:00 no twitches. Inj L.E. 20 cc. Same reaction as at 12:40. 1:10 perfectly at rest. No tremors or twitches on bleeding.
	3:00	4.96	3.28	24.62	Normal except for some depressionaand tremors on fear or effort. Fed 1/5 of meal at 5:00 PM. *In tetany(spasmodic) 6:30. Inj 42 cc L.E. with same immediate symptoms noted above. Complete recovery in 3 min. Vomited* ½ at 7:15

Date	Time	Serum Ca	Inorg P	T.A.S.P.	
Feb					
27	2:20PM	5.65	4.02	25.00	2:15PM was in spasmodic tetany. Dog walked, fell and went into an asphyxiation spell. Severe extensor rigor in inspiratory phase, followed by rapid running movements during which control of breathing returned and became very fast for 2 to 3 min. followed by complete subsidence. 2:30 and 2:40 PM Inj
	3:40		2.83	22.73	21 cc L.E. Momentary increase in resp. Some vomiting movements. Only depressed at 3:40. After bleeding dog was forced to extreme effort. He fell and went into another asphyxiation spell.
	4:30	4.91	4.61	23.25	No twitches elicitable on effort etc. Weak. 6:00 PM asphyxiation spell. Vomited at 6:40. Another attack
	7:55	5.46	5.51	25.73	at 7:35. 7:40 attack brought on by effort. Same at 7:55 after which 45 cc L.E. were Inj. Brought about ease in breathing. Dog was resting and was only de-
	8:30	4.58	5.52	23.76	pressed at 9:30 and effort brought forth no further attacks.
28	1:45PM	5.24	5.79	26.22	1:20 and 1:30 went into asphyxiation spells as noted on previous day. 1:40 another attack on handling. 1:45 while bleeding, the heart suddenly stopped. No tetany and the L.E. could not be Inj. Necropsy was done immediately and after the heart was excised, twitch occurred all over the body. gradually ceasing in 10 minutes. Teeth chattered for a while. Heart showed not the least sign of hemorrhage.

Dog 65. Male. 9 Kilo.

Feb				
15		10.32	3.79	25.45
16		10.36	4.08	25.67
17		10.83	2.55	24.11
18		10.62	3.99	23.65
20		10.68	4.16	26.91
22	9:20AM	10.70	4.14	24.16

Thyroparathyroidectomy. No meal. 500 cc water.

Date	Time	Serum Ca	Inorg P	T.A.S.P.	
Feb 23	5:05PM	7.85	5.91	25.52	No symptoms at 4:30PM. At 5:10 Inj. 25 cc L.E. Increased symptoms. 5:15 Inj of 22 L.E. Same as before. Marked signs of aleviation at 5:30. 5:40 200 cc water. 5:50 has only few twitches. Resp subsided. 6:00 dog has violent tetany but resp. not rapid.
	6:10	8.23	1.86*	29.26	Very violent tetany. Rapid resp. Inj 22 cc L.E. Symptons as above after which aleviation was only slight and fleeting.
	7:13				Dog in same condition. Inj. 50 cc L.E. Same immediate symptoms. 7:15 resp. very fast but tetany aleviated.
	7:35	8.72	2.27*	29.21	Death. Preceded by severe vomiting movement and the convulsions of asphyxiation. Otherwise no tetany. Heart was a flutter in last few minutes. Sample from heart right after heart stopped. Clotting time was very short.

*Standard had to be set at 10 instead of 20 and the readings were 21.500 and 17.500 respectively.

Dog 66. Male. 10½ Kilo.

Feb.					
16		11.58	4.04	25.47	
17		11.38	3.71	23.73	
18		11.80	3.70	23.68	
20		10.98	4.91	24.70	
22	9:30AM	11.24	4.57	24.28	Thyroparathyroidectomy at 3:30PM. No meal. 500 cc H_2O
23	3:00PM	9.13	5.52	24.52	Normal. Fed at 9:00PM.
24	3:00PM	7.73	5.27	27.08	Normal. Fed at 6:45PM.
25	1:00PM	7.26	5.48	26.57	Normal. Fed at 5:00PM
27	2:40PM	6.62	5.18	22.83	Normal. Fed at 5:30PM. Did not eat meal, only liquid part.
28	2:25PM	6.46	5.22	25.00	Had not eaten meal. Otherwise no symptoms. Inj 60 cc L.E. Causing deep breathing, tremors all over body, yelping, salivation, deep breathing, passing of Flatus
	2:30	6.52	4.56	26.67	defecation and urination. Recovery in 2 min. after which dog was prone to rest quietly, nevertheless normal & exhibited usual interest in other dogs.

~~Date~~	Time	Serum Ca	Inorg P	T.A.S.P.	
Feb.					
28	2:45PM	6.17	4.91	25.46	Normal
	3:15	5.29	4.74	23.09	"
	4:15	6.07	4.37	22.44	" Fed by stomach tube at 6:00 PM
29					Normal. Fed by stomach tube 7:00PM. Vomited some during night.
March					
1	2:40PM	5.89	5.50	28.96	Some twitches. Inj 50 cc L.E. followed by symptoms noted on 2/28 but slightly milder form.
	2:45	5.85	5.16	29.11	Depressed. No symptoms.
	3:00	5.67	4.87	27.64	Is responsive and active.
	3:35	5.52	4.82	26.72	" " " "
	5:00	5.54	5.18	26.14	" " " "
2	2:45PM	5.80	4.12	24.96	Severe tetany. Started at 1:30. Inj. L.E. 60 cc followed severely by symptoms as recorded on 2/28
	2:48	Broke tube	4.08	24.13	2:50 complete recovery. No depression.
	3:00	5.62	3.57	22.85	Normal
	3:30	5.38	3.74	23.17	"
	4:30	5.48	4.16	25.00	" Meal by stomach tube at 9:30 PM
3	8:05AM	6.44	5.16	26.26	Rather severe tetany. Inj 65 cc L.E. 8:05 to 8:09 followed by symptoms as noted above.
	8:11	5.83	4.84	26.13	Had only a few twitches.
	8:40	5.12	4.98	25.22	Respiration slightly above normal.
	9:55	5.26	5.19	29.32	Resp. labored. Twitches on effort. 10:13 Inj 43 cc L.E. with immediate symptoms in aleviated form
	10:19	5.46	5.31	26.67	
	11:45	5.42	5.93	24.93	Normal. Fed meal at 1:45. In tetany at 4:00 PM
4					No meal.
5					Fed at 4:00 PM. Vomited ½ of meal.
6	2:45	4.71	6.53	26.51	Depressed. Inj. 65 cc L.E. followed by immediate symptoms as noted above but no severe tetany.
	2:50	4.81	6.14	24.98	No tetanis symptoms.
	3:20	4.56	5.65	23.44	" " "
	4:20	4.58	5.14	22.10	" " " Fed 8:30PM. Vomited about ½ at 9:25) Fed at 5:30. Vomited same. Was in discomfort
7					
8	2:00PM	Found dead. At necropsy: The left ventricle contained what appeared to be a large old clot (had lost all its bloody appearance). The lungs were edematous and all the passages were filled with a frothy substance. Dog had vomited just before death and the vomit contained some blood.			

Date	Time	Serum Ca	Inorg P	T.A.S.P.	
Dog 66.		9½ Kilo.			
Date					
Feb.					
16		12.41	3.63	22.44	
17		12.31	3.89	23.26	
18		11.80	4.01	21.95	
20		11.30	4.23	22.67	
22		11.72	4.33	21.59	
24		11.56	4.12	21.78	
25		11.73	4.61	22.65	
27		11.65	4.45	21.05	
29	4:00PM				Thyroparathyroidectomy. No meal. 500 cc water.
March					
1	4:20PM	10.34	4.98	21.43	Inj of L.E. 15 cc at 4:20 & 33 cc at 4:45. Symptoms
	4:50	10.10	4.54	24.06	identical to those of Dog 66 on 2/28. Had very faint
	5:05	9.70	3.82	21.14	beat and most violent intestinal and abdominal move-
	5:35	9.54	4.32	20.80	Normal. ments
	6:30	9.31	4.53	20.24	" Fed at 9:00PM Blood was quite thin.
2	3:15PM	8.61	3.81	17.87	" Inj 53 cc L.E. Symptoms as on previous day
	3:19	8.42	4.26	23.39	"
	3:25	8.36	3.59	20.10	"
	4:05	8.18	3.58	19.63	"
	5:05	8.19	3.75	18.61	"
3	8:30AM	8.31	4.88	18.73	Inj 54 cc L.E. Symptoms as recorded above.
	8:34	8.28	4.31	24.31	Still more symptoms.
	9:00	7.74	4.09	21.84	Normal.
	10:00	7.70	4.03	19.65	"
4					Not fed.
5					Normal. Ate all of meal.
6	3:30PM	6.43	4.83	20.00	Normal. " " " "
7	3:00PM				Found dead. Apparently no tetany had preceded.
		Autopsy revealed no gross Pathological lesions.			

Dog 68. Male. 10 Kilo. Long hair. Reddish brown with white collar.

Feb				
27	3:00PM	12.08	5.09	25.69

Date	Time	Serum Ca	Inorg P	T.A.S.P.	
Feb 28	4:00PM	11.61	5.36	25.68	
March 1	3:00PM	11.56	5.16	25.67	
2	5:15PM	11.54	5.03	Spattered	
6	3:30PM	11.70	4.61	24.08	
7	3:50PM				Thyroparathyroidectomy.
8	2:35PM	9.63	5.54	25.94	Normal. Inj of 53 cc L.E. Brought about twitches salivation, urination, defecation and deep breathing. Then complete loss of tone and posture which returned at 2:48
	2:40	8.89	4.58	25.47	
	3:10	9.82	5.52	30.52	Depressed but not that of parathyroid deficiency.
	4:20	9.56	4.07	29.45	" " " " " " "
9	1:25PM	7.41	5.22	25.96	Normal. Inj 50 cc L.E. with symptoms as above.
	1:33	7.18	5.26	22.77	Difficult to bleed because of low pressure. Blood did not clot for a very long time.
	2:00	7.05	4.65	27.50	Quite normal.
	3:00	6.90	4.12	26.18	Resp increased. Yelped previously. Died at 3:13. Immediate necropsy showed the pericardial sac filled with blood so that heart could not relax. Due to this the last three samples may be mainly serum.

Dog 70. Male. 11 Kilo.

March 6		10.72	4.61	29.61	
8		10.69	4.50	29.75	
9		10.75	4.72	28.75	
10		11.03	4.98	28.92	
12		10.80	5.09	29.49	
13	3:50PM				Thyroparathyroidectomy.
14	2:45PM	8.67	5.45	29.36	Normal. Inj of 50 cc L.E. followed by deep breathing, & increased intestinal movements and great discomfort. Faint and rapid heart beat.
	3:00	8.31	4.37	29.41	Only depressed.
	3:30	8.32	4.36	27.66	Normal
	4:40	8.30	4.21	26.07	"
15					

Date	Time	Serum Ca	Inorg P	T.A.S.P.	
March					
15	10:48AM	7.31	6.02	27.40	Inj 50 cc L.E. Followed by symptoms as noted above
	11:00	7.13	5.16	27.88	Normal.
	12:50PM	6.95	5.19	26.65	"
	9:00PM				Ate heartily. Normal in every way.
16	6:00AM				Found dead. Had vomited. Necropsy showed no gross pathological lesion about the heart. Doubtful whether he was in tetany.
Dog 72. Male. 12.4 Kilo. White with brown collar.					
March					
8		10.96	3.74	24.40	
9		10.87	3.98	25.71	
10		10.93	3.93	24.38	
12		11.50	4.29	27.44	
14		10.80	4.24	24.09	
15	9:30Am	11.03	4.25	22.74	
16	1:30PM	10.60	4.10	23.06	4:00PM Thyroparathyroidectomy.
17	9:10AM	9.41	4.21	24.17	Inj of 75 cc L.E. Dog very sick. Forced defecation, urination, deep breathing, violent int intestinal movement, salivation, etc.
	9:20	9:30	3.69	25.73	Not over symptoms yet.
	10:00	9.52	3.15	24.70	Normal.
	11:10	9.51	3.15	23.95	"
18	11:05AM	7.53	4.97	22.85	" Inj 75 cc L.E. Symptoms as on day before but much aleviated and delayed.
	11:23	7.44	4.05	25.73	Some shivering. Not over symptoms.
	12:05PM	7.13	3.76	23.25	Normal.
	1:05	7.06	3.99	22.66	" Increased resp since 3:00PM. Same 9:00PM still increased resp. but no tetany.
19	2:00PM	6.18	6.17	23.52	Very pronounced heart-beat. Labored rapic resp. and slight twitches that cannot be felt. Inj of 75 cc L.E. Immediate symptoms are aleviated and delayed
	2:15	5.91			
	2:15	5.91	5.29	23.02	Some quivering of muscles. Dog sleeping.
	3:30	5.90	5.52	22.77	Sleeping, apparently only depressed. Deep resp. Muscle tremors barely noticeable. Rested quietly

until 6:30. Spry at 7:00. Meal by stomach tube. Deep and faster resp. Pronounced heart beat. Some twitches. Inj 75 cc L.E. Immediate symptoms increased but delayed.

Date	Time	Serum Ca	Inorg P	T.A.S.P.	
March					
20	2:25PM	5.60	5.57	22.60	
	2:40	5.54	4.72	22.62	Only depressed
	3:45	5.53	3.99	22.70	Deeper resp. Depressed. No twitches
21	2:30PM	4.87	4.91	23.32	Same as on previous day, with same results on Inj of 75 cc L.E.
	2:45	4.92	4.11	22.49	Quite normal. Very pronounced heart-beat
	3:45	4.77	3.28	21.60	Only depressed.
22	2:10PM	5.18	4.75	24.14	Tetany and rapid resp. Since after 7:00AM sometime Inj 75 cc L.E. Symptoms as above.
	2:25	4.88	3.76	20.56	Depressed.
	3:25	4.86	3.36	20.74	" Fed 2/3 meal at 4:30. Vomited 1/2.
23	2:00PM				" Inj 75 cc L.E. Immediate sym. aleviated.
24	9:00AM				" " " " " " " "
25	8:30				" . Dog has held no more than ½ of meal in stomach in last 3 days. Also on 26 and 27.
26	2:40PM	4.92	5.75	25.71	Depressed. Inj 75 cc L.E. Immediate symptoms much delayed.
	2:55	4.81	4.61	23.72	Only depressed.
	4:00	5.05	2.91	22.73	" "
27					Depressed. Bleeding from mouth. Indications are that it is blood vomited.
28	Used in B. P. experiment to determine effect of 75 cc L.E. Inj on Blood Pressure.--Blood Pressure fell 100 to 12 in 1' after which it rose to 134 in about 10' then gradually fell until death occurred in 20's more.				

Dog 73. Male. 9.5 Kilo.

March					
10		11.03	4.85	34.80	
14	2:00PM	11.53	4.39	32.57	
15	10:30AM	11.07	4.39	32.57	
16	2:00PM	10.90	4.70	29.12	5:00PM Thyroparathyroidectomy.

Date	Time	Serum Ca	Inorg P	T.A.S.P.	
March					
17	9:40AM	8.32	5.53	31.44	Normal. Inj of 53 cc L.E. followed by the immediate characteristic symptoms.
	9:55	8.16	4.98	31.44	Quite normal.
	10:30	7.36	4.72	30.52	Normal
	11:30	7.93	4.48	30.55	"
18	11:15AM	7.02	6.00	29.63	" Inj. 53 cc L. E. Immediate symptoms are aleviated and delayed.
	11:30	7.00	5.24	34.47	
	12:15PM	6.71	5.02	32.34	Normal
	1:15	6.70	4.92	30.79	"
19	2:10PM	6.02	5.23	27.58	Resp. is increasing. Rapid and violent twitching began in last ten minutes. Inj 53 cc L. E. Violent immediate symptoms.
	2:25	5.86	4.81	32.53	Apparently normal.
	3:30	5.72	4.18	27.14	Resp. above normal. Some tremors on fear.
	7:30				Normal but will not eat. Meal by stomach tube.
20					Was apparently well at 7:00 AM. Found dead at 11:30 AM.

THE INFLUENCE OF CALCIUM LACTATE ON DOGS SUFFERING FROM PARATHYROID DEFICIENCY.

The effect on calcium absorption from the intestinal tract when given orally has long been a matter of dispute, since Boggs (1908)(18a) announced an increase of 33 to 36% in the serum calcium by this method. Negative results were reported by others(Denis and Minot 1920 (57); Meigs et al 1919 (182); Clark 1920 (29); Salvesen 1924 (217); and others (172), (52), (151), (181), (237)). However, by a carefully controlled experiment Blum et al (1921) (18) was able to reestablish the original contention of Boggs and his work was subsequently affirmed by many investigators (231), (139), (127), (229), (136), (9), (150), so that there need be no question today about the effeciency of calcium salts by mouth in effecting the serum calcium. Finally Collip (41) has definitely shown that not only could the serum calcium be increased by intestinal absorption but that by frequent oral administration animals could be killed with their normal serum Ca and blood inorganic P doubled and trippled, respectively. The rise in serum calcium by the oral administration of the various calcium salts to parathyroidectomized and normal animal has most recently been reviewed and demonstrated by Hoyle (134).

The immediate relief from parathyroid tetany on injection of solutions of calcium salts were demonstrated by

Parhon and Ureche (1907) (200) and later by MacCallum and Voegtlin (169). This has been substantiated by all later investigators (17), (21), (157), (11), (163), (132), (216).

Luckhardt and Goldberg (1928) (163) by oral administration of Ca lactate and subsequently Compere and Luckhardt (1924) (44) by oral administration of $CaCO_3$, $Ca(NO_3)_2$ and $Ca(C_2H_3O_2)$ kept dogs alive and in good condition following a complete thyroparathyroidectomy whereas monobasic calcium phosphate seemed more likely to induce tetany rather than to prevent it. Dragstedt and Sudan (1926) (55) confirmed these results and pointed out the increased dosage necessary to prevent tetany in young dogs and pregnant animals.

METHOD.

After a brief control period of two to five days for daily blood analysis, dogs were completely thyroparathyroidectomized followed by the oral administration of calcium lactate (5% solution) in 10 to 15 gram doses twice daily with 3 hour interval or 2 hours before a meal and 4 to 6 hours after a meal. Occasionaly the dose had to be repeated for a third time to aleviate or prevent tetany. Some dogs were not treated until parathyroid deficient symptoms appeared and in some cases the treatment had to be supplemented with calcium intravenously either because the calcium was too irritant to the stomach even in 1% solution and was consequently vomited or absorption from

the intestine was not sufficient to keep the calcium above the tetany level. Blood analysis was made each day before calcium administration and at various times after its administration in the earlier experimental period wheras later the analysis was more infrequent and was usually made a few hours after calcium was administered or before its first daily administration.

RESULTS.

The results are given on eight dogs, five of which received no treatment until symptoms appeared (Dogs 83 to 86 and 88); the other three receiving treatment beginning with the first post-operative day (Dogs 89 to 91). All the dogs showed more or less severe tetany at some time during the experimental period except one (Dog 85) who showed only mild twitches and severe symptoms of distemper immediately after operation. This dog died in an exhausted state the third day after operation after only 1 day of calcium treatment. Another dog (Dog 84) of the group not treated until symptoms appeared developed a severe vomiting reflex on the sixth post-operative day or on the third day of treatment. He groaned, coughed and retched almost continuously for 3 more days without treatment, thus dying on the ninth post-operative day. This leaves 3 dogs that were not treated until symptoms appeared.

These 3 dogs not treated until parathyroid deficient

symptoms appeared showed tetany on the first (Dog 86), second (Dog 83) and second (Dog 88) days, respectively. The first two died in severe tetany on the third and sixth post-operative days, respectively. Both developed severe tetany during the night and died. Dog 88 was pregnant when the experiment was begun. She received treatment for 103 days--46 days to the time of birth of 6 healthy pups (she was however unable to carry them through the lactation period) and 57 days thereafter. Treatment was then discontinued having been decreased gradually for the last 2 weeks. This dog did not show any tetany subsequently, but a severe skin rash and joint ulceration developed and the animal was sacrificed 10 days later. The blood analysis of this dog is plotted graphically (Graph VIII)

It is thus obvious that it is difficult to free dogs from tetany and prevent fatality if calcium treatment is resorted to after symptoms appear. It is possible that the lives in at least 2 dogs (Dogs 83 and 86) could have been spared had treatment been vigorous enough to prevent the recurrence of tetany. However in the case of dog 83 not enough calcium could be given by stomach tube to prevent symptoms for any length of time, because of her vomiting. When parathyroid deficient symptoms are prominent it is often impossible to introduce anything into the stomach which will not be promptly returned. This then is an additional danger in waiting until symptoms appear before

treatment is begun, if such treatment is to be by the oral route.

The 3 dogs which received treatment from the time of operation were all benefitted by the calcium administration. All of them showed tetany at times in spite of the calcium treatment and in 2 cases intravenous calcium was resorted to a few times in order to save the lives of the animal. (Dogs 89 and 91).

Dog 89 soon developed anorexia and could not be forced to retain his food. Even calcium intravenously did not restore his appetite. He developed tetany several times and died in severe depression on the 19th post-operative day. Dog 90 never lost appetite for any length of time, could be kept quite normal by constant treatment, but developed symptoms upon discontinuation of treatment up to the 90th day when treatment was lessened day by day and discontinued on the 104th day. A week later he showed intermittent mild symptoms, and a violent attack of tetany ensued in the night from which he died 12 days after treatment was discontinued. Dog 91 was similar to Dog 90 but exhibited severer tetany at times from which only calcium if given intravenously would free him. He recovered after 60 days of treatment but after that never did exhibit a very good appetite. He was in a fairly good condition for 60 days after treatment stopped, but then began to decline, at times showing intermittant sharp

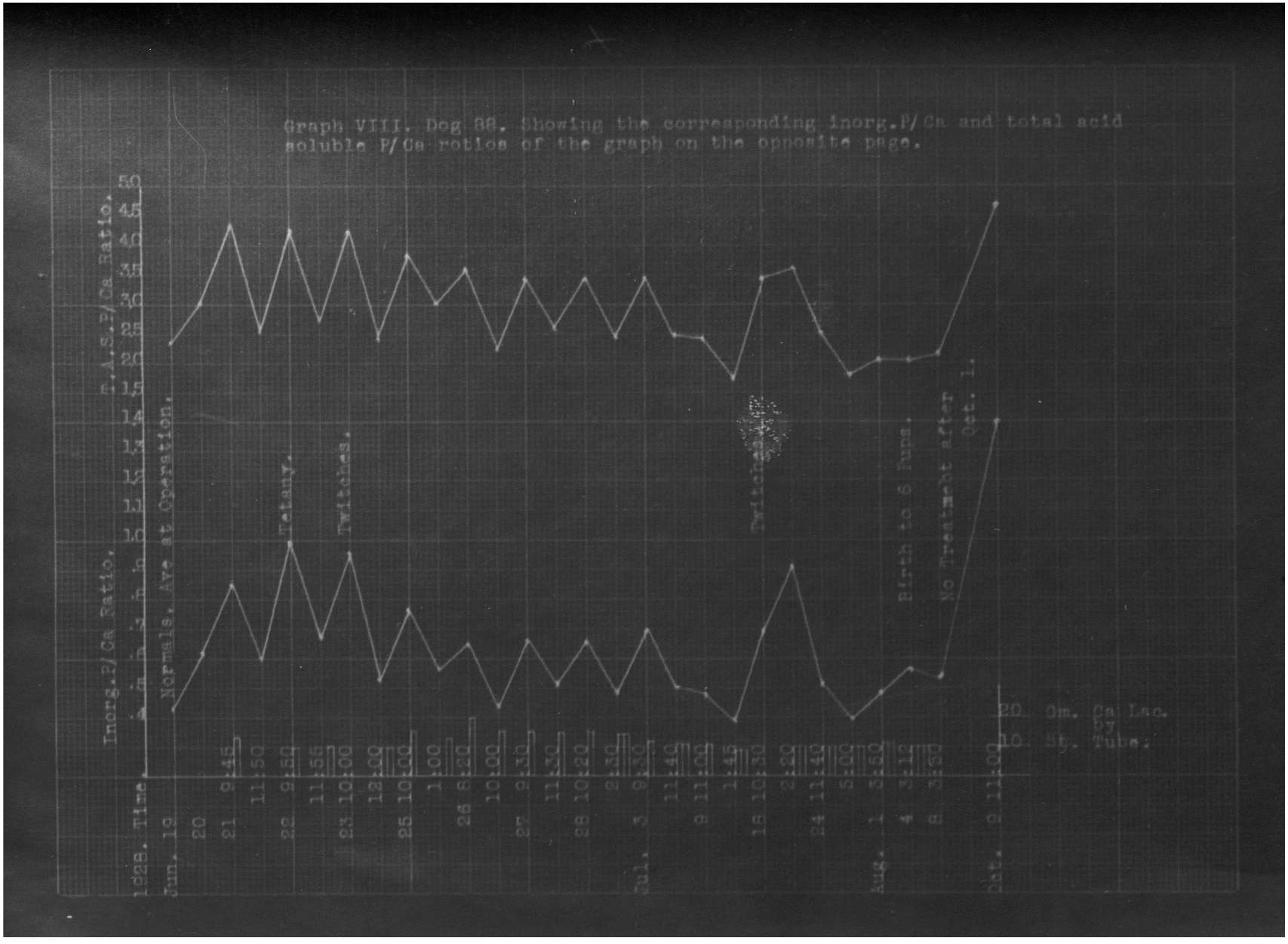
twitches of the jaw. He died in an extremely emaciated condition, almost hairless on the 153rd post-operative day.

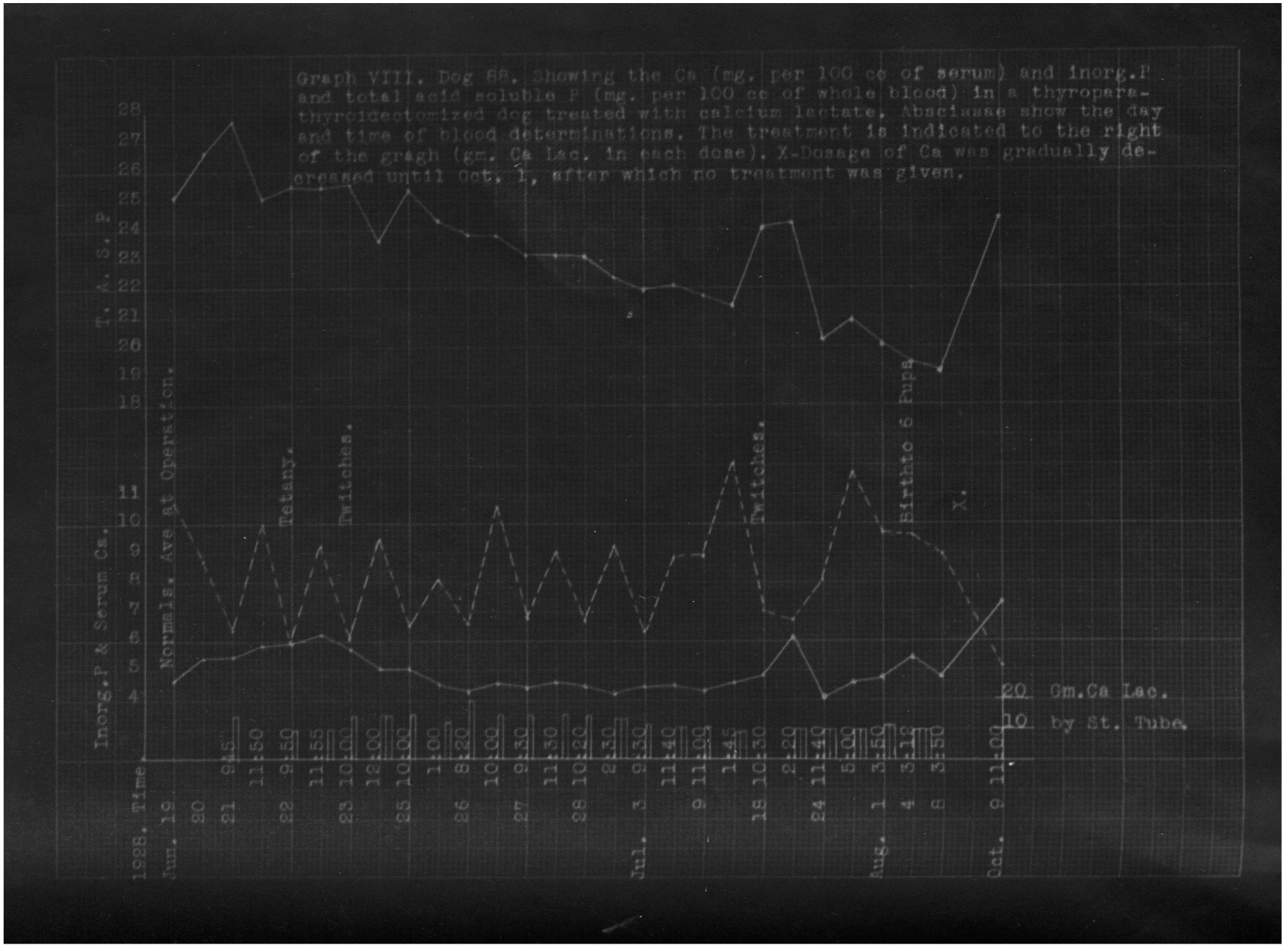
Our experiments would therefore not lend very strong support to the reports of Luckhardt and Goldberg (163) and those of Dragstedt and Sudan (55). We find that calcium therapy may keep the animal alive, but as to being in an excellent condition our results are at variance. Possibly our results are less encouraging because of the difference in diet which in our experiments consisted of Hamburger, bread, a small amount of kaolin and from 75 to 100 cc of milk daily. Their diet consisted of Bread and milk and even then some of their dogs died from the third to the 28th post-operative day of treatment. They also showed that a dog after recovery could be thrown into violent tetany at will by feeding a large amount of meat, especially if the meat was old. Our results suggest that dogs kept on a balanced meat diet from the day of operation are not apt to make a complete recovery from parathyroid deficiency as others have shown by the use of a non-meat diet during the experimental period.

BLOOD ANALYSIS.

The behavior of the serum calcium, whole blood inorganic and total acid soluble phosphorus and their ratios whenever symptoms appeared (Graph VIII Jun. 22 and

Graph VIII. Dog 88. Showing the corresponding inorg.P/Ca and total acid soluble P/Ca ratios of the graph on the opposite page.




Graph VIII. Dog 88. Showing the Ca (mg. per 100 cc of serum) and inorg.P and total acid soluble P (mg. per 100 cc of whole blood) in a thyroparathyroidectomized dog treated with calcium lactate. Abscissae show the day and time of blood determinations. The treatment is indicated to the right of the graph (gm. Ca Lac. in each dose). X-Dosage of Ca was gradually decreased until Oct. 1, after which no treatment was given.
T. A. S. P.
Inorg.P & Serum Ca.
Normals, Ave at Operation.
Tetany.
Twitches.
Twitches.
Birthto 6 Pups
X.
20 Gm.Ca Lac.
10 by St. Tube.
1928. Time
Jun. 19
20
21
22
23
25
26
27
28
Jul. 3
9
18
24
Aug. 1
4
8
Oct. 9

23, Jul. 18) and at the time of death (Graph VIII Oct. (), as a rule, was identical to that shown for dogs without any treatment. This therefore needs no further consideration. There remains to be considered the behavior of the phosphorus compounds when the calcium is kept above the tetany level or even above the normal value by calcium lactate administration. Dog 88 (Graph VIII) is representative of the results obtained by oral administration alone.

It will be seen from this graph that during the period of calcium administration (Jun. 25 to Jul. 18) when the animal is benefitted and parathyroid deficient symptoms are absent, the general trend of both the inorganic and total acid soluble phosphorus is progressively downward, even over a 40 to 45 per cent range of calcium variation. When twitches occurred on Jun. 18, the calcium was 7 mg per cent, having been as low as 6.3 mg per cent previously without tetany, but the total acid soluble P was up 2.5 mg per cent when twitches appeared. On the other hand raising the serum calcium markedly above the normal by intravenous administration raises both the inorganic and total acid soluble phosphorus by as much as 5 mg per cent (Dog 91, Jun 29). The rise in phosphorus compounds seems to follow the increase in calcium very closely. Take i.e. Dog 91 was in severe tetany on Jun 26 at 10:50 AM when 100 cc of 5% calcium lactate were injected intravenously. Calcium, inorg. P and T.A.S.P. values,

respectively, 5.82; 5.92; 28.80 mg per cent. (Non-tetanic levels were respectively 8.60; 4.81; 24.17 mg per cent.) In 10 minutes these repsective concentrations were 23.71; 9.25; 29.73 mg per cent. After complete recovery in an additional 20 minutes the respective concentrations were 19.78; 9.75; 31.00 mg per cent. The following morning the respective concentrations were again 7.03; 3.77; 24.10 mg per cent. This is in accord with the work of Collip (41).

With these relationships existing between the absolute concentrations of the calcium and phosphorus compounds it is obvious that both Phosphorus/Ca ratios will be more or less a function of the Ca content, that is the ratios vary inversely to the calcium concentration. This is actually shown to be the case in graph VIII.

CONCLUSIONS.

Under calcium therapy of parathyroid deficient dogs the inorganic phosphorus and total acid soluble phosphorus have a tendency to be below the normal so long as the animal is benefitted and the concentration of Ca is not markedly above normal. When the animal is not benefitted by the calcium administration or when the calcium is raised markedly above the normal both the inorganic and total acid soluble phosphorus compounds increase. In the former condition the rise in the latter is more constant and in the latter condition the rise in the former is more constant.

The phosphorus/Ca ratios are more or less a function of the serum calcium concentration.

DOGS TREATED WITH CALCIUM LACTATE.

Ca in mg per cent of serum and inorganic total acid soluble P in mg per cent of whole blood.

A= gm of Ca lactate by stomach tube.

Dog 83. Female. 9.8 Kilo. 1928	Time.		Ca	Inorg P	TASP.	A
June						
10			13.31	6.03	27.60	
11			12.05	5.84	31.87	
12			11.93	4.45	31.67	
14	2:40PM	Thyroparathyroidectomy				
15			8.36	5.93	27.52	
16	12:00	Twitches at least for two hours.	7.12	6.66	25.22	10
	1:10	Normal	8.60	5.75	23.98	
	2:15	"	9.29	6.05	23.78	
17	8:20AM	Labored breathing. Rapid respiration.	6.24	5.17	21.82	15
	9:40	Still some twitches on handling	7.97	4.97	21.87	
18	11:40AM	Very severe tetany.	5.70	5.52	24.04	15
	1:25PM	Still twitches	- --	- --	-- --	10
	2:30	Quite normal.	7.92	6.73	26.16	
19	10:05AM	Severe tetany.	5.54	4.94	24.38	10
	10:40 to 10:54 three successive attempts at 300 cc of Ca failed. Due to vomiting.					
	12:20PM	Tremors (cold)	7.85	6.34	27.38	
	3:00	Some vomiting	- --	- --	-- --	15
20	9:30AM	Had just died in severe tetany.				

Dog 84. Female. 12 Kilo						
June						
11			10.62	4.54	27.49	
12			10.70	4.44	24.32	
14			10.52	5.08	24.87	
15	2:20PM	Thyroparathyroidectomy				
16	11:40AM		8.21	6.20	27.34	
17			7.24	4.98	21.46	10
18	12:05PM	Twitches.	5.83	6.31	26.14	
	2:25	Normal.	6.72	6.34	23.68	
19	10:15AM	Begin tetany.	4.88	6.41	28.15	12.5
	12:25PM	Normal.	6.23	6.39	27.38	
	3:15	Had not eaten.				12.5
20	10:00AM	Faster Respiration.	5.32	4.46	25.75	15
	11:30					15
	12:20PM	Normal	7.53	4.48	24.21	
	1:45	Normal. Had not eaten. No twitches.	8.30	4.37	24.07	
21	10:15AM	Vomiting	5.13	4.68	25.71	20
	12:15PM	Normal.	6.90	4.39	24.77	

Date	Time		Ca	Inorg P	TASP	A
June						
22	10:00AM	Vomits. Twitches.	4.62	5.88	27.22	20*
	12:00M	Better	4.80	4.94	25.87	
23	11:00AM	Groaning. Coughing. Retching all day	4.45	6.25	27.42	
24	8:30AM	Dead. Was still warm.				

*Treatment discontinued due to severe vomiting & coughing reflex.

Dog 85. Female. 12 Kilo.

June						
11			11.48	5.48	30.96	
12			10.68	4.13	26.35	
14			10.62	4.02	26.94	
15	3:10PM	Thyroparathyroidectomy				
16	11:45AM		8.41	5.39	25.95	
17	9:30AM	Some intermittent twitches				
		Symptoms of distemper	6.73	5.17	23.42	
18	12:15PM	Twitches	5.68	5.44	25.27	10
	2:40	Very weak. Severe diarrhea.				
		Intermittent coughing.	8.65	9.73	26.61	
	6:15	Dead.				

Dog 86. Female. 5.6 Kilo.

June						
15			10.05	3.84	23.32	
16			10.08	3.68	23.78	
19	3:30PM	Thyroparathyroidectomy	10.46	3.73	22.54	
20	10:35AM		7.48	4.93	21.26	
	10:25	Had not eaten. Rapid Respiration. Twitches.	- --	----	---	7.5
21	10:00AM	Normal	6.74	4.70	19.75	10
	12:05PM	"	8.72	4.90	19.23	
22	9:35AM	Had just died in severe tetany.	5.93	6.50	25.22	

Dog 88. Female. 11.3 Kilo.

June						
15			10.74	4.87	26.84	
16			10.72	4.37	24.02	
19	4:40PM	Thyroparathyroidectomy	10.86	4.70	24.48	
20	10:40AM		8.74	5.44	26.65	
21	9:45AM	Some twitches	6.40	5.45	27.70	15
	11:50	Normal	10.00	5.86	25.09	
22	9:50AM	Tetany	6.00	5.94	25.46	17.5
	10:20	Vomited one-half.				
	11:55	Normal.	9.32	6.20	25.42	
	8:30PM					10
23	10:00AM	Twitches	6.00	5.75	25.55	15
	12:00M	Fed full meal. Normal.	9.84	5.08	23.60	
	6:00PM		- --	- --	-- --	10

Date	Time		Ca	Inorg P	TASP.	A
June						
24	8:30AM	Twitches				15
25	11:30AM	Beginning tetany				12.5
	10:00	Twitches	6.55	5.06	25.41	15
	1:00		8.10	4.57	24.32	
	6:00	Normal	- --	- --	-- --	12.5
26	8:20	Normal	6.60	4.31	23.83	20
	10:20	Normal	10.63	4.57	25.81	
	6:00	Normal	- --	- --	-- --	15
27	9:30		6.77	4.48	23.16	15
	11:30	Meal	9.07	4.60	23.09	
	3:00		8.57	4.19	20.22	
	7:30		- --	- --	-- --	15
28	10:30		6.70	4.48	23.10	15
	2:30	Meal	9.23	4.24	22.37	
	9:00	Had not eaten all of meal	- --	- --	-- --	15
30	3:00	Have been feeding twice daily 250 to 300 cc Ca lactate (5%) as listed in previous days.				
30 to July 6--This dog is normal and spry but does not eat but 2/3 of meal daily.						
July						
3	9:35		6.32	4.44	21.92	12.5
	11:40		8.89	4.47	22.12	
7		Did not give Ca lactate PM.				
9	11:00		8.93	4.33	21.72	11
	1:45		12.13	4.60	21.35	11
		Was not given the after meal 225 cc of Ca lactate on the 16th and 17th.				
18	10:30	Normal	7.00	4.82	24.06	
	2:30	A few twitches, otherwise reactive.	6.73	6.15	24.25	
	11:00	Moderate twitches ate very little.				11
24	11:40	Has always enjoyed a good appetite. Is in good condition but has intermittent fits and twitches.	8.07	4.08	20.25	10
	2:50	O. K.				10
	5:00	O. K.	11.75	4.57	20.95	
Aug						
1		Has had tetany almost every morning. Changed treatment for last two weeks to two doses, three hours apart and meal about three hours later.				
	11:00	Vomited a small part				12
	3:50	O. K.	9.72	4.67	20.10	
4	3:05	Had just given birth to four pups.				11
	3:12	Is in good condition	9.60	5.46	19.50	
	6:00	Had 2 more pups.				

Date	Time		Ca	Inorg P	T.A.S.P.	A
Aug.						
5 to 9		Gave 25 to 30 grms Ca Lact. daily in 2 or 3 doses. 20 would not keep her out of tetany.				
8	11:00	O. K. Disposed of 3 pups				10
	1:20	O. K.				12
	3:50	O. K.	8.94	4.75	19.20	
Oct.						
9		Dog has not been treated for a week. Before that dosage was gradually stepped down.				
	11:00	Weight 8.2 Kilo. Very poor. Has eruptions all over body but is otherwise well. Killed by etherization.	5.20	7.27	24.40	

Dog had diarrhea following each Ca administration until July 3. Same also with dogs 89 to 91.

Dog 89. Female. 9 Kilo.

June						
20			10.38	3.63	18.75	
21	7:20	Thyroparathyroidectomy	10.48	3.60	19.48	
22	11:00		7.84	4.14	24.37	
	1:20					15
	3:10		10.52	4.12	24.40	
23	10:00		7.22	3.88	25.19	15
	12:00	Did not eat. Vomited some	10.62	4.08	25.28	
	6:00					10
24	8:30					15
25	10:00	Severe tetany. Vomits some	5.22	4.90	24.02	15
	1:00	Recovered	7.82	5.08	31.55	
	6:00	Did not eat today.				12.5
26	8:20	Tetany	5.36	4.90	26.56	10
	9:25					7
	10:20	Had rested for a while but respiration became more rapid on bleeding.	12.82	4.33	26.61	
	6:00	No symptoms. Had not eaten				15
27	9:30	Had not eaten.	5.78	3.73	26.38	15
	11:30	Meal. Did not eat.	10.15	4.56	28.90	
	3:00	Had not eaten.	8.40	4.59	27.18	
	7:30					15
28	10:20	Had not eaten.	6.18	4.08	24.81	15
	2:30	Meal.	8.30	4.88	24.98	
	9:00	Had not eaten				15
30		Had not eaten	5.86	3.63	24.25	
July						
2	10:00	Had not eaten. Calcium intravenously as 5% solution.	7.21	4.12	26.20	2.5
		Treated same as dog 88 daily but dog seemingly never eats and is sick all the time.				
3	9:40		6.07	4.21	26.57	8
	1:40		11.53	5.13	27.91	

Date	Time		Ca	Inorg P	T.A.S.P.	A
July 5		Dog in convulsions with very little excitement.				
	8:45	Could not retain Ca Lact.				
		Ca by vein--5% solution				3
6	10:00	Ca by vein--5% solution				
		Depressed	10.30	7.53	29.56	3
	10:30	"	20.38	11.15	31.11	
7	10:10	Ca by vein--5% solution	9.22	6.66	30.75	
	10:30	Depressed	17.588	8.58	30.55	
8	12:50	Very depressed	6.92	6.06	29.73	
	12:55	Was in dying stages. Injected 25 cc 5% Ca Lact. into heart but respiration ceased and all efforts to bring it back failed. Dog had failed to eat or ate very little in last week or 10 days.				

Dog 90. Female. 12.5 Kilo.

June 20			10.46	3.37	23.47	
21	7:55	Thyroparathyroidectomy	10.42	3.49	22.85	
22	11:00		9.03	4.70	28.62	
	1:10					10
	3:00		9.48	4.56	26.53	
23	10:00	Some shivering	8.72	3.84	25.42	15
	12:00	Normal. Fed	10.62	4.26	23.32	
	6:00					10
24	8:30					15
25	10:00	Some shivering	8.90	3.38	23.80	15
	1:00	Normal	10:33	3.74	21.47	
26	8.20	Normal	8.03	3.90	23.25	15
	10:20	Normal	9.82	4.44	22.93	
	6:00	Normal				15
27	9:30		8.13	4.66	24.06	15
	11:30	Meal	10.51	4.73	23.58	
	6:00					15
28	10:20		8.31	4.00	21.18	15
	2:30	Meal	10.42	5.14	22.51	
	9:00					15
July 3	9:50	Treated same as Dog 88 and he eats all of meal and is normal.	8.83	3.77	23.61	12
	11:50		10.85	4.08	23.72	
7		No calcium P. M.				
8	12:00	Mild tetany and incoordination in walking				12
9	11:00		8.03	5.26	27.76	12
	1:45		10.21	5.59	27.78	12
		No appetite on July 12 and 13.				
16		Ca Lactate before feeding				10
17	10:20	A few tremors	7.60	5.33	29.31	12
	1:05	No appetite	7.50	4.47	26.14	

Date	Time		Ca	Inorg P	T.A.S.P.	A
July						
18	10:30	No appetite	8.35	4.80	27.80	12
	2:20	No appetite	11.20	5.51	28.35	
19		" "				
24	11:40	Is in good condition but has twitches, increased respiration but was well the day before.	8.46	4.27	25.84	10
	2:50	O. K.				10
	5:05	O. K.	11.66	5.02	25.45	
Aug						
1		Has had tetany almost every morning. Changed treatment for last two weeks to 2 doses of 10 gms 3 hrs. apart and meal 3 hrs. later.				
	11:00	No tetany in last week				10
	1:50	O. K.				10
	3:50	O. K.	11.18	5[illegible].29	27.30	
5		Good condition. Eats but not with appetite				10-11
8	11:30	Good condition				10
	3:50	Good condition	10.60	4.73	26.65	
Oct.						
9	11:00	No treatment since Oct. 4. Was in mild tetany. (Treatment had been reduced before but always followed by severe tetany. Wt. 10.2 Kilo.	5.64	5.57	22.45	
16		Had intermittent periods of twitching since Oct. 9. Lost appetite in last week. Found dead at 11:00, evidently having been in tetany. Wt 9.5 Kilo.				

Dog 91. Male. 10.7 Kilo						
June						
20			10.48	4.48	23.48	
21	8:50	Thyroparathyroidectomy	10.35	4.73	23.47	
22	11:00		8.61	4.34	23.61	
	1:10					15
	3:10		10.58	4.64	23.80	
23	10:00		8.08	4.88	27.00	
	12:00	Normal, fed	10.47	4.73	25.30	
	6:00					10
24	8:30AM					15
25	10:00		7.05	4.28	24.47	15
	1:00		8.60	4.81	24.17	
26	8.20	Severe tetany for at least one hour	4.42	6.43	28.88	15
	4:20	Tetany				12
	10:50	Severe tetany. L00 cc 5% Ca Lact. intravenously, cessation of tetany, immediately				5
	11:00	Only rapid respiration	23.71	9.25	29.73	

Date	Time		Ca	Inorg P	T.A.S.P.	A
June						
26	11:20PM	Complete recovery	9.78	9.75	31.00	
	6:20PM	Had eaten some				15
27	9:30		7.03	3.77	24.10	15
	11:30	Meal	8.36	4.39	24.40	
	6:00					15
28	10:20		6.13	4.68	23.63	15
	2:30	Meal	7.23	3.79	23.97	
	9:00	Had eaten about 1/3 of meal or less				15
29	10:00	Tetany. Ca Lact 5% by vein				4.5
			6.24	3.95	22.23	
	10:30		18.40	5.87	27.02	
July						
3	9:55	Treated same as 88 but is not so spry. Seems de-pressed and eats only about 2/3 meal daily.	6.20	3.84	20.00	
	11:55		8.05	3.83	20.70	
7	PM	No calcium lactate.				
8	12:00	Mild tetany				13
9	11:00		6.51	4.72	25.41	12
	1:45		9.03	5.59	25.00	12
		Little appetite on July 12 and 13				
16		Did not give Ca Lact. until 5 PM. When he was in extensor position and exhibited moderate twitching.				
17	10:20	Moderate tetany. 250 cc 5% Ca Lact which he vomited, followed followed by 200 cc at 12:00				
			4.82	7.18	28.39	
	1:05PM	Still extension and some tetany. 25 cc Ca Lact intravenously which quieted dog in few minutes.	9.00	6.37	28.35	
	9:30					12
18	10:30	No tetany symptoms. No appetite.	5.35	5.48	27.99	12
	2:20	No tetany symptoms. No appetite.	7.56	5.63	29.04	
19		No tetany symptoms. No appetite.				
24	11:40	Has had periods of moderate tetany and tetany is becoming severe right now due to only one dose of Ca the day before. Dog has exhibited no appetite and has eaten very little. Vomited a small part at 11:45	6.20	6.95	27.14	10
	11:50	5% Ca Lact intravenously				1
	2:50	O.K.				
	5:10	Ca Lact.	9.62	6.25	22.70	

Date	Time		Ca	Inorg P	T.A.S.P.	A
Aug						
*1	11:00	No tetany in last week				10
	1:55PM	O. K.				10
	3:55	O. K.	9.60	6.25	22.70	
5 to 9						10to 11 daily
8	11:30	Good condition. Eats, but not with good appetite				10
	3:50	Good condition.	8.42	6.35	25.27	
Oct.						
9	11:00AM	O. K. (No treatment since Aug. 20. Wt. 11.3 Kilo)	8.61	6.10	25.03	
16	11:00	Quite well, appetite not very good.	8.30	6.06	24.33	
25	11:00	Quite well, appetite not very good.	5.88	6.24	23.59	
Nov.						
15	12:00PM	Has occasional sharp snap of the jaw. Is very poor, has been developing ulcers and is almost hairless. Wt 8.2 Kilo.	4.58	6.02	25.42	
20		Found dead.				

*Changed treatment for last 2 weeks to 2 doses of 10 gm 3 hrs. apart and a meal 3 hrs. later.

Dog 98. Male. 6.4 Kilo

June					
28	3:00		10:40	2.97	25.41
29	5:00	Thyroparathyroidectomy	10:00	2.95	23.25
30	2:00	Tetany. 200cc Ca. Lact. by stomach tube. Dog aspirated it into lungs. I hardly think that the tube was in the trachea. Died shortly after. Do not know whether due to aspiration or slow heart rate. The latter may be due to the asphysiztion.	9.80	4.38	29.30

THE INFLUENCE OF STRONTIUM LACTATE ON DOGS SUFFERING FROM PARATHYROID DEFICIENCY.

Berkeley and Beebe (1909) (10) were the first to call attention to the effect of intravenous strontinu chloride in the alleviation of parathyroid tetany. They found that the symptoms were promptly relieved and that though calcium salts acted quicker there was scarcely any difference between the action and usefulness of the two. They could keep the symptoms under control but the dogs died in a few days of nutritional disturbances.

The following year Voegtlin and MacCallum (169) in their work stated that this salt intravenously produced the same effect as the calcium except that the lowering of the excitability of the motor nerves to electrical stimulation is not quite so marked. Only one animal survived 15 days otherwise their results were in accord with those of Berkeley and Beebe (10).

In 1926 Dragstedt and Sudan (56) treated 8 dogs by the oral administration of 1 to 1.5 g per Kilo body weight. The longest duration of life was 24 days. In other dogs when persistent vomiting and tetany occurred the treatment was supplemented by injection of strontium Ringer's solution (800 to 1200 cc daily). One dog was thus saved 18 days and another only 9 days. These authors came to the conclusion that Calcium lactate is more effectatious in preserving life, although it may be just as effective in preserving or relieving tetany for several days.

as was noted by Berkeley and Beebe. [illegible] (256).

The same year Swingle and Swingle and Wenner (1926) (236) gave their reports on the oral administration of strontium salts to 27 dogs. The chloride was found too irritative for the gastrointestinal tract. The lactate was then used exclusively in 5% solution, 200 cc daily for 40 days following the operation. A meat diet did not produce tetany after the 50th day. They concluded on the basis of this work and that of Salvesen that strontium prevented the excretion of Ca by decreasing the permeability of the intestinal mucosa so that the latter is not permitted to escape. Greenwald and Gross (109), however, have shown that the low serum Ca in parathyroid deficiency was not due to increased excretion. It is possible that Wenner and Swingle erred because the method of calcium determination that they used also measures the strontium. This is shown by Fay (66).

Dogs allowed to go into severe tetany were difficult or impossible to control by strontium alone. Wenner and Swingle conclude further that tetany is also aleviated and prevented by the sedative effect of strontium on the nervous system whereby the excitability of the motor nerves is greatly diminished. In this mode of action and by decreasing intestinal permeability they include also intravenous sodium chloride, Ringers, magnesium, lactose and galactose. They theorize on each as the unpublished results of W. F. Wenner et al would show.

Since one-half of one parathyroid gland is able to keep animals alive, they suggest, (as does Dragstedt and others) the possibility of undetectable parathyroid tissue. After 3 weeks the parathyroid is hyperplastic enough to compensate for its functional demand. Our results on the dogs that recovered without treatment would not subscribe to such a theory.

EXPERIMENTAL RESULTS.

The procedure for the dogs treated with strontium lactate was the same as described for calcium lactate treatment (p 100) except that intravenous therapy was never resorted to. Also since the literature emphasized the importance of keeping the calcium up in order to make strontium treatment effective, the animals were first freed from all symptoms by calcium lactate. This was also done in the dogs treated with magnesium lactate and ammonium chloride as we shall see later.

Only two dogs were treated with strontium lactate (Dogs 113 and 114), of which Dog 113 is represented graphically (Graph IX). In both cases the strontium was found effective in alleviating the tetany but not completely and it did not prevent other symptoms of parathyroid deficiency. Both of these dogs exhibited Laryngismus Stridulus as one of their parathyroid deficient symptoms.

Dog 114 developed symptoms on the third post-

Graph IX. Dog 113. The animal was brought out of tetany by oral treatment of calcium lactate on the 28th and 29th; received no treatment on the 30th. From then on he received daily two 8 gm. doses of strontium lactate by stomach tube, 2 to 3 hours apart followed by a rest period of 2 to 3 hours subsequent to which the animal was bled and then fed.

Ca in mg. percent of serum. Inorganic and total acid soluble P in mg. per cent of whole blood.

Inorg.P/Ca and T.A.S.P/Ca ratios of the graph to the left.

operative day and responded well to calcium lactate treatment. On the 6th day he was put on strontium lactate treatment which abolished all the symptoms except that of the laryngeal stridor. On the following day he developed severe diarrhea, vomited some, ate nothing and died in complete exhaustion late that day without any tetany symptoms.

Dog 113 developed severe tetany on the third post-operative day and responded well to calcium lactate treatment. When he was put on strontium treatment on the 6th day he was at first benefitted in every way. But late on the 7th day he showed again some laryngismus stridulus and from the 8th day on developed anorexia, joint stiffness, intermittent twitches, and even severe tetany and laryngeal stridor on the 10th day. Death was eminent without other treatment. He again responded to calcium lactate treatment, but after 2 more days on strontium treatment the above symptomatology repeated itself resulting in death on the 13th post-operative day.

In both of these cases, again as long as the calcium or strontium treatment benefitted the animal, the inorganic and total acid soluble phosphorus of the whole blood remained very nearly the same or decreased. As the symptoms leading to death became more severe the total acid soluble phosphorus increased in both cases by 6 to 7 mg per cent while the inorganic P was increased by 2 mg per cent only in Dog 113, remaining the same in

the other dog. Since the known method for calcium determinations have been shown to include also the strontium content not much significance should be attached to the high calcium findings even at the time of death (12.90 and 11.20) and consequently the P/Ca ratios lose their importance but still exhibit the property of being a function of calcium and strontium content, varying inversely. The high value for calcium at the time of death indicates that strontium cannot replace Ca in its biological functions.

Our results are too few to draw any definite conclusions from, at least they are not at variance with what we have found by other methods of experimentation concerning the relationship of the phosphorus compounds to the symptomatology.

DOGS TREATED WITH STRONTIUM LACTATE

Ca in mg per 100 cc serum, inorg P and total acid soluble phosphorus in mg per 100 cc of whole blood.
A is treatment in gm of strontium lactate by stomach tube.

Date	Time		Ca	Inorg P	T.A.S.P.	A
1928						
July	Dog 113. Female. Wt. 918 Kilo.					
24	3:45AM		10.10	4.10	24.62	
25	11:30AM	Thyroparathyroidectomy	10.20	6.96	28.15	
28	10:30	In tetany since before 6:00AM. Not very severe	6.45	5.80	25.75	10
	2:45	O. K.				8
29	7:40	O. K. Not fed				8
	5:00PM	O. K.				8
30	7:30AM	O. K. Ate full meal				
31	11:40AM	Had some twitches	6.00	4.83	25.00	10
	5:00PM	O. K. Ate full meal				5

Date	Time		Ca	Inorg P	T.A.S.P.	A
Aug						
1	10:40	O. K.				7.5
	2:00AM	O. K.				10
	4:20	Seems to have laryngx trouble	7.50	5.36	25.45	
2	11:40AM	O. K. but had not eaten May have few twitches				8
	3:40	O. K. but had not eaten				8
	5:00	O. K. but had not eaten	7.87	5.35	27.20	
3	10:30AM	O. K. except for marked stiffness on handling				8
	1:40	Same				8
	3:30	Did not eat. Otherwise same	6.84	5.00	27.52	
4	11:00	Same				8
	1:40	"				8
	3:30	Had some temporal twitches on effort	8.10	5.13	29.20	
	6:15	Rapid resp. & beginning tetany. Excessive.				
	8:00PM	Laryngeal stridor very severe				5
5	7:00	Improved but weak. No tetany. No food				8
6	12:00	Stiff and some twitches				8
7	11:00	Extension & twitches on handling				8
	1:00	Same				8
	3:40	Stiff jointed Died during following night.	11.20	7.08	31.37	
Dog 114 Male. Wt. 10.5 Kilo.						
July						
24	4:05PM		10.70	4.08	23.08	
25	11:30AM	Thyroparathyrodectomy	10.95	5.02	25.18	
28	9:00PM	Begin sym. of laryngeal stridor				10
29	7:45AM	O.K.				10
	5:00PM	O.K.				7.5
30		No tetany all day.				
31	11:40AM	Rapid Resp. Tetany quite severe. Almost complete recovery in 10 min.	5.60	5.16	23.40	10
	2:15PM	O.K.		5.40	23.05	
	3:00	O.K. Began irregular resp. and laryngeal stridor at intervals from 7:30 to 9:00				5
	9:00					7
Aug						
1	10:45AM	May be some intermittent Resp. symptoms				8
	2:00PM	O.K. Vomited most of it in diarrhea spell				10
	4:25	Very weak	12.90	5.40	30.75	
	7:40	Was weak but responsive to stimulus. Lay in exhausted position as at 4:25 PM.				
	10:00	Found dead. Must have died at least an hour ago. Apparently no tetany.				

THE INFLUENCE OF MAGNESIUM LACTATE ON DOGS SUFFERING FROM PARATHYROID DEFICIENCY.

Berkeley and Beebe (1909) (10) made a detailed study of salts other than calcium upon the tetany syndrome. They found that magnesium was a marked depressant causing a rapid disappearance of the neuromuscular disturbance. Its injection aleviated tetany but when given in such amounts as to abolish tetany life was endangered.

Voegtlin and MacCallum (1911) (242) confirmed the work of Berkeley and Beebe. They decreased motor excitability and produced a general state of anaesthesia in both normal and parathyroidectomized dogs by intravenous injection of magnesium. Although the dogs could be kept free from tetany the life span was only 7 days at the longest.

Essentially the same studies were made on parathyroidectomized dogs by Luckhard, Waud and Brannon (1926 (164) and by Wenner (1927) (249). These investigators found essentially the same symptomatic results by magnesium salt feeding as did their predecessors. Luckhardt et al found a progressive decrease in the serum calcium and that the animals may be kept free from tetany at a level of 4 mg per cent for a period of 6 days by the oral administration of magnesium chloride. He concluded that the action of magnesium is essentially due to its central depressing effect preventing thereby the rapid fatal convulsions.

Wenner (249) found that treatment by oral administration of magnesium lactate was effecatious if dogs were not allowed to go into tetany. However once they went into tetany it was impossible to save the life of the dog unless the treatment was supplemented by milk feeding except in 1 dog. All the dogs received enemas at various occasions. In every case he found that the serum Ca had to be maintained above or brought back to above the tetany level in order for the magnesium treatment to be effective. Under these conditions the magnesium seemed to act in maintaining the Ca level. No treatment was necessary after the 27-73 day. He suggests that the magnesium when in excess takes care of the increased phosphates or in some way brings the calcium back into solution alluding to Greenwalds work (109) as its basis.

Wenner also found that the lactates of sodium, cadmium and potassium were of no therapeutic use in this condition. Potassium up to 300 cc in 5% solution was inert and cadmium and sodium were so irritative even in 1/2% solution that they were vomited at once, thus causing an alkalosis by loss of gastric juice whereby tetany is brought on even sooner.

Perhaps the best results obtained by the use of magnesium salts is illustrated by the work of Jung and Cook (1927) (143). The sulfate injected intraperitonially in doses of 5 cc 1% solution hourly for 5 hours can be

tolerated by a parathyroidectomized rat 150 gm in weight and is effective in curing and preventing parathyroid tetany in less than a week of daily injections of 5 cc of 1% solution of magnesium sulphate.

The efficiency of these various treatments by strontium, calcium, magnesium, non-protein diet, lactose diet, acidosis, whatever the action of these substances may be it is suggested by Wenner (249) that the ultimate readjustment that occurs in the organism after 40 or so days of a given trea tment, must be the same. Suggestions have been made that this readjustment is by hypertrophy of accessory parathyroid tissue or that other organs take over the function of the parathyroid tissues.

If we take the action of any of these agents in particular, as f or example the magnesium, there is a wide discrepancy in the understanding of this ion in the body. In reviewing the literature this becomes very evident and is shown to be mostly due to a misunderstanding of the conditions under which any given set of results were found to be true.

Hay, 1882, (125) and Wallace and Cushny, 1898, (244) showed the cathartic action of magnesium due to delayed absorption in the intestinal tract. But it was Meltzer and Auer (184) who gave us so to say the internal action of the magnesium ion with respect to the calcium. They state:

"Intravenous infusion of various calcium salts is capable of completely reversing the pronounced inhibitory effect brought on by various magnesium salts. The respiratory paralysis, the lost lid reflex, the motor paralysis, the lost general reflexes, the general anesthesia, the loss of consciousness, the depression of the cardio-inhibitory action of the vagus, the lowering of the blood pressure--all are reversed and completely restored in a very short time by injection of comparatively small quanities of calcium salt. This statement does not hold good for conditions brought about by large doses of magnesium. Calcium effeciently antagonizes the abnormal activity of its three inorganic associates in the animal body, magnesium, potassium, and sodium be the activity an over-inhibition or an over-excitation."

Beginning with this report by Meltzer and Auer much work has been done by the same and other investigators on the probable action of these salts, magnesium in particular. This is adequately reviewed by Baumecker (1923) (6).

While Wiki (1906) (258) followed by Guthrie and Ryan (1910) (112) showed that the action of magnesium was at the myoneural junction, Meltzer and Auer (185) showed its narcotic effect on both the central and nerve trunk portions of the nervous systems. That magnesium did not act peripherally exclusively was affirmed by Starkenstein (228). Soon Wiechmann(253) added to these findings

his own which showed the depressive effect on the brain and smooth muscles including all synapses. This was followed by the hypothesis of Gottlieb (91) that all parts of the nervous system were effected of which the central action was greatest and that of the respiratory apparatus least.

That the magnesium content of the brain did not increase after a singular injection was shown by Mansfeld and Bosanyi (174), [illegible]sky, Schütz (222) and Stransky (233). Schütz showed an increase in the brain upon repeated injections and Stransky an increase in the blood plasma but practically none in the muscles. The latter also showed that magnesium had a decreasing effect on the plasma calcium but that this same effect could be produced by sodium and potassium. He came to the conclusion that the narcosis resulted from a disturbance of the Ca/Mg ratio; that it was not a colloidal phenomenon was shown by using various concentrations of the magnesium and calcium in several biological experiments.

Stransky (233) found shrinkage of the brain cells when treated with concentration of magnesium or calcium salts as they were found in the blood stream. The same was found by Wiechmann (253) for calcium in finely divided muscle while magnesium had the opposite effect. This is not true for the isolated muscles according to

Loeb (159) who found that both in isotonicity decreased the weight of muscle whereas Overton (194) found that only in a dying muscle is the weight increased by stronger magnesium solutions.

Finally the work of Baumecker (6) by taking solutions in which the concentration of calcium, magnesium or sodium or any combination of these was varied and applying them to the isolated nerve or muscle at rest and at work, or to the finely divided muscle, or to fibrin, brought out the following points. Magnesium and calcium both have a swelling effect on fibrin; they are antagonistic on finely divided muscle, give swelling by magnesium and shrinkage by calcium. In the isolated muscle calcium antagonizes the narcotic effect in the myoneural junction until magnesium is added to the extent where the muscle begins to swell whereupon calcium has no effect, being otherwise a dehydrant. Thus in the muscle itself there is no such reversible antagonism between magnesium and calcium. He also showed that in calcium free Ringers the magnesium was withoug effect on the nerve endings and also that the fatigue of a muscle caused by indirect stimulation was always hindered by calcium both in the presence and absence of magnesium but had no effect on the fatigue produced by direct stimulation. This may be the explanation for the fact that the parathyroidectomized animal's serum calcium must be kept up in order to save his life by magnesium treatment.

Baumecker believes that the action of magnesium is not to be interpreted as being a de-ionizer of calcium but can be explained by magnesium calcium exchange in the myoneural junction. This is the only self evident fact since the amounts of these elements here are too small for change in detection.

The facts shown by this review may be closely linked with the review of Neuwirth and Wallace (1929) (192) who bring out the fact that the action of magnesium is related to its actual concentration in the blood plasma and is thus dependent on the ratio: $\frac{\text{Rate of Absorption}}{\text{Rate of excretion}}$ as suggested by Meltzer (183). Thus oral or rectal injections are often withoug full anaesthetic or narcotic effect in normals, whereas in abnormal conditions magnesium salts are of more effect by these routes or if injected subcutaneously, intravenously or intraperitonially.

There are other factors which may cause a variation in the concentration of these cations in the blood. Thus Haag and Palmer (114) showed that in a high calcium and phosphorus diet or high in either P or Ca, magnesium depressed P or Ca retention much less than when both Ca and P or either were low. High calcium also had a depressing effect on both P and Mg retention.

Mathews and Austin (180) have shown that the animal was much more tolerant to magnesium when in an hypercalcemic condition due to parathormone injection and far less

tolerant when hypocalcemic due to parathyroidectomy.

Obviously, it is not clear just what relationship there exists between calcium and magnesium or their combinations with phosphate in the body or the various structures in the body. Whatever these relationships may be it is fairly certain that the beneficial effects of magnesium salts in tetany is due to its general depressant action of all nervous structures and in larger amounts slows up general metabolism and all bodily activity including a depressant effect on the vital functions that maintain life. This latter fact is perhaps the cause of death in the prolonged and excessive use of magnesium salts in preventing tetany, especially when the calcium salts are low.

RESULTS.

The experimental procedure and method of treatment by magnesium lactate is identical to that described for strontium.

After primary restoration to normalcy by means of calcium treatment, magnesium lactate by stomach tube was used exclusively. Two dogs were used (Dogs 111 and 112). They lived , respectively, 23 and 11 days after operation and 17 and 6 days on exclusive magnesium lactate treatment. Dog 111 received no treatment during

the last two days because of his narcotized condition. Both died extremely weak and comatous, exhibiting no signs of tetany. However, both showed some intermittent twitching during the earlier part of the magnesium treatment, but the animals soon lost their appetite, refused food entirely, became progressively weaker (with loss of muscular tone) until death ensued.

Under magnesium treatment the total acid soluble phosphorus of the whole blood fell (1.7 mg per cent) during the first 2 days in dog 111 (Graph X, Aug. 2 & 3) but from thereon it was higher, reaching 32.46 or 8 mg per cent above normal when treatment was terminated. The other dog showed a similar 8 mg per cent rise without a preliminary fall. The whole blood inorganic P showed a marked increase up to 90% above the normal but it was not entirely progressive from day to day and fell a mg the last day. In both dogs there was a slow progressive decrease of the serum calcium from the time that magnewium treatment was begun until death or its termination.

Because of the varying higher level in both inorganic and total acid soluble phosphorus on the one hand and the progressive decrease of the serum calcium until death on the other hand, both the T.A.S.P./Ca and the Inorg P/Ca ratios will vary from time to time but there will be a general trend upward except in the last day or two for the

Grsph X. Dog III. Tetany was prevented until Jul. 31, by oral administration of calcium lactate. From then on the animal received daily two 4 to 8 gm. doses of magnesium lactate by stomach tube, 2 to 3 hours apart, subsequent to which the animal was bled and fed.

Inorg.p/Ca and T.A.S.P/Ca ratios of the graph to the left.

Ca in mg. per cent of serum. Inorganic and total acid slouble P in mg. per cent of whole blood.

the Inorg P/Ca ratio. The latter ratio will thus finally decreases somewhat due to the final inorganic P fall. But both ratios are trebled or doubled at the time of death.

DISCUSSION AND CONCLUSIONS.

These results indicate that magnesium is unable to prevent a calcium decrease in the blood in parathyroidectomized dogs. However, it could not be said that in these dogs magnesium has a decreasing effect on the serum calcium as was found by Schütz (222) in normal animals, since the calcium fall was no faster than in certain untreated dogs. The results also indicate (contrary to the supposition of Wenner (249) that the magnesium does not act in making the calcium more available by replacing it from its phosphate combination, since the calcium falls progressively and the inorganic and total acid soluble phosphorus are both markedly increased after the second day even in dogs completely narcotized by magnesium. Thus, whatever other inter-relationship there may be between magnesium and other ions in the body, its beneficial effects are largely if not entirely due to its generalized nervous and metabolic depressant effects.

DOGS TREATED WITH MAGNESIUM LACTATE.

A = Treatment used in gm of substance named (by stomach tube)

Date	Time		Ca	Inorg P	T.A.S.P.	A
Dog 11. Male. 13.6 Kilo.						
July.						
24	3:30PM		11.10	3.96	26.84	
25	11:30AM		10.95	4.61	21.90	
	5:30PM	Very spry. Gave a little hamburger by hand				10Gm Ca L.
28	9:00	Moderate tetany				
29	7:45	O.K. Not fed				10
30	4:00PM	O.K. Ate full meal at 7:15 PM.				5
31	11:40AM	Symptoms of beginning tetany	5.95	5.59	24.25	5CaL 5MgL
	5:00PM	O.K. Ate all of meal				8 "
Aug						
1	10:35	O.K				7.5
	2:00PM	Had a few minor twitches				7.5
	4:10	Increased resp. More "	6.30	5.56	25.00	
	5:30	Rap. resp. Severe tetany Had not eaten				8
2	11:40AM	O.K.				6 Mg Lac
	2:40	O.K				8
	4:55	O.K. Ate ½ meal	5.80	5.63	24.40	
3	10:30AM	O.K.				8
	1:40PM	O.K.				6
	3:39	No tetany sym. Did not eat	5.40	5.46	23.25	
4	11:00AM	No tet. Sym. Did not eat				7
	1:40	" " " " " "				8
	3:30		5.05	6.15	26.65	
5	7:00AM	" " " " " "				80 gms
6	12:00M	Vigorous twitches. Did not eat				10
7	11:00	No tet. sym. Weak				10
	1:00	" " " "				8
	3:30	Very weak. Putrid odor	4.90	8.16	31.50	
8	11:00AM	Same				7
	1:20	"				8
	3:30	".. Drew 40 cc of blood more than usual	5.42	7.08	29.16	
9	11:50	Weak. May have eaten a little				8
	2:00	"				7
	4:00	"	5.44	7.48	31.00	
10		Same procedure as day before. Weak, very putrid odor.				
11	11:00	Seems slightly stronger				8
	1:15PM					7
	2:45	Same. Does not eat.	5.20	7.55	29.45	

Date	Time		Ca	Inorg P	T.A.S.P.	A
Aug 12 to 14		Became progressively weaker under treatment as above.				
15	10:30	Very weak.				8
	2:30	Very weak. Comatous. Wt. 10.2 Kilo. Limp but assumes posture on being aroused vigorously.	4.95	6.50	32.46	8
16		Same as above. Drank water.				
17	9:00AM	Found dead, not having had tetany.				

Dog 112 Male. 10.5

July 24	3:30PM		10.94	6.76	27.88	
25	11:30AM	Thyroparathyroidectomy	10.20	3.42	24.85	
28	9:00AM	Ca prophylactically				10 Ca Lac
29	7:45AM	O. K.				10
	8:00PM	O. K.				7½
30		No tetany all day.				
31	11:35AM	A few twitches on excitement	6.82	7.66	29.77	4 Ca L. 4 Mg L.
	5:00PM	O. K. Vomited about ½ Did not eat				8
Aug 1	10:35AM	Some temporal twitches Vomited a large part				7.5
	2:00	Some temporal twitches. Vomited a large part				7.5
	4:15	O. K.	6.10	8.38	30.26	
2	11:40AM	May have some tetany symptoms. Vomited at least ½ immediately. Did not eat				8
	3:40	Vomited at least ½ immediately				8
	5:00	Twitches on handling. Did not eat.	5.80	8.79	32.85	
3	10:30AM	Twitches on handling Did not eat (Mild)				8
	1:40PM	Twitches on handling (Mild)				6
	3:30	No twitches. Did not eat	6.34	9.46	32.65	
4	11:00	" " Vomited large part in few minutes				8
	1:40	Same				8
	3:30	Has not eaten	5.70	8.65	33.30	
5	7:00AM	Very weak. Vomited large part in few min.				8
	11:00	Had died. Not in tetany.				

INFLUENCE OF MOORPHINE SULPHATE ON DOGS SUFFERING FROM PARATHYROID DEFICIENCY.

The work on the depressant effect of magnesium in preventing tetany has been reported. It seems that long before this, it was known that the action of morphine was synergistic with magnesium and that other depressants have been used to prevent tetany. One such method was the use of KBr to prevent tetany in thyroparathyroidectomized dogs by Gley (1892) (89). He had only 2 dogs, both lived so shortly after operation that the beneficial effects are generally doubted. Consequently, the work was repeated by Sloan (1926) (227) who also tried the effects of sodium barbital and morphine on the tetany of parathyroidectomized dogs. He found that bromides injected intravenously in effective doses were rapidly fatal and by mouth they were too irritant to the gastro-intestinal tract in the required dosage. The depressant effect of sodium barbital was too prolonged, extending into the period of depression after tetany; the two agencies being great enough to interfere with the vital functions, therefore hindering recovery. Morphine sulphate was found to have distinct advantages even in the cases where the animals were in the last stages of tetany. It could not be used over longer than 5 or 6 day periods because of its action in producing constipation and certain other gastro-intestinal disturbances.

According to Sloan the beneficial effects of morphine are two-fold; it acts as a central nervous system depressant and it acts as a primary respiratory stimulant (necessary in spasm of respiratory muscles) and a secondary respiraatory depressant. The depression comes on after the animal has regained the power of respiration. This prevents the alkalosis of the blood due to hypernea which in itself is capable of causing tetany (Grant and Goldman (94); Collip and Bachus (33)).

Sloan showed that serum calcium was not affected by morphine treatment even when dogs were between tetany stages and were also free from the effects of morphine.

METHOD.

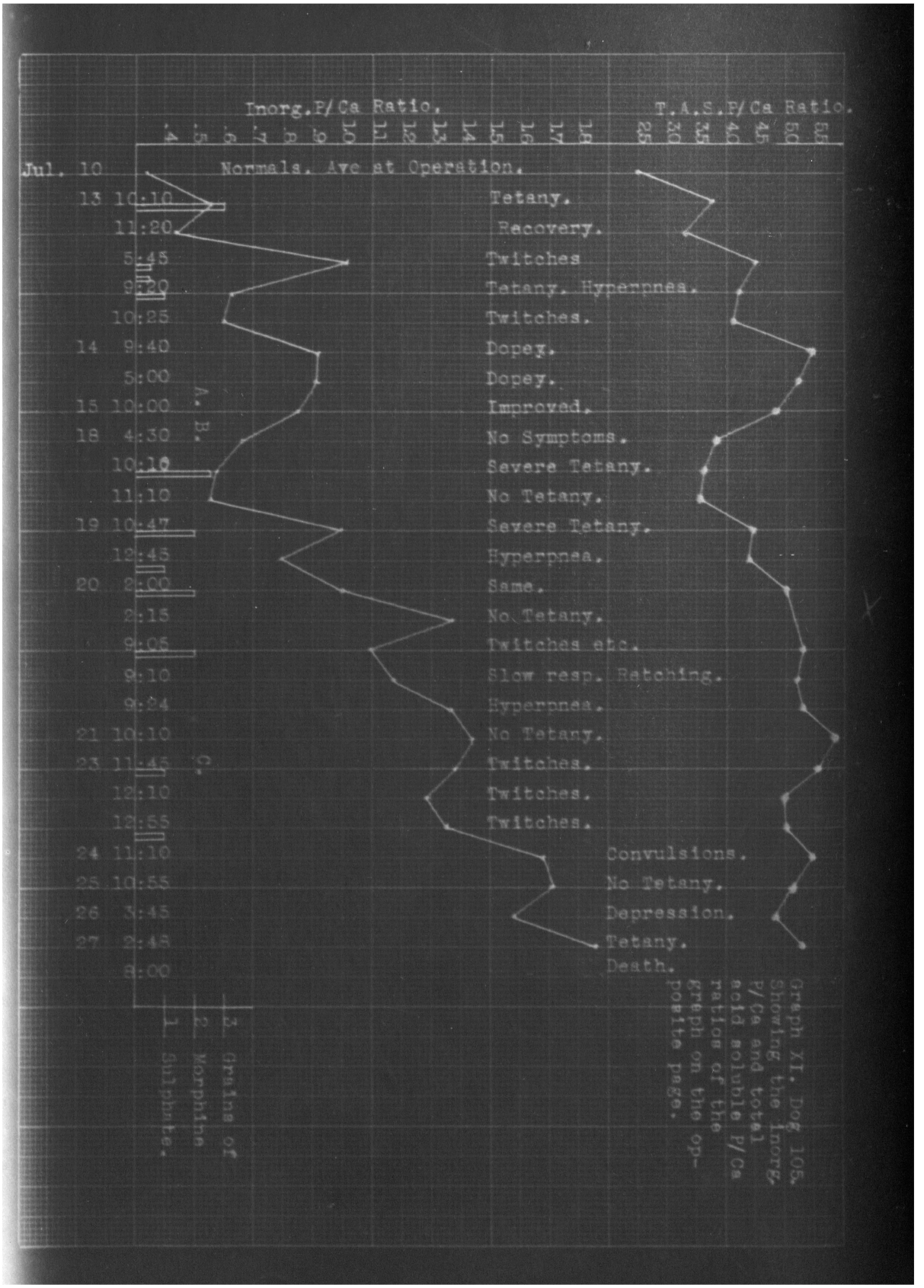
After a brief control period dogs were thyroparathyroidectomized, allowed to go into tetany and then treated by the intravenous injection of morphine sulphabe in $\frac{1}{2}$ to 3 grain doses. The highest ever injected in 1 day was 5 grains. Blood analysis for inorganic P and T.A.S.P. and serum calcium were made at various times after the injection of morphine and when the animal was free from the effects of morphine. To prolong the life of the animal beyond 5 days it was necessary to supplement the treatment with calcium by mouth.

RESULTS.

The symptoms and times of injection are well indicated on the protocols and the graph (Graph XI). They need no further comment. The symptoms after morphine administration according to the dose were those described in standard texts superimposing on or aleviating the symptoms of parathyroid deficiency.

There are 3 dogs (103, 104 and 105) in this series but only one in which the treatment could be prolonged. One (Dog 103) died by accident when he jumped through the window and the other (Dog 104) died on the first day of treatment, probably because of too large a dose of morphine (5 grains). Both these dogs showed a slight rise in the serum Ca (.4 to .9 mg per cent) in 7 to 8 hrs., a rise in inorganic P (2 to 3.5 mg per cent) and after a n initial fall of 3 to 4 mg during the first hour the T.A.S.P. showed a rise of 4 to 13 mg per cent in 6 to 7 hours.

The other dog (Dog 105, Graph XII) where treatment was prolonged showed essentially the same reaction on the first day of treatment as did the other two dogs. After a few days of calcium treatment (Jul. 14 & 15), the dog was again allowed to go into tetany on Jul. 18. Morphine sulphate repeated the above picture except for the serum calcium which did not vary markedly. Frequent determinations (Morphine sulphate grains 3 divided into 2 doses,



Graph XI. Dog 105. Showing the Inorg. P/Ca and total acid soluble P/Ca ratios of the graph on the opposite page.

Graph XI. Dog 105. Showing the effect of morphine sulphate on a thyroparathyroidectomized dog. Treatment indicated at bottom of graph in grains per dose, daily. A-350 cc H2O by st.tube: B- 2 dosse of 12 gm. Ca Lac. on the 15th at 11:30 and 7:00; C- 8 gm. Ca Lac. on 21rst and 22nd. Ca in mg. per cent of serum. Inorg.P and total acid soluble P in mg per cent of whole blood.

daily for 2 more days July 21) showed a practically constant calcium value with the inorganic P (up to 8.20 mg per cent) and the T.A.S.P. (up to 31.75 mg per cent) increasing from time to time. Calcium was again resorted to in order to save the life of the animal, but upon return to the morphine sulphate treatment, the inorganic P (6.68 to 8.38 mg per cent) and T.A.S.P. again rose (23.92 to 28.14 mg per cent) and the animal died in tetany however 3 days after all treatment had been withdrawn (Inorg P 9.35 and T.A.S.P. 26.65 mg per cent). The graph (Graph XI) shows very well the amounts of morphine sulphate injected and when the experiment was interrupted by calcium treatment.

With the calcium remaining practically the same and the phosphorus values increasing, it is clear that the P/Ca ratios must rise markedly in the later days of morphine treatment. This is well illustrated in Graph XI.

There thus appears to be a striking similarity in the behavior of the phosphates of the whole blood when magnesium and morphine treatment are compared: A primary fall followed by a rise in a few hours in case of morphine and a few days in the case of magnesium treatment.

DOGS TREATED WITH MORPHINE SULPHATE

B = grains of morphine sulphate injected subcutaneously.

Calcium lactate was given by stomach tube.

Date	Time		Ca	Inorg P	T.A.S.P.	B
Dog 103. Male. 18.6 Kilo						
July						
9			10.91	4.26	25.43	
10	3:25	Thyroparathyroidectomy	10.46	4.39	24.55	
14	9:30AM	Moderate tetany. Resp. increased	5.88	4.00	24.17	1½gr
	10:05	Twitching much aleviated				
	10:30	No twitching. Resp. almost subsided	5.57	3.63	21.93	
	4:30	Quite normal. Can walk well but lays down readily and rests.				
	6:30	400 cc water. Twitches on handling.				
	7:30	Beginning tetany. 250 cc Ca Lact 5%				
15	11:30	300 cc Ca Lact 5%				
	7:00PM	" " " " "				
16		No symptoms				
17		No symptoms				
18	12:30M	Exhibited some twitching. At 2:00PM when I returned dog had broken out of cage, jumped through the window thus killing himself.				
Dog 104 Male 12.2 Kilo						
July						
9	3:00PM		10.52	3.26	24.08	
10	2:30PM	Thyroparathyroidectomy	10.53	3.11	22.73	
13	9:10AM	In severe tetany since before 6:00 AM. Twitches were gone in about 10 min. after injection but soon began again	4.81	3.92	24.67	3gr
	9:45					2
	10:40	No twitches but resp. still rapid		3.26	20.40	
	5:35PM	Respiration jerky. Very comatous	45.72	7.48	23.60	
	7:20	Found dead.				
Dog 105. Female. 9.7 Kilo						
July						
9	7:25PM		10.71	4.16	28.19	
10	4:00PM	Thyroparathyroidectomy	11:05	3.73	26.50	

Date	Time		Ca	Inorg P	T.A.S.P.	B
July						
13	10:10	Tetany	6.24	3.48	23.37	3gr
	11:20	Complete subsidence. Very sleepy		2.70	20.40	
	5.45PM	Seems very much hallucinated. But has twitches again and will assume a certain curved posture of the neck	6.13	6.24	27.40	½gr
	8:30	Tetany becoming quite severe Dog is very irritable and still under influence of drug as noted above				½gr
	8:33	Hypernea				
	9:20	Hypernea continues. Tetany		3.92	26.12	1gr
	10:25	Still extension and fibrilation and rapid respiration	6.20	3.68	25.45	
	11:30	Twitches but no rapid real Tetany. Was too weak to stand or walk upright				
14	9:40AM	Animal has doppy appearance. Is so weak in the joints that he can hardly walk	5.41	4.98	20.63	
	5:00	Same doppy appearance. But walks and runs, however with much incoordingtion.	5.61	5.09	25.98	
	6:30	250 cc water by St. tube				
15	10:30AM	Improved	5.36	4.56	25.98	
	11:30	250 cc Ca Lact. 5%.				
	7:00	250 cc Ca Lact. 5%.				
16		No symptoms				
17		No symptoms				
18	4:30PM	No symptoms. Had eaten one-half meal	6.02	3.96	22.77	
	10:10	Severe tetany. Rapid resp	5.66	3.20	20.38	½gr
	11:10	Entirely quieted down	- --	3.02	19.35	
19	10:47AM	Extension, tetany and rapid resp. 2 min after inj. vomited	5.24	5.26	23.40	2gr
	12:45PM	Resp. still above normal	5.30	4.14	23.22	
	5:30	Resp. still faster. Twitches in head & neck				1gr
20	2:00PM	In discomfort all morning, yelping, has now rapid respiration, muscular fibrilation and twitches. Never seemed to have recoverdd from morphine	5.40	5.52	26.90	2gr

Date	Time		Ca	Inorg P	T.A.S.P.	B
July						
20	2:04	Powerful retching and extensor rigidity followed by complete subsidence of resp. Twitches of head and neck.				
	2:15	Resting. No tetany. Resp. increasing at 2:17	6.02	8.23	30.75	
	9:05	Diaphagmatic twitches. Groans with each expiration. Resp. much faster than normal. Dog is limp and will not stand. Inj. followed by sym. as above				
	9:10	Resp. slow. Retching		7.02	31.13	
	9:24	Resp fast again and under full influence of drug		8.20	31.75	
21	10:10	No tetany. Resp. quite normal for hot day. Groans with each expiration and shows signs of discomfort	5.42	7.55	31.82	
	3:00	Does not stand or walk. Dog in misery. 10 gm Ca Lact				
22		Tetany. Respiration normal				7
23	11:45	Some twitches. Inj. followed by symptoms as above	4.83	6.68	26.73	1gr
	12:10	Resting except for sudden single, violent twitches of all four legs, neck and jaws at intervals of 20 to 50 seconds		6.15	23.62	
	12:55PM	Same as 11:45		6.49	23.92	
	8:00	Has convulsions with inhibitions of resp. Aleviated by inj. plus sym as above				1gr
24	11:10	Convulsions on handling Is weak and will not stand. Has extreme eye symptoms. (enophthalmus)		8.38	27.14	
25	10:35	Blood is thin and literally black. Has no tetany sym. Can stand and walk	5.17	8.90	26.80	
26	5:45	Enophthalmus, depressed but no tetany symptoms. Later in day had some convulsions.		8.21	25.07	
27	2:40PM	Tetany on handling, eye symptoms.		9.35	26.65	
	8:00PM	Found dead.				

THE INFLUENCE OF AMMONIUM CHLORIDE ON DOGS SUFFERING FROM PARATHYROID DEFICIENCY.

The use of ammonium chloride in the treatment of parathyroid tetany was perhaps suggested by itsbeneficial effects in infantile tetany. (Freudenberg and György, 1922 (81 to 84); Gamble and Ross 1923 (86); and Anderson and Graham (3)) a nd the favorable results obtained by Youmans and Greene (1925) (260) by its intravenous administration in gastric tetany.

In 1921 Haldane (115) showed that ammonium chloride produced an acidosis in the body. This work was subsequently extended by Haldane, Hill and Lusk (116) who showed that ammonium chloride caused a marked diuresis. Since then it has been used in the treatment of edema and as a corrective in the alkalosis of tetany. An acidosis produced by several different ways (notably ammonium chloride, HCl and pathological acidosis, such as may be caused by nephritis, rickets and acute gastroenteritis) was effective in preventing tetany when the Ca was as low as 3 to 1.5 mg per cent are among the cases reported by Anderson and Graham.

They showed in 3 cases of infantile tetany that the Ca rose coincident with the fall of CO_2 as the tetany disappeared in 2 cases, while in the other, the tetany disappeared without affecting the serum Ca. In this case

the alkaline reserve fell only to 46.7 vol. per cent. But Gamble, Ross and Tisdall (86) obtained a much more striking fall in alkaline reserve with no increase in the ionized Ca. They suggested that in these cases an increase in the ionized Ca was responsible for the beneficial effect. Anderson and Graham, and Gamble and Ross thus found no constant effect on the total serum Ca.

They showed that at least in idiopathic tetany, the serum inorganic P bears no relation to the Ca level or the symptoms, though Salvesen (217) holds that the blood phosphorus level is high in parathyroid tetany, while Binger (14) even advances the theory that the increased blood P produces the Ca fall and hence the symptoms. This has been totally disproven by the work of Greenwald (100), Tisdall (238) and others, by phosphorus injections and raising the P as much as 20 times the normal level (100) and though the calcium fell, there were no untoward effects upon the animal unless the sodium salt was raised to a high value. Anderson and Graham (3) also show that Bingers contention cannot be true because in rickets, P may be low and the Ca normal. Nevertheless, Bingers work seems to show that the reaction of the solution injected rather than P content determines whether tetany appears.

Wilson, et al, (256), (257) showed that by HCl administration intravenously, the symptoms of parathyroid

tetany were prevented or allayed. They showed no permanent recovery but an intolerance to acid administration by mouth. Sodium bicarbonate appeared to aggravate tetany.

Boyd, Austin and Ducey (19a) in following the blood Ca for 6 hrs after the oral feeding of ammonium chloride found no consistent serum Ca rise. Out of a series of 11 dogs, 1 showed a rise of 8.2 to 12.1 and another 8.4 to 13.1 mg per cent and for the remaining experiments variations were from 1.5 below to 1.9 mgoper cent above the initial level. They found that ammonium chloride by mouth reduces the frequency and severity of tetany attacks; that the period of survival is considerably prolonged, but recovery does not as a rule occur; and that death is commonly preceded by a period of several days of anorexia and depression without tetany.

Wenner and Muntwyler (251) clearly demonstrated that a condition of alkalosis does not exist at any period following parathyroidectomy in dogs. The CO_2 content of plasma and the H ion concentration remain within normal range. After recovery from convulsions the p H and alkali reserve of blood may fall considerably. At this low p H 7.09 and low CO_2 content 26.8 vol. per cent all tetany symptoms disappeared.

Swingle and Wenner (236) by bleeding to a considerable extent showed the aleviation of symptoms but coincidentally they noted a marked rise in the serum Ca in 1½ to 7 hrs.

Tetany again occured on the following day. Bennett (8) later showed a fall of p H from .02 to .12 within 4 or 5 hours on withdrawal of $\frac{1}{4}$ to $\frac{1}{2}$ of the blood. On the following day the p H was .01 to .11 above normal values.

Wenner (250) affirms the work of Austin et al (19a). They state, however, that they were able to keep the dogs alive after 30 to 40 days of treatment. They state that ammonium chloride probably exerts its action by rendering the blood more acid thereby producing a rise in the serum calcium and a disappearance of the symptoms of tetany.

RESULTS

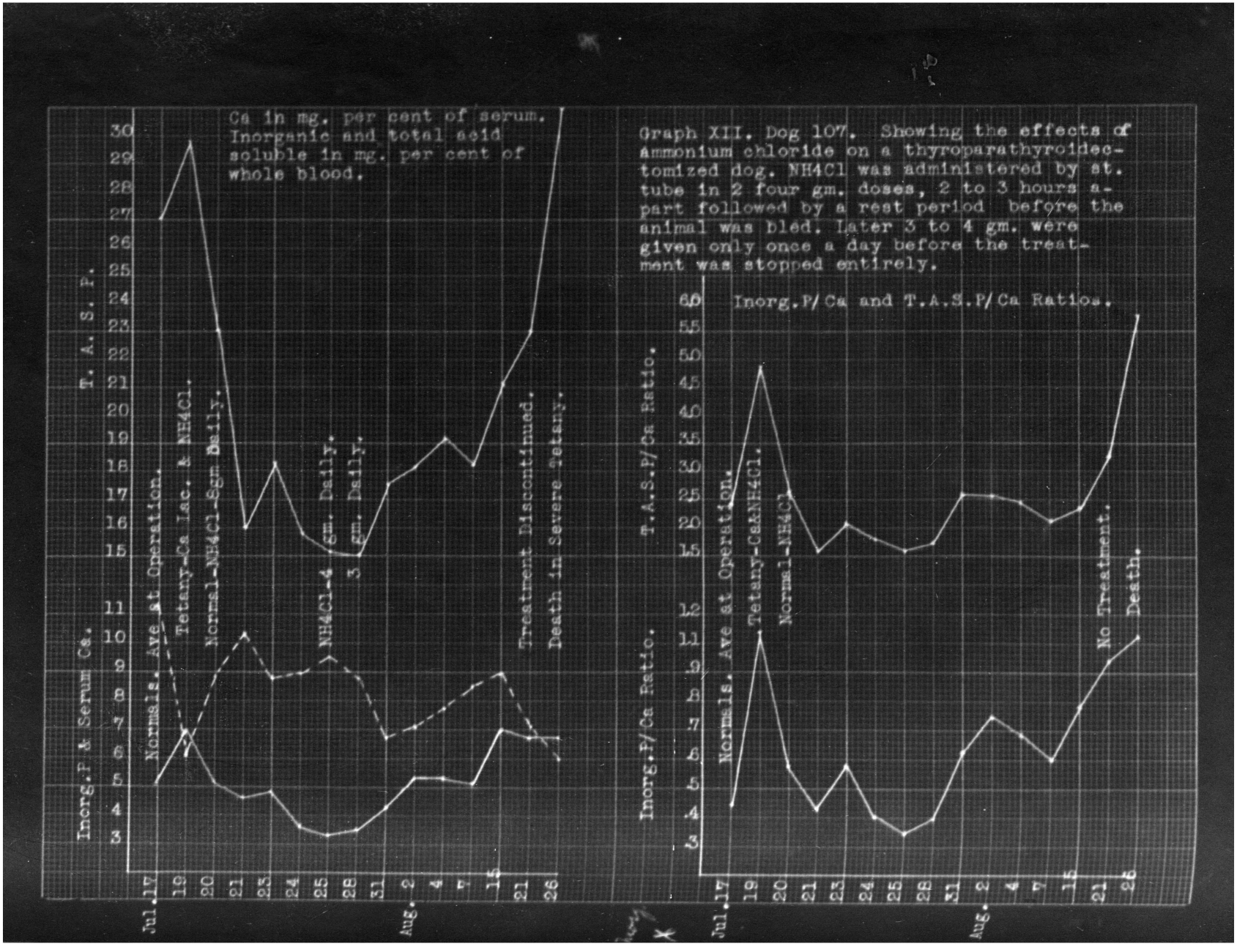
The experimental method and the method of treatment for ammonium chloride was identical to that outlined for strontium lactate treatment.

Only four dogs were treated with ammonium chloride (Dogs 106 to 109) of which dog 107 is represented graphically (Graph XII). In all of these dogs ammonium chloride was effective in aleviating tetany but it rarely prevented all other symptoms of parathyroid deficiency. All of the dogs exhibited tetany or twitches from once to several times during the experimental period, vomited frequently and had a mild or severe degree of anorexia.

All four dogs developed tetany on the first or second day and responded well to calcium treatment. Their span of life with ammonium chloride treatment was 1, 3, 8, and 38 days, (Dog 107, Graph XII), respectively. The latter was treated 33 days, but lived 6 days beyond that time.

In these dogs the phosphorus changes largely depend upon the length of ammonium chloride treatment that the animal will survive. Dog 106 exhibiting the severest tetany on the second post-operative day received morphine sulphate (gr $\frac{1}{2}$) subcutaneously and 12 grams of Ca lactate by mouth followed in one hour by 5 grams of ammonium chloride. Eleven hours later, shortly before death the calcium had risen from 6.04 to 11.22 mg per cent, the inorganic P from 5.51 to 8.51 mg per cent and the T.A.S.P. from 27.56 to 36.53 mg per cent. The serum showed marked hemolysis (due to ammonium chloride--Haldane et al (116)) and the dog had a rapid respiration and increased salivation though no other signs of parathyroid deficiency were present.

Dog 108, by essentially the same initial treatment followed by ammonium chloride treatment, exclusively, lived 3 days. In this dog the calcium stayed at a level of from 9.- to 9.6 mg per cent, the inorganic P was decreased from 0 to 4 mg per cent in 1 to 2 hours after each ammonium chloride administration.


Ca in mg. per cent of serum.
Inorganic and total acid soluble in mg. per cent of whole blood.
Inorg.P & Serum Ca.
T. A. S. P.
Normals. Ave at Operation.
Tetany-Ca lac. & NH4Cl.
Normal-NH4Cl-5gm Daily.
NH4Cl-4 gm. Daily.
3 gm. Daily.
Treatment Discontinued.
Death in Severe Tetany.
Jul. 17
Aug.
Graph XII. Dog 107. Showing the effects of Ammonium chloride on a thyroparathyroidectomized dog. NH4Cl was administered by st. tube in 2 four gm. doses, 2 to 3 hours apart followed by a rest period before the animal was bled. Later 3 to 4 gm. were given only once a day before the treatment was stopped entirely.
Inorg.P/Ca and T.A.S.P/Ca Ratios.
Inorg.P/Ca Ratio.
T.A.S.P/Ca Ratio.
Normals. Ave at Operation.
Tetany-Ca&NH4Cl.
Normal-NH4Cl
No Treatment.
Death.
Jul. 17
Aug.

Dog 109 was restored to normalcy by the same treatment used in Dog 108. The ammonium chloride maintained the Ca at a level of 8.18 to 9.13 mg per cent; the inorganic P varied from .5 below to 1 mg per cant above normal and the T.A.S.P. decreased 12 mg per cent (30.55 to 18.69) until the fourth day of ammonium chloride treatment on which day ammonium chloride was not administered. The following day this dog had tetany symptoms with values of serum Ca Inorg P, and T.A.S.P., respectively, 5.60; 5.12; and 23.50 mg per cent Ammonium chloride treatment from then on was still able to reduce both the Inorganic P and T.A.S.P. to the low values noted above but it could raise the calcium only to 7 mg per cent. The dog thus died on the eighth day of ammonium chloride treatment, however with no signs of tetany. Previous to death he was weak, emaciated and had bloody vomit and stools.

Finally, Dog 107 (Graph XII) after initial recovery from tetany was kept in good condition and at least free from any of the severer symptoms of parathyroid tetany by 33 days of ammonium chloride treatment. The Ca level was maintained between 6.73 and 9.45 mg per cent. The inorganic P was kept from .3 to 1.7 mg per cent below the normal until the 14th day of treatment from which time it gradually increased above the normal (Aug 2) as the treatment was lightened, but did not increase beyond that after treatment was withdrawn (6.77 as compared to the normal 5.01 mg per cent). The T.A.S.P. showed similar changes

but did not exceed the former normal value until the time of fatal tetany, six days after treatment was entirely withdrawn. Normally it was 27.0 mg per cent; in tetany 29.82 mg per cent; from there it fell to 23 mg per cent and 16.00 mg per cent on the following 2 respective days. It then stayed in the neighborhood of 19 to 15 mg per cent until the 10th day of treatment (Aug 29) from which it began to rise as the treatment was lightened. It was only 3 above normal (31.00 mg per cent) at the time of death in severe tetany, 6 days after withdrawal of treatment.

Graph XII, therefore indicates clearly that the phosphorus decrease is not wholly due to the calcium rise but is more a function of the ammonium chloride itself, since the decrease in the phosphorus compounds was proportionate to the dose of ammonium chloride used (Jul. 20 to 28) and the subsequent increase of the phosphorus compounds was proportionate to the decrease of ammonium chloride administered (Jul 28 to Aug 27) regardless of whether the serum calcium was above 9 mg per cent (Jul. 21 to 28, Aug 15) or below 7 mg per cent (Jul. 31)

From the above results, it must be obvious that both the inorganic P/Ca and the T.A.S.P./Ca ratios must decrease markedly where the dog is kept free from tetany by ammonium chloride and increase just as markedly when the dog is not initially benefitted by the ammonium chloride or when the ammonium chloride treatment is finally withdrawn and the dog is allowed to go into tetany.

DISCUSSION AND CONCLUSIONS.

Thyroparathyroidectomized dogs that survive the treatment by oral administration of ammonium chloride shbw a diminution in the Inorg P and the T.A.S.P. of the whole blood (Dogs 107 to 109). One dog (Dog 106) not surviving the treatment showed a marked increase in these substances. If the dog survives ammonium chloride treatment and is also benefitted and kept free from severe tetany by the ammonium chloride, the serum calcium is found to be above 7 mg per cent (Dogs 107 and 109) Even a dog (Dog 109) dying from severe overdosage showed a marked fall in inorganic and total acid soluble phosphorus but a normal serum calcium. Thus, it follows that whenever the dog is freed from parathyroid deficient symptoms by means of ammonium chloride treatment, both Inorg P/Ca and T.A.S.P./Ca ratios decrease to or below the normal.

Our results confirm those of Wenner that the ammonium chloride probably exerts its action by rendering the blood more acid, thereby producing a rise in the serum calcium. In addition it may be possible that the NH_4' ion is synergistic with Ca'' and Mg'' in certain functions of the body in which the lactic acid produced by muscular contraction also plays an important role. That such a condition does exist is shown by the workers in Pawlow's laboratory. The work of this Russian school has recently

been reviewed and translated by Prawdicz-Neminski (203a). From this extensive review, including the works of many Russian authors and investigators, it is concluded that the NH_4' in all forms of muscular and nervous activity unites with Mg'' and PO_4''' to form the triple phosphate and may be demonstrated in crystaline form in the tissues, thus removing these ions from solution and its ionic relationships. It is shown at the same time that excess of organic acids, notably lactic acid, redissolve the triple phosphate. The latter fact would seem of extreme importance in explaining why ammonium chloride alone is unable to maintain animals once in tetany free from tetany and death. The lactic acid already present would keep the NH_4' from uniting with Mg'' and PO_4''', thus making it necessary for more Ca'' to be in equilibrium with the excess PO_4''' ions. This same explanation may be attached to the fact that Mg'' treatment is effective only when the Ca'' is kept high. The Mg then acting as a pure depressant of all nervous elements, whereas, once the low Ca causes tetany to precipitate, the lactic acid so formed draws additional phosphate ions to the excess Mg'' ions thus increasing the phosphates of the blood markedly.

DOGS TREATED WITH AMMONIUM CHLORIDE.

Ca. Treatment--Morphine Sulphate subcutaneous, and ammonium chloride and Ca Lac. in gm by stomach tube.

Date	Time		Ca	Inorg P	T.A.S.P.	C
Dog 106. Female. 11.1 Kilo.						
July						
11			10.88	4.95	25.72	
12			11.10	4.99	24.70	
17	4:55PM	Thyroparathyroidectomy				
19	9:40PM	The severest tetany. Rapid respiration.	6.04	5.51	27.56	½gr Mor. Sul.
	9:55	250 cc Ca Lact 5%				
	11:00	Rapid resp. Less tetany.				5 gm NH_4Cl
20	10:00AM	Dog was very weak and resp. was still moderately rapid.				
	10:30	Had just died. Serum showed much hemolysis and had some red cells in it	11.22	8.51	36.53	
Dog 107 Female 11.1 Kilo						
July						
11			11.32	5.03	26.65	
12			11.33	4.99	27.40	
17	4:10PM	Thyroparathyroidectomy				
19	9:45PM	Tetany. No rapid resp. as yet.	6.13	7.00	29.82	5%CaLac
	11:00	Rap. resp. No extension				5 gm NH_4Cl
20	11:15AM		8.33	6.13	23.00	6 gm
	1:30PM		8.81	5.13	23.10	
	7:30	Vomited about ½ with meal 15 min later				6 gm
21	10:30	Normal. Bleeds from sight of operation	10.35	4.63	16.00	5 gm
	11:00	Vomited about ½				
	11:30	Normal. Not Fed				
22		Normal. Not fed. No medication.				
23	10:50	Apparently near tetany symptoms. Vomited some	7.76	4.19	19.48	6 gm NH_4Cl
	11:55	Normal		3.84	18.72	
	3:30	Normal. Vomited some at 3:40. Fed at 5:30 when he ate full meal but had vomited most of it by 7:30PM	8.30	4.82	18.33	5 gm
24	12:15PM	In good shape. Vomited some 12:45	8.90	3.85	17.02	4 gm
	2:55	Vomited a small part at 3:50				4 gm
	4:55	O.K. Ate ½ of meal when fed at 9 PM	8.96	3.59	18.91	

Date	Time		Ca	Inorg P	T.A.S.P.	C
July						
25	10:20	Slight muscular fibrilation; more like that of fear. Vomited ½ at 10:50	9.45	3.33	15.15	
	1:35PM	Ate ½ meal at 7 PM		3.63	15.27	
26	10:55	O.K. Except for some tremors as above.				4gm
	3:50	Vomited most of it at 11:12. O.K. Did not eat		3.90	16.52	
27	9:35	Vomited a small part immediately. Is otherwise O.K.				
	2:50PM	O.K. Did not eat		4.16	16.53	
28	10:05AM	O.K. Has fibrilations and tremors as of fear or cold				4 gm
	10:18	Vomited about ½				
	12:05PM	O.K. 5 PM ate ½ meal	8.78	3.52	15.06	
29	7:30AM	Vomited a larg part at 7:45. Not fed				3 gm
30	3:50PM	Ate entire meal at 7:30				3
31	11:30AM	Has some muscular fibrilations. May have vomited a small part				3
	2:00PM	O.K. better than ever since operation. Ate full meal	6.73	4.27	17.50	
Aug						
1	10:25AM	O.K. Ate full meal at 7:30PM				3
2	11:35AM	O.K.Vomited some at 11:45				3
	3:30PM	O.K. Ate with good appetite	7.10	5.36	18.15	
3	10:40	O.K.				3
4	11:00	O.K.				3
	3:40	O.K.(3 gm NH_4Cl and meal daily 5 to 6)	7.80	5.30	19.20	
7 to 11		O.K. Very well				3
	3:40PM	At 8:30PM ate meal with excellent appetite	8.52	5.14	18.25	
8	11:00AM	Ate meal at 8:30 with excellent appetite				3
9	11:00	Ate meal at 8:30 with excellent appetite		5.71	17.63	3
10	12:00M	At 5:30 ate meal with excellent appetite				3
11	11:00AM	At 4:30 ate meal with excellent appetite				3
12 to 14		Same as above with same treatment.				
15	10:30	Same as above with same treatment.				3
	2:30		8.96	6.96	21.15	
21		Discontinued treatment	7.12	6.722	23.08	
26	7:30AM	Had been in a very severe tetany for some time. Was in exhaustion.		6.36	30.75	
	7:50	Had just stopped breathing. Ca samples lost by misplacement in the ice-box.		6.77	31.00	

Date	Time		Ca	Inorg P	T.A.S.P.	C
Dog 108 Male 13.2 Kilo						
July						
13	5:30PM		10.21	3.24	30.42	
17	11:30AM	Thryoparathyroidect-	10.82	2.77	29.74	
18	11:50PM	omy at 3:45 PM				
18	11:50PM	Tetany with marked laryn-				1 gr Mor. Sul.
		geal stridor. Very				12 gm Ca Lact.
		rapid resp.	7.50	5.10	31.67	
19	11:00AM	Resp. above normal and				
		some muscular fibrilation	8.94	4.50	30.26	10 gm NH_4Cl
	12:50PM	Quite normal	9.16	3.17	30.10	
	7:00	Beginning tetany. Rap.				
		Resp. Had not eaten				12 gm Ca La
		" alleviated immediately				
	11:00	Active and had eaten some.				
		Vomited about 15 min. later				5 gm NH_4Cl
20	11:15AM	Normal	9.40	3.39	27.56	6 gm
	1:30PM	Normal. Resp. Faster	9.41	3.48	25.03	
	7:20	Drank about 600 cc water				6
		water immediately following				
		and in about 10-15 min vomited some.				
		Dog was weak & resp. fast				
21	10:25	Normal except for faster resp.				
		Vomited about ½ at 10:47	9.02	5.71	29.85	5 gm
	11:30	Normal faster resp.				
		12:30 vomited				
	7:20	Drank about 600 cc water immediately				6
		following and in about 10-15 min				
		vomited some. Dog was weak and				
		his resp. fast.				
21	10:25	Normal except for faster resp.				
		Vomited about ½ at 10:47	9.02	5.71	29.85	5
	11:30	Normal faster resp. 12:30				
		vomited some on return-				
		ing to cage	9.62	2.95	25.60	
22	10:30AM	Dog not active but otherwise				
		O.K.				
	5:00PM	Dog found dead and rigid.				
Dog 109. Female. 14.3 Kilo						
July						
13	5:30PM		11.25	4.29	28.23	
17	11:30AM	Thyroparathyroidect-	11.40	3.92	27.30	
		omy at 3:00 PM				

Date	Time		Ca	Inorg P	T.A.S.P.	C
July						
19	10:00AM	Beginning twitches				
	1:30	Severe tetany. Rapid resp	6.71	5.76	29.00	1grMS
	1:50	Tetany. Rap. rest. Very marked salivation				10gm Ca Lact
	3:10	Tetany. Rap. Resp.				" " "
	5:15	Recovered from tetany and rapid respiration but not mor. Sul.	11.90	4.08	30.55	
	11:00	Still a little dopey				5 gm NH_4Cl
20	10:30	Was quite normal. Had vomited some between 12:00-12:30	8.18	3.45	21.72	10 gm
	1:40	Normal	8.88	4.54	22.45	
	9:45	Vomited some meat on passing of St. tube.				6 gm
21	10:30	Normal	9.13	5.08	18.95	5 "
	11:30	" Not fed. 3:00PM 200 cc Ca Lact	7.42	4.69	17.69	
22		Normal Not fed. No appetite				
23	10:40AM	Some twitches and resp increasing.	5.60	5.12	23.50	6
	11:50	No tetany symptoms		4.70	22.85	
	3:20	" " " Ate only a part of meat at 5:30 PM	6.30	4.70	21.81	5
24	12:15PM	No symptoms on table and on passing of St. tube. Vomited much mucous material.	6.74	4.28	20.00	4
	2:50	Vomited about ½ containing much mucous at 2:57. Tried to add more whereupon he vomited the rest and another 4 gms was then given				4
	3:05	Exhibited a few twitches at 3:30				
	4:50	O. K.	6.80	3.52	19.50	
25	10:20	A muscular twitching some times	7.10	3.40	19.30	
	1:35	O. K.		3.45	18.69	
26	10:55	A few twitches. Had exhibited marked diarrhea during night and bloody vomit. Vomited about ½ at 11:00				4
	3:45PM	O.K. as far as tetany. Weak and emaciated. Did not eat		3.68	18.33	
27	9:00AM	Found dead. Was still warm in curled up position with no symptoms of tetany.				

THE INFLUENCE OF URANIUM NITRATE ON DOGS SUFFERING FROM PARATHYROID DEFICIENCY.

MacNider (1918) (171a) in making studies on Uranium Nitrate Intoxications on dogs noticed in the liver a cloudy swelling followed by edema, a fatty degeneration and infiltration and necrosis. These changes started from the central vein and migrated to the periphery of the lobule. The severity and rate of these changes did not depend upon the dose used but very strikingly upon the age of the animal, the older animals being much less resistant than the younger. Associated with these changes there developed an acid intoxication directly related to the extent of the liver changes.

Since other modes of creating an acidosis are but fleeting and always decrease from the time of each administration of the acidifying agents (reviewed in ammonium chloride section), Uranium Nitrate was resorted to by Swingle (1928) (235a) for its prolonged acid effect. He found that the effects of Uranium Nitrate upon tetany were striking, for within 12 to 24 hours after injection, all tetany symptoms had disappeared and the animals ran about, ate and played in normal fashion. A week to ten days elapsed before dogs again developed tetany when fed on a heavy meat diet. The injected dogs showed a lowered CO_2 capacity, CO_2 content and a slightly lowered p H. The serum Calcium remained the same or increased somewhat,

(never more than 1 mg per 100 cc of blood). Despite the low tetany calcium, the dogs appeared entirely normal. He suggests that a disturbance of the acid-base equilibrium with a shift in reaction toward the acid side, relieves tetany by rendering the serum calcium more diffusible and also probably takes care of any excess of phosphorus which may be present by stimulating its excretion.

METHOD.

Dogs were completely thyroparathyroidectomized, allowed to go into tetany and then treated by subcutaneous injection of uranium nitrate (.3 to 5 mg per K body weight) according to the apparent age of the animal. Blood analysis was made several times on the normal, at the time of tetany and more or less frequently after injection of uranium nitrate until recovery. After this the blood was analyzed not more than once a day.

RESULTS.

The symptoms described by Swingle conform to our findings and need no further comment. They are fully recorded on each protocol.

There are 9 dogs in this series of which one, to serve as a control, was not thyroparathyroidectomized.

Of these 8 dogs 2 (Dogs 96 and 94) died on the first and third days respectively, following the injection of uranium nitrate. Dog 94 had a severe rash and must have died from a complication, for he had no uranium nitrate overdosage symptoms. But dog 96 died from the immediate effects of uranium nitrate poisoning. The other 6 dogs showed typical recovery lasting from 1 (Dog 95) to 8 days (Dog 97). From this time on these dogs gradually or quite suddenly lost their appetite, began to vomite a green slimy substance, became progressively weaker, exhibited some typical convulsion or tetanic twitches intermittently in the course of 7 (Dog 99) to 20 days (Dog 102). Dog 97 did not die but had to be killed on the 52nd day because of severe joint and skin ulceration. The normal dog (Dog 110, Graph XVI) treated with uranium nitrate showed practically the same terminal symptoms as did the tetany dogs; convulsions, temporal and leg twitches, extreme weakness and death.

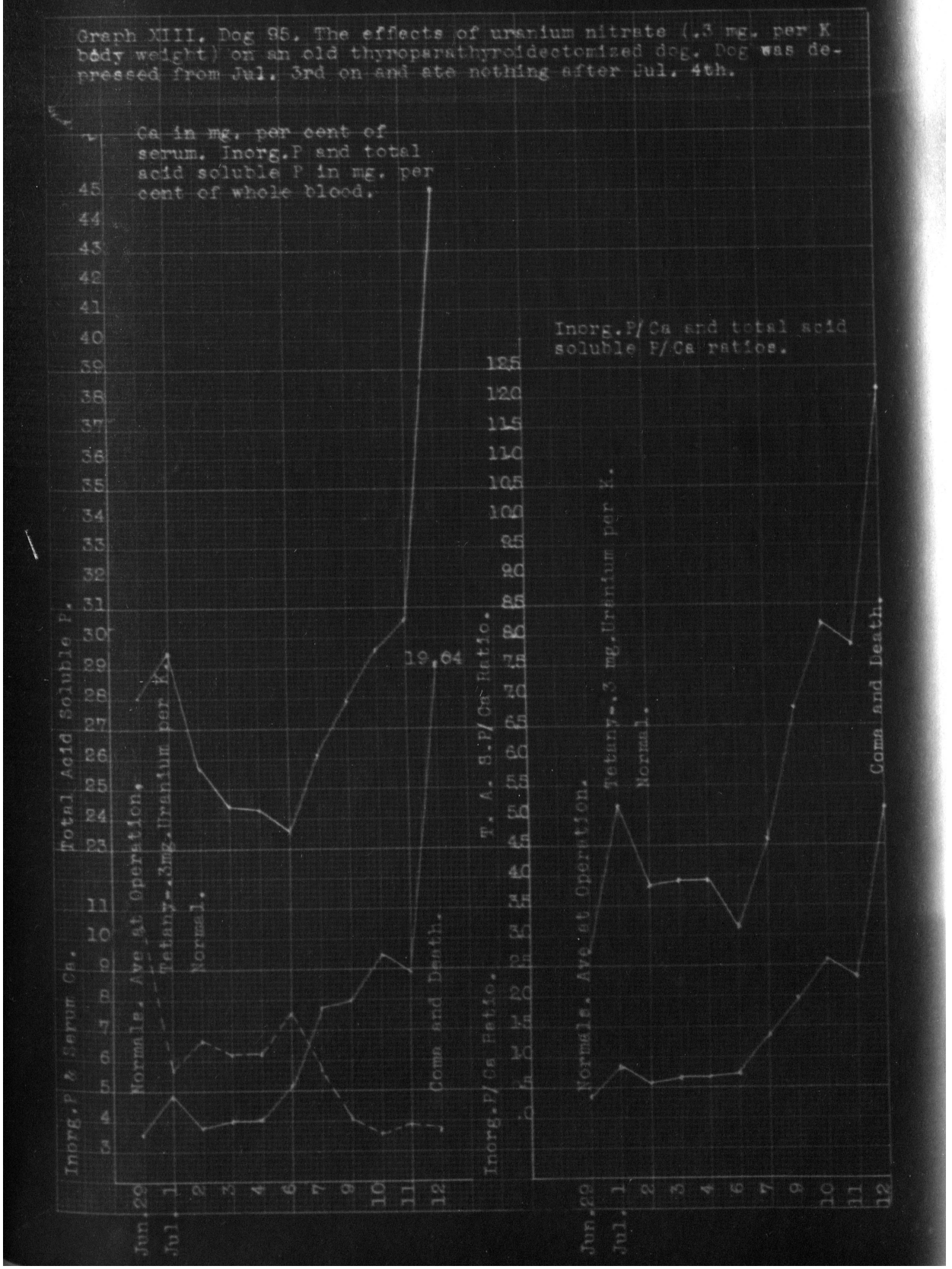
The serum calcium hardly ever varied more than ± 1 mg per cent after the administration of uranium nitrate to tetany animals. The most striking and unexplainable exception is that in Dog 97 (Graph XV) when on Jul. 7 (6 days after the uranium nitrate injection) the serum calcium had risen from 5.3 to 9.3 mg per cent and from thereon fell slowly in the course of 7 more days (Jul. 7 to 14).

However, in the normal dog (Dog 110, Graph XVI), there was a fall of nearly 3 mg per cent in the last 2 days of life.

However, in the blood chemistry the most striking thing is the change in whole-blood inorganic and total acid soluble phosphorus paralleling the symptomatology. That age is a very important factor in determining the optimal dose to be administered to a dog is shown by a comparison of Dogs 94 and 95. Dog 95 (Graph XIII) had the appearance of being very old. Therefore only .3 mg of uranium nitrate per K body weight were injected, which benefitted the animal for 6 days (Jul 1 to 6) and a marked decrease in the P compounds resulted. From there on a progressive phosphatemia (both inorganic P and T.A.S.P.) occurred for 5 days Jul. 6 to 11) and on the next day the inorganic P rose from 9 to 19 mg per cent and the total acid soluble P from 30 to 45 mg per cent and the animal died in coma. But dog 94, appearing young was given a dose of 5 mg per K which terminated his life in the course of 18 hours. In this dog the inorg P was only slightly decreased at first but the T.A.S.P. rose progressively and the values an hour before death were 8.70 and 45.30 mg per cent, respectively.

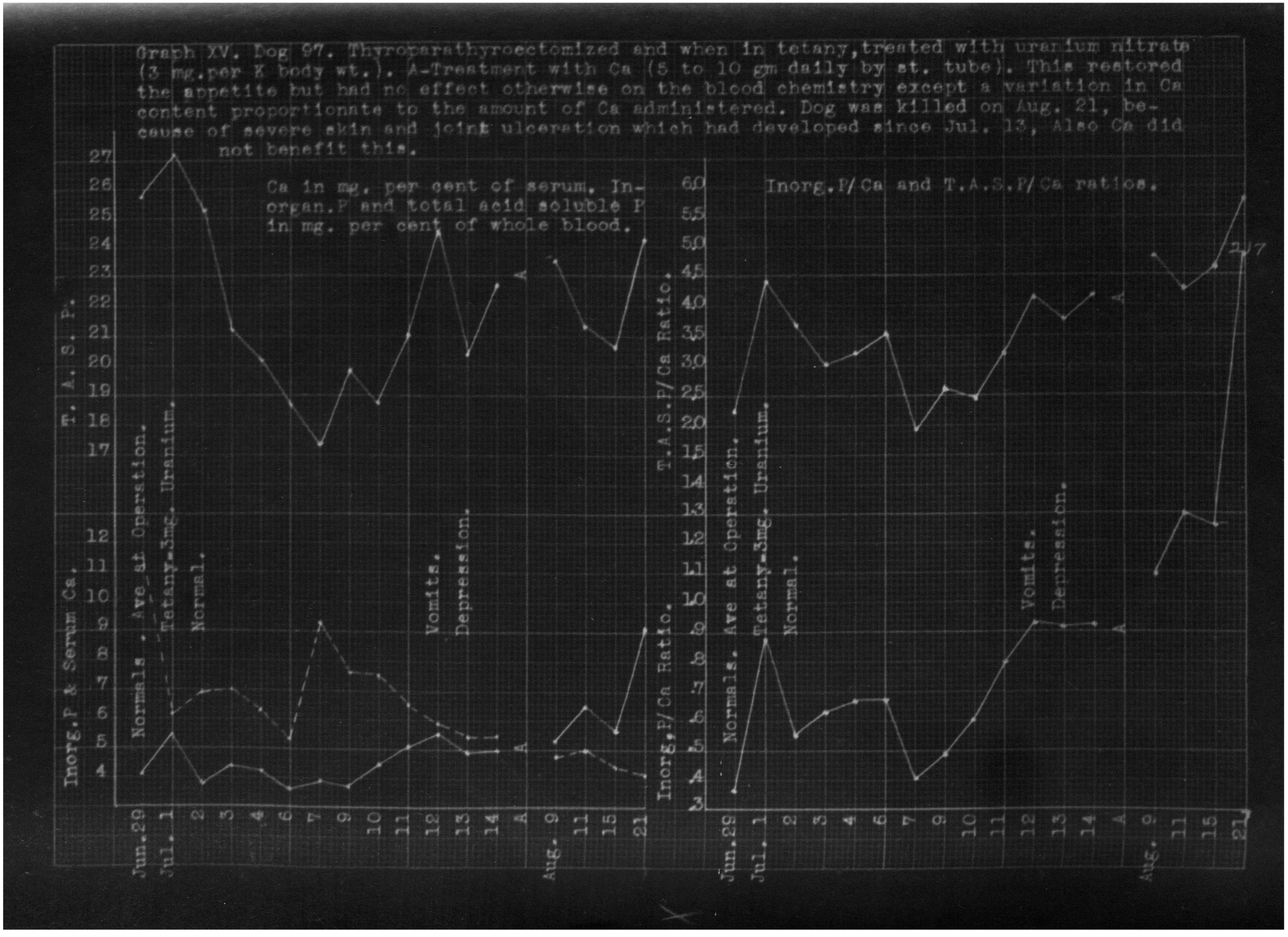
For the remainder of our discussion on the tetany dogs, Dogs (97) (Graph XV) and 102 (Graph XIV) will serve as valuable examples to bring out the contention that change in phosphorus concentrations accompanies the

Graph XIII. Dog 95. The effects of uranium nitrate (.3 mg. per K body weight) on an old thyroparathyroidectomized dog. Dog was depressed from Jul. 3rd on and ate nothing after Jul. 4th.



symptomatology. Immediately following the injection of uranium nitrate there was a progressive drop in the total acid soluble phosphorus to the neighborhood of 17 mg per cent (10 and 16 mg fall) in both dogs in the course of 2 or 3 days. This was accompanied or followed by a 2 mg per cent drop in inorganic phosphorus. Soon, however (11 days later) in dog 102 (Graph XIV, Jul. 23) symptoms began to appear again and from then on the phosphorus compounds were progressively increased and death ensued 5 days later with values of inorg P and T.A.S.P. 22.20 mg, and 55.00 mg per cent, respectively. Not so with Dog 97 (Graph XV). He continued to eat, though the phosphorus concentrations varied widely from day to day; the T.A.S.P. never even reached the normal concentration whereas the inorganic P was above the normal after the 20th day (Jul 10 to Aug 21) and from thereon showed a general trend upward, having a concentration of 9 mg per cent when the animal was killed on the 52nd day after the uranium nitrate injection. In both of these dogs and in dogs 99 and 100, calcium lactate by mouth did not cause a decrease in the blood phosphorus. On the other hand in all but dog 97 (Graph XV) the phosphatemia increased in spite of the calcium therapy. Since dog 97 responded also by regaining his appetite the treatment of 5 to 10 gm calcium lactate daily was continued for 25 days in an effort to clear up his skin eruptions and ulcerations. This proved unsuccessful. The ulceration became progress-

Graph XIV. Dog 102. A thyroparathyroidectomized animal treated with uranium nitrate (4 mg. per K body wt.) showing the decrease in P compounds in the blood in recovery from tetany (Jul. 10 to 23) and subsequent phosphatemia leading to death. (Compare with Graph XV.)


Graph XV. Dog 97. Thyroparathyroectomized and when in tetany, treated with uranium nitrate (3 mg. per K body wt.). A-Treatment with Ca (5 to 10 gm daily by st. tube). This restored the appetite but had no effect otherwise on the blood chemistry except a variation in Ca content proportionate to the amount of Ca administered. Dog was killed on Aug. 21, because of severe skin and joint ulceration which had developed since Jul. 13, Also Ca did not benefit this.
Ca in mg. per cent of serum. Inorgan. P and total acid soluble P in mg. per cent of whole blood.
Inorg. P & Serum Ca.
T. A. S. P.
Inorg. P/Ca and T.A.S.P/Ca ratios.
Inorg. P/Ca Ratio.
T.A.S.P/Ca Ratio.
Normals. Ave at Operation.
Tetany-3mg. Uranium.
Normal.
Vomits.
Depression.
Jun. 29
Jul. 1
Aug. 9

ively worse and the animal was killed 12 days after calcium treatment had been withheld. It will be seen from the protocol of Dog 97 that the phosphorus concentrations even in this dog exhibited the same variations during Ca therapy as before and after.

The T.A.S.P. concentration was only slightly decreased while the Inorganic P was increased by 1 mg per cent during the first 5 days in the control dog (Dog 110, Graph XVI). From thereon both phosphorus compounds rose rapidly and progressively until death ensued 9 days later. The last determinations were made on the day previous to the day of death. At that time the Inorg P was the same as in Dog 102 (Graph XIV) at the time of death whereas the T.A.S.P. was higher by 11 mg per cent than found in any other dog at the time of death (Dog 102 Graph XIV). As will be seen from the protocol, the most striking thing in this dog was that he exhibited very nearly the same symptoms in the terminal days as did the parathyroidectomized dogs by the same treatment.

Since the calcium remains very nearly the same after uranium nitrate administration and since the symptomatology is accompanied by marked phosphorus changes it is shown in these graphsddiscussed above (Graphs XIII to XVI) that the T.A.S.P./Ca and the Inorg P/Ca ratio are largely a function of the P changes. That is to say that these ratios rise or fall whenever their respective P compounds rise or fall. Thus there is a marked fall in these ratios

Graph XVI. Dog 110. Uranium nitrate injected into a normal dog of the 20th of July (5 mg. per K body wt.).

Ca in mg. per cent of serum. Inorg.P and total acid soluble P in mg. per cent of whole blood.

Inorg.P/Ca and T.A.S.P/Ca ratios.

T.A.S.P.

Inorg.P and Serum Ca.

T.A.S.P/Ca Ratio.

Inorg.P/Ca Ratio.

Normals.

Mild Tetany. See Protocol.

Death.

22.7

Jul. 20 23 25 28 31 Aug. 2

below the normal as long as the animal is benefitted, but the ratio rises as soon as the terminal symptoms of uranium poisoning come on in both normal and parathyroid-ectomized dogs.

DISCUSSION AND CONCLUSIONS.

If Dog 107 (Graph XII) treated with ammonium chloride and Dog 102 (Graph XIV) treated with uranium nitrate are compared, there appears a striking similarity in the blood phosphorus compounds as a result of these two methods of producing an acidosis. That is during recovery there is a remarkably lower Inorganic and total acid soluble phosphorus in the whole blood so long as the animal is kept in an acid condition and the terminal symptoms of uranium poisoning do not develop. These facts may thus give proof to the supposition of Swingle (235a) and Wenner (249); (250) who suggested that a shift to the acid side relieves tetany by lowering the phosphorus concentration. Our results, of course, do not show whether the P reduction in the blood is the result of increased P excretion. Neither do our results in the uranium nitrate dogs show that the beneficial effects results from an increase in calcium of the serum--still the calcium present may become more diffusable, and still not increase in concentration.

However the terminal symptoms of depression or tetanic seizures cannot be identified with parathyroid deficiency as suggested by Swingle (235a), but rather as the result of metabolic changes caused by the uranium poisoning. It is well known that a severe nephritis follows the administration of uranium which has a tendency to terminate in anuria. It produces a generalized anasarca and ascites (Leconte, (156), Richter (208)); a highly albuminous fluid transuding mainly into the serous cavities, but also into the other tissues. The anuria is not the whole explanation, since there is an altered permeability in the capillary walls (Richter). There is in this nephritis a retention of water (which parallels the anatomic injuries) (Watanabe et al (245) and non protein nitrogen coupled with an increase in tissue destruction (Mosenthal, (189)). According to the work of MacCleod (170) phosphorus excretion, as a rule, varies in the same direction as does the nitrogen excretion. Thus the increased retention of nitrogen and increased destruction of protein would furnish the source and cause of the high P which may attribute to the later symptoms. The convulsions seen in the later stages may be due to the high urea content since they were the same in both the control and parathyroidectomized dogs and did not stimulate the tetany found in parathyroid deficiency.

It is concluded that the serum calcium content of

thyroparathyroidectomized dogs in tetany is not primarily affected by subcutaneous injection of uranium nitrate. It may vary ±1 mg (relative to the concentration ffound at time of uranium nitrate injection; in one case (+3 mg) during some time after recovery from tetany. The T.A.S.P. and Inorg P decreases progressively and remains low until the severer symptoms of uranium poisoning set in when a progressive increase takes place until death ensues. After treatment with uranium nitrate the P/Ca ratios become largely a function of the respective phosphorus compounds, that is the ratios change in the same direction as do the phosphorus compounds since the divisor remains fairly constant.

DOGS TREATED WITH URANIUM NITRATE.

D--Subcutaneously.
Ca Lact in gm (by stomach tube)

Date	Time		Ca	Inorg P	T.A.S.P.	D
Dog 94	Female	9.3 Kilo.				
June						
20			11.21	3.48	25.51	
22			10.46	4.00	26.77	
23			10.42	3.52	26.63	
26	3:45PM	Thyroparathyroidectomy				
27	10:30		8.50	4.96	31.50	
28	11:00	Ate full meal at 2:30PM	7.01	6.20	29.04	5 per
	5:10PM	Severe tetany. Rapid respiration	6.65	2.97	27.40	5 mg per K
	7:40	Apparently no twitches. Rapid respiration	6.52	2.23	32.95	
	8:50	Respiration normal. Severe convulsions on handling.		2.58	35.43	

Date	Time		Ca	Inorg P	T.A.S.P.	D
June						
28	11:30PM	Still convulsive attacks. Much defecation, urination, and vomiting.				
29	10:15AM	Resting. Too weak to stand.	6.58	8.70	45.30	
	11:10	Dog had just died in extreme coma. Autopsy showed excess intrapericatdial hemorrhage.				
Dog 95 Male 9.8 Kilo						
June						
27	11:00		10.62	3.61	27.92	
28	11:00		10.43	3.53	28.19	
29	3:10	Thyroparathyroidectomy				
July						
1	10:00AM	Tetany	5.73	4.87	29.45	.3 mgper K
	3:30	No tetany	5.96	4.45	29.83	
	9:30PM	No tetany	5.80	4.45	29.33	
2	10:00AM	Normal	6.70	3.80	25.67	
3	10:30	Normal. Eats very little	6.21	4.00	24.39	
4	10:50	Normal. Does not eat	6.21	4.00	24.31	
6	10:20	Normal. Does not eat	7.57	5.12	23.55	
7	9:50	Severe depression. Does not eat.	5.68	7.65	26.20	
9	11:30AM	Severe depression. Does not eat	4.10	7.89	27.87	
10	11:30	Severe depression. Does not eat	3.61	9.39	29.57	
11	3:00PM	Does not eat. In extreme coma	3.91	8.90	30.59	
12	10:30	In extreme coma. Does not eat.	3.72	19.04	45.05	
	2:00PM	Found dead. During last days had vomited green slimy substance.				
Dog 96 Female 9.1 Kilo						
June						
27	2:30	Had eaten at 12:30	10.05	4.86	25.88	
28	3:00		10.43	4.63	25.87	
29		Thyroparathyroidectomy				
July						
1	9:30	Tetany. Looks like recovery stages where twitches are absent	6.82	5.06	31.00	3 mg per K
2	10:00		5.73	5.60	31.25	
3	10:30	Depressed. Suffering from very raw rash. Eats very little				
4	10:35AM	Very bad condition, but is not weak.	6.48	6.86	33.71	
	7:00PM	Dead. No tetany.				

Date	Time		Ca	Inorg P	T.A.S.P.	D
Dog 97	Male	17.5 Kilo				
June						
27	2:40	Had eaten at 12:30	11.40	4.44	25.67	
28	3:00		11.41	3.86	25.79	
29	2:25PM	Thyroparathyroidectomy				
July						
1	9:30	Tetany. Looks like recovery stages where twitches are absent.	6.18	5.44	27.20	3 mg per K.
2	10:30	Normal	6.92	3.78	25.34	
3	10:30	"	7.00	4.39	21.18	
4	10:40	"	6.32	3.58	20.22	
6	10:30	"	5.30	3.58	18.69	
7	10:00	"	9.24	3.84	17.35	
9	11:30AM	"	7.62	3.71	19.95	
10	11:30	"	7.53	4.55	18.67	
11	3:00PM	"	6.56	5.16	21.05	
12	10:30AM	" . Green slimy vomit. Apprently ate very little	5.92	5.52	24.55	
13	10:30	Somewhat depressed	5.41	4.91	20.40	
14	10:00	" " Had not eaten.	5.43	4.97	22.76	
	2:50PM	350 cc milk by St. tube.				
	7:20	350 cc " " " "				
15	10:00	Had not eaten. Depression but not in parathyroid defeciency. Had not eaten	5.78	4.46	21.43	
17	10:30AM	Wt. 14.4 K. Weak and walks badly. Had not eaten	5.20	5.08	21.65	
18	10:30	Weak and walks wabbly. No food	5.05	5.80	23.80	
	4:30	Twitches				10 gm Ca Lact.
	10:30	Normal. Had not eaten. Heart	7.22	6.04	23.25	10 gm
	1:00	beat only 22 to 26 per min. and is irregular. PM ate most all of meal	9.57	5.93	21.05	
20	3:30	Ate nothing. Is reactive	5.69	5.67	20.38	
21	11:00	Has some twitches. No food. No tetany symptoms	5.48	5.40	20.30	11 gm
22		No tetany symptoms. No food.				
23	11:00	Twitches in legs. Wt 13.8 K. Ate most of meal at 5:30	4.83	5.54	21.32	10 gm
24	12:15	No symptoms. Vomited about ½	5.80	5.73	22.70	10 gm
	9:00	Ate entire meal				
25	2:00PM	O.K. Vomited part immediately		5.21	20.00	5 gm
	7:00PM	Ate all of meal.				
26	9:20	O.K. Ate all of meal. Vomits over ½ of injection by stomach tube.				5 gm
27	3:30	O.K. Ate all of meal		5.57	22.20	

Date	Time		Ca	Inorg P	T.A.S.P.	D
July						
14	4:45PM	150 to 200 cc 5% Ca Lact by St. tube	- --	16.00	41.69	
	5:30	Only respiration above normal	12.20	10.66	48.75	
	7:20	Found dead. Had considerable difficulty in bleeding last time, but there was no clot even in the heart nor intrapericardial hemorrhage.				

Dog 100 Male 11.6 K.

July						
3	3:00PM		10.03	3.73	26.30	
4	10:15AM	Thyroparathyroidectomy	11.20	4.18	26.72	
7	9:40	"	6.48	5.61	28.80	
8	12:30PM	Indications are that he has gone through a siege of tetany	6.02	5.04	27.68	
9	7:20	Rapid respiration. Groaning and beginning symptoms of tetany	5.41	4.10	25.52	4 mgm per K
10	11:00AM	Still yelping and other symptoms.	6.12	4.11	25.51	
11	3:00PM	No signs of tetany but groans occasionally and yelps on handling. Did not eat	6.19	4.57	25.98	
12	10:30	No tetany symptoms. Did not eat.	5.23	4.68	24.02	
13	10:30	Same.		4.85	19.10	
14	10:30	Same	5.08	5.35	22.32	Severe infect
15	10:00	Same.		5.75	23.72	" "
16		"				" "
17	10:30AM	Wt 9.9 K. Extension on standing	4.92	8.49	22.60	" "
18	10:30	Some tetany symptoms. Extension which gave way on bleeding and respiration became rapid.				
	4:30PM	Moderate tetany. Ca Lact. by St. tube				9 gm
	10:40					12 "
19	11:00	Still some temporal twitches on passing St. tube				13 "
	1:00PM	No tetany symptoms. Wt 9.2 K Heart rate 132	8.32	13.56	42.00	
	9:30PM	Found dead. Still had a partial infection of the neck. Wt. 8.9 K. Was O.K. at 7:30 PM.				

Dog 101 Male 8.8 Kilo

July					
3	3:00PM		10.00	3.35	22.83
4	10:20	Thyroparathyroidectomy	10.24	3.74	22.85
7	9:30AM		6.71	5.29	23.98

Date	Time		Ca	Inorg P	T.A.S.P.	D
July						
8	12:30PM	Indications are that he has gone through a siege of tetany.	6.71	7.27	28102	
9	7:00PM	Severe tetany	5.13	5.89	27.44	5 mg per K
	11:00	No tetany symptoms		4.80	24.52	
10	11:00AM	" " " Did not eat	5.32	4.44	22.82	
11	3:00PM	No tetany symptoms. Did not eat	4.80	3.81	20.95	
12	3:00	Same	4.93	4.00	18.64	
13	10:30AM	Same		3.91	17.62	
14	10:30	"	4.80	5.27	20.00	
15	10:00	"	5.58	6.86	24.03	
16		"				
17	10:30	" . Wt 7 K. Weak and walks wobbly.	4.95	8.42	27.60	
18	10:30	Very weak	4.46	11.53	32.80	
	5:30PM	Very comatious	4.50	11.53	32.74	
	9:40	Found dead, no tetany having occured. Wt. 6.4 K.				
Dog 102 Female Wt 14.3 K						
July						
3	3:00PM		10.52	3.14	25.73	
4	10:25AM	Thyroparathyroidectomy	10.52	3.26	24.53	
7	9:45		7.18	4.97	27.60	
8	7:00PM	Tetany, rapid resp.	6.62	4.73	27.60	4 mg per K
9	11:00AM	Normal	5.87	5.22	27.87	
10	11:00	" Did not eat	6.20	5.35	26.40	
11	3:00	Same	5.63	3.45	18.68	
12	5:00	Same	5.43	3.42	18.50	
13	10:00AM	"		3.63	18.64	
14	10:30	"	5.44	3.63	18.60	
	2:50PM	400 cc milk by St. tube				
15	10:00	Normal. Did not eat	6.31	3.63	18.60	
16		" " " "				
17	10:30	" " " "				
		Wt 11.8 K.	5.90	4.16	18.85	
18	10:30		5.40	4.03	20.00	
	4:30PM	Ca Lact by St. tube				13 gm
19	10:30	Normal. No appetite	8.82	4.81	18.00	10
	1:15	" Heart rate 66 and somewhat irregular	12.80	5.19	20.40	
20	3:30	Normal. No food	9.10	4.33	19.50	
21	7.20	" " "				
23	11:30	" " "	5.75	4.85	18.83	
	5:10PM	Had a violent and sudden attack of convulsions				

Date	Time		Ca	Inorg P	T.A.S.P.	D
July						
24	12:30PM	Apparently has had some attacks during the night, but is not depressed.	5.62	5.96	22.70	
	8:45	By st. tube about 400 cc of hot milk. Vomited about ½				
	10:45	Wt 10.5 K. Walks some and responds to call. Some tremors.	5.45	8.25	27.00	
25	10:30PM	Has fibrilations and twitches and respiration is increased slightly.				
26	4:10PM	Can still stand but is very weak.		11.68	37.34	
27	2:45	Can stand and walk though very wobbly. Pretty far gone. Wt 9.2 K. Drinks much water		13.98	41.20	
28	12:00AM	Very comatous	6.42	22.22	55.20	
	12:13	Found dead.				

Dog 110. Female 23 K

July						
20	4:00PM		11.72	4.65	25.02	5 mg per K
23	3:30		11.40	5.98	23.25	
25	1:30	Has some very marked tremors as those of cold or fear.				
28	12:00M		5.45	5.25	24.25	
31	2:15PM	Not active. Weight 22.1 K. No tremors	11.21	16.00	45.57	
Aug.						
2	4:30PM	Had marked twitches of the diaphragm. On handling exhibited a very tender abdomen. More so than rest of body and pressure brought about abdominal spasms. Twitches of the jaw, neck and legs could also be elicited.	8.50	22.74	66.60	
3	11:00AM	Showed excessive incoordination in walking and exhibited the symptoms noted above, being very weak.				
	2:00PM	Found dead, having died within last hour. Weight 18.2 Kilo.				

THE INFLUENCE OF PARATHORMONE ON NORMAL AND PARATHYROIDECTOMIZED DOGS.

The use of the active principle of the parathyroid gland, parathormone, (Collip) since its initial discovery has largely turned to its employment clinically. The literature therefore consists almost entirely of its clinical application or its use in producing overdosage phenomena in animals. Parathormone overdosage both in normal and parathyroidectomized animals brings about a marked rise in inorganic phosphorus which is secondary to a marked calcium rise to above the normal value (Fisher & Larson 1925, (70); Collip 1926 (41)). Salvesen (1925)(218) observed in parathyroidectomized dogs and cats a decrease in Inorg P (6 or 7 to 4 mg per 100 cc) with a terminal rise as in the normals. Collip found in parathyroidectomized rabbits that with the calcium almost normal, injection of parathormone may bring about a rapid high inorganic P accompanying fatal tetany. They found increased excretion of Ca and P in the urine. These results have been affirmed by Greenwald and Gross (1925) (109 to 111) Grollmann (1927) (92) and others. It can thus be concluded that given a low serum calcium level, the effects of parathormone on the blood inorganic phosphorus is opposite to that caused by parathyroidectomy. No reports are available, as far as I have been able to find, on the behavior of the total acid soluble P of the blood by the use of parathormone.

Overdosage of Parathormone brings about certain pathological changes that are especially prominent in the gastro-intestinal tract. Collip (41) found a dark and hemorrahgic mucosa of the stomach as one of the most singular findings. Matthews and Austin (1927) (180) specified that this change was confined to the fundus region. This was affirmed and its microscopical study extended by Heuper (1927) (126 a).

The therapeutic uses that this hormone is being put to is out of the scope of this paper. However to emphasize the importance of the function of the parathyroids in many diseased conditions, a brief list of pathological conditions in which it has been found of benefit follows: Ca mobilization (Collip 1927, (43 A)), experimentally produced exudates (43 b), as a diuretic in generalized cases of edema with nephritis (181 a), in obstinate cases of edema not yielding to digitalis or other diuretics (206 a), chronic nepnrosis (128 a), osteomalacia (202 a), epilepsy (171 b), infantile tetany (196) (187 a) (235 b) (86 a) (157 a), bronchospastic conditions (204 a) (140 a) (193 a), Maternal tetany (158 b), Idiopathic menstrual bleeding (2 a), peptic ulcer (194 a), hemorrhage (90 a), lead poisoning (134 a) and cases of syphilis, tuberculosis and such skin diseases as urticaria. This list is by no means complete but comprises some of the literature that I have run across in the course of this problem.

The mode of action of this hormone is not understood. Its action has been attributed to its ability of changing water and mineral metabolism in which the calcium plays its major role. Just how this is brought about is today entirely a matter of opinion and dispute and is outside of the scope of this research.

SYMPTOMS OF PARATHYROID OVERDOSAGE

The symptoms produced by parathormone overdosage are the same in normal and parathyroidectomized dogs. These symptoms together with the physical and chemical findings have been aptly summarized by Collip (1926) (41) from which most of the following is taken.

There is an enormous variation in the response of different normal animals to injections of parathormone. Single small doses produce no objective effects. The response to repeated injections at short intervals of time is much different. Some animals exhibit a typical train of symptoms which end fatally if the injections are continued past a certain point, while others are relatively immune. Compare for example Dogs 120 to Dog 131 or Dog 121. Dog 120 (Graph XIX), five kilos in weight, showed no severe symptoms even with 185 units per day whereas Dog 131 (Graph XXI), 9.5 kilos in weight, died of overdosage on the seventh day from a total of 80 units divided into 3 doses of 40, 20 and 20 units, respectively, and ex-

tending over 3 days. Dogs are said to be the most susceptible to poisoning by overdosage. The cat is relatively more resistant, whereas rabbits and hens are practically immune to repeated injections of the hormone. The main response following single injections of parathormone into dogs is a rise in serum calcium (Dog 120, Oct 12, Graph XIX). For some hours following an injection the blood serum calcium gradually increases until a peak ppint is reached (usually 15 to 24 hours; Dogs 120 and 122), a return to normal is then gradually accomplished. The slope of the descending curve is somewhat the same as that of the ascending one.

The increase in blood calcium in 15 hours after injection is almost directly proportional to the dose administered in a given dog. Thus only by using a large number of animals nearly of the same weight and under the same conditions can the parathormone be standardized. Young animals seem to respond better than old animals.

Single injections of parathormone have no ill effects unless the dosage is excessive. Calcium levels of 15 mg per cent may cause vomiting which in itself is not serious; should it reach 20 mg per cent or higher the animal may die on the second or third day. We found that in Dog 131 (Graph XXI) death ensued after it had reached 16 mg per cent. It is possible that it was higher the day before when no determinations were made.

Dogs injected at 3 to 4 hour intervals with 30 or more units of parathormone manifest a typical line of symptoms (Dog 122), run a characteristic blood calcium curve and die within forty-eight to seventy-two hours. Certain blood constituents other than calcium run a characteristic curve. The physical properties of the blood are also altered. Somewhat similar results are obtained when larger or smaller dosage is administered and when the time interval between injections is varied to a considerable degree (Dogs 121 (Graph XVII) and 131 (Graph XXI)). The symptoms manifested and the order of their occurrence are somewhat as follows: Some hours after the injections have begun the animal has attacks of vomiting followed by diarrhea (See dog 122, Oct. 25 to 27); (In our animals this was preceded by anorexia and polyphasia) a certain uneasiness of manner may be manifested at this time but otherwise the animal is quite normal in its behavior. During this period (approximately 24 hours) the blood calcium curve is steadily rising at a uniform rate (Dog 123, Oct 9). The peak point of the blood calcium curve is reached at about 20 mg (Dog 122, Oct 26). It is maintained at this level for some hours and then the blood calcium starts to fall (Dog 123 Oct. 9 and 10). The animal meanwhile may continue to have occasional attacks of vomiting and diarrhea, and is physically becoming more and more depressed; there is respiratory distress, polyphasia, vomiting and passing of blood

by bowel and mouth, faint heart beat and a marked drop in peripheral temperature and collapse (Dogs 121, 122 and 131). Death follows in a few hours. During this period of urgent symptoms the calcium falls and the inorganic phosphorus rises abruptly. We find also an abrupt rise in the total acid soluble phosphorus at the same time. (Dogs 121, Graph XVII; 122; and 131, Graph XXI). The blood urea and non-protein nitrogen also increase several hundred per cent. There is a marked decrease in blood volume and a characteristic thickening of the blood. (At times it was hardly possible to obtain 2 cc of serum from 20 cc of the blood). The coagulation time was decreased. The circulation gradually fails and blood samples are obtained from peripheral veins only with great difficulty. We found that even from the heart it is difficult to obtain blood for the necessary determinations. All the above as recorded by Collip (except for N.P.N. and urea) were abundantly affirmed and the additional findings have also been noted.

Collip gives us certain additional facts that may be of importance in our discussion later on. They follow: "The carbon dioxide content and combining power of the blood serum are as a rule definitely and gradually increased during the first half of such experiments. the pH of the blood serum as determined by the colorimetric method of Cullen may be coincidentally increased very

slightly. This would indicate that in this period there is a tendency towards alkalosis which is however well compensated. The increase in carbon dioxide content of the blood serum is maintained for several hours, then this value gradually decreases and in the terminal stage is greatly reduced. The pH on the other hand remains stationary until within a few hours of death when it decreases very rapidly. The general effect therefore of parathormone overdosage upon the acid-base balance is to produce a condition of compensated alkalosis on the first day, this then passes over into a condition of compensated acidosis which in turn is followed by an uncompensated acidosis just prior to death.

"The urinary findings in parathormone over-dosage are also of interest. The kidney practically ceases to function very abruptly at about the time that the serum calcium curve has reached its peak point. There is a sudden decrease in the volume of urine produced and, as a rule, both a relative and an absolute decrease in the rate of excretion of phosphorus, ammonia, and titrable acid. Coincident with this abrupt decrease in kidney function the curves for whole blood P, urea and non-protein nitrogen start to ascend."

Of interest is the fact that Collip was able to simulate the pathological findings recorded above for parathormone overdosage by careful injection of $CaCl_2$

and NaH_2PO_4. The symptomatology was essentially the same too. This was only on one dog.

METHOD OF EXPERIMENTATION.

After a brief control period one-half the dogs in this series were injected with massive (50 to 120 units) or a number of repeated small doses (10 to 20 units) of parathormone to test its effect on the normal animal. After return to normalcy these dogs together with the other dogs were completely thyroparathyroidectomized. Only a few dogs were allowed to go into tetany before treatment was started. The remaining dogs received treatment from the day following the operation. Both single daily massive doses and smaller doses at several hour intervals were injected, usually hypodermically. In some cases over-dosage was produced. The blood analysis was made at various times before and after the injection of parathormone and the protocols fully indicate the times of injection and blood determination. Complete autopsies were done in nearly all cases to substantiate our clinical and chemical findings.

RESULTS.

This report contains the data on 11 dogs. One of these dogs (Dog 115) was not treated with parathormone

until three months after operation or two months after showing no symptoms of parathyroid deficiency. This dog had recovered from typical depression, mild tetany, and laryngeal stridor without any tetany whatsoever. The purpose was to note the effects during and after parathormone treatment on a parathyroid deficient dog not suffering from such deficiency. One other dog (Dog 124) was discarded as abnormal after some days of pre-operative treatment. Of the remaining 9 dogs, 2 were not treated until tetany had developed. The other 7 were treated from the day following the operation. Of these 9 dogs, 2 (Dogs 120 and 125) died pf parathyroid deficiency on the 12th and 2nd days, respectively; 3 (Dogs 121, 122 and 131) died of parathormone overdosage on the 4th, 9th, and 7th, days, respectively; 2 (Dogs 123 and 130) died of undetermined cause on the 15th and 63rd days, respectively; and 2 dogs were killed--Dog 128 on the 45th day (see protocol) because of severe ulcerations at the sight of calcium injection, Dog 129 on the 34th day by accidental puncture of a large coronary vessel in the process of obtaining a blood sample.

DOGS NOT TREATED UNTIL TETANY APPEARED: Of the 2 dogs not treated until tetany appeared one (Dog 121, Graph XVII) recovered completely, but died 3 days later of parathormone over-dosage; the other (Dog 125, Graph XVIII)

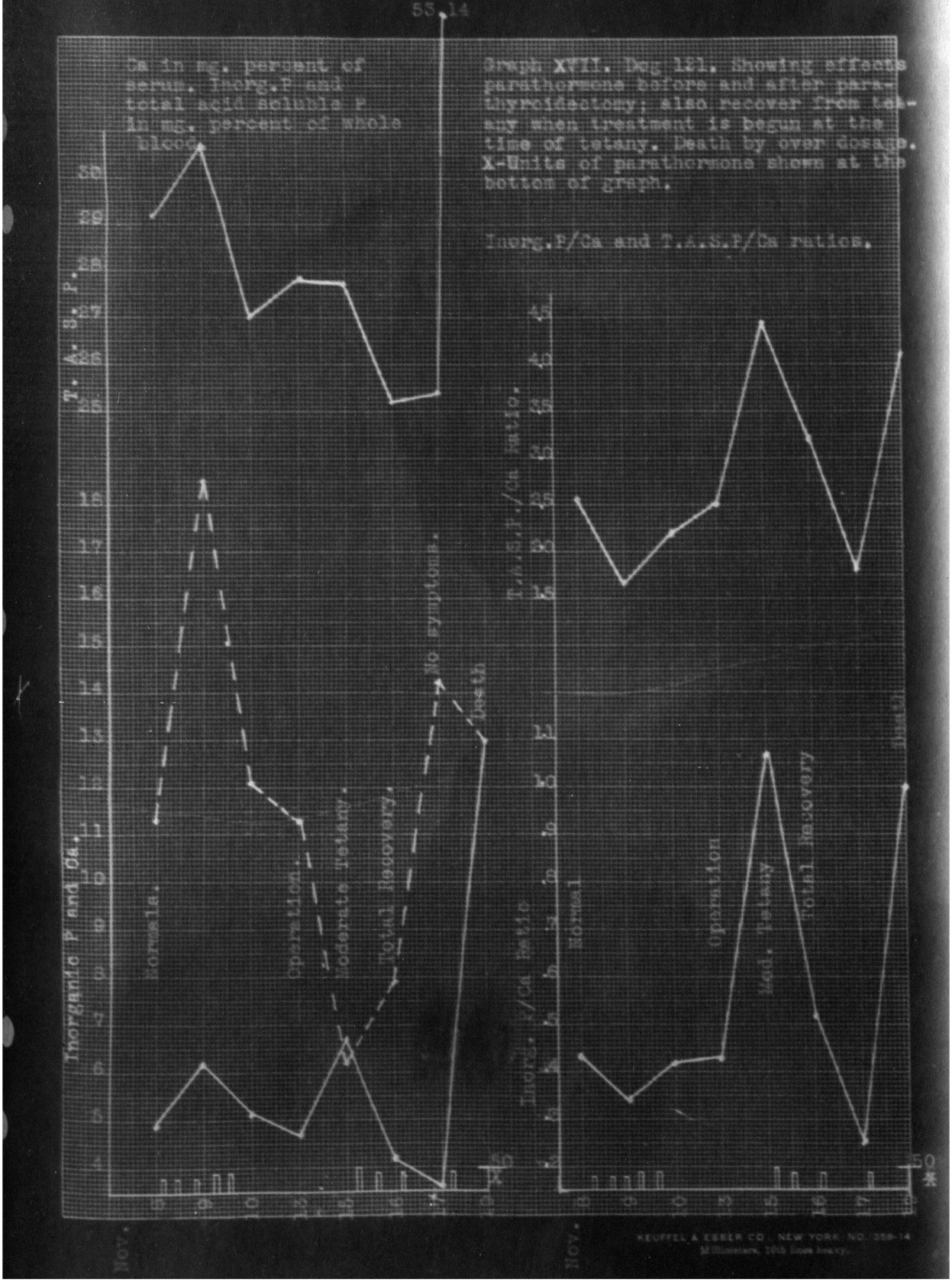
showed aleviation of tetany but died 6½ hr. after an initial injection of 120 units parathormone or 3 hours after an additional injection of 40 units parathormone. The difference in the behavior of the whole blood phosphorus compounds in these 2 animals is very striking. From the time of tetany to complete recovery, in dog 121 (Gr aph XVII, Nov. 15 & 16) the changes in the concentration of serum Ca and whole blood Inorg P and T.A.S.P. were, respectively, 6.23 to 8.08; 6.66 to 4.03; and 27.76 to 24.76 mg per cent as compared to these respective concentrations in Dog 125 (Graph XVIII, Nov 15) at time of tetany and just after the animal had died 6½ hours later, 5.16 to 6.12; 6.25 to 17.08; and 26.50 to 32.45 mg per cent. The tetany of course, was more severe in the latter case than in the former before treatment was begun.

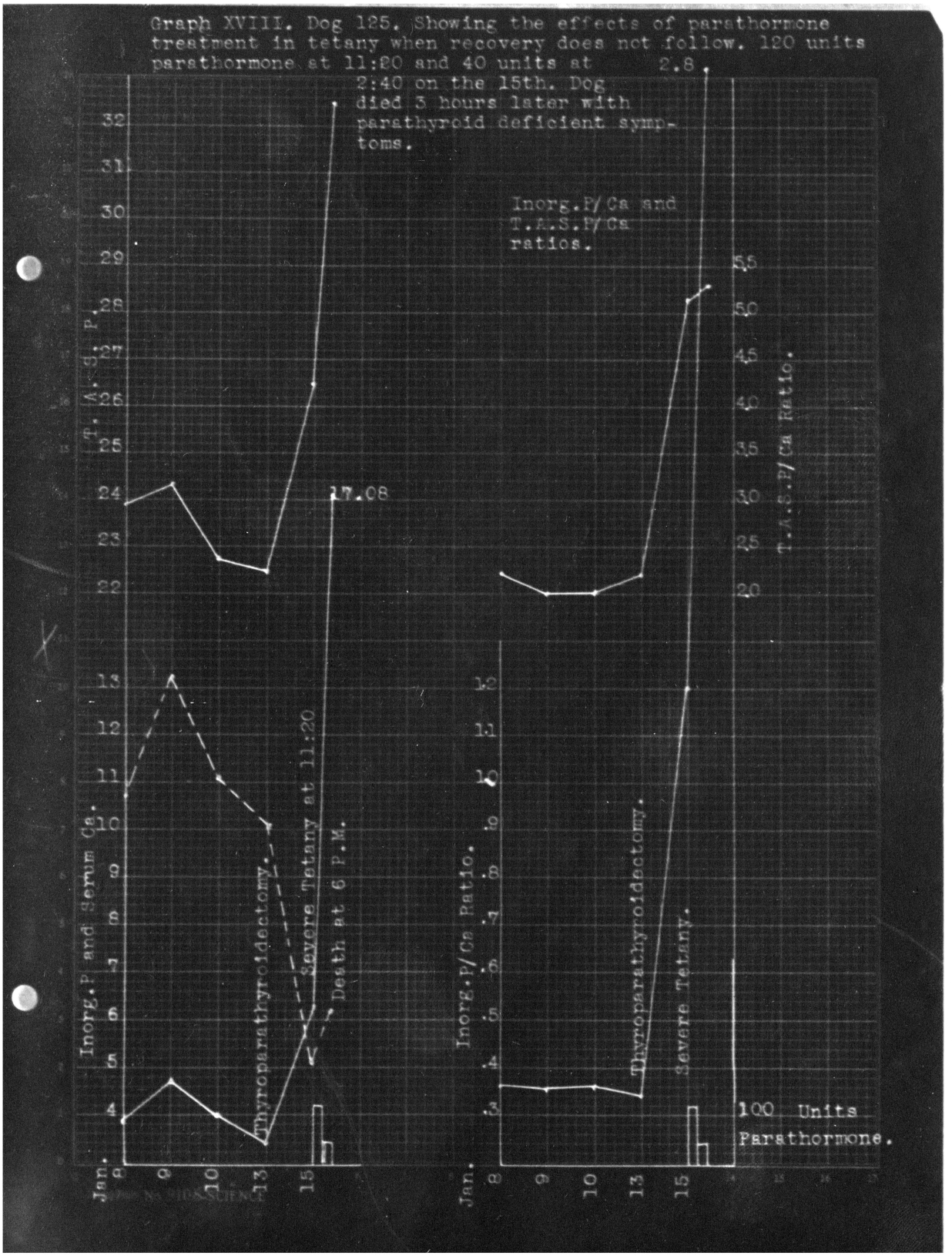
It seems from this that just as Collip (41) observed in his parathyroidectomized rabbits that died despite the parathormone treatment, so it is also in dogs; an abrupt and sudden rise of the inorg P of the whole blood (300% in this case) with only a very slight change in the calcium content of this dog treated after severe tetany had begun. The T.A.S.P. rose only 6 mg per cent. This would probably have been much higher had the determination been made at least a half or one hour before death. I have found several times that the total acid soluble P at the

Ca in mg. percent of serum. Inorg.P and total acid soluble P. in mg. percent of whole blood.

Graph XVII. Dog 121. Showing effects parathormone before and after parathyroidectomy; also recover from tetany when treatment is begun at the time of tetany. Death by over dosage. X-Units of parathormone shown at the bottom of graph.

Inorg.P/Ca and T.A.S.P/Ca ratios.




Graph XVIII. Dog 125. Showing the effects of parathormone treatment in tetany when recovery does not follow. 120 units parathormone at 11:20 and 40 units at 2:40 on the 15th. Dog died 3 hours later with parathyroid deficient symptoms.
Inorg.P/Ca and T.A.S.P/Ca ratios.
T. A. S. P.
T.A.S.P/Ca Ratio.
Inorg.P and Serum Ca.
Inorg.P/Ca Ratio.
17.08
2.8
Thyroparathyroidectomy.
Severe Tetany at 11:20
Death at 6 P.M.
Thyroparathyroidectomy.
Severe Tetany.
100 Units Parathormone.
Jan.
8
9
10
13
15

instant of death is much decreased compared to its concentration a half or one hour preceding death (in one instance a drop from 40 to 29 mg per cent when drawn after death). These results would indicate that an abrupt and sudden rise in the inorg P and T.A.S.P. without a comensurate rise in serum Ca after parathormone administration results in death, whereas if parathormone administration results in recovery, the serum calcium is primarily increased accompanied by an inorg P and T.A.S.P. fall. The latter 2 remain low unless the calcium is raised markedly above the normal (Graph XVII, Nov 17) when these values rise abruptly (Nov. 17 to 19--Inorg P 3.55 to 12.90 mg per cent; T.A.S.P. 25.38 to 53.14 mg per cent) and death ensues.

DOGS TREATED FROM DAY FOLLOWING THE OPERATION: The results obtained on the 7 dogs treated from the day following the operation are shown by 3 representative dogs in the form of 3 graphs: (A) Dog 120 (Graph XIX) shows the effects of a high calcium before (Oct 13) and after parathyroidectomy (Oct 26) as a result of parathormone treatment followed by the effects of a low calcium after parathormone treatment was withdrawn (Oct 27 to Nov. 1); (B) Dog 129 (Graph XX) shows the effect of parathormone when the treatment is sufficient to keep the dog from any severe symptoms of parathyroid-deficiency; (C) Dog 131 (Graph XXI) shows the effects of parathormone over-

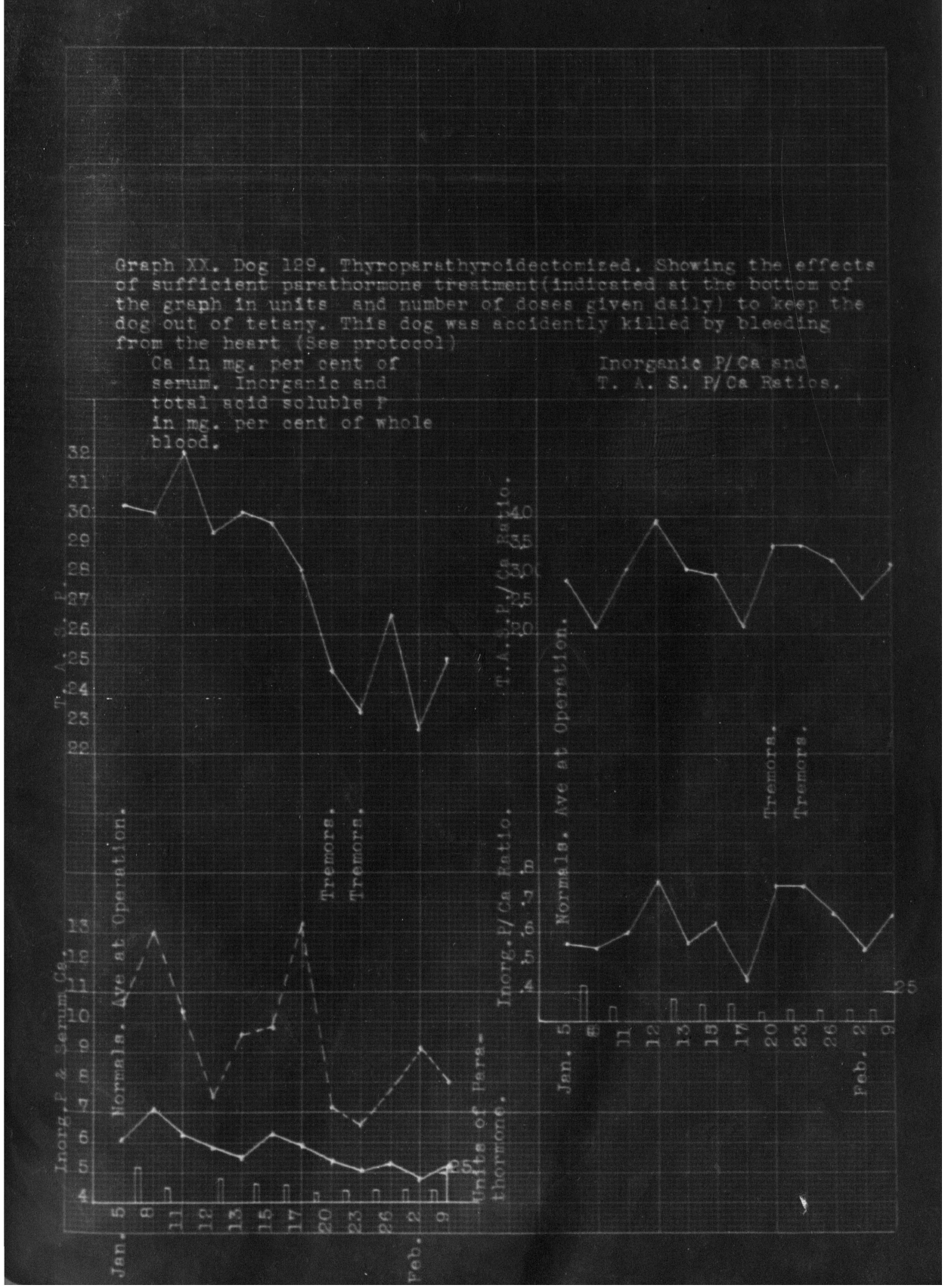
dosage after parathyroidectomy even if treatment is withdrawn (No treatment after Jan. 9) before symptoms of overdosage appear (Jan. 11). The clinical symptoms were those of parathormone overdosage up to the time of death (Jan 13) despite the fact that the calcium was low.

The effect of parathormone on the whole blood inorganic and total acid soluble phosphorus can best be studied by a careful consideration of these graphs. It is shown in Graph XIX (Oct 12 to 13) that a moderate rise (3 mg per cent) of calcium in the normal dog is accompanied by a fall in the T.A.S.P. (2.3 mg per cent) and Inorg P. (.5 mg per cent) following the administration of a single massive dose (100 units). This whole relationship is reversed in the following days when the calcium returns to its normal level (Oct. 18); the T.A.S.P. (6 mg per cent) and Inorg P (2 mg per cent) rise. (See also Dog 122, Oct 12 to 16). This primary fall in the blood phosphorus compounds did not take place if the massive dose was divided into 30 unit doses administered several hours apart. Both inorganic P and T.A.S.P. may then only exhibit a slight rise of 1 to 2 mg per cent with a return to or slightly below the normal in the course of a few days when the calcium is again at the normal value. (Dog 121, Graph XVII, Nov. 8 to 13; Dog 123, Nov. 8 to 13; Dog 125, Graph XVIII Nov. 8 to 13).

After thyroparathyroidectomy, much the same relation-

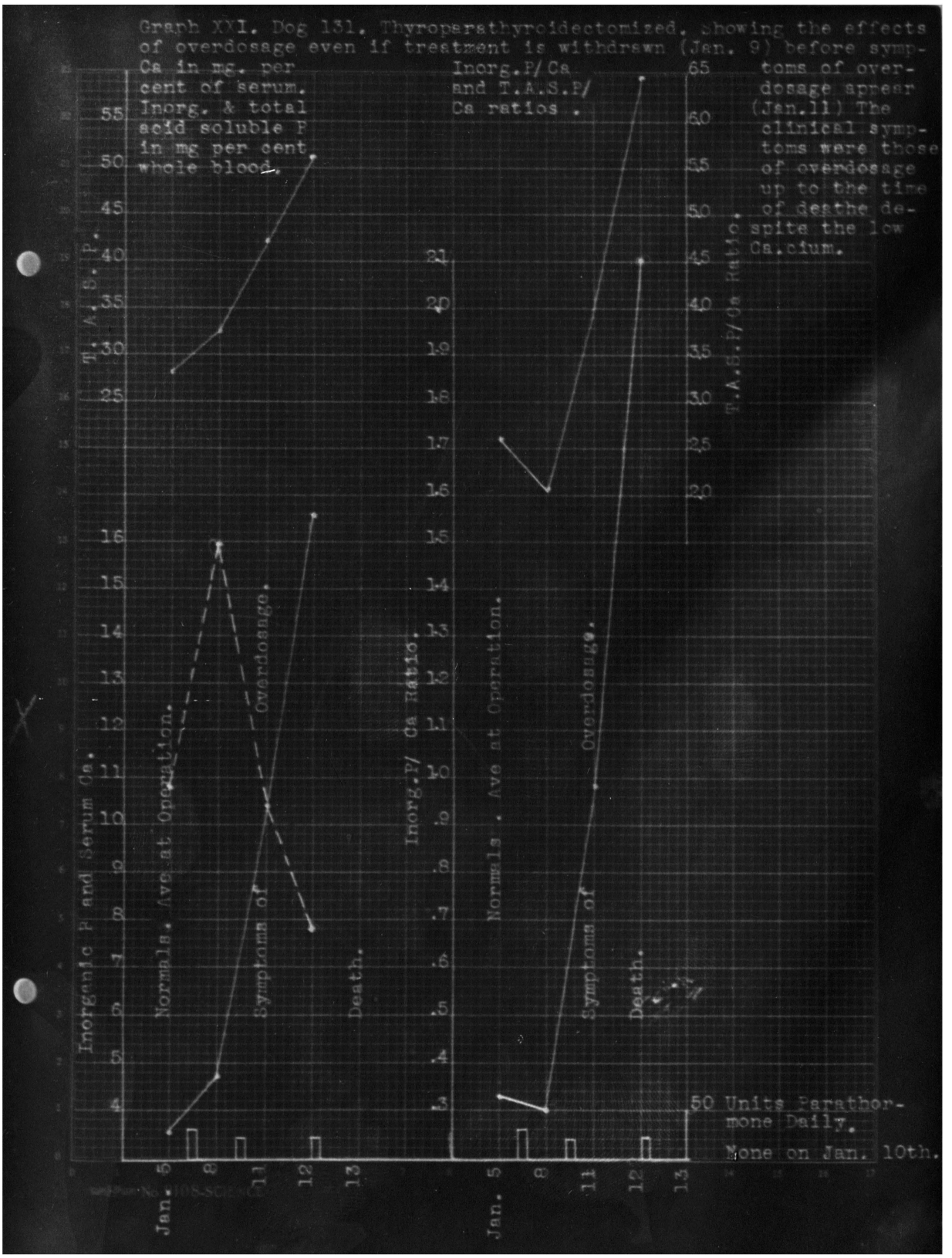
Graph XIX. Dog 120. Showing the effects of high Ca before and after thyroparathyroidectomy by parathormone treatment and followed by the effects of low Ca after treatment was withdrawn. X-100 units parathormone 26 hours before operation. Otherwise the parathormone administered is shown at the bottom of the graph in units and number of doses given daily.

Graph XX. Dog 129. Thyroparathyroidectomized. Showing the effects of sufficient parathormone treatment (indicated at the bottom of the graph in units and number of doses given daily) to keep the dog out of tetany. This dog was accidently killed by bleeding from the heart (See protocol)



ship exists between the blood phosphorus compounds and the serum calcium under parathormone treatment. In all these cases (as shown by Graph XX) the general trend of both blood phosphorus compounds is progressively downward from day to day so long as the calcium does not vary markedly beyond ± 2.5 to 3 mg per cent from the normal level. The inorganic P as is shown on Jan 6 and 15 (Graph XX) forms exceptions to this more often than does the T.A.S.P. of the whole blood. As a rule the T.A.S.P. tends to vary opposite to that of the serum calcium (Graph XIX, Oct. 18 to 24); that is as the calcium falls, the T.A.S.P. rises and vice versa. But when this variation in the serum Ca is markedly below the tetany level (Graph XIX, Oct. 30 to Nov. 1) or markedly above the normal (17.6 mg per cent on Oct 26) the T.A.S.P. increases in both of these conditions. If this is preceded also by a marked rise in the inorganic P, (particularly in parathormone over-dosage) then both the Inorg P and T.A.S.P. rise progressively until death ensues, regardless of the behavior of the serum calcium. (Graphs XVIII and XXI). These graphs (XXIII & XXI) indicate that in parathormone overdosage death is not only independent of the final serum calcium level but also that the inorganic P may be more than quadrupled and the T.A.S.P. more than doubled at the time of death.

It may be of interest here to study the results obtained by parathormone administration to a female dog


Graph XXI. Dog 131. Thyroparathyroidectomized. Showing the effects of overdosage even if treatment is withdrawn (Jan. 9) before symptoms of overdosage appear (Jan.11) The clinical symptoms were those of overdosage up to the time of death, despite the low Calcium.
Ca in mg. per cent of serum. Inorg. & total acid soluble P in mg per cent whole blood.
Inorg.P/Ca and T.A.S.P/Ca ratios.
T.A.S.P.
T.A.S.P/Ca Ratio.
Inorganic P and Serum Ca.
Inorg.P/ Ca Ratio.
Normals. Ave.at Operation.
Symptoms of Overdosage.
Death.
Normals . Ave at Operation.
Overdosage.
Symptoms of
Death.
50 Units Parathormone Daily.
None on Jan. 10th.
Jan. 5 8 11 12 13
Jan. 5 8 11 12 13

(Dog 115) 60 days after this dog had made a complete recovery from parathyroid tetany without any treatment whatsoever. The serum calcium, Inorg P and T.A.S.P. were respectively, (Nov. 8) 7.52; 4.86; and 19.50 mg per cent. (For data on this dog previous to parathormone treatment see p 62). 170 units of parathormone divided into 30 to 40 unit doses with 3 to 5 hour intervals were injected in the course of 20 hours. This brought the calcium back to normalcy in the neighborhood of which it stood for 4 days. It then decreased progressively for nine days until it reached below the pre-injection level. (Dec. 22). The inorganic P varied within the normal range whereas the T.A.S.P. varying between 17 and 20 mg per cent before this day (Nov 9 to 17) was now (Dec. 22) 15.15 mg per cent. After this the animal became progressively worse exhibiting more and more the symptoms of parathyroid deficiency until she died on Dec. 24 in severe convulsions. Unfortunately I was unable to tend to my dogs at that time because of illness and consequently no blood analysis were available after Dec. 7 when both inor g P (6.66 mg per cent) and T.A.S.P. (20.58 mg per cent) were on the incline, no conclusions can be drawn from this one dog. Since this dog was a female the fatal convulsions may have been due to a period of heat (54). On the otherhand, the results suggest that parathormone tends to maintain a balance between the blood phosphorus compounds and the serum Ca

It is obvious that the T.A.S.P./Ca and Inorg P/Ca ratios must exhibit a wide range of individual variations, since the serum calcium may range ±3 mg from the normal before the phosphorus compounds are affected in relation to the serum calcium. This is shown on Graph XX. These ratios exhibit no variations from those discussed under parathyroid deficiency without treatment when the calcium falls more than 3 or 4 mg per cent. However when parathyroid over-dosage occurs there must alway be a marked rise in both of these ratios, since both phosphorus compounds increase progressively until death and the serum calcium decreases because of withdrawal of parathormone treatment.

DISCUSSION AND CONCLUSIONS

Our results on the symptomatology as related to the serum calcium and whole blood inorganic phosphorus upon administration of parathormone to normal and parathyroid deficient animals affirm and extend those reviewed and established by Collip (41)

Parathormone administration to normal and thyroparathyroidectomized dogs causes a progressive increase in the serum calcium, beginning 2 hours after the injections have started and reaching a maximal in 15 to 24 hours. After some hours it begins to decrease and the course of decline is similar to that of the rise. One dog not injected until severe tetany occurred did

not show this rise in the 6 hours before he died.

In thyroparathyroidectomized dogs when by means of parathormone treatment the serum calcium is not allowed to vary beyond± 2.5 to 3 mg per cent the inorganic P of the whole blood varies slightly from just above to 1 or 2 mg per cent below the normal, whereas the whole blood T.A.S.P. has a tendency to decrease at first markedly and then slowly and progressively. When these variations in the serum Ca are more or less beyond ±3 mg per cent from the normal, marked variations in the behavior of the inorganic P and T.A.S.P. take place. When the calcium variation is negative the results are the same as noted in the section on untreated animals. When the serum calcium variation was on the positive side and did not excede 5 or 6 mg per cent (from the normal) the T.A.S.P. change was opposite to that of the serum Ca; that is, when the serum calcium increased the total acid soluble P decreases and vice versa. Should the serum calcium rise still higher accompanied by an abrupt increase in the whole blood inorganic P, then death ensues in 48 to 72 hours while the calcium falls progressively, and the inorganic P and T.A.S.P. are as much as quadrupled and more than doubled, respectively, at the time of death. Death then occurs of over-dosage symptoms even if the calcium level is at or below the tetany value. The abrupt and rapid increase of the inorganic P was the most constant finding when parathormone

overdosage led to death, even in the dog that died 6 hours after tetany began and showing no increase in serum calcium. The increase in T.A.S.P. was just as constant but was not always so extensive and sometimes no higher at the time of death than when death occured without treatment. At any rate, the inorganic P increase preceded the T.A.S.P. increase in those dogs that died of over-dosage.

In consequence to the above the Inorg P/Ca and T.A.S.P./Ca ratios vary markedly when the Ca does not vary beyond ±3 mg per cent from the normal, but beyond this ±3 mg per cent variation these ratios are both increased and at the time of death due to over-dosage the Inorg P/Ca ratio may be increased by 3 to 7 times and the T.A.S.P./Ca by .5 to 3 times.

DOGS TREATED WITH PARATHORMONE.

Date	Time		Ca	Inorg P	T.A.S.P.
Dog 115. Female. 13.7 Kilo.					
July 31		Started on diet.			
Aug. 1	3:30PM		11.70	5.13	24.85
2	4:10		11.80	5.19	23.50
3	4:00		11.54	5.02	22.52
7	11:30	Thyroparathyroidectomy			
11		Normal	6.60	5.89	24.70
14		Had vomited. Showed increase in resp. and laryngismus strid. symptoms.			
15		Same		5.75	26.92

Date	Time		Ca	Inorg P	T.A.S.P.
Aug.					
21		Had occasional twitches	5.33	7.02	27.20
Oct.					
9		Was sym. free since Sept. 10			
		O.K. Wt. 15.7 K.	8.40	5.16	21.05
16		O.K.	8.22	5.10	19.80
Nov.					
8	11:00AM	O.K. 30 units parathormone intravenously	7.52	4.86	19.50
	3:00PM	O.K. 30 units parathormone intravenously			
	9:00	O.K. 30 units parathormone intravenously	10.52	5.75	20.37
9	3:00AM	40 units parathormone intravenously.			
	8:00	O.K. 40 units parathormone intravenously	11.41	4.77	18.60
	3:00PM	Looks very well	12.05	5.93	20.37
	11:45PM	O.K.	11.76	5.44	19.05
10	9:00AM	O.K.	*16.41	4.88	18.37
13	10:30	O.K.	9.12	4.53	16.85
15	12:00M	O.K.	8.42	5.45	18.05
17	9:30AM	O.K. Wt. 16 K.	7.82	5.33	17.72
22	11:40AM	O.K. Has been shivering at times	7.08	5.47	15.15
Dec.					
7	10:30	O.K.Appetite decreasing. Died in morning. Has severe paradepsient symptoms-- including convulsions		6.66	20.58

Dog 120. Female. Wt. 5 Kilo.					
Oct					
9		Caged			
11	1:00PM		11.02	4.00	25.66
12	12:00M	100 units of parathormone subcutaneous.	11.20	3.96	25.15
	8:30	Tender over sight of inj. Not so spry.	12.80	3.70	25.00
13	8:00AM		14.30	3.55	23.10
16	1:00PM	O.K.	10.96	4.53	24.33
17	8:00PM	O.K. 100 units parathormone intraven.			
18	10:00AM	O.K. Thyroparathyroidectomy 7:30PM No meal	11.83	5.44	29.20
19	10:00AM	O.K. 20 units parathormone intraven.	9.08	6.08	29.89
	1:00PM	O.K. 20 units paratormone intraven.			
	5:30	O.K. 50 units parathormone intraven.			
	12:00	O.K. 55 units parathormone intraven.	13.08	5.48	24.25

Date	Time		Ca	Inorg P	T.A.S.P.
Oct.					
20	10:00AM		13.08	5.48	24.25
21		O.K. No meal			
22	6:00PM	Moderate twitching. No rapid resp. Ate allof meal 25 units parathormone			
23	1:15	25 units parathormone. Same as Oct. 22	7.10	6.05	27.36
	3:30	Still twitching (marked)			
24	8:40AM	Had eaten whole meal. Some twitches. 30 units parathormone.			
	2:30PM	50 units parathormone			
	5:30	55 units parathormone			
	10:30	50 units parathormone			
25	10:00AM	O.K. 30 units parathormone	9.36	6.93	25.00
	2:30PM	Vomits white slimy material 40 units parathormone. Loss of appetite.			
	9:30	Vomits white slimy material 55 units parathormone. Loss of appetite			
26	11:00AM	Quite spry. Had eaten about 60% of meal	17.36	5.15	27.60
	8:00PM	Very well but does not eat	15.70	4.33	27.14
27	11:00AM	Same	15.21	4.54	23.50
28-29		Ate very little. Had no symp. of tetany.			
30	2:00PM	Severe seizures of tetany No rapid respiration	5.96	6.00	29.55
31		Seizures of tetany during day. Did not eat.			
Nov					
1	12:20PM	Seizures of tetany Had not eaten	5.20	5.30	27.76
	2:20	Had just died. Autopsy showed little of gross pathological importance. The small gut was void of foecal material and showed only a trace of hemorrhage in few places. The liver was dark and considerably notched. The lungs showed a few areas of hemorrhagic infiltration mostly in the area where blood was taken from the heart. Dog was the laryngismus stridulus type.			

Dog 121. Female. 11.25 Kilo

Oct.					
9		Caged			
11	1:00PM		11.84	5.00	29.00

Date	Time		Ca	Inorg P	T.A.S.P.
Oct					
12	12:00M		12.10	4.92	30.10
	8:30		11.80	4.94	30.10
13	8:00AM		11.82	4.44	29.20
16	1:00PM	O.K.	11.10	5.17	29.45
18	10:00AM	O.K. No meal	11.68	4.34	29.78
19	10:00AM	O.K.	10.62	5.38	31.00
20	10:00AM		11.05	4.90	28.55
21		Normal			
23	1:20PM		10.95	5.10	28.24
25	10:20AM		11.02	5.91	29.77
26	11:00		11.20	4.96	28.55
	8:00		11.72	4.86	26.96
27	11:00AM		11.91	4.87	29.61
Nov					
1	1:00PM		10.88	4.91	29.61
8	11:00AM	Slight skin rash. O.K. 30 units parathormone intrav.	10.68	4.52	28.35
	3:00PM	O.K. 30 units parathormone intravenously.			
	9:00	O.K. 50 units parathormone intravenously.	13.04	5.63	28.80
9	3:00AM	O.K. 40 units parathormone intravenously			
	8:00	O.K. 40 units parathormone intravenously		6.24	29.20
	3:00PM	Apparently well. Ate heartily at 6:00PM	18.55	6.25	30.75
	11:45	O.K.	14.14	5.41	28.92
10	9:00AM	O.K. Ate well	12.15	5.14	26.92
13	10:30AM	Very well. No meal	11.23	4.70	27.87
	3:30PM	Thyroparathyroidectomy			
15	11:30AM	Developing moderate tetany 50 units parathormone	6.23	6.66	27.76
	12:30	Tetany very severe. Respiration rapid			
	2:40	Almost recovered. 40 units subcutaneously			
	6:00	Total recovery	8.08	4.03	24.76
16	4:30	O.K. 40 units subcutaneously	7.87	4.12	25.26
17	9:00	O.K. " " "	14.22	3.55	25.38
18	1:30	O.K. " " "			
19	6:30PM	Salivation (Thick & slimy) Blood per rectum. Cold body, Rapid exhausted respiration. Heart beat is imperceptible.			
	6:40	Dead.			

Date	Time		Ca	Inorg P	T.A.S.P.
Dog 122 Male Wt. 11.8 Kilo					
Oct.					
9		Caged			
11	1:00PM		11.33	6.00	28.55
12	12:00M	100 units or parathormone subcutaneously.	12.08	5.40	26.30
	8:30	Extremely infiltrated and painful at sight of inj.	13.00	4.48	22.77
13	8:00AM		14.82	4.97	23.10
16	1:00PM	O.K.	11.42	5.89	24.40
17	8:00PM	O.K. 100 units parathormone intravenously			
18	10:00	O.K. No meal			
	8:30PM	Thyroparathyroidectomy	11.40	4.73	24.10
19	10:00AM	O.K. 20 units intraven.	9.94	5.56	25.15
	1:00PM	O.K. " " "			
	5:30	O.K. 50 " "			
	12:00	O.K. 55 " "			
20	10:00AM	O.K.	14.57	5.47	24.55
21		O.K. No meal			
22	6:00PM	O.K. 25 units intraven.			
23	1:15	O.K. " " " Few twitches	9.43	6.56	25.91
24	8:40AM	O.K. 30 units intraven.			
	2:30	50 " "			
	5:30	55 " "			
	10:30	55 " "			
25	10:00	O.K. 30 " "	9.36	6.40	27.20
	2:30	O.K. 40 " "			
	9:30	O.K. 55 " "			
		Loss of appetite. Diarrhea Much water and vomiting White slimy substance.			
26	11:00	Same as above. Had eaten nothing.	20.45	8.97	31.00
	8:00	Very weak, almost in coma. Walks very wabbly, and with great difficulty. Rapid respiration. No appetite, No thirst. Low surface temp. Faint heart beat. Salivation.	13.58	11.56	36.20
26		Died during night.			
Dog 123 Male 12.6 Kilo					
Oct.					
9		Caged			
11			12.20	5.56	27.95
12	12:00M		11.90	6.02	28.32
	8:30		11.80	5.60	28.11

Date	Time		Ca	Inorg P	T.A.S.P.
Oct.					
13	8:00AM		12.20	5.56	28.15
16	1:00PM		11.96	5.89	27.00
18	10:00AM	No meal	11.62	5.59	27.14
19	10:00AM		11.30	6.02	26.10
20	10:00AM		11.68	5.48	27.40
21		O.K. Normal			
23	1:20PM		12.96	6.11	26.65
25	10:20AM		11.62	6.10	27.20
26	11:00		11.40	6.01	27.10
	8:00PM		12.10	6.23	26.16
27	11:00AM		12.30	5.88	25.61
30	2:00PM		11.84	6.06	26.90
Nov.					
1	1:00PM		11.52	6.27	26.84
8	11:00AM	Skin rash for some time			
		O.K. 30 units para. intra.	11.50	5.67	26.82
	3:00PM	O.K. " " " "			
	9:00	O.K. " " " "	13.97	6.06	28.22
9	3:00AM	40 " " "	13.84	6.46	27.00
	8:00	40 " " "			
	11:00	Polyphasia; diarrhea and vomiting.			
	3:00PM	Quite well. Ate meal but with little appetite between 7 and 11 AM	14.61	7.01	29.56
	11.45	O.K.	16.11	5.93	27.72
10	9:00AM	O.K. Ate well	14.12	5.97	26.07
13	10:30	O.K.			
	5:00PM	Thyroparathyroidectomy	11.92	5.16	26.14
15	11:40	O.K. 20 units para. intra.	7.12	7.01	28.94
	6:00PM	O.K 40 " " "			
16	4:30PM	O.K. 40 " " "	8.30	5.45	25.72
17	9:00AM	O.K. 40 " " "	12.16	5.04	25.56
18	1:30	O.K. 40 " " "			
19	6:30	O.K. 40 " " "	16.80	5.43	26.96
20	2:30PM	O.K. 20 " " "			
21		O.K. 20 " " "	12.50	4.86	26.30
23				3.54	25.45
30		Found dead. I was not in town and from indications related to me I can not establish whether death was from over-dosage or unknown cause. 1cc of parathormone had been administered daily (20 units.)			

Dog 124	Male	Wt 26 Kilo			
Oct.					
23		Ca ged			
25	11:00AM		10.53	3.48	22.27
27	11:00		11.32	3.58	24.85
30	2:00PM		10.92	3.55	24.766

Date	Time		Ca	Inorgq P	T.A.S.P.
Nov.					
1	1:00PM		10.64	3.64	23.50
8	11:00AM	O.K. 30 units para. intrav.	10.65	3.51	23.06
	3:00PM	O.K. 30 " " "			
	9:00	O.K. 30 " " "	11.85	5.02	24.46
9	3:00AM	O.K. 40 " " "			
	8:00AM	40 " " "	15.33	5.16	24.85
	11:00	Polyphasia			
	3:00PM	Looks well. Ate only about one-third meal	13.02	5.54	28.31
	11:45PM	O.K.	11.17	4.29	25.06
10	9:00AM	Does not look as well. Did not eat. Wt. 23.2 K.	10.81	2.91	24.78
13	10:30AM	Does not look so well. Has not eaten since 10th. Has diarrhea, distemper and polyphasia.	10.71	3.36	25.66
		Dog was not used in further experimentation because of his abnormal condition probably arising from kaolin feeding in the diet.			

Dog 125 Male Wt 20 Kilo

Oct.					
23		Caged			
25	11:00AM		10.70	3.74	29.77
27	11:00		10.61	3.90	21.93
30	2:00PM		10.93	3.15	18.95
Nov.					
1	1:20PM	Has diarrhea. Due to Kaolin Blood very thick	11.05	4.56	26.02
8	11:00AM	30 units para. intraven.	10.10	3.77	22.77
	3:00PM	30 " " "			
	9:00	30 " " "	11.21	5.04	24.73
9	3:00AM	40 " " "			
	8:00	40 " " "	13.23	4.69	24.63
	3:00PM	Looks well. Fed full meal	12.25	5.49	24.31
	1:45	O.K.	11.24	4.28	22.76
10	9:00AM	O.K.	11.15	3.98	22.72
13	10:30	O.K.	10.08	3.41	22.45
	5:30PM	Thyroparathyroidectomy.			
15	11:20	Has been in tetany for some Rapid resp. salivation. 120 units intraven. para	5.166	6.25	26.50
	2:40	Relieved but still in bad shape. 40 units subcut.			
	6:00	Dead. Blood not clotted.	6.12	17.08	32.45

Date	Time		Ca	Inorg P	T.A.S.P.
Dog 128 Male. Wt 15 Kilo					
Jan.					
3	1:00PM		10.20	5.21	25.98
4	1:30		10.62	6.15	26.38
5	1:30	Thyroparathyroidectomy			
6	3:30	40 units subcutaneously			
7	3:00	20 " "			
8	2:30	20 " " at 6 PM.	13.05	6.96	27.80
9	1:00	O.K.			
10	6:30	O.K. 20 units subcutaneously			
11	4:30	O.K. Ate ½ meal. Spry.	14.52	7.08	29.16
12	4:30	O.K	12.00	7.07	29.45
13	2:15	O.K.	10.90	5.38	24.73
14		O.K.			
15	3:30	O.K. 10 units subcutaneously	8.22	6.25	24.73
16	3:30	O.K. 15 " "			
17	2:30	O.K. 10 " "	8.10	4.96	21.78
18	4:00	O.K. 10 " "			
19		O.K.			
20	4:00	O.K. 20 " "	7.42	6.53	24.10
21		O.K.			
22	5:00	O.K. 10 " "	7.23	5.43	23.70
23 to 25		10 " "			
26	5:00	O.K. 10 " "	11.25	5.76	23.80
27 to Feb 1		O.K. 10 " "			
2	5:00	O.K. 10 " "	10.75	25.03	23.10
3 to 5		O.K. 10 " "			
6		O.K. No parathormone.			
7	11:30	O.K. 10 units subcutaneously			
8	4:00	O.K. 10 " "			
9	5:00	O.K. 10 " "			
10		O.K.	7.10	5.40	23.77
11	10:30AM	Moderate tetany. 20 units and .5 grains morphine sulphate at 12:45. Dog seemed worse. 20 more units and 1.5 grains of morphine sulphate were injected at 4:00PM. Tetany had ceased but the dog was unconscious and the abdomen was exceedingly distended with gas. Soap enema was given.			
	5:00PM	Blood sample was drawn. As dog seemed beyond help a laporatomy was done with no relief of distension. Finally a stomach tube was inserted into the stomach by mouth. This released the gas. The stomach was aspirated and the tube left in place over night. Two days later dog was again in tetany despite 10 to 15 units parathormone daily. Ca lactate (5%) was given by leg vein, a small amount subcutaneously. Here an extensive ulceration developed in a few days involving about 5 to 6 sq in of flesh exposure. The dog had been paralyzed below the knee in the front fore leg since the 12th of Feb. Dog was killed on the 20th.			

Date	Time		Ca	INORG P	T.A.S.P.
Dog 129. Male. Wt. 13.2 Kilo					
Jan.					
3	1:00AM		10.51	6.06	29.90
4	1:30		10.71	6.01	31.25
5	2:30	Thyroparathyroidectomy			
6	3:30	40 Units			
7	3:00	20 "			
8	2:30	20 " at 6 PM	13.00	7.14	30.22
9	1:00	O.K.			
10	6:30	O.K. 20 Units			
11	4:30	O.K. Ate very little	10.34	6.31	32.20
12	4:30	O.K. 20 Units. Did not eat	7.57	5.94	29.52
13	2:15	O.K. 10 " " " "	9.62	5.51	30.06
14	4:30	O.K. 20 " Ate ½ meal			
15	6:30	O.K. 10 " " " "	19.95	6.28	29.87
16	3:30	O.K. 20 " " " "			
17	2:00	O.K. 10 " " Little	13.23	5.90	28.15
18	4:00	O.K. 10 " " "			
19		O.K. " "			
20	4:30	20 " Tremors and labored breathing	7.05	5.42	24.77
21		O.K. Ate little			
22	2:30	20 units. As on 20th. Did not eat	6.62	5.06	23.40
23 to 25		10 " Ate more every day			
26	5:00	10 " " all of meal	7.75	5.21	26.65
27 to Feb 1		10 units. Ate all of meal			
2	5:00	10 units. O.K.	9.10	4.88	22.85
3 to 5		10 units. O.K.			
6		No parathormone. O.K.			
7	11:30	10 units, O.K.			
8	4:00	10 units, O.K.			
9	2:30	O.K.	8.00	5.36	24.22
	2:45	Died. Wt. 13.6 K. Autopsy showed that death was due to a large blood clot between the pericardium and the heart. No blood in heart chambers. The large coronary artery had been punctured in bleeding.			

Dog 130. Male. Wt 26 Kilo.					
Jan					
3	1:00AM		10.61	4.14	26.26
4	1:30		10.88	4.34	26.92
5	3:30	Thyroparathyroidectomy			
6	3:30	40 units			
7	3:00	20 "			
8	2:30	20 " at 6 PM	13.10	3.85	26.26
9	1:00	O.K.			
10	6:30	20 units.			
11	4:30	Not spry. Did not eat	18.24	5.57	31.17
12	4:30	10 units. Looks very well. Ate double meal.	10.55	4.11	27.28

Date	Time		Ca	Inorg P	T.A.S.P.
Jann					
13	2:00	O.K.	13.24	4.05	27.68
14	4:30	O.K. 10 units			
15	4:30	O.K. 10 units	8.72	4.155	25.75
16	3:30	O.K. 15 "			
17	2:00	O.K. 10 " Ate only two-thirds of meal	11.23	3.85	24.43
18	4:00	O.K. 10 units.Ate only two-thirds of meal			
19		O.K. Ate only 2/3 meal.			
20	3:00	O.K. 20 units. Tremors, twitches	6.96	4.27	25.52
21		O.K. Ate 2/3 meal			
22	2:30	20 units. As on 20th	6.53	5.36	29.20
23 to 25		10 units. Ate most of meal			
26	5:00	O.K. 10 units. Ate well	11.95	5.06	24.55
27 to Veb 1		10 units. O.K.			
2		10 " O.K.			
3 to 5		10 " O.K.			
6		No parathormone. O.K.			
7	11:30AM	20 units. Mild tetany			
8	4:00	10 " OLK.			
9	5:00	20 " O.K.			
10 to 23		10 units daily or 20 units on alternate days. Some twitches being noted at times (20 units on Feb. 22)			
23	2:00	O.K. 10 units	6.70	4.85	23.00
24 to Mar. 9		10 units daily. No treatment until Mar. 20 when he died, having eaten well up to the last day. Had no tetany.			

Dog 131. Female. Wt. 9.6 Kilo.

Jan.					
3	1:00PM		10.68	3.58	28.15
4	1:30		10.91	3.53	28.31
5	4:30	Thyroparathyroidectomy.			
6	3:30	40 units.			
7	3:00	20 "			
8	2:30		15.91	4.73	32.65
9	1:00	20 units			
10	6:30	Not very spry			
11	4:30	Had vomited blood. Did not eat. Resp. rapid and shallow. Depressed. Dark viscous blood	10.53	10.28	42.05
12	4:30	As above, only much worse	7.87	16.58	51.04
	6:30	20 units.			
13	5:00AM	Found dead apparently had all the symptoms of a previous over-dosage of parathormone as described above and in other dogs. Blood from mouth and rectum were evident.			

GENERAL SUMMARY.

LITERATURE: The phosphoric acid compounds of the blood have been divided into three main groups: protein, lipoid and acid soluble. The protein and lipoid phosphoric acid signifies the P that is in organic combination with proteins or fats, respecitvely. Both of these compounds are removed from the blood by acid-protein precipitants such as trichloracetic acid and may be separated from each other by well known processes. The protein free filtrate then contains what is called the total acid soluble phosphorus and includes all the phosphoric acid (inorganic and organic) that is not in combination with fats or proteins. This total acid soluble phosphorus is further divided into (1) an inorganic portion which is free (not in organic combination) and can be determined in the protein free filtrate without further treatment of the filtrate; (2) an organic acid soluble portion which is further divided into at least two compounds (a) one that is easily acid hydrolizable and is liberated by hemolysis and broken up by the esterases of the blood and (b) the other which is quite acid stable and cannot be liberated by the blood esterases. These organic acid soluble phosphoric acids are ester-like compounds of a heterogenous composition of which the main portion is di-phospho-levo-glycenic acid belonging entirely to the

second group (2b) of the organic acid soluble phosphoric acid compounds. All of these organic acid soluble phosphoric compounds are completely reduced to the inorganic phosphoric acid by prolonged boiling with concentrated sulphuric and nitric acids. Thus the total acid soluble phosphorus of the whole blood includes all the inorganic phosphoric acid and all the organic phosphoric acid that is not in lipoid or protein combination.

The errors in previous phosphorus determinations are pointed out. It is finally shown that the serum and plasma contain only negligible amounts (.1 mg per cent) of organic acid soluble phosphorus, if any at all; that there is no unanimity of opinion on the division of the inorganic phosphorus between the serum, plasma and cells (Some maintain that all the inorganic P is found in the plasma and serum, while others hold that up to 37% has been found in the corpuscles); and that the plasma has only lipoid phosphorus as its organic combination, whereas serum has in addition a trace of protein phosphoric acid which is liberated into the serum when the platelets break up.

Variations in the acid soluble phosphorus compounds of the blood, serum or plasma are then pointed out including the agents or conditions whereby these changes are brought about. Most of these changes are limited to the inorganic phosphorus, not much work having been done

on the now established organic acid soluble phosphorus. The acid soluble inorganic phosphorus compounds exhibit marked variations from individual to individual and from time to time within the same individual. Difference in altitude, in amount and slant of sun's rays striking the animal, in irradiation, in vitamin D content of food, caging of animals, laboring on an unaccustomed task, varaiations in sugar metabolism, variation in adrenal and insulin function, increasing age, pregnancy, lactation, change in rations, diet content in all vitamin, relative concentration of P and other ions in the digestive tract, injection of acids and alkalies, and kidney function (insufficiency); all of these are pointed out as being important factors in varying either or both the inorganic and total acid soluble phosphorus of the blood.

It is shown that normally plasma inorganic PO_4 is chiefly influenced by change in ration and that the blood derives its PO_4 from the digestive tract in the form of inorganic PO_4. It is indicated that each cell manufactures its own phosphoprotein within its self, no phosphoprotein being free in the plasma. The theory is advanced that notably the mammary gland and skeletal muscle can obtain its fat and P only in the form of phosphatids.

An increase in the inorganic P of the whole blood following the fall in serum calcium as a constant finding in parathyroidectomized dogs has been established as well

as the urinary P retention and the retention of calcium which parallels the decrease of calcium in the serum. The retention of Na and K is secondary to the phosphorus retention. A slight rise in total acid soluble phosphorus of the whole blood has been reported. Although the inorganic P/Ca ratio is always markedly increased in parathyroid deficiency, it does not run parallel with the severity of the symptomatology or tetany alone.

Certain chemical formulas that tend to show ionic relationships in the blood or their disturbance in the production of tetany have been reviewed. It is revealed that changes in ionic ratios cannot be only a function of the H ion concentration. The possibility of a K' Ca'' antagonism finds favorable comment because of their physiological effect on the isolated heart, the intestine and the "sleep center" as well as many other parts of the brain.

Parathormone raises the serum calcium of normal and parathyroidectomized dogs which is followed by a primary decrease in inorganic phosphorus with a secondary rise should the calcium rise markedly above the normal. The total acid soluble phosphorus has not been determined under these conditions.

Concerning the parathyroid glands themselves, a brief summary of their anatomy, embryology and histology with certain pathological findings in diseased conditions has been made, followed by a short historical sketch of

their discovery and the investigations made concerning their function. Finally, the clinical symptoms following removal of the parathyroid glands have been recorded.

Because of numerous references in the literature indicating a relationship between blood P content and tetany and because of the close chemical relationship between P and Ca, we have been led to investigate their relationships in a systematic way under various conditions of parathyroid deficiency. For this method of approach and for constant help and encouragement all credit with my sincerest gratitude, goes to Dr. O. O. Stoland, Head of the Department of Physiology, University of Kansas.

THE WHOLE BLOOD INORGANIC AND TOTAL ACID SOLUBLE PHOSPHORUS AND SERUM CALCIUM AND THE PHOSPHORUS/Ca RATIOS OF NORMAL DOGS? AND DOGS UNDER VARIOUS CONDITIONS OF PARATHYROID DEFICIENCY: After an adequate control period, dogs were completely thyroparathyroidectomized. They were then treated with (1) heparmone (18 dogs); (2) calcium lactate (9 dogs); (3) strontium lactate (2 dogs); (4) magnesium lactate (2 dogs); (5) morphine sulphate (3 dogs); (6) ammonium chloride (4 dogs); (7) uranium nitrate (9 dogs); (8) Parathormone (11 dogs). Twelve other dogs were allowed to run their course without any treatment. Of these 70 dogs, 40 received no treatment, (including the 12 that received no treatment

at all throughout the experimental period) until parathyroid deficient symptoms appeared, whereas 30 received treatment from the time of operation.

The blood analysis throughout the experimental period was made from one to four and even seven times a day, daily, 2 to 5 times a week, weekly, bi-weekly, etc., according to the nature of the results and the method of treatment employed. The blood analysis extends over the experimental period of each dog lasting from several days to weeks, months and even a year.

The serum calcium was determined by the method of Kramer and Tisdall as modified by Clark and Collip. The inorganic phosphorus and total acid soluble phosphorus (T.A.S.P.) were determined by the method of Subbarow and Fiske.

NORMAL P AND Ca CONCENTRATIONS: The data includes 261 determinations made on 71 dogs under normal conditions. The average of all the normal determinations was 10.84 mg per cent for calcium (mg per 100 cc of serum); 4.44 mg per cent for inorganic P; 26.65 mg per cent for T.A.S.P. (per 100 cc of whole blood); 0.41 for the Inorg. P/Ca ratio; and 2.42 for the T.A.S.P./Ca ratio. The serum calcium is quite constant from animal to animal and especially from time to time--however one dog had a constant calcium as low as 8.54 mg per cent and another a constant high calcium, 12.55 mg per cent. The inorganic P

varies markedly from time to time (up to 2 mg per cent) and from animal to animal (up to 2.5 mg per cent). The T.A.S.P. also varies from time to time (usually 1 to 2 mg per cent but may be up to 6 mg per cent) and from animal to animal (up to 14 mg per cent). Due to the above, both the inorganic P/Ca (.29 to .57) and the T.A.S.P./Ca (1.83 to 3.44) ratios may vary markedly from animal to animal but less so from time to time within the same animal. However, taking the average of each dog and comparing this to the average values found for the 71 dogs, the variation is much less and hardly ever excedes ±.3 mg per cent for the serum calcium, ±.5 mg per cent for the inorganic phosphorus, ±2 mg per cent for the T.A.S.P., ±.05 for the Inorg P/Ca ratio, and ±.3 to .35 for the T.A.S.P./Ca ratio.

CONCENTRATIONS OF P AND Ca AT THE TIME WHEN SYMPTOMS APPEARED IN UNTREATED THYROPARATHYROIDECTOMIZED DOGS: The T.A.S.P. of the whole blood tends to vary directly with the severity of the symptoms manifested and inversely with the time of their post-operative onset. (In very severe tetany dogs this does not always hold true.) For example a dog showing symptoms of parathyroid deficiency the first or second post-operative day will have a rise of 1 to 5 mg per cent in the T.A.S.P. whereas another dog not showing the same symptoms of parathyroid deficiency until the 4th or 5th post-operative day may show a normal or a fall of 1 to 6 mg per cent in the T.A.S.P. In the dogs that

developed severe and sudden attacks of tetany, the T.A.S.P. was from 5 to 8 mg per cent above the normal even when these symptoms did not appear until the 4th and 5th day. On the other hand, as a rule, there was progressively a decrease of T.A.S.P. content at the time when symptoms appeared in going from dogs showing severe and sudden tetany to those showing mild tetany and to those showing depression.

Under the same conditions, the inorganic phosphorus of the whole blood is always above the normal when symptoms of parathyroid deficiency appear (as a rule .5 to 2 mg per cent) but the exceptions to paralleling the T.A.S.P. changes are numerous.

The rate of serum calcium fall and not the absolute content runs parallel with the parathyroid deficient symptoms, but bears no relationship to the type and severity of symptoms manifested. A dog showing a serum calcium fall of 3 to 5 mg per cent within 12 to 24 hours after operation showed symptoms of parathyroid deficiency within 30 hours of operation whereas if the fall in serum calcium was slower, from 3 to 5 days may pass with the calcium reduced by 6 mg per cent before symptoms appeared. However, severe tetany, mild tetany or depression does not depend upon this rate of serum calcium fall, that is, severe tetany, mild tetany, or depression may occur at a fall of 3 or 6 mg per cent no matter whether such fall occurs at the rate of 1 or 5 days.

The T.A.S.P./Ca ratio, as a rule, tends to vary directly with the severity of the symptoms manifested and the time of their post-operative onset. That is since the calcium decreases progressively from day to day its decrease will be relatively greater even than the decrease in T.A.S.P. found in the dogs where mild tetany or depression is delayed for 3 to 5 days. This ratio varies from 3.18 to 6.50, the usual range being between 4.25 and 5.25 at the time when symptoms appear.

The inorganic P/Ca ratio tends to parallel the T.A.S.P./Ca ratio, exhibiting less constancy in extent of change. It is usually doubled and sometimes trebled at the time that symptoms of parathyroid deficiency appear.

One thing that is striking is that, particularly where the symptoms are delayed, the serum calcium may be lower, or the Inorg. P, or the T.A.S.P. may be higher and hence either or both of these ratios may be higher at some time before symptoms appear when compared with the time when symptoms were manifested.

CONCENTRATIONS OF P AND Ca AT THE TIME OF DEATH IN UNTREATED THYROPARATHYROIDECTOMIZED DOGS: The conclusions drawn above for the changes taking place until symptoms appear apply equally well to the changes taking place in the blood from the time that symptoms appear until death. That is the more severe the tetany is and the sooner

death follows the appearance of symptoms of parathyroid deficiency the greater will be the rise in the T.A.S.P. of the whole blood, whereas if the symptoms are milder and death is delayed for several days, the T.A.S.P. may be below the symptomatic and even below the normal value at the time of death. The inorganic P simulates the changes of the T.A.S.P. but is never below the normal, and only once below the symptomatic, concentration at the time of death.

The serum calcium may be lower between attacks of tetany than at the actual time of tetany but in all the dogs there is a progressive decrease from day to day until death occurs except in the dogs that died shortly after the first severe attack and one dying on the 7th day which showed a rise of 1 mg per cent. It seems that in the former the tissue acidosis produced by the severe tetany may be the cause of the rise, whereas in the latter case where only depression was present some other compensatory mechanism may have already come into play.

Though (with one exception) they are always higher at the time of death than when symptoms appeared, both P/Ca ratios may be considerably lower at the time of death than at some previous time. Moreover dogs which recover as we shall see in the next paragraph show a maximal disturbance in their ratios without terminating fatally.

CONCENTRATION OF P AND Ca UP TO THE TIME OF RECOVERY: Two dogs recovered without any treatment whatsoever. They showed in every way the symptoms of severe depression and mild tetany accompanied by all the changes in serum calcium and blood phosphorus compounds and P/Ca ratio that were noted above for the dogs that died. However, in the process of recovery the calcium rises and a decrease in inorg. P and T.A.S.P. is very favorable for recovery. But after recovery if the serum calcium is at 7 mg per cent or above, an increase of 1 mg per cent inorg. P or 6 mg per cent T.A.S.P. causes no detectable symptoms in the animal. One such dog has now, one year after recovery, Inorg P/Ca and T.A.S.P./Ca ratios, respectively, of .46 and 2.84 as compared to his normals .40 and 2.15.

This certainly suggests very strongly that neither calcium fall alone nor its relationship to the phosphorus content of the blood can be the only factors involved in the symptomatology and death of parathyroid deficient dogs.

CONCENTRATIONS OF P AND Ca IN PARATHYROID DEFICIENT DOGS TREATED WITH LIVER EXTRACT: Dogs were completely thyroparathyroidectomized and treated with liver extract (heparmone), intravenously; 17 dogs not until parathyroid deficient symptoms appeared and 6 from the day following the operation. Seven of the former 17 received 5 to 15 cc doses of heparmone at 10 to 30 minute intervals not exceeding a total of 40 cc. The other 10 received large massive

doses (40 to 110 cc a day) as did also the last 6 dogs treated from the time of operation.

We found that injection of liver extract (in larger doses) into dogs suffering from tetany brought on more violent tetany for a period of 2 to 5 minutes after which the tetany subsided. This primary increase in tetany was accompanied by autonomic reactions in the dogs that were benefitted by the liver extract characterized by a fall in blood pressure, faint pulse, salivation, vomiting, retching, borborigmus, passing of flatus, forced micturition, and violent intestinal movements resulting in defecation. The coagulation time was also increased markedly during this time. This syndrome was as a rule followed by a slight decrease in serum calcium, a primary rise in total acid soluble phosphorus, and a variable change in the inorganic phosphorus (more often reduced). The serum calcium rose again in the course of several hours whereas the behavior of the inorganic P and T.A.S.P. was as a rule reversed in 5 to 30 minutes,--that is a fall took place in the T.A.S.P. until it was even down to 5 mg per cent below the normal. This primary increase in tetany accompanied by the autonomic reactions became less with each successive injection and was almost totally absent after about the 6th injection. This was paralleled by the decrease and final absence of the primary changes in calcium and a fall of the T.A.S.P. from the beginning.

There were 3 dogs in very severe tetany that were not benefitted by the liver extract. All 3 did not show the visceral reactions and all three showed a slight rise in serum Ca (up to 1 mg per cent) and a rapid increase in the T.A.S.P. until death.

The T.A.S.P. level was ultimately lowered in all animals benefitted by the liver extract. If the total acid soluble phosphorus was no longer lowered by the injection of liver extract the animal was as a rule no longer benefitted.

Since the serum calcium rises with an increase in the total acid soluble phosphorus of the whole blood in dogs that run an acute course and since those that are benefitted show a progressive decrease in the serum calcium altogether with a marked fall in the total acid soluble phosphorus it seems again that the lowering of the calcium is not the only factor in producing tetany.

We would suggest that the recovery from tetany brought about by liver extract may be due to a neutralization of toxic substances since the calcium level remains at or below tetany level.

METHOD OF TREATMENT FOR THE REMAINING EXPERIMENTS: The method of treatment followed in the remaining experiments consisted of twice daily administration by stomach tube (spaced so they would not interfere with a daily

meal) in doses of 3 to 12 gm of calcium lactate, strontium lactate, magnesium lactate, or ammonium chloride. The dogs treated with uranium nitrate were given .3 to 5 mg per Kilo body weight subcutaneously; those treated with morphine sulphate received subcutaneously, gr. $\frac{1}{2}$ to $2\frac{1}{2}$ as necessary but not exceeding 5 gr. a day; and those treated with parathormone received 10 to 185 units a day (according to the amount of parathyroid deficiency or excess desired) either subcutaneously or intravenously.

DOGS TREATED WITH CALCIUM LACTATE: Dogs may recover from the symptoms of parathyroid deficiency after at least 60 days of treatment by calcium lactate, orally. The treatment must be started before the animal exhibits severe tetany. Two dogs receiving treatment from the time that symptoms appeared died on the 3rd and 6th day, respectively, while a third dog that was pregnant at the time of operation received 103 days of treatment (46 days before and 57 days after partuition) and was killed 2 weeks later because of a severe skin rash. Three dogs receiving treatment from the day following the operation died on the 18th, 112th, and 153rd days, respectively, and received treatment 18, 104 and 60 days, respectively.

Under calcium therapy of parathyroid deficient dogs the behavior of the serum calcium, whole blood inorganic and total acid soluble phosphorus and the P/Ca ratios whenever parathyroid deficient symptoms appeared and at

the time of death was identical to that shown for dogs without any treatment.

Under calcium therapy of parathyroid deficient dogs, the inorganic P and T.A.S.P. have a tendency to be below the normal so long as the animal is benefitted and so long as the calcium concentration is not markedly above the normal. When the animal is not benefitted by the calcium administration or when the calcium is raised markedly above the normal, both the inorganic P and the T.A.S.P. increase. In the former condition (tetany) the rise in the latter is more constant and in the latter (above normal) the rise in the former is more constant.

The P/Ca ratios are more or less a function of the serum calcium concentration--that is the changes in serum Ca are so marked by calcium administration that they hide the lesser change in the numerator and therefore vary inversely with the change of the denominator.

DOGS TREATED WITH STRONTIUM LACTATE: Strontium lactate treatment was not nearly so effective as calcium lactate in bringing about recovery from tetany without depression or in saving the life of the animal. The dogs died on the 10th and 13th post-operative days but not in tetany.

As in the case of calcium lactate treatment so it is with strontium; so long as the animal was benefitted by the treatment, the inorganic P and T.A.S.P. remained the same or decreased. However as the symptoms that led

to death increased, the T.A.S.P. rose by 6 to 7 mg per cent while the inorganic P varied.

It is felt that since the method used for Ca determination includes also that for strontium that this is the cause for the high calcium values found at death. The high calcium values would thus cause low or very nearly normal P/Ca ratios even if there is a marked rise in the T.A.S.P.

It is suggested that the high calcium value, though it abolished tetany cannot replace Ca in its biological relationship since death followed just the same.

DOGS TREATED BY MAGNESIUM LACTATE: The lives of 2 dogs could not be maintained beyond 11 and 23 days, respectively, by magnesium lactate treatment.

The results indicate that in parathyroidectomized dogs magnesium treatment neither prevents nor promotes a decrease in the serum calcium. The results also indicate (contrary to the supposition of Wenner (248 to 250) that the magnesium does not exert its beneficial influence to a great extent, by making calcium more available as a result of replacing the latter from its phosphate combination, since the serum calcium falls progressively (no faster than in the normal) and the inorganic P and T.A.S.P. are both markedly increased after the second day even in dogs completely narcotized by magnesium.

But since the phosphorus compounds do not rise until the second or third day after magnesium treatment is begun it appears that the phosphorus rise may be due to the lower calcium or the effects of high magnesium content, and that therefore initially the magnesium may act by replacing the Ca from its phosphate combination, but certainly not later.

Thus, whatever other relationship there may be between magnesium and other ions in the body, its beneficial effects in parathyroid deficiency are largely if not entirely due to its generalized nervous and metabolic depressant effect.

DOGS TREATED WITH MORPHINE SULPHATE: It is impossible to keep a dog longer than 5 days at a time on morphine treatment alone because of its systemic effects.

The effect of prolonged morphine sulphate treatment on the blood picture is very nearly identical to that produced by magnesium except that the inorganic phosphorus rises to greater dimensions, particularly terminally and the serum calcium varies within a mg per cent. It seems as if the calcium is kept from decreasing farther by morphine treatment whereas magnesium did not have this property. Also the total acid soluble phosphorus rises earlier in morphine treatment than it does in magnesium. Whenever calcium lactate was given, orally, the phosphorus compounds decreased and reached as far as 3 to 8 mg per

cent below the normal in T.A.S.P. content whereas the inorganic P was less affected and never even decreased to the normal concentration.

Since the calcium remains so very nearly the same throughout the period of morphine treatment it is evident that the direction and extent of change of both P/Ca ratios will be dependent and nearly directly proportional to the change in concentration of the respective P compounds. Thus the ratios increase or decrease according to whether the numerator increases or decreases.

The beneficial effects of morphine have been attributed to its depressant action on the central nervous system and its effect on respiration by primarily stimulating it when it has become paralyzed and secondarily depressing--thus preventing the alkemia of hyperpnea.

DOGS TREATED WITH AMMONIUM CHLORIDE: It seems that dogs may be freed of tetany by the oral administration of calcium lactate followed by ammonium chloride and still not survive. Such dogs die in a curled up position as if suffering from cold. Previous to death they become weak and emaciated, their vomit contains blood and they have a watery diarrhea. In such dogs the tendency toward hemolysis is strong, the serum calcium may be normal or below the tetany level with an inorganic P that is 2 mg per cent below to 3.5 mg per cent above the normal and a T.A.S.P. that has been reduced by 12 mg per cent

or raised by 9 mg per cent at the time of death.

Only one dog was brought to complete recovery by ammonium chloride treatment (33 days) and died in tetany 6 days later. Two other dogs were benefitted for 3 and 7 days respectively. Another dog died the first day without tetany.

All four dogs treated with ammonium chloride show that the ammonium chloride has a tendency to keep or raise the serum calcium above the tetany level. In the 3 dogs benefitted by the treatment the inorganic P (1 to 2.5 mg per cent) and T.A.S.P. (6 to 14 mg per cent) are markedly reduced. Both phosphorus compounds increase correspondingly upon decrease or withdrawal of ammonium chloride treatment regardless of the serum calcium content. The behavior of the phosphorus compounds is therefore due to the NH_4' itself and not through the agency of affecting the serum calcium.

Both the P/Ca ratios decrease markedly, even to below the normal, when the animals are benefitted by ammonium chloride treatment and vice versa when the treatment is withdrawn.

Our results confirm those of Wenner (1927) that the ammonium chloride probably exerts its action by rendering the blood more acid, thereby producing a rise in serum calcium. But since the behavior of the P compounds has been shown to be a function of the NH_4', it is possible

that the NH_4' is synergistic with Ca'' and Mg'' in certain functions of the body in which the lactic acid produced by muscular contraction also plays an important role.

That such a condition does exist is shown by the workers in Pawlow's laboratory. The work of this Russian school has recently been reviewed and translated by Prawdicz-Neminski(203 a). From this extensive review, including the works of many Russian authors and investigators, it is concluded that the NH_4' in all forms of muscular and nervous activity unites with Mg'' and PO_4''' to form the triple phosphate and may be demonstrated in crystalline form in the tissues, thus removing these ions from solution and its ionic relationships. It is shown at the same time that excess of organic acids, notably lactic acid, redissolve the triple phosphate. The latter fact would seem of extreme importance in explaining why ammonium chloride alone is unable to maintain animals once in tetany free from tetany and death. The lactic acid already present would keep the NH_4' from uniting with Mg'' and PO_4''', thus making it necessary for more Ca'' to be in equilibrium with the excess PO_4''' ions. This same explanation may be attached to the fact that Mg'' treatment is effective only when the Ca'' is kept high. The Mg then acting as a pure depressant of all nervous elements, whereas, once the low Ca causes tetany to precipitate, the lactic acid so formed draws

additional phosphate ions to the excess $Mg^{''}$ ions thus increasing the phosphates of the blood markedly.

DOGS TREATED WITH URANIUM NITRATE: Eight thyroparathyroidectomized and 1 normal dog were treated with single injections of uranium nitrate. The symptomatology paralleled by the blood findings varied inversely with the age of the animal and directly with the dose administered.

Dogs can be rendered free from tetany and other symptoms of parathyroid deficiency for a period of 3 to 10 days before the severer symptoms of uranium poisoning appear. During this time the blood findings are similar to that found in the recovery period of the dogs treated with ammonium chloride except that the serum calcium does not show a tendency to rise. The inorganic P and T.A.S.P. reach the same low level and are paralleled by the P/Ca ratios. The ratios however never reach the normal since the Ca does not increase.

The symptoms that appear after the 3 to 10 day (in one case 45 days) period of recovery are not identical to those found in parathyroid deficiency (as reported by Swingle and Wenner (235 a)) but must be traced to the uremia or other injuries caused by the poisoning, since normal animals also show the same symptoms. When these symptoms of poisoning begin and as they progress to fatality (usually 5 to 10 days) both inorganic P and

T.A.S.P. rise progressively and may be up to 7 and 3 times the normal, respectively, at the time of death.

This terminal increase in P paralleling the degree of uranium poisoning is attributed to excess tissue destruction caused by the uranium.

It is possible that here too the acidosis causing a decrease in the blood phosphates prevents tetany, but if the serum calcium content is an index of available Ca for functional activity, the uranium does not act by making the calcium more available to the tissues and blood.

DOGS TREATED WITH PARATHORMONE: Our results on the symptomatology as related to the serum calcium and whole blood inorganic phosphorus upon administration of parathormone to normal and parathyroid deficient animals affirm and extend those reviewed and established by Collip (41).

Parathormone administration to normal and thyroparathyroidectomized dogs causes a progressive increase in the serum calcium, beginning 2 hours after the injections have started and reaching a maximum in 15 to 24 hours. After some hours it begins to decrease and the course of decline is similar to that of the rise. One dog not injected until severe tetany occurred did not show this rise in the 6 hours before he died.

In thyroparathyroidectomized dogs when by means of parathormone treatment the serum calcium is not allowed

to vary beyond ±2.5 to 3 mg per cent the inorganic P of the whole blood varies slightly from just above to 1 or 2 mg per cent below the normal, whereas the whole blood T.A.S.P. has a tendency to decrease at first markedly and then slowly and progressively. When these variations in the serum Ca are more or less beyond ±3 mg per cent from the normal, marked variations in the behavior of the inorganic P and T.A.S.P. take place. When the calcium variation is negative the results are the same as noted in the section on untreated animals. When the serum calcium variation was on the positive side and did not excede 5 or 6 mg per cent (from the normal) the T.A.S.P. change was opposite to that of the serum Ca; that is, when the calcium increased the T.A.S.P. decreases and vice versa. Should the serum calcium rise still higher accompanied by an abrupt increase in the whole blood inorganic P, then death ensues in 48 to 72 hours while the calcium falls progressively and the inorganic P and T.A.S.P. are as much as quadrupled and more than doubled, respectively, at the time of death. Death then occurs of over-dosage symptoms even if the calcium level is at or below tetany value. The abrupt and rapid increase of the inorganic P was the most constant finding when parathormone over-dosage led to death, even in the dog that died 6 hours after tetany began and showing no increase in serum calcium. The increase in T.A.S.P. was just as constant but was not

always so extensive and sometimes no higher at the time of death than when death occured without treatment. At any rate, the inorganic P increase preceded the T.A.S.P. increase in those dogs that died of over-dosage.

In consequence to the above the Inorg P/Ca and T.A.S.P./Ca ratios vary markedly when the Ca does not vary beyond ± 3 mg per cent from the normal, but beyond this ± 3 mg per cent variation these ratios are both increased and at the time of death due to over-dosage the Inorg P/Ca ratio may be increased by 3 to 7 times and the T.A.S.P./Ca ratio by .5 to 3 times.

GENERAL DISCUSSION.

The facts in the literature together with this work have led to the opinion that the inorganic and total acid soluble phosphorus changes in the whole blood are not primarily etiological in the symptomatology and death of parathyroid deficient dogs. In thyroparathyroidectomized dogs the inorganic P always increases but the total acid soluble phosphorus tends to vary inversely with the time of post-operative onset of symptoms and the time of death after symptoms appear, and directly with the severity of the symptoms manifested. That is to say, as a rule, the earlier and severer the symptoms after operation and the severer the symptoms and the the shorter the time leading to death after symptoms appear the higher is the rise in total acid soluble phosphorus of the whole blood, but if the symptoms are mild and delayed and several days in their onset and if death is delayed several days after onset of symptoms, the total acid soluble phosphorus of the whole blood may be markedly below the normal at the time when symptoms appear or at the time of death.

A low blood inorganic and total acid soluble phosphorus (particularly the latter) is highly favorable to recovery. This is true when it occurs without treatment or when it occurs in the treatment by heparmone, calcium

lactate, ammonium chloride, uranium nitrate, primarily in magnesium lactate, and parathormone when the calcium does not vary beyond ±3 mg per cent relative to the normal.

The beneficial effects of prolonged treatment with magnesium lactate or morphine sulphate despite the secondary marked progressive increase in inorganic and total acid soluble phosphorus is attributed to the general and central depressant effects of the former and the central depressant effects of the latter and the depressant effect on respiration by both.

The rate of calcium change and not so much its absolute concentration is related to the onset of parathyroid deficient symptoms but seems to bear no relationship to the type and severity of symptoms initially manifested. That is to say if the serum calcium drops 3 to 4 mg per cent in 24 hours, parathyroid deficient symptoms appear at the end of that period, as a rule, whereas if the calcium fall is spread over several days the decrease is usually as much as 5 to 6 mg per cent before symptoms appear, but the symptoms initially manifested whether they be severe tetany, mild tetany or depression does not depend on whether the fall in serum calcium is 3 to 4 mg per cent in 24 hours or 5 mg per cent in five days.

It follows therefore that the changes in concentration of neither the inorganic P nor the T.A.S.P. in the whole

blood are definitely and constantly related to the concentration of the calcium in the serum either in extent or direction of change.

Still, when the symptoms were those of parathyroid deficiency or whenever death was directly due to the parathyroid deficiency and not to any toxic over-dosage in treatment, both P/Ca ratios were increased or decreased opposite to that of the calcium showing that the ratios changed largely as a result of the calcium change. Hence, when symptoms of parathyroid deficiency appeared or at the time of death (due to parathyroid deficiency) the ratios vary from 90 to 300% (inorg P/Ca) and from 60 to 150% (T.A.S.P./Ca) above the normal.

But 2 dogs receiving no treatment showed in every way the same blood picture and clinical symptoms that ordinarily resulted in death (high inorg P and T.A.S.P. and low serum calcium accompanied by mild tetany and severe depression), yet recovery occurred.

These facts would tend to show that the changes in serum calcium and in the acid soluble phosphorus compounds of the blood cannot be the only important factors that determine the symptomatology and death or recovery of parathyroid deficient dogs. Suggestions have been made that the ionic concentration of $Mg^{''}$, $NH_4^{'}$ and particularly the $K^{'}$ as well as poisonous metabolites play a role in this whole syndrome.

Our knowledge concerning the various phosphorus compounds and the manner in which they are related to each other in the soft tissues and body fluids is at present hopelessly inadequate to draw any weighty conclusions. From all indications, the body can withstand a wide range of variation in both inorganic and total acid soluble phosphorus of the blood without any apparent effect on the organism as a whole. Greenwald (100) has increased the inorganic phosphate 20 times by phosphate injections without any very untoward effects. The conditions that cause a variation in these blood phosphorus compounds are so numerous even under physiological conditions that it seems presumptuous to estimate the functional and pathological importance of any given phosphorus compound of the blood until the chemistry and the possibel source of variation of all the phosphorus compounds of the body have been determined.

From the most recent work of Irving and Bastedo (1928) (137) and that reviewed and extended by Sella (1928) (225) it seems that the functional metabolism of muscle itself cannot be a direct source of inorganic phosphorus compounds of the blood. Moreover, Meyerhof and Lohmann ((1928) (186)), Nachmansohn ((1928) (190)), and Ferdmann and Feinschmidt ((1928) (68)) followed independently by Fiske and Subbarow ((1929) (75)) and Irving and Bastedo (137) have established a mechanism of phosphorus metabolism within the muscle fiber that normally neither contributes

to nor subtracts from the inorganic phosphorus compounds of the blood. In this intramuscular mechanism calcium and potassium are highly involved but their action has not been explained.

The whole mechanism hinges about a newly discovered compound called phosphocreatine--a phosphoric acid of methyl guanidine acetic acid $(OH)_2OP \cdot HN-C:NH-N(CH_3 \cdot CH_2 \cdot COOH$ which forms salts with K and calcium, both secondary and tertiary. The secondary salts but not the tertiary salts of calcium are easily given to hydrolysis under anaerabic and acid conditions, such as is brought about by muscular contraction. Under these same circumstances optimal conditions are created for the reformation of lactacidogen which involves the incorporation of phosphate. In this anaerobic and acid hydrolysis of phosphocreatine, creatine and calcium and potassium phosphate are probably formed. This whole process is reversible so that in the aerobic and more alkaline condition of muscular rest or between contractions the phosphocreatine is reformed. It is evident that if the easily hydrolizable K' and secondary Ca'' phosphates are formed, the phosphates become readily available for the incorporation into lactacidogen leaving an excess of well balanced Ca/K base for neutralization of the acids formed by muscular contraction. However, under abnormal conditions an excess formation of the tertiary calcium phosphate that is

hardly hydrolizable in the muscle fiber will bring about an excess of the excitable K' ions which will in turn draw excessively upon the Ca'' in the blood and cause increased diffusion of K' into the blood.

It stands to reason that the parathyroids may function primarily in keeping this reversible reaction (phosphocreatine $\rightleftharpoons$ secondary K' + Ca'' phosphates $\rightleftharpoons$ tertiary Ca'' phosphate) at an optimal sensativity in the muscle and perhaps other tissues.

Since a disturbance in the Ca/K ratio has such a marked biological effect on the premability and irritability it also stands to reason that metabolites otherwise ineffective may now have excess to the cellular protoplasm perhaps too in increased amounts. Thus by a variation of cellular intoxication wide variations may be introduced into the syndrome of parathyroid deficiency.

In parathyroid deficiency the primary decrease in the serum calcium followed by a P retention would supply the demand of calcium and PO_4 in the tissue. The secondary retention of K and Na and their increase in the blood and tissues would be necessitated for the replacement of Ca'' which is being taken out of its ionic and chemical relationship with other compounds by being precipitated as the tertiary phosphate in the tissues.

It is thus obvious that it is very unlikely that the phosphates that are found in the muscle fiber and are

directly related to its functional metabolism can be a source of acid soluble phosphorus increase in the blood. It is also obvious that the lower the phosphate concentration in the blood the less will be the extramuscular supply of phosphate to form the tertiary Ca phosphate in the muscle fiber and hence by the law of mass action more calcium will become available for its other functional relationships. Hence the beneficial effects of a low blood phosphate in parathyroid deficiency. Hence also, since the calcium supply in the body is so limited the PO_4 ion need not be in great excess to precipitate most of the Ca'' as the tertiary phosphate.

Since according to the above facts and postulations the phosphate is progressively precipitated in the tissues as the Ca phosphate in parathyroid deficiency, it may also explain the low phosphate in animals that do not show parathyroid deficient symptoms until several days after operation, particularly, if the symptoms are mild.

It would seem then as Greenwald (97 etc.) stated that the phosphate increase in the blood in parathyroid deficiency resulted from an excess destruction of tissue proteins and we would add that this and the terminal anuria found in both parathyroid deficiency and over-dosage are probably responsible for the increase not only in the inorganic P but also of the T.A.S.P. of the whole blood.

CONCLUSIONS.

1. The average of 261 determinations on 71 normal dogs showed the following concentrations: Calcium 10.84 (mg per 100 cc of serum), inorganic P 4.44, total acid soluble P 26.65 (in mg per 100 cc of whole blood), inorganic P/Ca ratio .41, and total acid soluble P/Ca ratio 2.42.

2. Although the phosphorus compounds, particularly of the skeletal muscles, may play a leading role in the symptomatology and death of parathyroid deficient dogs, the inorganic and total acid soluble phosphorus changes of the whole blood are not primarily etiological.

3. In thyroparathyroidectomized dogs the inorganic P always increases, but the total acid soluble P tends to vary inversely with the time of post-operative onset of symptoms and the time of death after symptoms appear and directly with the severity of the symptoms manifested.

4. A low blood inorganic P and particularly a low total acid soluble P is highly favorable to recovery from parathyroid deficiency.

5. The beneficial effects of magnesium lactate and morphine sulphate despite a secondary progressive rise in

inorganic P and total acid soluble P are attributed to their depressant action on the respiratory center and other nervous structures.

6. The rate of calcium fall, and not so much its absolute concentration in the serum, is related to the onset of parathyroid deficient symptoms but seems to bear no relationship to the type and severity of symptoms initially manifested.

7. As a rule both P/Ca ratios largely varied opposite to the calcium change and at the time of death or when symptoms of parathyroid deficiency appeared were increased by 90 to 300% (Inorg P/Ca) and 60 to 150% (T.A.S.P./Ca) above the normal.

8. Two out of 12 thyroparathyroidectomized dogs, none of which were treated, made a complete recovery though the blood picture and clinical symptoms were identical to those that died of parathyroid deficiency (high inorganic P and T.A.S.P. and low serum calcium accompanied by mild tetany and severe depression).

9. It is concluded that the behavior of the calcium and acid soluble phosphorus compounds in the blood of dogs suffering from parathyroid deficiency is largely due to a disturbance of phosphocreatine metabolism within the muscle fiber (and perhaps other tissues) which

greatly involves the Ca/K ratio thereby affecting also the permeability and irritability of tissues whereby metabolites otherwise non-toxic occur in excess and gain access to the cellular protoplasm which results in the various clinical manifestations found in parathyroid deficiency.

10. The marked increase of the blood P compounds in early and severe parathyroid deficiency and parathormone over-dosage is contributed to the increased destruction of tissue proteins.

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