THE EFFECT OF POTASSIUM DEFICIENCY ON GASTRIC SECRETION

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by

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A McGill University thesis submitted in partial fulfillment of the requirements for the degree of Master of Science in Experimental Surgery.

August, 1950

ACKNOWLEDGEMENTS

To Dr. D.R. Webster I wish to express my sincere gratitude for his constant supervision, encouragement, interest and advice during the course of this investigation. I am indebted to Dr. T.R. Waugh for assistance in the interpretation of the microscopic sections, and to Dr. C.C. Birchard for help in reviewing the electrocardiograms.

I wish to thank Mrs. K. Wright for the typing of this thesis, Miss Carol Philip for secretarial assistance and other services, and Miss Hope Thompson for numerous tasks related to the biochemical investigations. Mrs. K.A.C. Elliott has cheerfully performed all potassium and sodium determinations with the flame photometer at the Allan Memorial Institute. Microscopic slides were made by Mr. Hans Torunski of the Department of histology, McGill University.

The majority of the photographic work was made made by Mr. Paul Roustan. Special thanks is also due him for technical assistance in the operating room. My thanks are also due to Mr. James Byers for the supply and care of animals and Mr. Leo Groulx for care in the animal rooms.

It has been a real pleasure to work in the same laboratory with Dr. R.A. Forse, Dr. D.W. Miller, Dr. Helen Henrikson, Dr. Stan Skoryna, Dr. Andrew Chau, and Drs. Toovey and Rutis, and I wish to thank them for constructive criticisms and operative assistance. (I wish to thank

Dr. R.A. Forse in particular for constant help and co-operation throughout the whole year and particularly in final months.) The high degree of cooperation and companionship that exists in these laboratories has made this past year a most enjoyable one.

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The Effect of Potassium Deficiency on Gastric Secretion

ILLUSTRATIONS

CHAPTER 1

INTRODUCTION

In October 1946 a dog was prepared in these laboratories with a large partially innervated gastric pouch. The pouch was a modification of the Cope operation (30), a pouch made from the lesser curvature of the stomach. The dog was standardized to the various gastric function tests and was maintained on a normal kennel diet of minced meat. Within 48 days the volume of gastric juice secreted by the pouch increased from an average of 50 c.c. to an average of 135 c.c. daily. There was also noted an increase in the amount of water taken and in the volume of urine excreted. After the 82nd day the dog gradually lost its appetite and became thin and weak. On the 98th day the head was found arched downwards and it was described as having a spastic paralysis of neck muscles. The hypersecretion of gastric juice, polydipsia and polyuria persisted. On the following day the dog was found paralysed but this paralysis was described to be of the flaccid type. Tetany, with both tonic and clonic movements, was observed. On the suggestion of Dr. J.S.L. Browne, the serum potassium level was found to be low - 15 mg. per 100 c.c. Other biochemical studies revealed findings within normal limits, except for a moderate alkalosis. The CO_2

combining power of the plasma was 85.1 volumes per 100 cc. Potassium chloride solution was administered under electrocardiographic control and the dog made an immediate and dramatic recovery although the polydipsia, polyuria, and hypersecretion persisted. Seven days after the administration of potassium the carbon dioxide combining power was 64.3 and four days later 42.3 volumes per 100 cc. The dog was fed potassium chloride by mouth in large doses thereafter but did not return completely to normal.

During the following year attempts were made to reproduce the condition. Dogs were prepared with Heindenhain pouches (63) and the gastric secretions were standardized. Desoxycorticosterone acetate was given to these dogs in order to produce potassium deficiency and although hypersecretion, polydipsia and polyuria followed, tetany was not reproduced.

Because a diligent search through the literature failed to reveal any previous report of the effect of potassium deficiency on the gastric secretion, the problem for this investigative work was conceived. Further, the only report found in the literature on the appearance of tetany in association with potassium deficiency is the paper by Moehlig and Jaffe (97) who described a patient who had several pellets of desoxycorticosterone acetate

implanted subcutaneously in the treatment of myesthenia gravis and developed tetany in several weeks time apparently from overdosage as one of the pellets was accidentally crushed during implantation.

The method used in the investigation of this problem in general will be as follows. Suitable gastric pouches will be prepared in dogs and an attempt will be made to produce potassium deficiency by diet alone; the gastric secretions will be refed. A second attempt to produce potassium deficiency by diet, desoxycorticosterone acetate and the loss of gastric juice will be made. The water balance, potassium balance and blood chemical findings in these dogs will be followed. The gastric secretions will be studied for volume, pH, pepsin and potassium content.

CHAPTER 11

A. REVIEW OF THE LITERATURE

POTASSIUM METABOLISM IN GENERAL

That Potassium is essential to the living organism has been known for many years, yet investigations of the role that this element plays in the many physiologic and pathologic reactions in which it has been found, are quite incomplete.

The distribution of potassium in Nature is interesting and unique. It is found in abundance in soil, intracellular fluid and erythrocytes of rats, rabbits and humans but relatively scarce in seawater, extracellular fluid and erythrocytes of cats and dogs. Explanations of this peculiar distribution are lacking. Mond and Netter (98) in 1932 first proposed the theory that the cell membrane is permeable to potassium and not to sodium and supported this theory with evidence gained from studies following the injection of potassium to potassium depleted animals. Further evidence has been presented recently from the study of the fate of radioactive isotopes of potassium after injection into animals. In spite of the fact that this concept is contrary to the basic principles of cell membrane permeability, it seems

apparent that the cellular membrane is more permeable to potassium than it is to other cations, in particular sodium, and possibly potassium may remain intracellular because the anions to which it is combined are unable to escape (47).

Potassium is the chief basic ion (cation) of the cell and its concentration is 140 - 160 M.Eq. per litre of cell water. In contrast, the concentration of potassium in the extracellular fluid is only 4.0 - 5.5 M.Eq. per litre in the human. Between these two fluid compartments there must be ionic, osmolar and acid-base balance, according to the Gibbs-Donan effect (50). There are three known isotopes of potassium present in the normal body and these have atomic weights of 39, 40 and 41. The chief isotope (atomic weight 39) constitutes 93% of the body potassium. Almost all of the remaining 7% has an atomic weight of 41. The isotope with an atomic weight of 40 is a natural radioactive isotope and seems to be of no importance (137).

Studies following the injection of radioactive isotopes have thrown light on the fate of potassium when injected into the body. The artifically radioactive isotope K^{42} is usually used (half life of 12.8 hours). Joseph, Cohn and Greenberg (80) found that the

isotope was largely absorbed from the bloodstream in the first half hour, that the portal of entry was the small bowel, that the liver uptake was early and marked, yet transitory and that the muscle uptake was slow over the first four hours, relatively stable for 22 hours and that after this time the isotope was slowly lost. Levitt and Gaudino (85) found that after injection, 75 - 80% of the final equilibrium was reached in 3 hours. During the first 24 hour period the urinary loss varied from 2 - 12% of the total isotope injected. Thus, this radioactive isotope leaves the extracellular fluid space rather rapidly. Noonan, Fenn and Haege (101) again found that the potassium uptake was good in the gastro-intestinal tract, liver, heart, kidney, lung, diaphragm, moderate in muscle and skin, and poor in the testes, erythrocytes and brain.

In a human the ingestion of 2 gm. of potassium chloride caused a serum potassium level of 6.3 M.Eq./L., 10 gm. resulted in a serum potassium level of 7.7 M.Eq./L. and 15 gm., a serum potassium level of 8.9 M.Eq./L. There were no symptoms but typical electrocardiographic changes were noted. The maximum increase was found in two hours and the change had disappeared by three and a half hours (160). Thus it may be seen that within these transitory

variations the serum potassium level remains relatively constant. Potassium Iodide will not cause an immediate rise in serum potassium as potassium chloride does and the rise will not be as marked but potassium acetate will cause a rise with as little as 2.5 gm. in diet (104). The 61% rise in the serum potassium level 2 hours after the ingestion of 12 gm. of potassium chloride has been confirmed by Norn (103). After the ingestion of these salts potassium is excreted quite rapidly in the urine, so that the value of potassium salts as diuretics is easily realized (1).

The efficiency of the body in disposing of potassium is best seen when potassium is administered intravenously. Such potassium rapidly disappears from the bloodstream, the rate of disappearance being proportional to the efficiency of the liver, gastro-intestinal tract and kidneys in absorbing or excreting this element (71) (72). In man it is safe to inject only 0.79 - 1.02 M.Eq. (3 - 4 mg.) per kilo of body weight (122) (116). This is less than 0.2% of the total of 641. M.Eq. of potassium present in one kilogram of body substance. However, with slower injection, over an hour or so, using isotonic potassium chloride solution the potassium content can be increased by 56 M.Eq./Kg.

or by about 9% of its normal content before the lethal level in serum of 15 M.Eq./L. is reached (103). Amberg and Helmholz (3) found that the toxicity of intravenously injected potassium chloride was much less when given with sodium chloride or glucose than when given alone. Potassium when injected intra-arterially causes a marked vasoconstriction but is actually less toxic than when given in the same concentration intravenously. In large doses, potassium will cause slowing of the heartrate, auriculo-ventricular block, fibrillation and finally death (90) (61) (69). These few facts are presented not only for their physiologic significance but also for therapeutic value in the correction of potassium deficiency states.

Probably the best indication of the state of potassium balance is the chemical analysis of muscle for potassium. Heppel (67) found that rats raised on a low potassium diet may lose up to half of their muscle potassium although their liver content remained normal. The potassium lost was replaced by sodium. In both man and rats on low salt diets the depletion of potassium was made more pronounced if a little sodium chloride was given. It was found that animals on low potassium diets required more sodium chloride than normal animals.

Darrow, Schwartz, Iannucci and Colville (37) have shown that high serum bicarbonate content and low serum chloride level invariably accompany low potassium content of muscle and the concomitant high sodium content of muscle whether the potassium deficiency be produced by diet, desoxycorticosterone acetate or the administration of large amounts of sodium salts. Low potassium and high sodium content of muscle has been found in acidosis and alkalosis by the chemical analysis of biopsies by Mudge (99). He also found that flaccid muscular paralysis was not invariable with low serum potassium and low intracellular potassium levels. Although the chemical analysis of muscle tissue for potassium will give the best indication, the state of potassium deficiency can also be shown by a study of the intake and excretion of potassium. The human body contains 0.11 - 0.35% potassium by weight according to various reports. Assuming an average of 0.25% which happens to be the same as the value found for the rat (68) (84) (87), a 70 Kg. man has 175 gm. of potassium in his body. Of this 175 gm. (45.385 M.Eq.), the blood will have 8 gm. (2051 M.Eq.), the plasma 300 mg. (77 M.Eq.) and the extracellular space 3 gm. (769 M.Eq.). The faeces contain on an average 300 mg. (77 M.Eq.) over a 24

hour period and the urine 3.1 gm. (795 M.Eq.) in the same period. As one would expect the average daily intake in this study was found to be 3.4 gm. (872 M.Eq.) of potassium because the subject was in potassium balance; i.e. 795 M.Eq. (urine) plus 77 M.Eq. (faeces) is equal to the dietary intake of 872 M.Eq. of potassium (123).

After fasting for six days the uring excretion of potassium drops to 1.08 gm. (279 M.Eq.) in 24 hours and after 30 day fasting to 0.6 gm. (154 M.Eq.). During these periods of fasting the nitrogen-potassium excretion ratio remains the same as the nitrogen-potassium ratio of muscle, which is 10. This is undoubtedly due to the unavoidable loss of potassium with nitrogen from endogenous metabolism due to a gradual destruction of cells. This could therefore give rise to a considerable error in potassium balance studies if there was any great degree of tissue breakdown for any reason. The error could be realized by analysis of the urine for nitrogen (43) (29) (40) (123).

Apparently the kidney plays a primary role in the production of potassium deficient states in humans. Studies made on patients with gastro-intestinal disorders with secondary potassium deficiency have shown

that although certain amounts of potassium may be lost through vomiting or diarrhea, the deficiency is really caused by excessive loss of potassium in the urine (138) (139). Under such conditions of maximum need for the conservation of potassium the renal tubules do not reabsorb potassium sufficiently to prevent excessive loss. Such patients with gastrointestinal disorders and "secondary" potassium deficiency show no impairment of renal function by the usual clinical kidney function tests. The mechanism of the failure of the kidneys to reabsorb potassium remains unknown and no feasible theories have been offered (139).

There is some evidence that a high content of potassium in the tissues is related to a rapid rate of growth. Rapidly growing tumors have been found to contain more potassium and less calcium than normal or even slowly growing tumors. However, with aging of the tumor the high potassium falls and the low calcium content rises (47). Carcinomata in humans have shown this same change and actually clinicians have advised low potassium diets in the treatment of such patients! It is more likely in these cases that the higher potassium concentration is a secondary rather than a primary effect (47).

The interelationship of potassium and sodium in the living body has been widely studied and certain concepts have changed as a result of recent studies. In summarizing one of these studies, Elkinton, Winkler and Danowski (44) state that (1) sodium unlike potassium can enter the serum from the cells even though the renal function is greatly impaired, (2) in contrast to potassium, large increases in cell sodium are not dependent upon the exogenous supply of this cation, (3) Exchanges of Potassium for sodium do occur; however this is not an invariable finding in any particular experimental procedure nor are the transfers when present of equivocal magnitude, (4) alterations in the osmotic activity of the cations of cells are not correlated closely with either the direction or the magnitude of the transfers of sodium or potassium, (5) Potassium leaves the cell in significant amounts only if it can be excreted; hypertonicity and cellular dehydration are frequent though not invariable findings in such cases, and (6) transfers of large amounts of potassium into cells have been observed only when exogenous potassium is available. These concepts have been supported by evidence from numerous studies by these same workers (43) and others (138) (139) (29).

It is easily seen then that potassium, along

with other cations and anions is essential in the maintenance of normal water balance, acid-base balance, osmotic equilibrium and muscle irritability, that it is the main intracellular cation yet is permeable to the cell membrane, that it exists in skeletal muscle in constant relationship to the nitrogen content and is unavoidably lost when nitrogen is lost, that in deficiencies, although one would expect the loss through other routes, potassium is lost in greatest quantity through the kidneys, that potassium is toxic only if given in excessive quantities and these excess quantities are excreted rapidly in the urine, and that in the normal animal the intake of potassium in the diet is balanced by the urinary excretion in addition to a small quantity of potassium lost in the faeces.

Potassium Metabolism - The Gastrointestinal Circulation

Potassium is excreted in considerable quantities in the various juices of the upper gastrointestinal tract and is reabsorbed through the small intestine. The total exchange is quite large; in humans an average of 321 M.Eq. circulates through the gastrointestinal tract in every twenty four hour period. By calculation all of the potassium in the plasma changes every six hours and an amount equivalent to the amount of potassium present in the serum at any one time is excreted through the kidneys

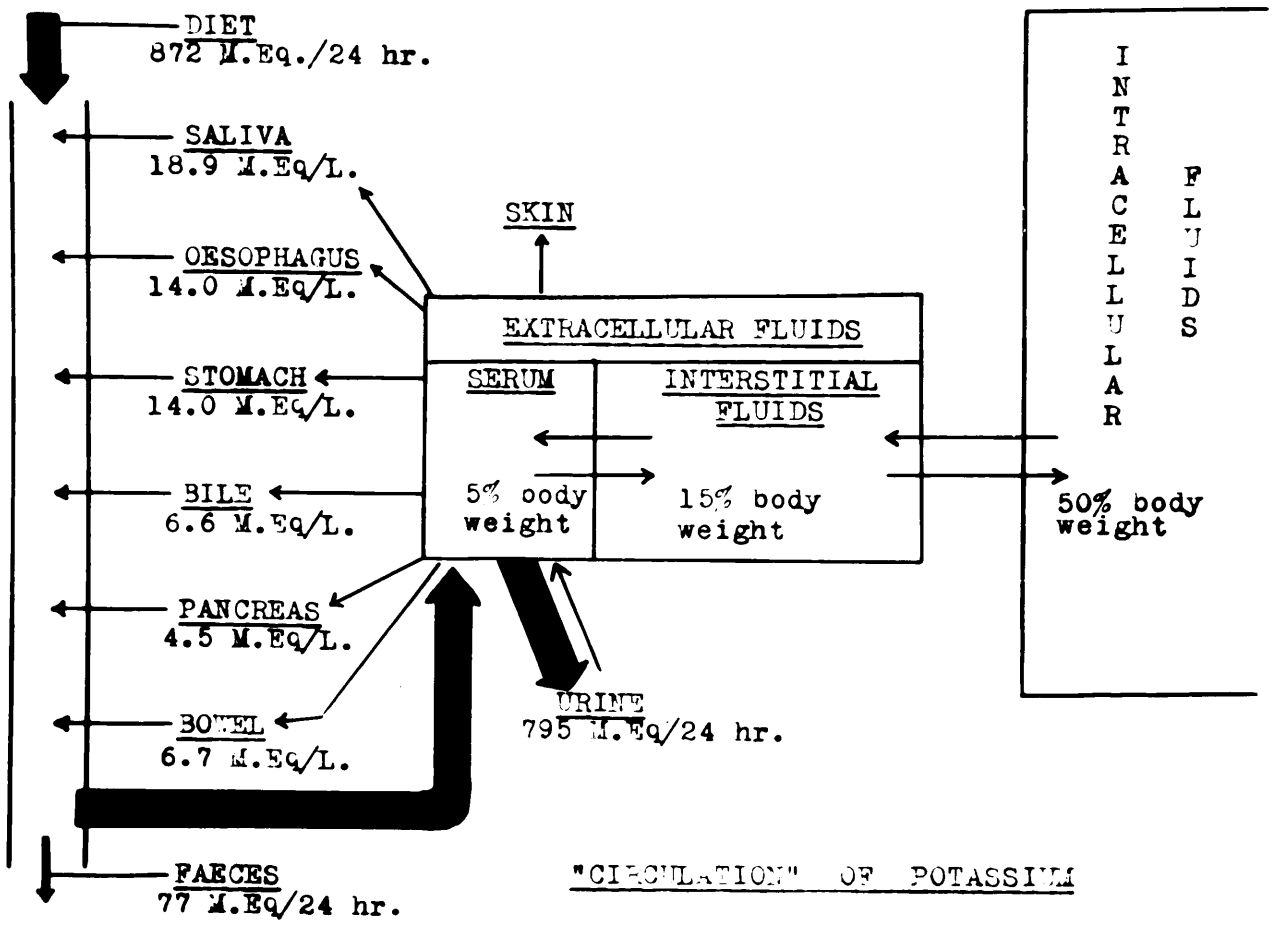


Illustration 1. CIRCULATION OF POTASSIUM

every 2½ hours (47). The circulation of potassium in the body is schematically represented in Illustration 1.

Normal human saliva contains 18.9 M.Eq./L. of potassium and appears to be in constant relationship to the amount of calcium in the ratio of 10:1 (154). Vineberg and Komarov (153) found that the concentration of potassium in the oesophageal secretions was 14.0 M.Eq./L. on an average. The average potassium content of the gastric juice according to Austin and Gammon (5) is the same as that of the oesophageal juice and is 14.0 M.Eq./L. The bile contains 6.6 M.Eq./L. of potassium on an average (110). The pancreatic juice contains 4.0 - 5.0 M.Eq./L. of potassium which is the same as the concentration in the serum. Curious, too, is the fact that after the injection of potassium chloride the increase of potassium in the pancreatic juice exactly imitates the increase in the serum potassium level (78). DeBeer, Johnston and Wilson (40) found the concentration of potassium in the pooled secretions of the jejunum, ileum and colon was 6.2 - 7.2 M.Eq./L.

Most of the potassium in the above secretions is reabsorbed through the small intestine. As stated before, only 77 M.Eq. of potassium is lost in the faeces over a 24 hour period so that by calculation more than

76% of the potassium in these secretions is reabsorbed. It is also easily seen that by either vomiting or by diarrhea fairly large quantities of potassium may be rapidly lost by way of the gastrointestinal tract. As stated before in such deficiencies the primary loss of potassium is through the kidneys, no matter how great the loss from the gastrointestinal tract. Another interesting point is the fact that the secretions of the upper gastrointestinal tract contain potassium in higher concentration than the blood serum with the exception of the pancreatic juice which contains the same amount.

CHAPTER 111

POTASSIUM DEFICIENCY IN DISEASES

The clinical condition which has received by far the most attention as far as potassium is concerned is Addison's Disease. Many excellent reviews have been published on the general treatment of this condition (144) (93) (150) (24) and on the specific treatment and management of such patients with desoxycorticosterone acetate (149) (92) (49) (147) (54) (162) (27). The syndrome is due to chronic adrenal cortical insufficiency which may be secondary to either adrenal tuberculosis or simple adrenal cortical atrophy. The predominant signs and symptoms are asthenia and fatigue, pigmentation of the skin and mucous membranes, anorexia, nausea and vomiting, loss of weight, hypotension and small heart, dizziness and syncopal attacks, decreased resistance to cold (hypometabolism), collapse with dehydration and circulatory failure. The diagnosis is made on the recognition of progressive asthenia, increasing pigmentation, loss of weight, gastrointestinal irritability, hypotension, decreased basal metabolic rate, a low 17-ketosteroid excretion in the urine, a positive Kempler-Power water test, a decrease in serum potassium level, hypoglycemia with a flat glucose

tolerance test and abnormal electro-cardiographic changes. As will be seen in a later chapter these changes are simulated by adrenalectomy in animals and correction of this state as well as that of the syndrome of Addison's Disease lies in replacement therapy by the administration of either aqueous extract of the adrenal cortex or synthetic desoxycorticosterone.

Of particular interest in the problem in this thesis is the report of a patient who received desoxycorticosterone acetate and developed tetany. In 1942, Moehlig and Jaffe (97) described a male patient who received desoxycorticosterone acetate for myesthenia gravis. On the occasion reported the patient received several pellets of the synthetic hormone and one pellet was accidentally crushed during the subcutaneous implantation. Within two weeks he developed tetany with Chvostek's and Trousseau's signs and paraesthesias. The serum calcium and phosphate levels remained normal and the serum potassium was low and the sodium level slightly increased. The weakness due to myesthenia gravis improved after the pellets were implanted but disappeared when the tetany developed. The signs of tetany persisted for two months. These same workers tried to reproduce these signs in dogs by the administration of

desoxycorticosterone acetate. These dogs developed diabetes insipidus-like signs of polydipsia and polyuria but showed no signs of neuromuscular hyperirritability. They found pituitary extract did not control these symptoms and believed the syndrome was due primarily to thirst because witholding fluids did not cause dehydration. Actual muscular weakness and polydipsia and polyuria were produced in only two of five dogs. They were unable to reproduce tetany in their dogs by the administration of desoxycorticosterone acetate as they had in their case of myesthenia gravis.

In spite of the fact that desoxycorticosterone acetate produces polydipsia and polyuria there seems to be no relationship between true Diabetes Insipidus in humans and potassium metabolism. However, gastric upsets have been described in cases of Diabetes Insipidus. Blotner (16) describes nausea, vomiting, heartburn, wretching and anorexia in such patients. He found that these patients secreted greater volumes of gastric juice which were more acid than normal and contained increased amounts of pepsin and renin. After the administration of pituitrin to these patients their symptoms improved and the findings in the gastric analyses returned to normal. No potassium determinations were done in this study. Mattei (91) has described non-specific treatment

of gastric upsets in cases of Diabetes Insipidus.

Another clinical condition that has been studied with regard to potassium metabolism is familial periodic paralysis. In a rather complete review of the literature on this disease, Talbot (136) stated that there was always a decrease in the potassium concentration in the extracellular fluid during attacks of paralysis and an associated decrease in the amount of potassium excreted in the urine without any evidence that the extracellular volume had expanded. Therefore the potassium from the extracellular fluid must pass into the intracellular spaces. This has been confirmed by Danowski, Elkinton, Burrows and Winkler (33) who studied the sodium, potassium and water exchanges in two patients with familial periodic paralysis. They found that during attacks there was a sharp decline in the extracellular potassium and that during recovery large amounts of administered potassium were taken up by the intracellular fluids before the extracellular potassium was replentished. No significant changes were found in the volumes of the total body water and extracellular fluid, and concluded that the diminution in the extracellular potassium was responsible for the attacks of paralysis.

Potassium deficiency has been observed in two patients with chronic nephritis by Brown, Currens, and Marchand (18). These patients developed a flaccid paralysis similar to the paralysis seen in cases of familial periodic paralysis, low serum potassium levels and electrocardiographic changes characteristic of potassium deficiency. They felt that the glomerular filtration of potassium was probably normal but the defect lay in the impaired tubular reabsorption although they were unable to present supporting evidence for this concept. Sherry, Eichna, and Earle (124) described another case of chronic nephritis with the low potassium syndrome. They were unable to bring the serum potassium level back to normal by the prolonged daily administration of 25 gm. of potassium chloride by mouth but when this salt was given intravenously the serum potassium level soon rose and slow steady improvement in muscle strength began several hours later.

Patients recovering from diabetic acidosis or coma retain considerable amounts of administered potassium as well as water, sodium, chloride, carbohydrate and nitrogen (34). In every patient studied potassium was found to enter the cells far in excess of the amounts which could be ascribed to changes in cell protein.

Here again, the study of potassium metabolism is important in clinical practice for, although orally administered potassium salts are usually harmless to normal individuals, patients recovering from diabetic acidosis or coma may develop potassium intoxication from this treatment. In this regard one interesting biochemical problem arises. It is known that when the liver stores glycogen, the potassium content of the liver is raised. The mechanism of this uptake of potassium by the liver is not known; the potassium may be bound to glycogen or may be contained in the water which enters the liver cells along with glycogen. If for any reason glycogen is liberated from the liver, potassium too may enter the extracellular fluids and so the danger of potassium intoxication arises. Other conditions in which potassium metabolism has been studied and found important include diseases of allergy, obesity, Meniere's disease, hypertension, diarrhea (155) cardiac disease and certain surgical conditions to be described (32) (137).

The importance of potassium in parenteral therapy has been realized only recently following carefully controlled electrolyte balance studies. Elman, Lemmer, Weichselbaum, Owen and Yore (45) have recently reported a study of forty surgical patients while on

complete parenteral therapy for the first four post-operative days. They found that in most cases a total volume of 2000 c.c. of intravenous fluid was adequate and resulted in a urinary output of 1000 c.c. daily which was considered sufficient. Parenteral fluids without electrolytes resulted in a loss from the body of potassium and phosphate but to a lesser extent sodium and chloride ions. When patients were given 9 gm. of salt a day there was a lag in the secretion of sodium chloride so that of the 36 gm. over the four day period an average of 14 gm. was retained. However the loss of potassium was still the same. They concluded that adequate electrolytes were provided by 4 gm. of sodium or potassium gluconate in 2000 c.c. a day. In calculating the potassium nitrogen excretion ratio it was found that only part of the potassium loss resulted from the breakdown of tissue protoplasm. Randall, Habif, Lockwood and Werner (109) studied surgical patients who received intravenous fluids for three days preoperatively and four days postoperatively; some were given the usual solutions while others received 50 M.Eq. of potassium daily. They found that with no potassium the serum potassium always fell to levels below normal. With potassium therapy they found no drop in the serum potassium level except

on the operative day. These patients were in positive potassium balance for the whole period.

Blixenkrone-Moller (15) stated that blood loss at the time of any operation always results in some loss of potassium and that tissue damage usually causes a similar loss. He believes that in cases of mild dehydration the proper replacement of fluid does not result in potassium loss but if more than the necessary amount of fluid is given potassium salts should be added to the intravenous solutions. These observations have been suggested by earlier studies (46) but their importance has not been realized. In this latter study, Falconer, Osterberg and Bargen (46) suggested the use of potassium in all intravenous fluids because even in normal individuals an intravenous of saline only will decrease the level of serum potassium. They showed that potassium may be lost in diarrhea, vomiting or suction of juices from the gastrointestinal tract and this loss was always exaggerated by intravenous sodium chloride solution. Burnett, Burrows, and Commons (19) studied alkalosis in five patients who had duodenal ulcers with pyloric obstruction and severe vomiting. They found that severe depression of renal function usually occurs during alkalotic episodes regardless of

whether the patient suffered from previous renal insufficiency or not. This attack of renal impairment resulted in a depletion of body water, sodium, chloride and potassium. Of course alkalosis does not necessarily accompany potassium deficiency due to loss of gastric juice.

Of practical importance is the method of administration of potassium to patients requiring such therapy. When the salt can be taken by mouth no problem arises for fairly large quantities (5-10 gms a day) may be given quite safely providing the kidney function is known to be adequate and the patient is not recovering from diabetic acidosis (34). A child with potassium deficiency due to diarrhea tolerated up to 3.8 M.Eq. in every 1,000 c.c. of intravenous fluid when the tolerance was measured by the electrocardiogram (155). One may give 3.5 M.Eq./kgm. of body weight / day over a period of more than 6 hours parenterally to adults but this should not be given faster than 20 M.Eq. / hour (139). In summary, Howard and Carey (73) recommend the oral administration of potassium in solutions of 40-80 M.Eq. of potassium chloride per litre (3-6 gm. of KCl) which may be given in 50-100 c.c. amounts with or without fruit juices. Parenterally, solutions of KCl

containing 40-90 M.Eq./L. at rates not greater than 180 drops (12 cc.) per minute; usually 120 drops (8 c.c.) per minute. Electrocardiographic control is recommended. An adaptation mechanism has been demonstrated by Thatcher and Radike (141). They found that by progressively increasing the amount of potassium chloride given by mouth, the animal was able to adapt more readily and the serum potassium rose less readily in response to the intake. Further, adrenal cortical extract and desoxycorticosterone acetate were found to produce an increased resistance in the animal to the ingestion of potassium salts. The mechanism was not fully investigated in this study; it was not shown whether the kidneys became more efficient in excreting potassium or whether the muscle cells or liver increased their intake more readily.

In summary, the role of potassium has been investigated in many physiological and pathological states. Potassium has been studied in relation to electrolyte balance, radioactive tracers, dietary needs, toxicity, in growth, muscle contraction, neuromuscular transmission, in asphyxia, haemorrhage, shock, carbohydrate metabolism, central nervous system function, water balance, and in relation to adrenocortical function. Clinical studies

have been made in hypertension, edema, Addison's disease, obesity, diabetic acidosis and coma, dermatitis, familial periodic paralysis, Menières disease, infantile diarrhea, pernicious vomiting, colitis, intestinal obstruction and cases of alkalosis. Although much is known there are many questions left unanswered and further study in every field will be required.

CHAPTER 1V

STUDIES ON EXPERIMENTAL POTASSIUM DEFICIENCY

Relationship to Endocrine System.

Of most importance, is the relationship of potassium metabolism to the adrenal cortex. The adrenal cortex produces a hormone "Cortin" found in adrenal cortical extract which will maintain animals in normal state after adrenalectomy. A synthetic substitute has been found, desoxycorticosterone, which will have the same effect. Both of these substances, as mentioned before, are used in the "replacement" treatment of cases of hypoadrenalcorticism such as Addison's Disease.

Adrenalectomy will cause an increase in the urinary excretion of sodium, chloride and water, a decreased excretion of potassium, a rise in the level of serum potassium, a decrease in the level of serum sodium and chloride, haemoconcentration, dehydration, circulatory collapse, coma and death. The administration of adrenal cortical extract or desoxycorticosterone will prevent this syndrome. If desoxycorticosterone is given to normal animals, the body will retain sodium, chloride and water and a diuresis of potassium occurs (146). Incidentally, desoxycorticosterone acetate was first

prepared from stigmasterol by Steiger and Richstein and has the formula delta-4-pregnene-21-ol-3, 20-dione acetate, 21-acetoxy-progesterone (146). Darrow, Harrison and Taffel (35) studied the tissue electrolytes after adrenalectomy and found an increase in intracellular water and no change in the cellular concentration of potassium in skeletal muscle, heart, liver or kidney. An increase in intracellular water was not found in cardiac muscle. However the concentration of potassium in skeletal muscle was found to be raised in terminal adrenal insufficiency and in total nephrectomy. However, Miller and Darrow (95), showed that the intracellular concentration of sodium was inversely proportional to the concentration of potassium and that administration of desoxycorticosterone acetate may cause a fall in the amount of intracellular potassium and a rise in intracellular sodium. After the injection of potassium chloride, any rise in concentration of potassium in muscle cells is always transitory.

Prolonged administration of desoxycorticosterone acetate to normal dogs will produce polydipsia, polyuria and depletion of intracellular potassium. Tbese "toxic" effects of desoxycorticosterone esters were studied by Kuhlman, Ragan, Ferrebee and Atchley (83) as early as

1939 because some patients with Addison's disease were observed to develop signs of cardiac failure on prolonged administration. They gave dogs 20-25 mg. of desoxycorticosterone acetate daily for long periods and found that the level of serum potassium soon dropped, the level of serum sodium rose slightly and the levels of serum protein and non-protein nitrogen dropped slightly. Later a curious periodic paralysis developed which could be cured by 1 gm. of potassium chloride in a 2% solution intravenously daily. It was periodic because it appeared several hours after meals but cleared in 8-10 hours. All dogs developed the diabetes insipidus-like symptoms of polyuria and polydipsia and curiously the administration of potassium chloride increased this effect. Chest radiographs showed no increase in cardiac size but electrocardiograms revealed irregular variations in the T waves. All of these signs disappeared when the administration of desoxycorticosterone acetate was discontinued.

This study was followed by another a year later by Ragan, Ferrebee, Phyfe, Atchley and Loeb (108). They confirmed the previously made observations that in 6 weeks dogs would increase their water exchange from 400 to 1,000 c.c. daily on the daily administration of 25 mg. of desoxycorticosterone acetate. They found

that sodium was not retained but the level of serum sodium was raised. Sodium chloride by mouth increased the severity of the symptoms and caused the animal to develop muscular weakness. Potassium chloride by mouth was followed by a rise in the specific gravity of the urine but little further change. Pitressin was given and this caused a slight decrease in the exchanges of fluids with a slight decrease in the level of serum sodium. Within 7 days of the withdrawal of desoxycorticosterone acetate, the water exchanges returned to normal. They concluded that this polydipsia and polyuria was not true diabetes insipidus because pituitrin was ineffective in controlling the symptoms and because fluid restriction did not result in dehydration in these dogs. They believed the polyuria was secondary to the polydipsia and suggested the polydipsia might be a result of the increase in extracellular sodium or a disturbed osmolar balance between the extracellular and intracellular fluid spaces. It may be that the polyuria enables a normal dog to avoid the retention of sodium by an increased flow of urine through the renal tubules and so counteract the increased sodium absorption caused by desoxycorticosterone acetate.

Mulinos, Spingarn and Lojkin (100) repeated

these experiments and in general confirmed the above observations. They found in addition that the speed of onset and intensity of the diabetes insipidus-like signs were proportional to the dose of desoxycorticosterone acetate and to the salt intake. Water by mouth was eliminated more rapidly than normal but not in greater quantity whereas saline was eliminated both more rapidly and in greater quantity. Large doses of pitressin in oil reduced the water intake, and the urine volume, raised the specific gravity and the chloride concentration. However, the prolonged administration of desoxycorticosterone acetate produced no weakness or paralysis in their animals.

Another study was made by Ferrebee, Parker, Carnes, Gerity, Atchley and Loeb again in 1941 (48). They reviewed the shole problem and made further observations on the electrolyte changes in skeletal muscle and serum. They found that the typical paralysis was invariably accompanied by a replacement of intracellular potassium by sodium. Symptoms of polydipsia and polyuria were consistantly associated with an elevation of serum sodium level. Potassium chloride by mouth could prevent paralysis and the associated replacement of intracellular potassium by sodium but would not affect

either the symptoms of polydipsia and polyuria or the elevated serum sodium level. It would then seem that the diabetes insipidus-like symptoms are associated with the elevated level of serum sodium and the muscular weakness with the lowered level of intracellular potassium.

In 1929, Teel (140) observed a diuresis in dogs from a neutralized alkaline extract of the anterior hypophysis but further work has disproved any such effect; it is probable that the effect was brought about by the inclusion in his extract of contaminating substances from the posterior lobe of the pituitary which have been shown to cause polyuria. The posterior pituitary, however, is linked to the clinical condition of diabetes insipidus because pitressin will relieve the symptoms of polydipsia and polyuria. As stated before pitressin fails to relieve the symptoms of polydipsia and polyuria produced by the prolonged administration of desoxycorticosterone acetate. Silvette and Britton (126) (127) first advanced the theory that diabetes insipidus was caused by a hormonal imbalance - a pathologic preponderance of the diuretic effect of the adrenal cortical hormone over the antidiuretic effect of the posterior pituitary hormone, pitressin. They offered no direct supporting evidence apart from the facts that pitressin relieved

the symptoms of true diabetes insipidus and that adrenal cortical extract produced diabetes insipidus-like symptoms in normal opossums. Opossums were used because of the ease in passing a catheter and collecting the total urinary secretion. In 1941, Britton and Corey (17) confirmed this latter study and substituted desoxycorticosterone acetate for adrenal cortical extract; hypophysectomized and adrenalectomized rats were substituted for the opossums. Winter and Ingram (164) in 1943 supported these studies using dogs. However, they showed that although polydipsia and polyuria was marked on the prolonged administration of desoxycorticosterone acetate, these signs were not relieved by the administration of pitressin. That the syndrome is related to both adrenal cortical and posterior pituitary function is beyond doubt; however, this relationship is not clear cut and the pathogenesis of the syndrome remains unknown.

An interesting study has been made on the effect of gastric secretion in hypoadrenalcorticism produced in rats by adrenalectomy. Tuerkischer and Wertheimer (151) showed that adrenalectomized rats had neutral gastric juice and that the volume, acidity (both free and total acids) and enzyme content were

diminished on stimulation with "Doryl". The mucin concentration was increased. They further showed that neither adrenal medullectomy alone, shock produced by either narcosis and laparotomy or ether anaesthesia and fracture of a femur, nor desoxycorticosterone acetate and added salt mixtures in the diet would restore the gastric secretions to normal. Adrenal cortical extract did restore the normal gastric secretions.

Relationship to Other Systems in the Body

It has been shows that desoxycorticosterone acetate in prolonged administration would produce cardiac dilatation and circulatory failure in humans, polydipsia and polyuria with signs of potassium deficiency in dogs but Carnes, Ragan, Ferrebee and O'Neil (23) found no signs of toxicity in the albino rat. They found the adrenals were smaller, occasionally the testes and pituitarys were smaller but no other significant changes. Darrow and Miller (36) however have produced the signs of polydipsia and polyuria in rats by both desoxycorticosterone acetate alone and by a potassium deficient diet. They were able to demonstrate myocardial fibrosis in potassium deficient rats and offered this as a reason for the findings of edema, cardiac failure and increase in volume of the extracellular fluids in patients with Addison's Disease under treatment by

desoxycorticosterone acetate. The rats on a low potassium diet alone showed only a slight drop in the serum potassium level in spite of a moderate reduction in the concentration of potassium in the cells of skeletal muscle. The concentration of potassium in liver tissue remained unchanged.

Numerous observations on the effect of potassium deficiency on various tissues and functions of the various systems in the body have been made and no attempt is made to review all such reports. Suffice to report here certain interesting studies; others will be reviewed in later sections on the pathology of potassium deficiency and relationship of potassium deficiency to gastric secretions. For more detailed consideration of the effect of potassium deficiency or intoxication on various systems, the review by W. O. Fenn (47) is suggested.

Bisgaard, McIntyre and Osheroff (13) have studied the electrolyte balance in patients with various conditions of surgical importance. They found that with adrenalin and ether anaesthesia there were transient variations in the level of serum potassium, in traumatic shock there were no consistant changes in electrolyte balance, and in high intestinal obstruction there were no consistant changes in sodium and potassium but there

was an invariable lowering in the concentration of serum chlorides. They were unable to present any evidence that potassium contributed to the production of either symptoms or death. This last observation has since been refuted in studies by Bellet, Nodler, Gazes and Lanning (11). These workers found in all of 15 patients with protracted vomiting a low level of serum potassium which was made worse by the intravenous administration of glucose and saline solutions. These patients showed typical electrocardiographic changes of potassium deficiency and their clinical condition improved markedly on the administration of potassium. Intracellular potassium stores in these patients was believed depleted because of a relatively small rise of serum potassium level shortly after the injection of moderately large doses of potassium chloride. It seems only reasonable that patients with loss of even moderate quantities of the gastrointestinal secretions, be it by vomiting, diarrhea, Wangensteen suction or intestinal fistulae, will develop relative potassium deficiencies since all of these juices are known to contain significant amounts of potassium and will certainly do so if the dietary intake is low or impeded. Early deficiencies have not been recognised

because, apart from electrocardiographic and biochemical studies, there are no warning signs or symptoms. When general weakness and muscular paralysis develop the deficiency is marked indeed. Other effects have been shown by Henrickson (66) who has demonstrated a decrease in mobility of the smooth muscle of the gastrointestinal tract, a dilatation of mesenteric vessels, distension of the small and large bowel and, at postmortem, ascites and associated hydrothorax in rats in the potassium deficient state.

As far as the skeletal muscular system is concerned, few studies have been made. It is known that the paralysis of potassium deficiency is identical with that in familial periodic paralysis. Dogs on deficiency diets develop the paralytic picture with the same type of periodicity - that is, at first it occurs after heavy meals (in humans at night, in animals during the day if fed in the morning) but later becomes constant and progresses until the animal dies usually due to respiratory failure. Baetzer (8) showed that if the blood supply to a limb was reduced so that less than 80% of the blood returned, the serum potassium level rose and this was thought to be due to loss from the intracellular potassium stores in the limb. However this loss caused

no loss of muscle irritability but, as one would expect, some loss of motor power. Similarly after a fracture of a bone in the limb a loss of potassium occurs and again it is in proportion to the nitrogen loss in a fixed ratio and is probably due to endogenous metabolism (31).

Potassium appears essential in neuromuscular transmission and so affects muscle irritability. Neuromuscular irritability is apparently directly proportional to the ionic concentration of sodium and potassium and inversely proportional to the ionic concentration of calcium, magnesium and hydrogen ions (40). An increase in both potassium and acetylcholine has been found in venous blood draining from a stimulated muscle. Potassium is not believed to be a "neurohumor" although when applied to nerve trunks it has produced a motor impulse, and even tetanus-like contractions when applied directly to the nerve end-plate (47). These findings might shed light on the mechanism thereby paralytic attacks in familial periodic paralysis are relieved by the administration of potassium. The injection of potassium chloride has been shown to liberate acetylcholine in the superior cervical ganglion, the salivary gland, the tongue, the heart and in the placenta. However the increase in excitability at the neuromuscular junction

may result from the potentiating effect of potassium chloride on acetylcholine and from the inhibiting effect on cholinesterase as reported by Altamirans and Huidubro (47). Whatever the mechanism, potassium is closely associated with acetylcholine at the neuromuscular junction and a loss of potassium impairs neuromuscular transmission and so decreases excitability, irritability and power.

The toxic effects of excessive amounts of potassium on heart function are well known. Briefly, excessive amounts of potassium, unlike calcium, will progressively prolong the diastolic phase of the cardiac cycle until there is cardiac arrest in the relaxed state - the so-called potassium inhibition (12). However little is known of the changes in heart function in potassium deficiency apart from pathological changes and the effect on the electrocardiogram. In potassium deficiency there is a scattered patchy necrosis of myocardial cells. Healing takes place by fibrous tissue replacement in the dead areas (131).

Winkler, Hoff and Smith (163) showed that the changes in the electrocardiogram after the injection of potassium chloride intravenously were simply the reverse of the changes in potassium deficiency. They

further showed that potassium deficiency causes cardiac arrest in systole and that potassium affects both the myocardium in increasing relaxation and the conducting bundles by causing intraventricular blockage.

Electrocardiographic changes are well known and are described in standard texts (117) (57). In potassium deficiency, the T wave which normally is at least 1 - 2 millivolts in leads I and II is weaker and the QT duration which is normally $\frac{1}{4}$ - $\frac{1}{2}$ second may remain normal or be slightly prolonged. T waves may become inverted and show an increase in strength up to 6 millivolts. Incidentally, the only other circumstance which will show low T waves is a case in which the whole P Q R S complex is low or isoelectric (57). The progressive effects in potassium deficiency are characteristically a prolonged Q T interval, lowering of the T wave, sagging of the S T segment and finally depression of the S T segment (32). The changes in the various phases of the electrocardiogram in potassium deficiency and intoxication are shown in Illustrations 2 and 3.

Relationship to Water and Acid-Base Balance.

Only a very brief outline of water and acid-base balance will be attempted. There would be little to be gained here from a detailed review of the many

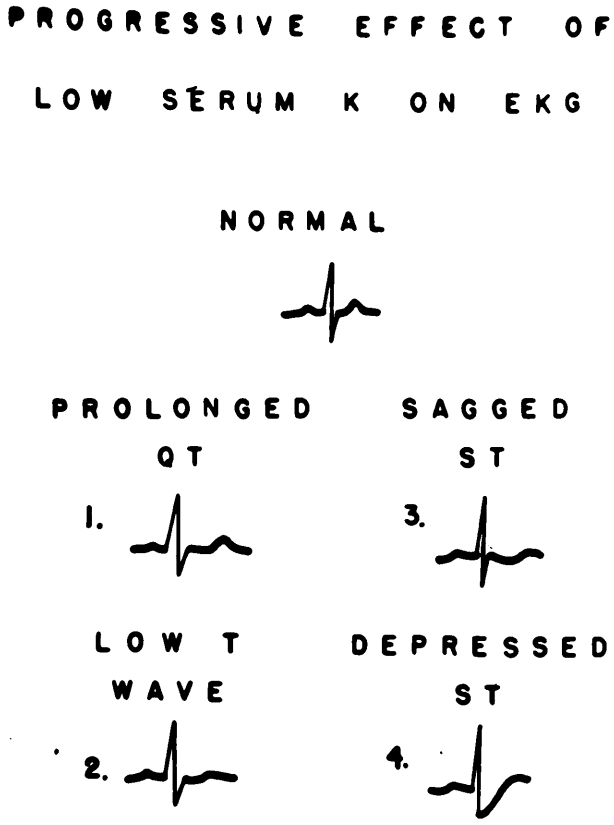


FIGURE 1

Illustration 2. ELECTROCARDIOGRAPHIC CHANGES

ELECTROCARDIOGHRAPHIC CHANGES

	Potassium Deficiency	Potassium Intoxication
Rhythm	Heart Block	Nodal Rhythm Conduction Defects
Rate	May be increased	May oe decreased
P wave	0	0
PR interval	May be prolonged	may oe prolonged
QRS wave	Voltage may be reduced May be prolonged	Voltage may be reduced Branch block possibly
ST segment	May become depressed	May become depressed
T wave	Usually lowered	May be taller, lower or inverted
QT duration	0	May be prolonged

Illustration 3. ELECTROCARDIOGRAPHIC CHANGES

intensive studies (52) (40) (12) from which this information is culled, but terms to be used must be defined and certain concepts should be outlined.

The units of measurement of the osmotic pressure and ionic concentration of body fluids are the milliosmole and the millequivalent. The osmotic pressure of a solution is the sum of the concentrations of all of the molecules or ions in solution as each of these exerts a pressure. Valency is disregarded because a divalent or trivalent ion exerts the same osmotic pressure as a monovalent ion. The unit of osmotic pressure is the milliosmole which is found by dividing the concentration of the molecule or ion in milligrams per litre of solution by its atomic weight.

The components of the body fluids must be expressed in terms of their chemical equivalence so that their relative magnitude and relationships may be easily seen. Therefore, the ionic concentrations are expressed in milliequivalents per unit of volume (1 litre) and this is found by dividing the concentration of the molecule or ion in milligrams per litre of solution by its atomic weight and multiplying the result by the valency. Thus the ionic concentration value in milliequivalents is equal to the value of the osmotic

presure in milliosmoles if the latter is multiplied by the valance of the molecule or ion in question. There are an equal number of cations and anions in the serum and these are listed below (52).

Cations	Value	Anions	Value
Sodium	142	Chloride	103
Potassium	5	Bicarbonate	28
Calcium	5	Phosphate	2
		Protein	16
Magnesium	3	Sulphate and organic acids	6

Total base = 155 M.Eq./L Total Acid 155 M.Eq./L.

The distribution of water and electrolytes in the various compartments of the body is dependent upon "semipermeable membranes", so-called because not all ions can pass through these membranes and those that cannot, exert an osmotic pressure in proportion to their concentration. Water can diffuse freely and by so doing always attempts to maintain a balance of osmotic pressures. The cellular membrane is relatively impermeable to sodium and chloride ions which are the main ions of the extracellular fluids, along with bicarbonate ions. The main intracellular ions and molecules are potassium, proteinates and phosphates. The osmotic concentration of body fluids is approximately 310 milliosmoles.

The input and output of fluids in the adult human may be outlined as in the following table.

Intake		Output		
Fluid drunk	1,200	Kidney	1,500	
"Food" water	1,000	Skin	500	(constant)
Water of oxidation	300	Lungs	350	
		Sweat	50	(inconstant)
		Faeces	150	(inconstant)
			2,500	cc/24 hrs.

Under normal conditions 20% of the body weight is extracellular fluid (5% serum and 15% interstitial fluid) and 50% intracellular fluid. However, this is a dynamic equilibrium because water and electrolytes are taken in periodically but excreted continuously. The plasma volume and concentration must obviously remain relatively constant and normally the intracellular fluid volume and composition remain the same so that the expendable fraction of the body fluid is the interstitial fluid. Therefore water exchanges are essentially changes in the interstitial fluid phase. The changes in the extracellular fluid phase are reflected in the concentration of sodium and chloride ions, and changes in intracellular fluid volume are reflected by changes in potassium excretion and to a lesser extent by changes in nitrogen balance.

Changes in body weight during short periods of time are due to changes in body water content. If this change were due to changes in the extracellular fluid phase, the change will parallel changes in the ionic concentration of sodium in the serum. If the weight loss were proportionally greater than the sodium loss then not all of the water loss could come from the extracellular fluid space but some must come from the intracellular fluids and these should be reflected by an increase in concentration of intracellular potassium and nitrogen presupposing that the concentration of these substances was known to be normal before the change in weight. If the weight loss was proportionally less than the sodium loss then one might assume that some of the water has shifted to other fluid compartments, i.e. that water has moved into the intracellular spaces and again the concentrations of intracellular potassium and nitrogen would be changed; in this case, lowered.

The aim of fluid replacement therapy is to provide not only the amount of fluid required but also the ions lost in their proper concentration depending upon the primary condition. Because sodium is the main extracellular cation intravenous saline will tend to remain in the extracellular fluid space and if

renal function is impaired will lead to edema. When cells require fluid they may gain water from the extracellular fluids by osmosis, by the consumption of protein and by the release of potassium which can be rapidly eliminated in the urine. Intracellularly, 3 gm. of water is associated with each gm. of protein and 6 gm. of water is associated with each millequivalent of potassium.

The gastrointestinal secretions are isotonic with the blood serum but vary in the ionic concentration of sodium, chloride, bicarbonate and potassium. Loss of these secretions can cause acid-base imbalance, for example alkalosis may result from vomiting and acidosis from diarrhea. By the release of potassium, base can be lost from the body so that in cases of alkalosis, besides the loss of potassium in the gastrointestinal secretions, potassium may also be lost in the urine in an attempt to correct the acid-base imbalance. In acidosis too, potassium is lost from the cells and is replaced by sodium (37). In these cases of acidosis due to diarrhea potassium is lost in the stool and this loss tends to aggravate the acidosis. In treating diarrhea with acidosis, it is easy to see that besides providing water and cations by intravenous sodium chloride or better, sodium lactate solution, one

must remember that in all probability a relative potassium deficiency coexists and should be treated by the administration of potassium chloride either by mouth, intravenously or subcutaneously. One other fact should be restated - not all the intracellular potassium is ionized and therefore not osmotically active for it has been shown that some potassium exists intracellularly bound to protein in a characteristic ratio to cell nitrogen (62) (40).

Pathological Changes in Potassium Deficiency

The pathological changes in potassium deficiency have been studied by several groups of works but no complete report on the pathological changes in dogs has been published except a short description by Smith, Black-Shaffer and Lasater (131).

One of the earliest reports of the pathological changes in potassium deficiency appeared in 1939 by Schrader, Prickett and Salmon (119). In potassium deficiency, their rats became lethargic, comatose and finally died. Hydrothorax and ascites were usually found and in some, the body tissues generally were edematous. The bowel was found dilated, "atonic" and edematous, the lower jejunum and ileum showing the most marked changes. Thickened annular areas were found in the region of Peyer's patches and this gave a

beaded appearance to the bowel. These areas were congested but the thinned intervening areas were pale. More than half of their rats had intussusceptions, and the mesenteric lymph nodes were enlarged. The kidneys were large and pale, the pancreas edematous.

Microscopically, Schrader et al. (119) found these thickened portions of the bowel were areas of intense congestion and edema. There were numerous lymphocytes and phogocytes found in distended mucosal villi and occasionally they found the mucosa ulcerated over the villi with passage into the lumen of lymphocytes and phagocytic cells. In the intervening tissues the submucosa was edematous and thickened but the mucosa thin and atrophic. In the heart endocardial erosions were found. The acinae of the pancreas were edematous and dissociated with a degree of cloudy swelling. Similar changes were found in the adrenals, kidneys and liver. One wonders, however, if all of these changes were due to potassium deficiency because in the following reports not all of these findings are confirmed. These findings might well be complicated by a vitamin deficiency. It may be of interest to note that whereas the potassium deficient rats became lethargic and comatosed before death, rats in magnesium deficiency became hyperirritable and actually developed

tonic and clonic convulsive movements before death. As will be seen it is reasonable to suppose that magnesium as well as potassium may be lost from the body with continuous loss of gastric juice (119).

In 1940, Miller and Darrow (95) described the pathological changes in rats dying in 22 days in potassium deficiency due to low potassium diet. Again, these animals had marked edema of all organs and frequently had hydrothorax, ascites, diarrhea and intussusceptions. Further, changes in the heart and kidneys were observed by Follis, Orent-Keiles, and McCollum (51). In the myocardium, necrosis with scars were found and in the kidney, the tubular epithelium was necrotic with evidence of regeneration and tubular dilatation but the mechanism of the latter changes was not shown.

Kornberg and Endicott (81) confirmed the findings of Miller and Darrow and Follis et al and added two observations. They demonstrated splenic congestion in most animals and urinary casts in many but the raison d'etre of these changes was unexplained. Recently Smith, Black-Schaffer and Lasater (131) reviewed the findings in potassium deficiency and described myocardial necrosis with healing by fibrosis and renal tubular dilatation. They further described a sticky character of the animal's fur, a finding they

thought due to atrophy of sebaceous glands which they felt they demonstrated adequately in histologic study of the rats tail and which they felt was due to an unknown vitamin B complex deficiency.

As stated before, the only pathological studies on dogs to date was reported by Smith, Black-Schaffer and Lasater (131). These workers found no lesions in the thoracic or abdominal viscera ascribable to potassium deficiency. However, they demonstrated Zenker's waxy degeneration in skeletal muscle characterized by loss of striations, disruption of sarcoplasm, invasion by macrophages and evidence of regeneration on the part of skeletal muscle cells. These findings appear irreversible and consequently are not entirely responsible for the paralysis due to potassium deficiency which is more or less completely reversible. Although other muscle cells appear histologically normal, they are functionally impaired in the potassium deficiency state.

Relationship of Potassium Deficiency to Gastric Secretion

In 1824, W. Prout (107) wrote "On the Nature of the Acid and Saline Matters Usually Existing in the Stomach of Animals" and first reported the demonstration of hydrochloric acid in gastric juice. Dunglinson

and Emmett as reported by Beaumont (10) in 1833 were the first to show the presence in gastric juice of the cations sodium, magnesium, calcium and potassium. During the following century, in contrast to the great advances in the study of the physiology of gastric secretion by Pavlov, Babkin, Wolf and Wolf and others, little actual progress was made in the biochemical study of the gastric juice. However, towards the end of this period, Rosemann (112) in 1920 reported a study of the ionic content of gastric juice and was able to show a relative constancy in the content of potassium in the normal juice.

In 1930, Bliss (14) found that potassium in the fasting human gastric secretion was 21 - 28% of the total base whereas in the dog potassium accounted for only 10% of the total base in the secretions from a Pavlov pouch. On stimulation the potassium curves and variations were small. They enunciated the oft quoted statement that the concentration of potassium in the gastric juice is 3 to 5 times greater than in the blood serum. A year later Austin and Gammon (5) found the average secretion of potassium in the gastric juice was 14.0 M.Eq./L. They further found that the secretion of potassium was relatively very constant and unlike sodium, does not

vary with the acidity of the juice. Actually, the sodium content of the gastric juice is inversely proportional to the concentration of hydrochloric acid (7). These observations were confirmed by Ingram and Visscher (76) who also demonstrated that there was an inverse concentration ratio for sodium and potassium in gastric juice and blood serum. Actually, the ratio of gastric juice to blood plasma for sodium content was 0.64 and for potassium content 2.33. This was also shown by Smotrov and Vasilien (137) and in part by Rudd (113) (114), Takata (135), and Gamble and McIver (53).

Gray and Bucher (56) studied the differences in secretion of the parietal and non-parietal (mucus) components of the gastric secretion. They were able to show that the non-parietal juice (or mucus) is secreted at a slow and constant rate whereas the parietal or acid juice is secreted at widely varying rates depending upon the stimulation used. However, as seen by previous workers, the rate of secretion of potassium remains uniquely constant in both the parietal and non-parietal components of the gastric juice.

Few other studies have been made of the potassium content of the gastric secretion which have any bearing on the problem at hand. However, one study

of incidental interest only might be mentioned. It has been shown that the calcium content of malignant tissue is low and the concentration of potassium is high. Dunham and Brunschwig (41) studied the calcium and potassium content of gastric secretions from patients with normal stomachs and others with carcinoma of the stomach and compared these observations with the mineral content of the mucosa and tumor tissue. They concluded that the mineral content of the secretions did not reflect the mineral content of the mucosa. They again confirmed the fact that the calcium content was low and the potassium high in malignant growths of the stomach.

Methods of Producing Potassium Deficiency

There are three methods available to produce potassium deficiency which lend themselves to investigative work. These are by either a potassium deficient diet, relying on the excretion of potassium in the urine faeces and sweat, by the administration of desoxycorticosterone acetate (or adrenal cortical extract) in which case the potassium is lost in the urine, or by interrupting the gastrointestinal circulation of potassium by removing from the body part of the digestive juices which contain considerable amounts of potassium. As seen before, the interruption of the so-called "gastrointestinal

circulation" of potassium is the cause of potassium deficiency in such clinical conditions as pyloric stenosis or upper intestinal obstruction with vomiting, continuous suction during intubation therapy, intestinal fistulae or diarrhea. Potassium deficient diet is the most direct method. This method obviates the possible loss of other substances in the digestive juices and so complicating the deficiency when one tries to produce the deficiency by the removal of gastrointestinal secretions. The effect of desoxycorticosterone has been studied in detail and is satisfactory if given in frequent small doses.

If one tried to produce a potassium deficiency by the removal of gastrointestinal secretions alone, the deficiency might be complicated by a loss of other substances. This probably happened in the dog observed in these laboratories three years ago. Although the dog was undoubtedly in a potassium deficient state, it was also deficient in other substances which are normally present in the gastric juice. Evidence of this is the fact that with added potassium the animal did not completely recover. Magnesium deficiency is a good possibility because it is present in the gastric juice (10) (112) and tetany is characteristic in the late stages of magnesium deficiency (119).

CHAPTER lV

EXPERIMENTAL METHODS.

Construction of a Suitable Synthetic Diet

It was quite obvious early in this work that an adequate synthetic diet must be designed as we were unable to find a suitable diet described in the literature. This diet was devised in collaboration with Dr. R.A. Forse who also required an adequate synthetic diet for research in the problem of pyridoxine deficiency.

In 1945, Seeler and Silber (121) described certain studies on adult dogs which were maintained over periods up to 4½ years on a synthetic diet which was apparently nutritionally adequate in all respects. However, on further examination the salt mixture was not entirely suitable and required changing. Therefore the main constituents only of this diet were adopted.

Casein is used as the source of protein because it is 98.5% utilizable, complete in its content of essential amino acids found necessary in quality for growth and adequate nourishment (133) and because it was found superior to all other proteins in promoting growth in other diet mixtures by Osborn and Mendel (104). Number 80 mesh-strained, acid free, triply washed casein was used. Dextrin is an easily utilized, commonly used source of carbohydrate for such mixtures. This was

generously supplied by the Canada Starch Company. Hydrogenated cottonseed oil is a good source of fat which is inexpensive, relatively stable in composition and again commonly used in diet mixtures. "Crisco" (Proctor and Gamble) was the cottonseed oil used, although this substance is known to contain in addition small traces of palm and olive oils. Bone ash as used by Seeler and Silber was deleted because it was necessary to know in detail the mineral composition of the diet.

The Salt Mixture

A careful study of salt mixtures as used in synthetic diets was made by Mendel, Hubbell and Wakeman (94). They fed young rats on diets containing five different percentages of four different salt mixtures and when the rats reached 200 gm. in weight, sacrificed them and took the mineral composition of their dried, defatted femora as an indication of the efficiency of the salt mixture. They found the old Osborn-Mendel mixture most efficient when 3% was added to the diet if this was supplemented by calcium carbonate in an amount as was contained in the 5% Osborn-Mendel mixture. Later, Hubbel, Mendel and Wakeman (75) again improved this mixture, by adding more calcium along with certain trace elements as shown in the chart. These trace elements

Synthetic Diet

Constituent	Percentage	Cal. per 100 gm.	Approx. Daily Requirement
Dextrin	42	168.0	3.6 gm. or 14.4 Cal./Kg.
Casein	30	120.0	1.0 4.3
Cottonseed Oil	21	189.0	
Corn Oil	0.15	1.35	3.0 27.3
Cod Liver Oil	2.0	18.0	
Mineral Mixture	5.0		

Vitamin Supplements	mg./day
Thiamine	1.
Riboflavin	1.
Pyridoxine	1.
Nicotinic Acid	10.
Calcium Pantothenate	10.
Alpha Tocopherol	2.8
Vitamin A, Vitamin D } IN C.L.O.	
Choline Chloride	200.

Mineral Mixture	Percentages
Sodium Chloride	14.6
Potassium Phosphate, Monobasic	40.8
Magnesium Sulphate	6.0
Calcium Carbonate	40.0
Ferric Sulphate	2.83
Potassium Iodide	0.083
Manganese Sulphate	0.467
Zinc Chloride	0.02726
Copper Sulphate	0.04994
Cobalt Chloride	0.00238

Illustration 4. COMPOSITION OF SYNTHETIC DIET

were added to the level of the 5% mixture and by these changes they were able to reduce the amount of the mixture required in the diet from 3 to 2%. A recent modification of this latter mixture was described by Jones and Foster (79) in which traces of cobalt and zinc were added and sulphur, fluorine and aluminum, which have not been proven essential, were removed. The proportions were varied slightly in an attempt to increase the efficiency. This mixture was shown to be quite adequate when added at the recommended level of 4%. Because the experiments to be carried out involved a certain accidental loss of gastric juice through spillage we decided to use a 5% mixture as a measure of safety. Therefore the final salt mixture chosen is shown in illustration #4.

The salt mixture used in these experiments for the low potassium diet is simply the above mixture with the potassium iodide substituted by sodium iodide and calcium phosphate substituted for potassium phosphate. In every other way the diets were the same. In order to keep the concentration of phosphate the same in these mixtures, 702.9 gms. of calcium phosphate were substituted for 816.6 gms. of potassium phosphate

	Osborne & Mendel	McCollum	Steinbock	Sure	#351 Hubbell Mendel Wakeman	#12 Jones & Foster
Calcium	0.462	0.276	0.296	0.322	0.870	0.576
Magnesium	0.0597	0.0581	0.0398	0.0681	0.0418	0.043
Sodium	0.128	0.136	0.226	0.159	0.1008	0.206
Phosphorus	0.279	0.412	0.458	0.482	0.204	0.334
Chlorine	0.444	0.114	0.233	0.132	0.382	0.319
Sulphur	0.0259	0.0766	0.0525	0.0897	0.01816	---
Iron	0.0112	0.0263	0.0101	0.0309	0.0206	0.020
Iodine	0.000131	---	0.0020	---	0.000244	0.0028
Manganese	0.000246	---	---	---	0.000508	0.00494
Fluorine	0.000961	---	---	---	0.001808	---
Aluminum	0.0000219	---	---	---	0.0000388	---
Copper	---	---	---	---	0.001432	0.00046
Cobalt	---	---	---	---	---	0.00002
Zinc	---	---	---	---	---	0.00047

Expressed in number of grams to be added to 100 grams of basal diet to give a 4% salt mixture in diet.

Illustration 6. MINERAL MIXTURES

in making up the stock mixture as shown in illustrations 4 and 5. The chemicals used to make up this mixture were all of C.P.grade. In illustration 5, the normal mineral mixture is shown on the left and the potassium free mixture is shown on the right hand side of the table.

The Vitamin Mixture

Only those vitamins have been used which have been proven essential in the diets of dogs for normal growth and maintenance. The mixture described by Seeler and Silber has been adopted unchanged as they showed that the mixture was adequate for adult dogs for long periods of time (121). Vitamin C (ascorbic acid) is unnecessary for dogs as it is synthesized in the bowel and again can be synthesized adequately in the bowel of a dog maintained on this artificial diet. The vitamin preparations used were generously supplied by E.R. Squibb and Son.

Methods and General Management.

The diet was mixed in dry form according to the proportions shown in illustration #5. The amount of diet required per day was calculated from the weight of the dog and from the requirements of carbohydrate,

PROPORTIONS FOR SYNTHETIC DIET - MODIFIED SEELER AND SILBER

		4 Kg.	12 Kg.
CASEIN	30%	1200 gm.	3600 gm.
DEXTRIN	42%	1680 gm.	5040 gm.
CRISCO	21%	840 gm.	2520 gm.
CORN OIL	0.15%	6 gm.	18 gm.
SALT MIXTURE	5%	200 gm.	600 gm.
COD LIVER OIL	2%	80 gm.	240 gm.

SALT MIXTURE

SALT	MOLES	GM.	MOLES	GM.
Sodium Chloride	5.	292.5	5.	292.5
Potassium Phosphate	6.	816.6	----	----
Calcium Phosphate	--	----	3.	702.9
Magnesium Sulphate	1.	120.3	1.	120.3
Calcium Carbonate	8.	800.8	8.	800.8
Ferric Sulphate	0.2	56.6	0.2	56.6
Potassium Iodide	0.01	1.66	----	----
Sodium Iodide	--	----	0.01	1.50
Manganese Sulphate	0.05	9.35	0.05	9.35
Zinc Chloride	0.004	0.545	0.004	0.545
Copper Sulphate	0.004	0.999	0.004	0.999
Cobalt Chloride	0.0002	0.048	0.0002	0.048

Illustration 5. PROPORTIONS IN SYNTHETIC DIET

fat, and protein. A stock mineral mixture was made and added to the diet mixture each time a new lot was made. The vitamin mixture was partly in powder form and partly in capsules (thiamine and riboflavin). Daily doses of vitamins were made up and added to the moistened diet just before feeding each day.

Dogs generally took this diet satisfactorily although occasionally the diet was refused. In this group, the dogs were not force fed. The usual reasons for refusal were a relative stenosis of the stomach in the early postoperative period, lower respiratory infection, or early in the experiment when the diet was first introduced to the dog. Although bland, tasteless and uninteresting the diet is quite tolerable and tastes like a pablum-water mixture. The amount of diet necessary was weighed for each dog each day, mixed with a measured quantity of warm water, with the vitamin preparation and with the previous day's gastric secretions if this was refed, and given to the animal in his cage at the same time each morning.

The secretion of gastric juice in dogs is intermittent and required a suitable stimulus (5). Dogs were found to secrete for a period of $4\frac{1}{2}$ hours but may secrete longer than $5\frac{1}{2}$ hours with a degree of

delayed emptying of the stomach due to narrowing which was occasionally found following the construction of certain types of gastric pouches. Therefore the dogs were fed early in the morning and left in stands for their full secreting period, 5 hours at least. Tests of the secretory function (histamine, insulin and teasing tests) were performed early in the morning and were completed before the regular feeding time. In this way, conditioned reflex secretion did not complicate these tests.

Water balance studies were carried out as follows. Dogs were given measured liberal quantities of water to drink freely over the full 24 hour period; the amount required to refill the pans to a determined volume was taken as the water intake for the previous day. The volume of water added to the diet mixture was added to this volume. The total urine volume was saved as carefully as possible, measured each morning at the same time and pooled so that each week a potassium determination could be made. Because the dogs had to be removed from their cages when the kennels were cleaned there was an unavoidable loss. As much as possible of this loss of urine was collected or calculated. Apart from this occasion, the dogs remained in their cages

all of the time and although the balance studies show a moderate difference between the volume of intake and output each day, the figures are believed to be of value in showing changes in the fluid exchange of the animal.

Potassium balance studies were carried out as follows. The concentration of potassium in the mineral mixture was constant and therefore the amount of potassium given could be calculated from the measured quantity of diet mixture consumed. There are 15 M.Eq. of potassium in every 100 gms. of synthetic diet. It was found by calculation, that the Ringer's solution used during operation contained 2.00 M.Eq. per 500 c.c.of solution. The output of potassium was calculated from the concentration of potassium in the weekly pooled uring samples and from the volume of urine recovered each day. Although it is known that small amounts of potassium are lost in the faeces, this loss was not determined or considered in these balance studies. None of the dogs had diarrhea during the experimental study and so significant losses by this route were not expected. However, several occasions, three of the four dogs were given small quantities of mineral oil to encourage bowel movements

when movements became alarmingly infrequent. Fecal concretions or impactions were never found although either might have been expected because of the low-residue diet or the possibility of loss of gastro-intestinal motility due to potassium efficiency.

Construction of Gastric Pouches and Management of Pouch Dogs.

Many types of gastric pouches have been described and used with varying suitability. Generally, these pouches are of two types. Enervated pouches are usually separated from the stomach and so constructed that few if any functioning parasympathetic nerve fibres reach the pouch and therefore do not respond to psychic stimuli but secrete only in the gastric hormonal or intestinal phases or to local stimulation of the mucosa of the pouch. Innervated pouches do have a functioning parasympathetic nerve supply so that they will respond to stimuli in all phases of gastric secretion. However, this is a relative phenomenon; in other words, the response to maximum stimulation will produce a variable response in different animals depending upon the number and area of distribution of the intact functioning parasympathetic fibres. These pouches are usually attached to the body of the stomach because the main nerve

trunks run over the stomach in the subserosal plane and this layer must be continuous from stomach to pouch.

The anatomy of the stomach in the dog is very similar to the anatomy of the human stomach except that in the dog the pylorus is longer and more mobile and the splenic artery passes in a more obliquely downward direction so that its rostral branches, the short gastric arteries, supply a greater portion of the body of the stomach and consequently the bare area is farther from the fundus than in the human (illustration #7).

The simplest, most satisfactory enervated pouch is that described by Heindenhain (63) (64) (65) in 1878. As illustrations (9) and (10) show, this pouch is made quite easily from the greater curvature portion of the body of the stomach in an area extending obliquely downwards from the bare area to the junction of the body and pyloric antrum on the greater curvature. All layers of the stomach wall are divided between rubber-shod intestinal clamps placed on either side of this line and the stomach is closed completely in two layers. The pouch is again closed in two layers beginning on the left but incompletely, leaving an opening on the right hand side from which a stoma is fashioned. The blood supply to this pouch is good; often one can feel both

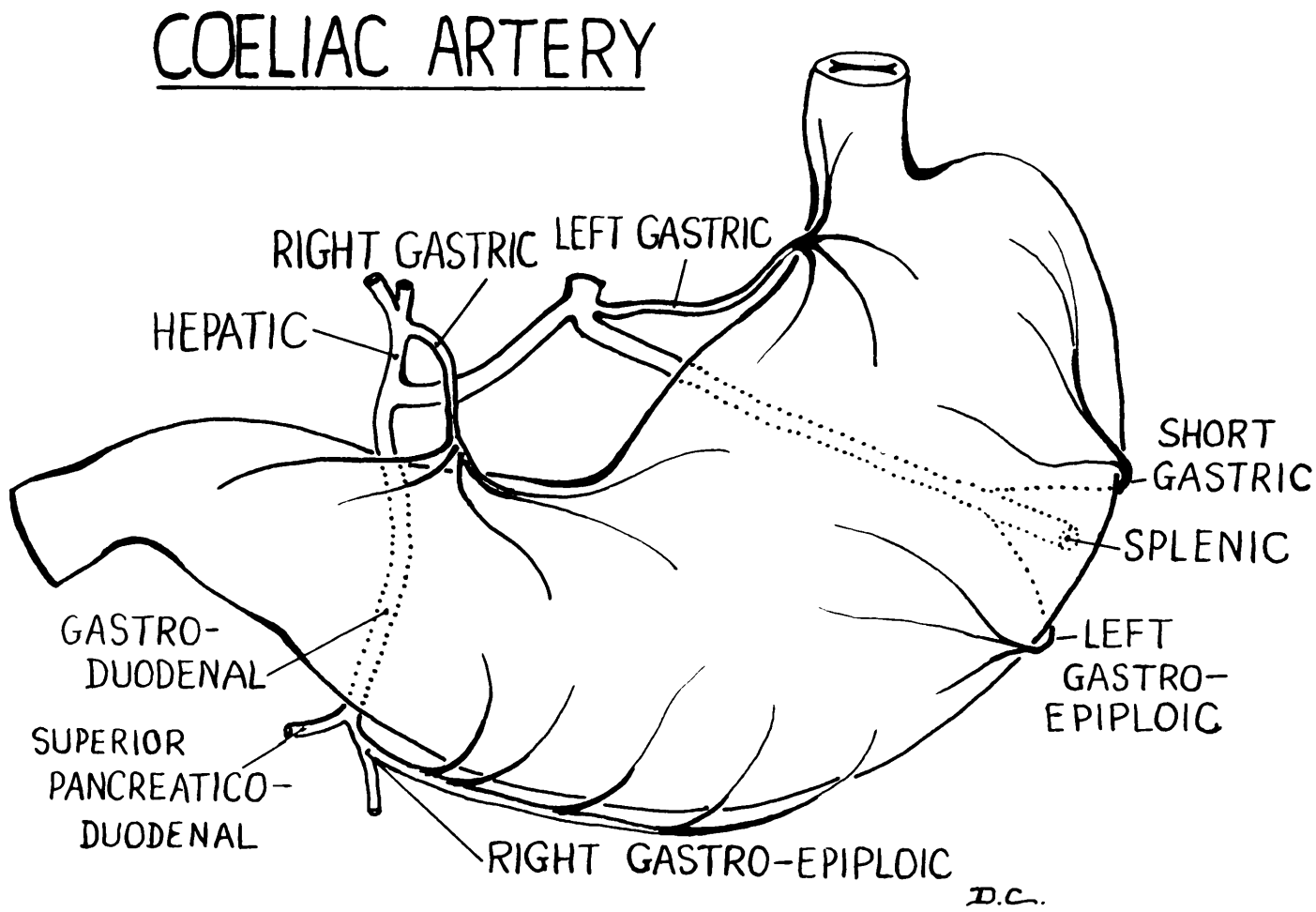


Illustration 7. THE COELIAC ARTERY AND BRANCHES

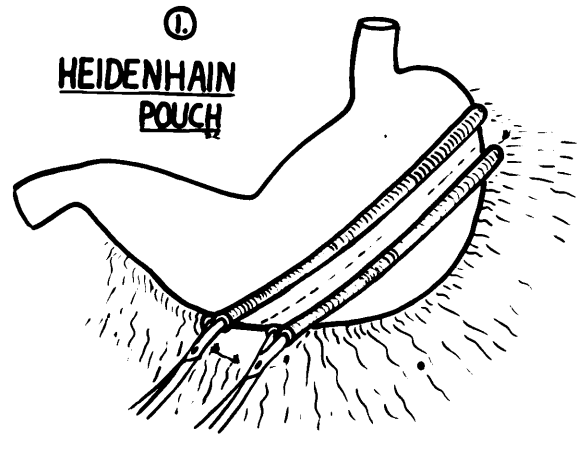


Illustration 9. HEINDENHAIN POUCH I

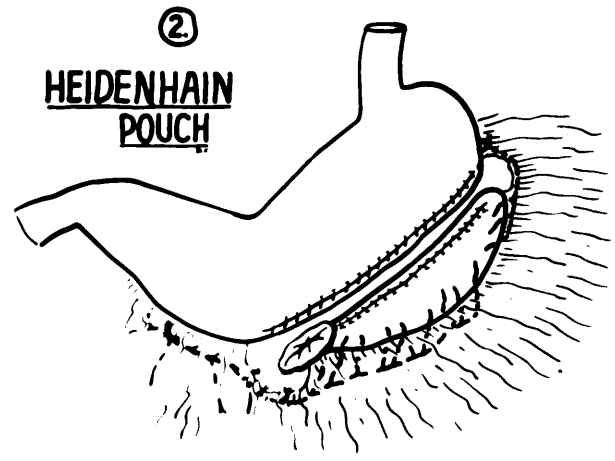
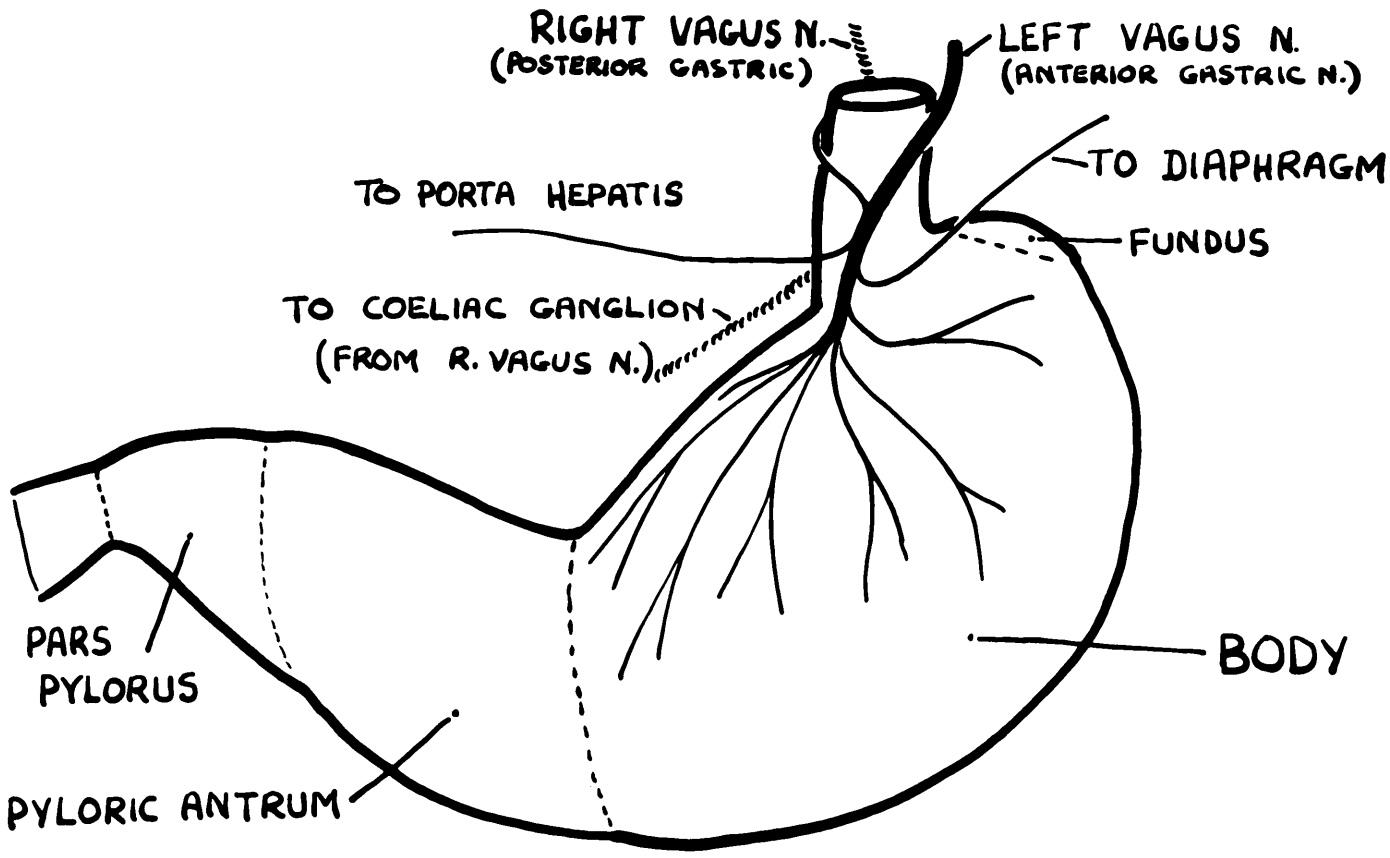


Illustration 10. HEINDENHAIN POUCH II

the right and left gastroepiploic vessels pulsating forcefully in the greater omentum which forms a mesentery for the pouch. The stoma of pouch is incorporated in the midline abdominal incision during closure so that it lies about two fingerbreadths caudal to the xiphoid cartilage. It is wise to anchor the pouch to the abdominal wall and so lessen the chances of prolapse.

Pavlov described a method of construction for an innervated gastric pouch. The method is well described in most texts of physiology. It has two great disadvantages. No matter how expert the construction a large percentage show little if any functional parasympathetic innervation. This might be expected because the pouch is made from the same portion of the stomach as the Heindenhain pouch and illustration 8 will show that this area of the stomach receives usually few major vagal trunks. The second great disadvantage is the frequency of a break in the mucosal partition between the stomach and pouch. Although this complication frequently occurs in all innervated pouches, the rate of breakdown in Pavlov pouches is almost 50%.

Thomas (142) has described a simplified Pavlov pouch in which the serosal and muscle layers are not incised, but again the difficulty of construct-



VAGUS NERVES AND DIVISIONS OF THE STOMACH

Illustration 8. VAGUS NERVES AND DIVISIONS OF THE STOMACH

ing a good mucosal partition is great and the rate of breakdown is again high.

Cope, McMahon, Hagstromer and Thompson (30) have designed a new type of innervated pouch. One important feature is that the area of stomach used is in the region of the lesser curvature and anterior surface, a portion which Armour (4) found highly innervated by parasympathetic fibres. Although Armour used a small saddle-shaped area of the lesser curvature, Cope used both the lesser curvature and the anterior wall or, in other words, that portion supplied by the larger trunks of the left vagus nerve. They claim a greater percentage of well innervated pouches. Another feature is the immediate implantation of the stoma into the pyloric antrum and at a later stage, in three weeks time, this stoma along with a tough ring of scar tissue from the pyloric antrum is transplanted into a stab wound in the flank near the spine so that the pouch, rather than the stoma, is dependent. In this way, continuous drainage is avoided and secretions may be aspirated at will by a syringe and catheter. The pouch is large as the whole width of the anterior wall is used, the blood supply is good as vessels enter by both the lesser and greater omenta, there are a high percentage of function-

ally innervated pouches, the care required is lessened, there is minimal distal denervation, quantitative collections may be made for long periods of time and the mucosal breakdown rate is less or at least no greater than with other innervated pouches. This type of pouch was tried on three dogs in this series and a discussion of the complications will be given later. Suffice to say that in a number of dogs in which this operation was performed this year, there was a relative stenosis of the remaining portion of the stomach causing delayed emptying, prolonged secretion and so more excoriation, and although the dogs did require less care the excoriation around the stoma in the flank was just as marked as that around ventral stomata. Little advantage could be seen in placing the stoma in the flank.

The Cope pouch is made in two stages. In the first stage, the incisions are made as outlined in illustration 11 from D to A to B to C and hence on to the anterior surface again until the most lateral branch of the left vagus nerve is encountered. This flap is elevated and the mucous membrane only along its base is incised carefully preserving the muscle and serosa as these layers carry the fibres of the vagus nerve (this step is depicted for another type of pouch in illustration

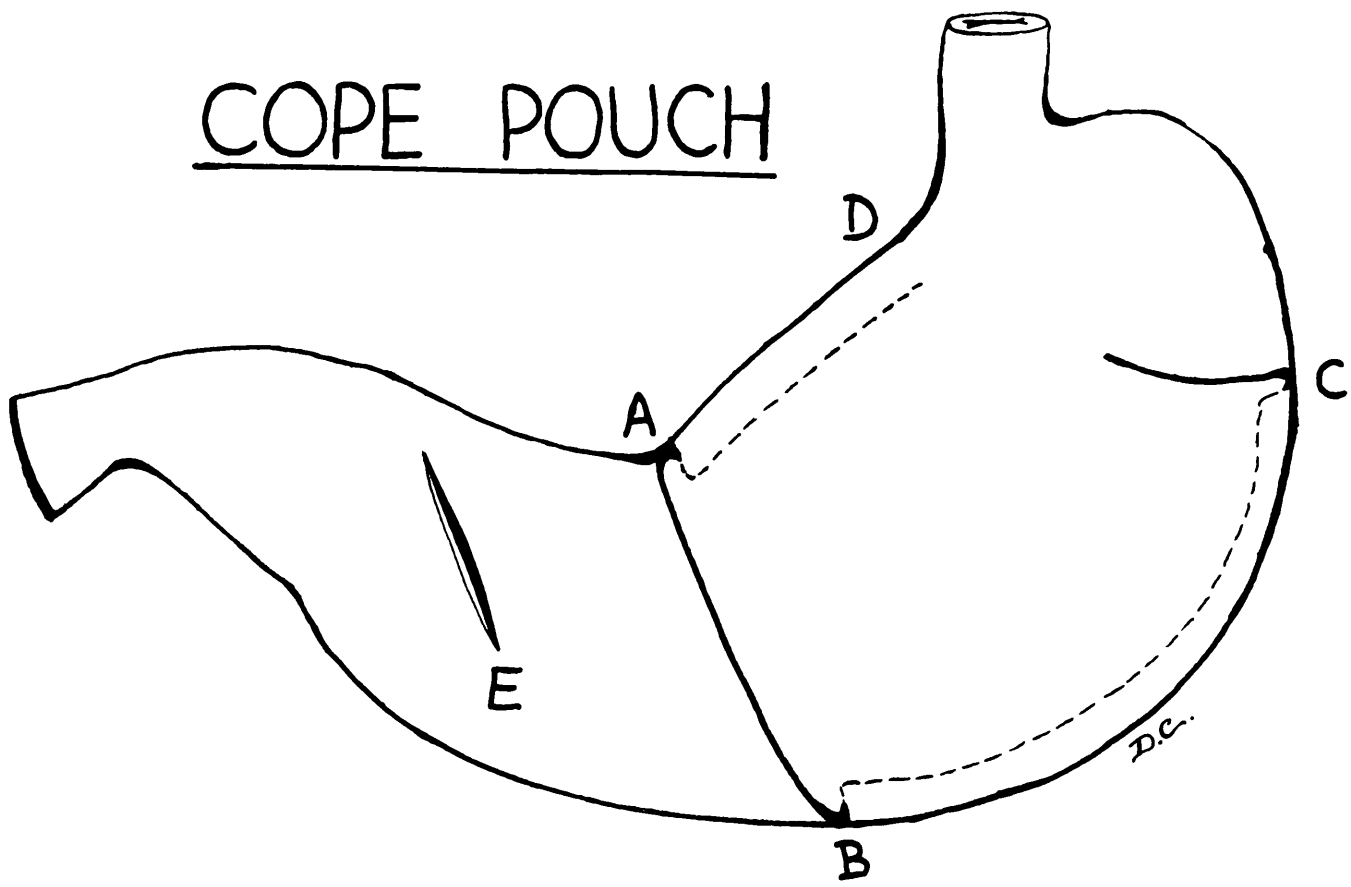


Illustration 11. COPE POUCH I

14.) The edges of the mucous membrane of the remaining portion of the stomach are now brought together with an inverting continuous Connell suture of intestinal chromic catgut and reinforced by a layer of interrupted non-absorbable suture. The edges of the mucous membrane of the flap are similarly brought together by a continuous inverting Connell suture of the same material beginning on the lesser curvature side and leaving the last part open so as to form a stoma. This stoma is then carefully implanted into a 2.5 cm. incision in the pyloric antrum as outlined in illustration 12. The usual two layer technique for intestinal anastomoses is used. Since the stomach is closed from A to C (illustration 11) B is brought to D as shown in illustration 12 and since the stomach is closed in the longitudinal direction, the remaining portion is invariably narrowed. The abdomen is closed in three layers without drainage.

In the second stage the abdomen is opened through a left paramedian incision. The stoma is excised from the pyloric antrum with a 0.5 cm. ring of pyloric antrum tissue which is tough because of scar tissue. The pyloric antrum is closed by the usual technique in two layers. A stab wound is made in the dorsal region in the angle between the twelfth rib and quadratus

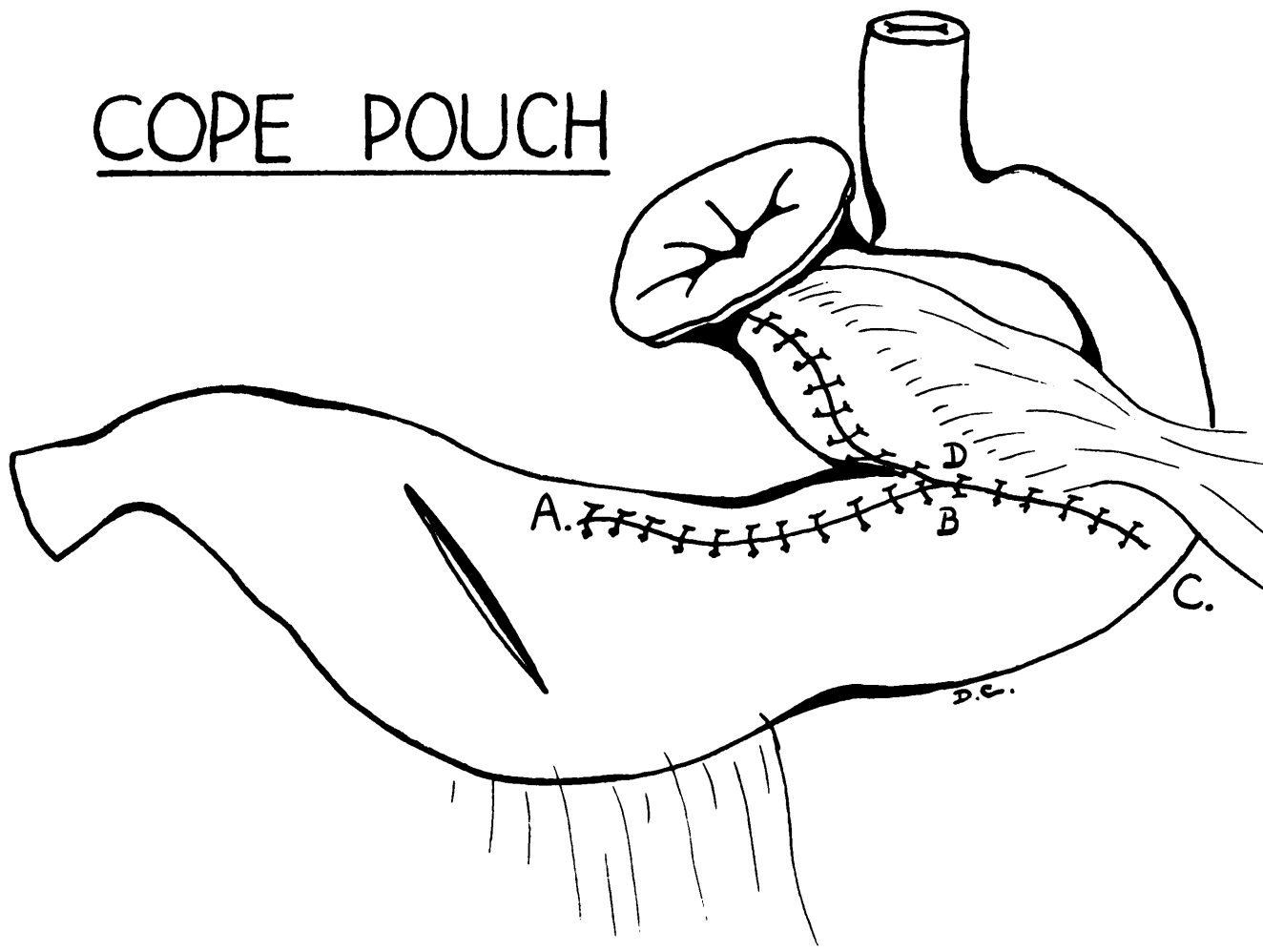


Illustration 12. COPE POUCH II

lumborum muscle and the stoma is carefully implanted here. The abdomen is closed in three layers. The post-operative care is the same as for other pouch dogs and will be described shortly.

Because of the disadvantages of the Cope pouch as outlined yet realizing certain advantages, a modified Cope pouch was designed and tried successfully on six dogs this year. The main modification was in the shape of the area of the anterior gastric wall used so that the remaining stomach will be closed in a transverse direction thus preventing narrowing and its sequelae. The operation is performed in one stage with a ventral stoma as no advantage was found in the dorsal position of the stoma.

It was realized that the resulting suture line AC (illustration 11) must be as long as possible and extend across the stomach in a transverse direction so that the remaining stomach would not be narrowed. To accomplish this, the site C was moved along the greater curvature towards the pylorus to a point opposite A which is on the lesser curvature and the two adjacent sides of this area which form either side of the suture line must be lengthened. Therefore the new design of the area to

be used was adopted and is shown in illustration 13. This quadrangular area happens to be that portion of the anterior surface of the stomach which receives the largest branches of the left vagus nerve as shown. Although the gastroepiploic vessels do not reach the pouch now, in the six dogs in which this operation was performed, the blood supply to the pouch was quite adequate in all cases. However, in one dog (#8 described later) in which the pouch was separated from the stomach because of a breakdown in the mucosal partition, the pouch sloughed. Apparently the lesser curvature vessels are sufficient if the pouch is left attached to the stomach but not so if it is separated later.

The description of the operative procedure will be given in some detail as it is original. The abdomen is opened through a midline epigastric incision. Point A is selected about an inch above the incisura at a convenient place between large vessels and nerves. The incisions as outlined are then made (illustration 13) and the flap turned back. The mucosa from A to D is then incised and freed from the underlying muscle for a short distance as shown in illustration 14. The edges of the mucous membrane of the flap are then brough together

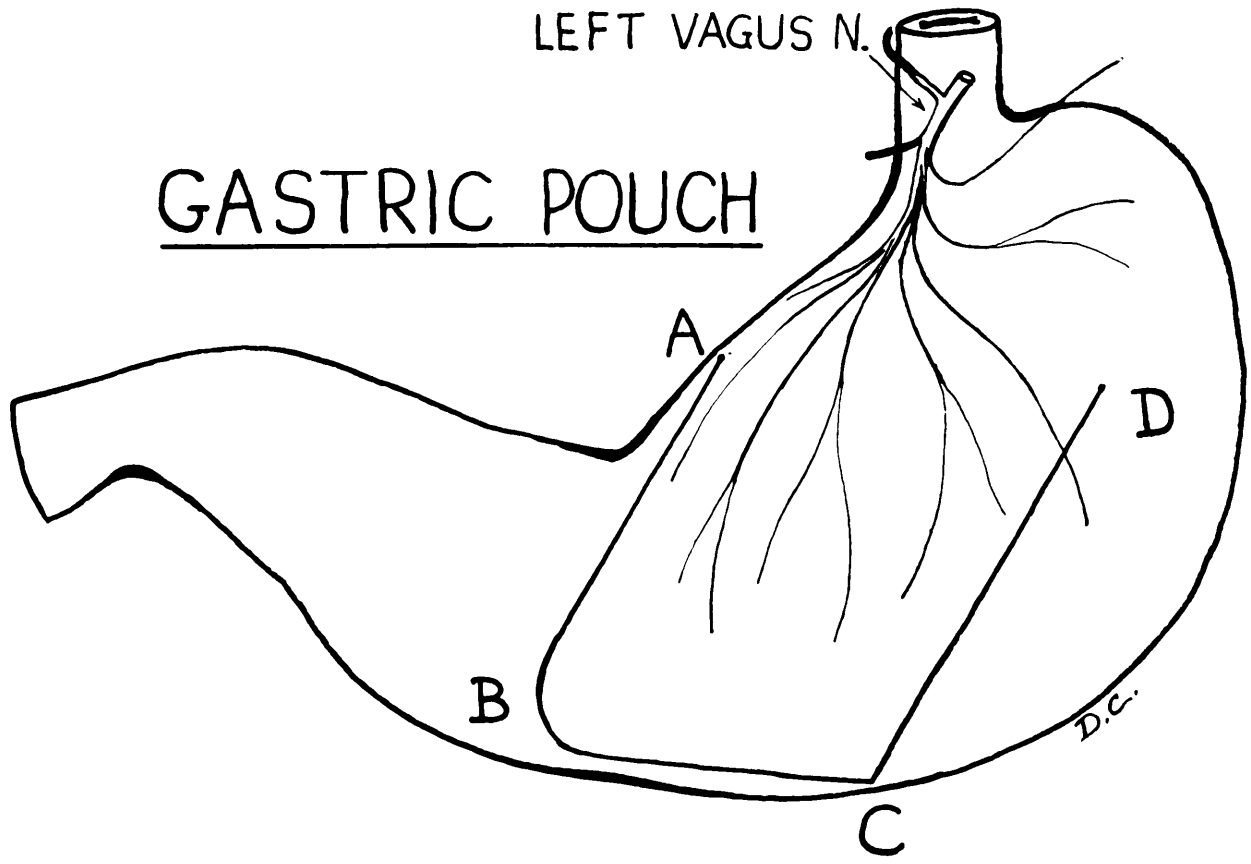


Illustration 13. NEW GASTRIC POUCH I

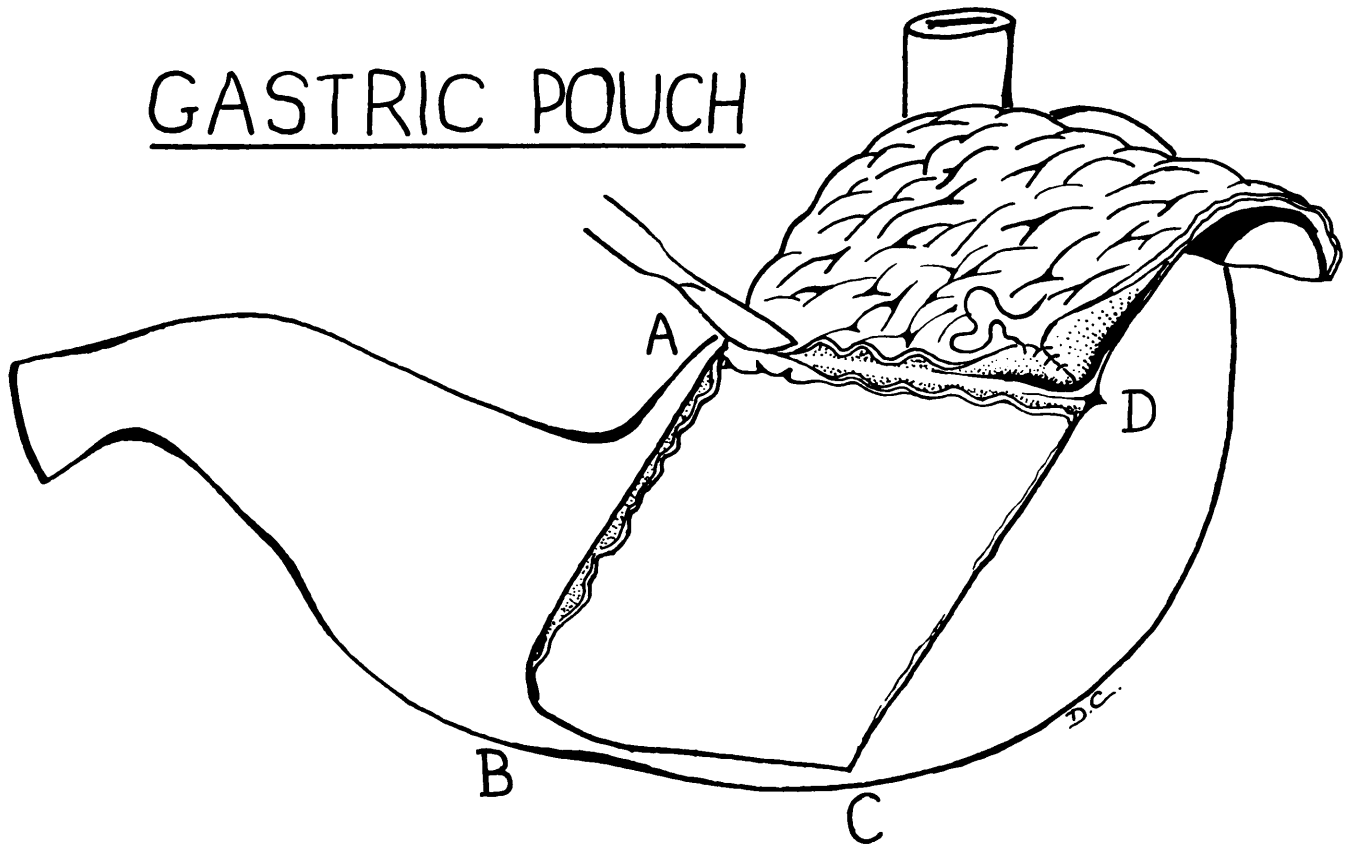


Illustration 14. NEW GASTRIC POUCH II

beginning at D by a row of continuous inverting Connell sutures of chromicized catgut, preferably 000 in size. The tip at B is left unclosed and this will form the stoma of the pouch. The stomach is then closed in a similar fashion beginning at A. Both of these suture lines are reinforced by a row of interrupted #40 cotton stitches. On closing the abdomen the stoma of the pouch is incorporated in the incision about two fingerbreadths below the xiphoid cartilage. As can be seen in illustration 15, the stomach is not narrowed but may actually be widened by placing the suture line in this transverse direction.

Pouch dogs are starved the day before operation and given intravenous fluids for the preoperative, operative and first postoperative days. In this series, the dogs were given Ringer's solution as it contained 2 M.Eq. of potassium per 500 c.c. These dogs were usually given penicillin for 2 days postoperatively. They were starved for the first postoperative day, given water four times a day on the second, milk and water ad lib on the third and then started on small quantities of synthetic diet mixture on the fourth. In about two weeks time the secretions became stabilized so that the dogs could then be standardized.

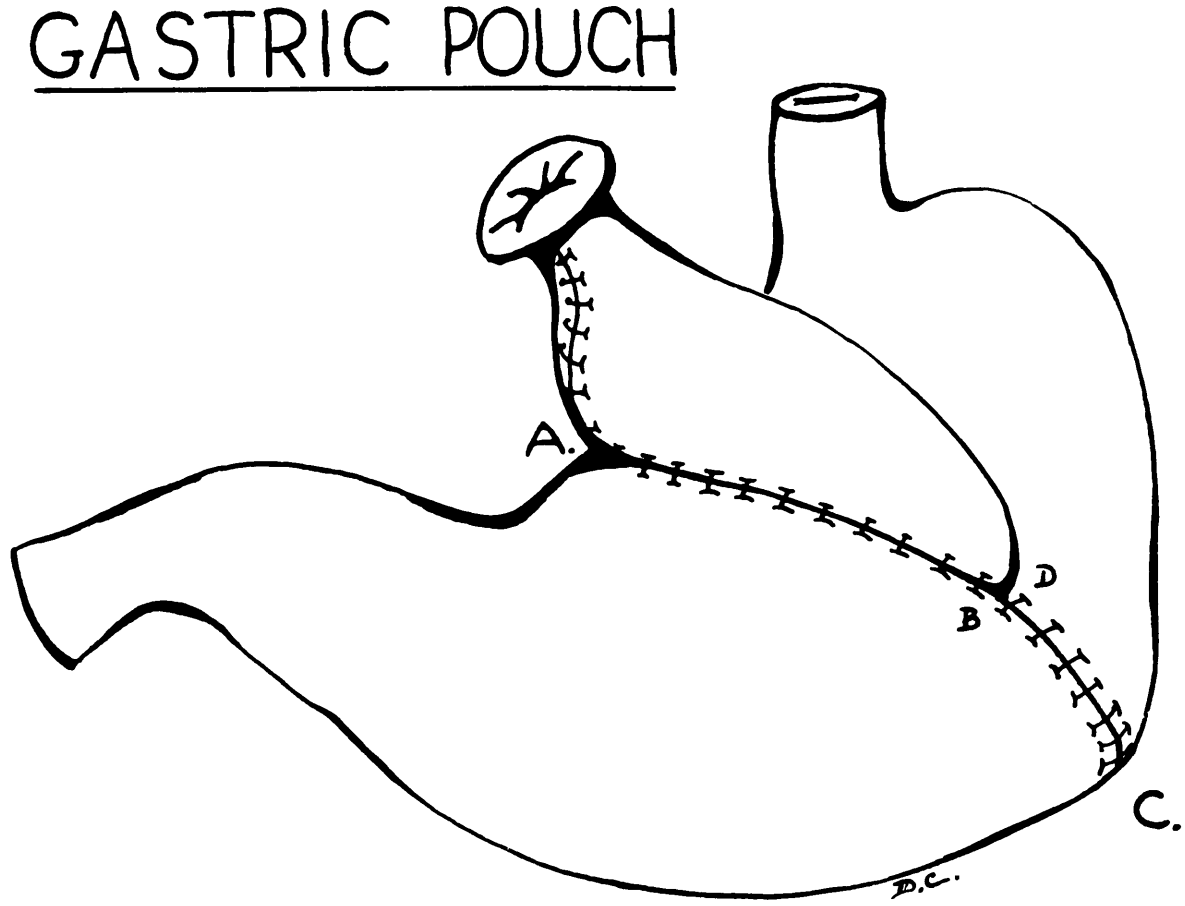


Illustration 15. NEW GASTRIC POUCH III

Dogs were tied in secreting stands or in their cages on the sixty day. The stomata were frequently smeared with aluminum hydroxide gel to prevent excoriation. Many types of collecting bottles were tried during the course of the year but the method found most satisfactory was actually the simplest. A four wing Malecot (butterfly) catheter of suitable size (#18 - 24) was placed in the pouch each day and a collecting bottle was suspended beneath by straps over the dog's body. The bottles were emptied several times during the day over the 5 - 5½ hour secreting period. Although the dogs required much care, this method was felt to be the most satisfactory.

Study of the Gastric Secretions - Biochemical Studies

The gastric secretion is actually a mixture of the secretions of several different types of cells found in the stomach. Globlet cells secrete the surface mucus, oxyntic cells secrete hydrochloric acid or the immediate precursor, chief cells secrete pepsin, neck cells secrete dissolved mucin and there are also argentaffin cells whose function remains unknown.

The secretion of gastric juice consists of the cephalic, chemical and intestinal phases. The

cephalic phase is initiated by sight, smell or taste of of food or by hypoglycemia.. Impulses apparently arise from the vagal centre and pass to the stomach and may be abolished by vagotomy or atropine injection. Insulin may serve as a test for this phase as it will produce hypoglycemia if given in sufficient amount. This secretion accounts for half of the total secretion and is rich in enzymes.

The general arrangement of the vagus nerves in the dog is similar to that seen in man (illustration 8). The left vagus passes to the anterior surface of the stomach, mostly in the region of the lesser curvature, and here in the submucosa is the cell station. Post-ganglionic fibres pass via the plexi of Auerbach and Meissner to the gland and muscle cells. The right vagus fibres pass through the coeliac ganglion uninterrupted and on to their cell stations in the effector organs which are the posterior wall of the stomach, pylorus and probably the rest of the intestinal tract at least to the splenic flexure of the colon.

Food in the stomach produces a flow of gastric juice of high acidity but weak in enzymes. This secretion is due to the liberation of gastrin from the mucosa of the pyloric antrum. This is part of the chemical phase

of gastric secretion. Another hormone called entero-gastrin is formed in the upper small bowel and this again stimulates a gastric secretion.

Derivatives of protein digestion after absorption from the small bowel stimulate gastric secretion to a minor degree and this is termed the intestinal phase. Carbohydrates and fats stimulate little secretion and in the case of the latter may actually inhibit secretion by the formation of enterogastrone.

In the study of gastric juice the volume, acidity and pepsin content are the important factors. These may be studied in juices secreted in response to standard stimuli such as histamine or a weighed standard meal and insulin and the sight and smell of meat in dogs with innervated pouches. These standard tests are well known (7) and will not be described.

In this study acidity was determined by the Beckman pH meter after the instrument was calibrated with buffer solutions of known pH value.

Pepsin determinations were performed by the method of Riggs and Stadie (111), a photoelectric method using the Evelyn photoelectric colorimeter. Enzyme activity is measured as the decrease in turbidity of a standardized homogenized suspension of coagulated egg

white under specified conditions. Protein hydrolysis so measured follows a monomolecular course and hence the enzyme activity is expressed as a velocity constant - "k", and this velocity constant is a curvilinear function of the pepsin concentration.

Specimens for potassium or sodium determination were suitably diluted and submitted to Mrs.K.A.C. Elliott of the Department of Biochemistry of the Allan Memorial Institute. Measurements were made on the flame photometer (Perkins Elmer, Model G, series 11) which checked with our determinations as done gravimetrically to within 1% in six specimens. Although the flame photometer has limitations, there are numerous interfering substances and the calibration is difficult, still it appeared satisfactory for this work in the determination of serum sodium and potassium, and potassium in urine and gastric juice. Discussions of the advantages and limitations of this instrument have been written by Hald (60), and Overman and Davis (105).

Other biochemical determinations were carried out in the Biochemical Laboratory of this Department by Miss Hope Thompson.

CHAPTER Vl

PROCEDURE.

Throughout the early part of this work many difficulties were encountered. Various types of gastric pouches were tried, numerous methods of caring for the animals had to be tried and in particular, an epidemic of atypical pneumonitis caused the death of many dogs under observation. Therefore the earlier experiments will be mentioned only briefly as little was shown; most of their value lay in their contribution towards the improvement of technique for subsequent experiments.

Dog #1. was operated on August 22/49 and a large Heindenhain pouch was made. The postoperative course was very slow, although vomiting was never observed, the dog ate but little and finally died two weeks later, on Sept. 12/49. At autopsy the suture line on the stomach was found doubled upon itself and this caused a midgastric stenosis and the dog died of inanation. No results will be mentioned.

Dog #2. was operated on Sept.14/49 and a first stage Cope pouch operation was performed. After a normal interoperative course of three weeks, the second stage was performed on Oct. 7/49. The postoperative course was excellent.

This dog was maintained on a normal synthetic diet and the gastric juice was not refed. Studies on the gastric juice and serum potassium were carried out. Unfortunately on October 15 the mucosal partition between the pouch and stomach perforated and on October 17 the pouch was liberated from the stomach and a free, denervated pouch was formed.

On November 9 the dog developed a fever and running nose which, in spite of "adequate" doses of sulphathiazole and penicillin, progressed to complete left pulmonary consolidation. The dog died on November 13, during the epidemic of lower respiratory infection in the kennels.

Dog #3. was operated on September 23/49 for the first stage and on October 13/49 for the second stage for the formation of a Cope type of gastric pouch. The early postoperative course was satisfactory and studies were made of the serum potassium and gastric juice, which was not refed. Later however the dog lost its appetite and by November 8/49 was given full minced meat diet, sulphathiazole and penicillin in an effort to save the animal. This failed and the dog died on November 15/49 with signs of right and left lower lobe pulmonary consolidation.

Dog #4. was operated on September 29/49 and October 21/49 for the two-stage formation of the Cope pouch. The dog was well for several weeks but by November 3/49 lost its appetite and in 2 days developed signs of pneumonitis. In spite of sulphathiazole, penicillin and aureomycin the disease progressed and the dog died on November 8/49. This dog was the first in the kennels to die of this pneumonitis and may have infected the other animals.

Dog #5. survived both stages of the Cope gastric pouch operation but developed signs of pneumonitis on the seventh postoperative day and died two days later. Autopsy revealed a haemorrhagic consolidation of the whole of the left lung. No results will be given.

Dogs #6 and #7 were found unsuitable for use and were not operated upon in this work.

Dog #8. is the first in the series of three dogs (#8 #9 and #10) which were studied for prolonged preoperative and long postoperative periods. Water balance and potassium balance studies were performed in addition to other biochemical studies of the blood including the level of blood potassium, and studies of the volume, pH, pepsin and potassium content of the gastric juice. Electrocardiograms were also taken.

This dog was studied for five weeks preoperatively beginning on November 16/49. The new type of gastric pouch was made in one stage on December 20/49 and the early postoperative period was satisfactory except for bleeding from the pouch,during the second week,for a five day period. The gastric secretions were refed. Fever and loss of appetite developed soon after this and unfortunately the mucosal partition perforated on January 10/50. The pouch was liberated from the stomach on January 18/50 and a communicating intra-abdominal abscess was removed. Postoperatively, pus only was expressed from the stoma of the pouch so on February 8/50 the whole pouch was excised with some difficulty. The dog died two days later, and a complete autopsy was performed.

Dog #9. was studied for four weeks preoperatively beginning on November 16/49. A new type of gastric pouch was made on December 14/49 and the gastric secretions were stabilized to various stimuli during the following $3\frac{1}{2}$ weeks. The gastric secretions were refed over the whole period. On January 10/50 the dog was given a potassium deficient diet and carried through the following six weeks in good condition. Periodic neck weakness developed on March 2/50 and gastric

secretory studies were repeated. On March 8/50 a diet containing normal amounts of potassium was given and the neck weakness did not reappear. On March 14/50 the animal was again placed on a potassium deficient diet and studied until loss of appetite, fever, and signs of pulmonary consolidation appeared on March 30. The dog died on April 2/50 and a complete autopsy was performed.

Dog #10. was studied for two weeks preoperatively beginning on November 21/49. On December 2/49 a modified Cope pouch was performed in one stage and the stoma was brought out through the midline epigastric incision. The animal ate poorly for the first twelve postoperative days probably because of a relative stenosis of the remaining portion of the stomach. Its appetite increased after this time and on January 10 was started on the potassium deficient diet after complete standardization.

The gastric secretions were refed over the whole period. A small amount of blood was found in the secretions for three days beginning on February 1/50 and the mucosal partition perforated on February 8/50. On February 10/50 the dog was operated upon and very fortunately the perforation could be repaired and the pouch left attached to the stomach. On February 28 and March 1 the dog was given 10 mg. of desoxycorticosterone acetate subcutaneously and developed neck paralysis one

day later. On March 3/50 the dog died suddenly following the intravenous injection of insulin for a test of the cephalic phase of gastric secretion. A complete autopsy was performed and sections were prepared for histological study.

Dog #11. was studied for one week preoperatively and was operated on April 5/50. A large Heindenhain pouch was made and the dog was stabilized on a normal diet postoperatively for two weeks. On April 17/50 the animal was started on a potassium deficient diet, the gastric secretions were studied but not refed, and 25 mg. of desoxycorticosterone acetate was given by subcutaneous injection daily. The dog was on complete water and potassium balance studies throughout the whole period. Finally intermittent head drop appeared on June 15/50 and this paralysis became severe on June 20. The dog died quite suddenly on the morning of June 23/50 for no apparent reason, the morning after an EGG and histamine test were performed. An autopsy was carried out two days after death. Formalin had been placed in the (L) ventricle and peritoneal cavities.

CHAPTER V11

RESULTS.

The findings gained from the first four dogs in this study are few. In general, the greatest problem was the epidemic of lower respiratory infection which affected the whole kennel during the month of November. It was believed to be an atypical type of "distemper" - that is, a haemorrhagic type of pneumonitis probably of virus origin and very infectious. There was a secondary invasion in the affected lobes of the lung by pus-forming bacteria because most dogs at the time of death dripped pus from their nostrils and at autopsy the worst portions of the lung were involved in a suppurative pneumonia whereas other portions showed haemorrhagic consolidation only. Microscopically (illustration 16) pus, bacilli, leucocytes and erythrocytes filled the alveolar sacs in the suppurating areas whereas engorged vessels and an edematous sanguinous fluid filled the remaining affected alveoli. The disease did not improve with adequate doses of penicillin sulphathiazole, or aureomycin, and caused the death of dogs #2, 3 and 4.

Dog #2. The results of the observations on this dog are outlined in tabular form in illustration

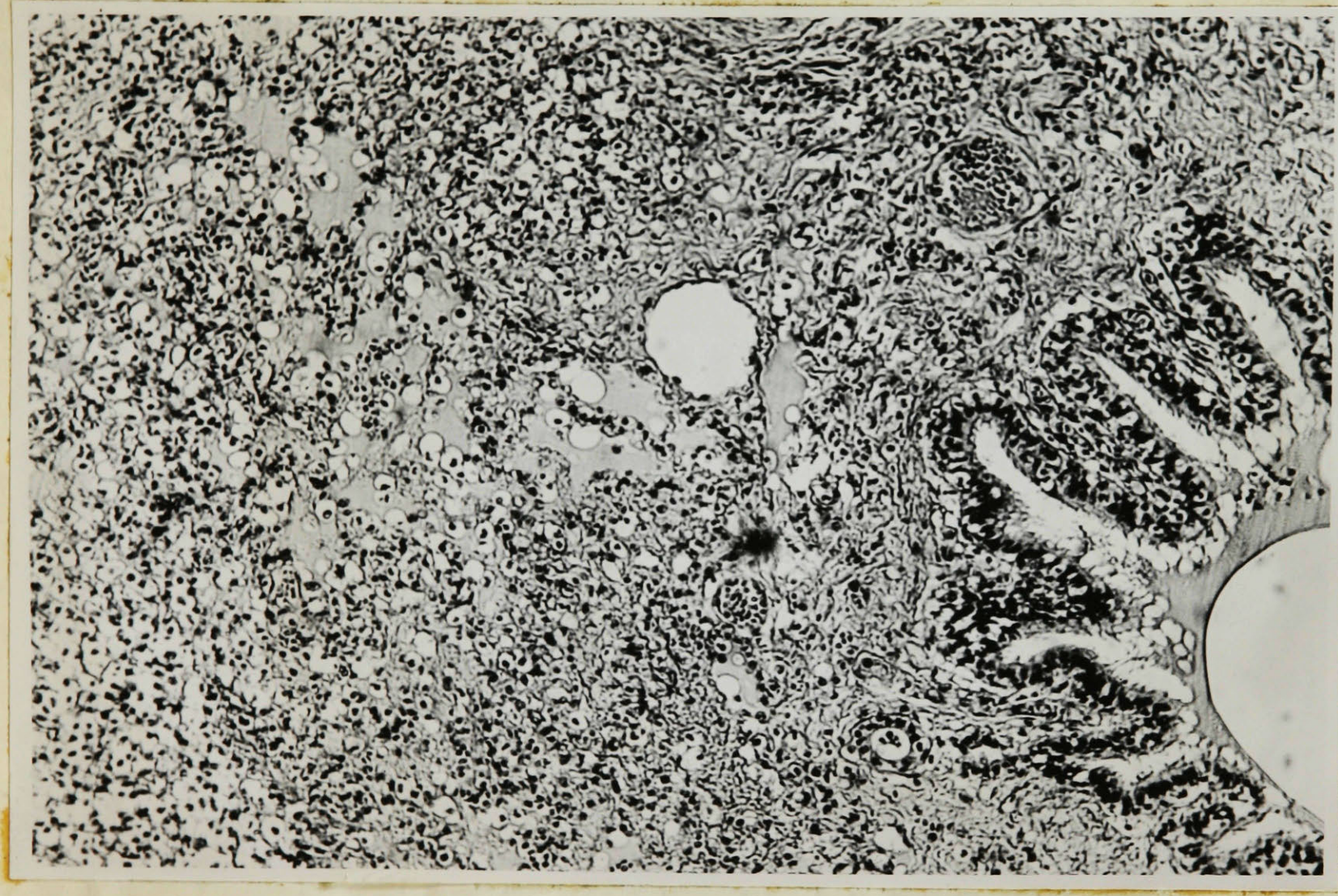


Illustration 16. LOWER RESPIRATORY INFECTION

(Photomicrograph)

17 and graphically in illustration 18. Note that there is a tendency to increase the volume of gastric secretion on continued loss of gastric juice while on a normal synthetic diet. The few serum potassium determinations would also tend to indicate a progressive loss of potassium but it is believed the number of determinations makes this latter finding of little significance. Late in the course the picture is complicated by the lower respiratory infection. Pepsin and pH determinations of the daily gastric secretions showed little change over the whole period. Autopsy revealed nothing more than the atypical pneumonitis affecting both right and left lower lobes of the lungs.

Dog #3. Results of the study are tabulated in illustration #19 and shown graphically in illustration #20. Again, continued loss of gastric juice while on a normal synthetic diet results in an increase in the volume of gastric juice secreted. On the second, fourth and seventh days, however, there was a greater volume of secretion than would be expected. Although the volume of gastric juice secreted day by day varies considerably, no explanation of why there is a very large volume of secretion on several days early in the

Happy - Dog #2

Date	Volume G.J. c.c.	MEq. K. in G.J.	MEq. K. Serum
Oct. 8	145	0.71	
9	120	0.59	
10	70	0.34	
11	150	0.74	
12	29	0.14	
13	113	0.55	
14	39	0.19	
15	47	0.23	
16	6	0.03	
17	4	0.02	
18	42	0.21	
19	8	0.04	
20	4	0.02	
21	11	0.05	2.10
22	16	0.07	
23	12	0.06	
24	51	0.25	
25	51	0.25	
26	74	0.36	
27	54	0.27	
28	97	0.48	
29	110	0.54	
30	125	0.61	
31	133	0.65	
Nov. 1	125	0.61	
2	144	0.71	3.45
3	175	0.77	
4	144	0.63	
5	209	0.92	
6	223	0.98	
7	304	1.34	
8	222	0.98	2.30
9	36	0.16	
10	17	0.08	
11	117	0.57	
12	8	0.04	
13	39	0.17	1.90

Illustration 17. TABLE OF RESULTS - Dog #2

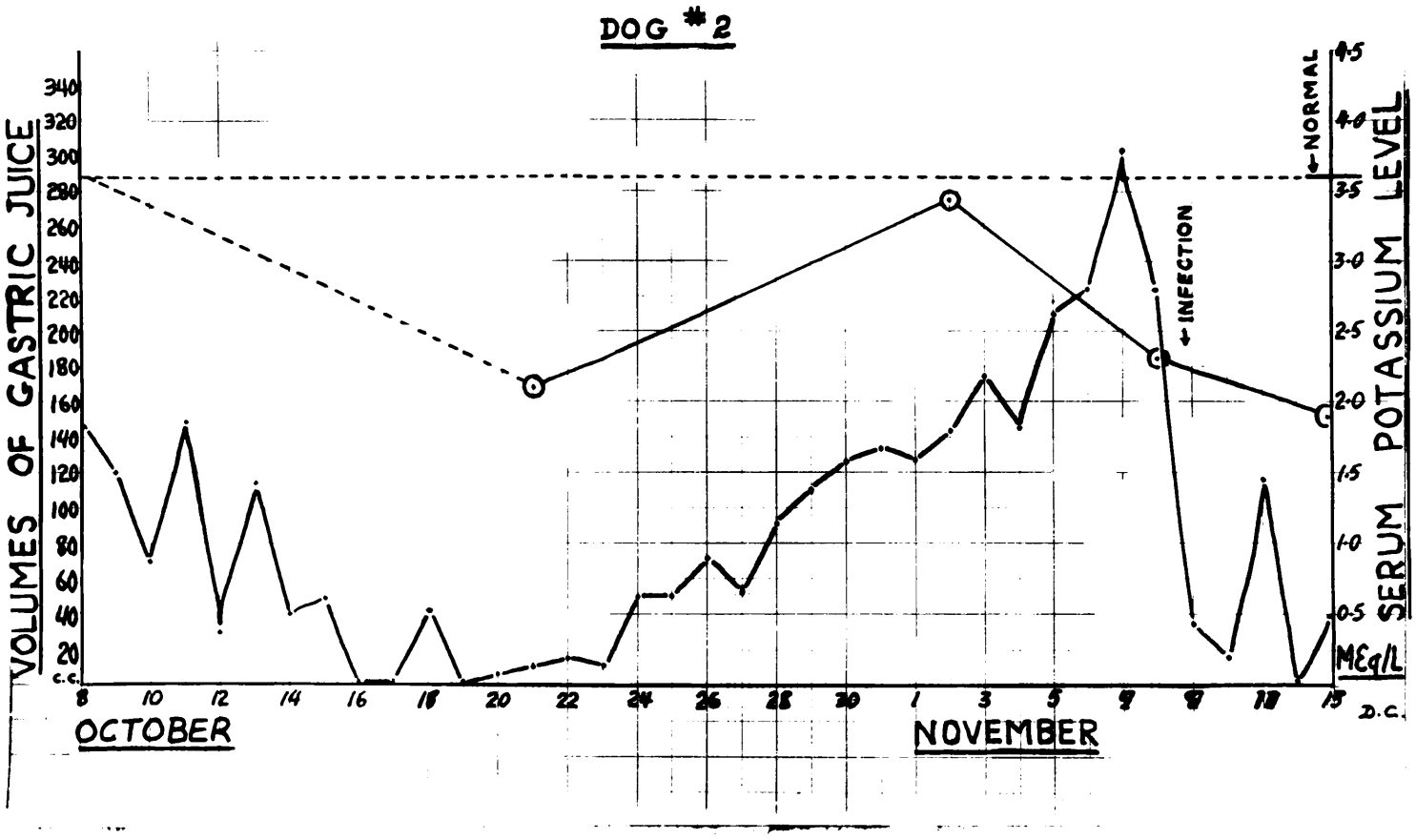


Illustration 18. GRAPH OF RESULTS - Dog #2

Skinny - Dog #3

Date	Volume G.J. c.c.	MEq. K. in G.J.	MEq. K. Serum
Oct.14	25	0.21	
15	330	2.81	
16	120	1.02	
17	199	1.69	
18	105	0.89	
19	18	0.16	2.81
20	263	1.71	
21	104	0.68	
22	127	0.83	
23	145	0.94	
24	60	0.39	
25	107	0.47	
26	60	0.26	
27	42	0.19	
28	159	0.70	
29	91	0.40	
30	125	0.55	
31	128	0.56	
Nov. 1	115	0.51	
2	120	0.53	2.68
3	219	0.97	
4	71	0.31	
5	248	1.09	
6	84	0.37	
7	266	1.17	
8	262	1.15	1.80
9	198	0.88	
10	207	0.91	
11	67	0.29	

Illustration 19. TABLE OF RESULTS - Dog #3

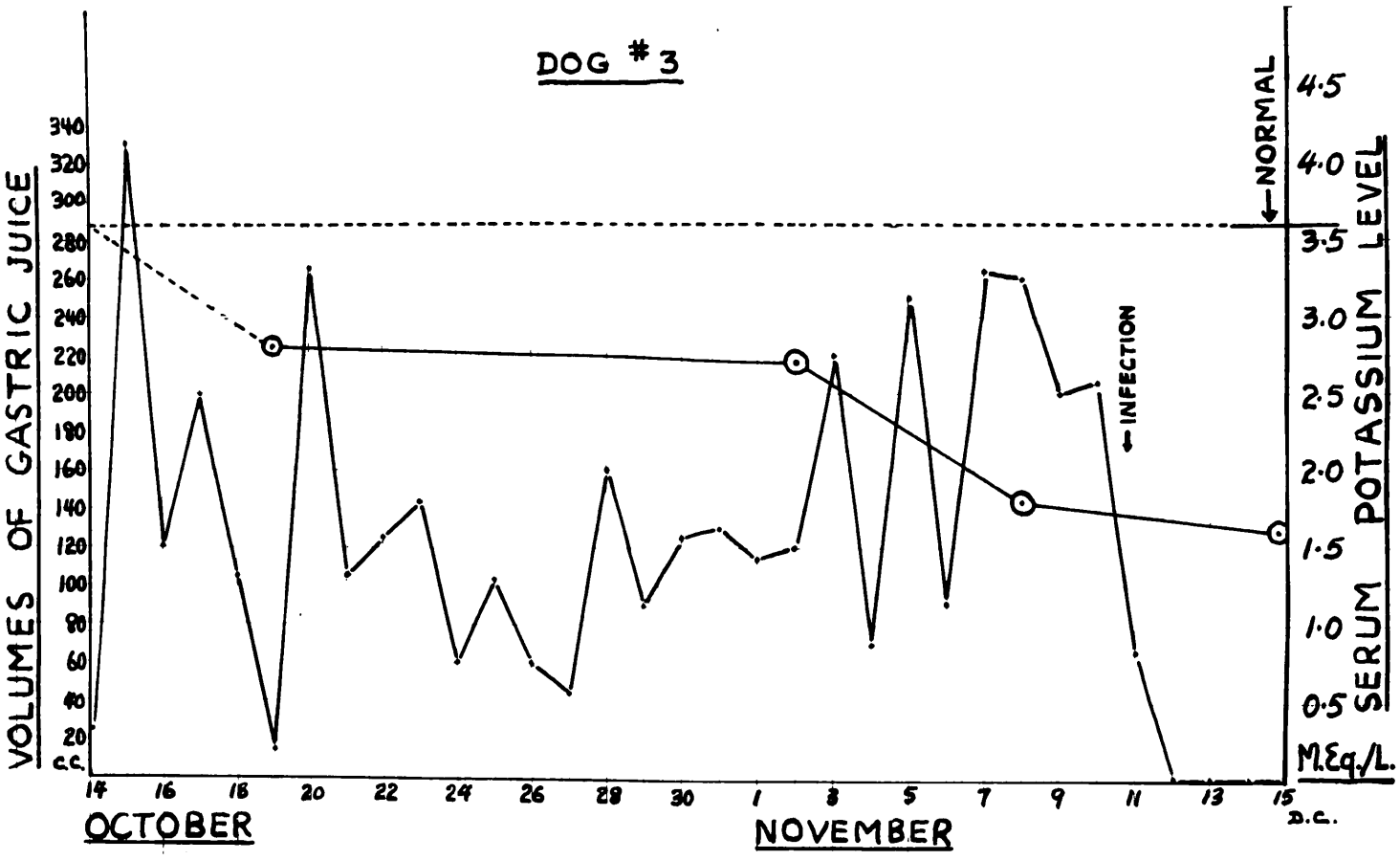


Illustration 20. GRAPH OF RESULTS - Dog #3

postoperative period can be offered. Again, there is a drop in the level of serum potassium with the continued loss of gastric juice in the few determinations recorded. The determination of pepsin content and pH value of the gastric juice showed no change over the period. Again autopsy revealed nothing more than an atypical bilateral lower lobe pneumonitis.

Dog #4. Results are shown in illustrations #21 and #22. This study was very short because of the early onset of the infection. This may have been the animal which infected the others as it was the worst affected and died first. The level of serum potassium dropped over the three determinations but this is of practically no significance. Autopsy revealed extensive bilateral pneumonitis.

Dog #8. Results are shown in tables in illustration #23 and in graphic form in illustration #24. As stated before this dog is the first of three studied in great detail. Because of complications of the pouch this dog did not survive long enough to be started on a deficient diet. During the early period of study numerous biochemical determinations were performed. On November 24 the plasma NPN was 25.2 mg. per 100 c.c.

Brownie - Dog #4

Date	Volume G.J. c.c.	MEq. K. in G.J.	MEq. K. Serum
Oct.22	37	0.23	
23	43	0.26	
24	106	0.65	2.56
25	131	0.80	
26	105	0.64	
27	38	0.23	
28	66	0.40	
29	52	0.32	
30	35	0.21	
31	29	0.18	
Nov. 1	8	0.05	
2	82	0.50	2.12
3	36	0.22	
4	10	0.06	
5	16	0.10	
6	4	0.02	

Illustration 21. TABLE OF RESULTS - Dog #4

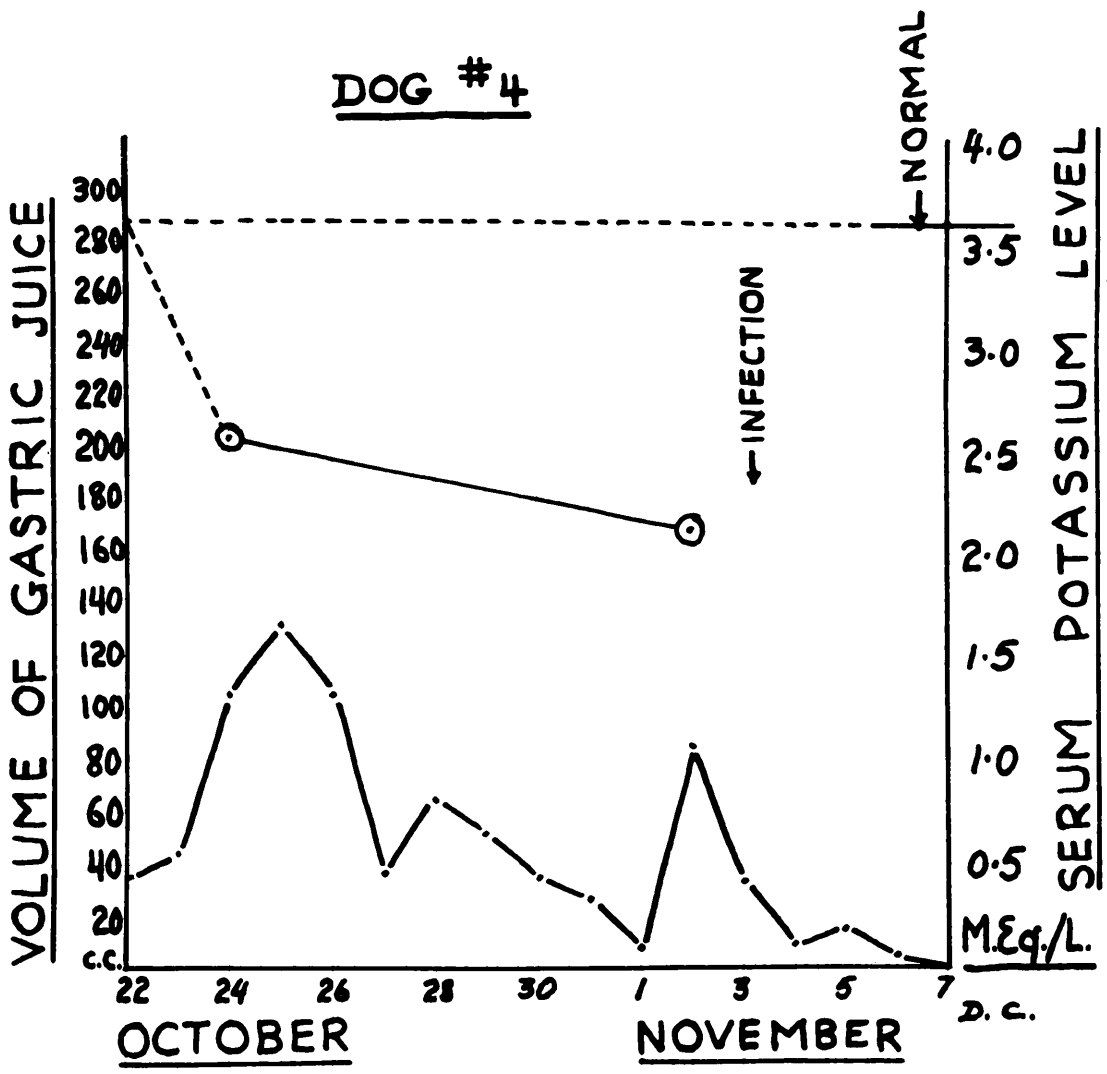


Illustration 22. GRAPH OF RESULTS - Dog #4

DOG # 8 - JUNIOR

Date 1949		Water c.c.	Diet gm.	K in Diet meq.	Urine c.c.	K in Urine meq.	Serum K meq/l	Gastric Juice c.c.	pH	meq	
Nov.	16	120	100	15.0	100	10.3	4.00				
	17	80	80	12.0	250	28.1					
	18	180	100	15.0	80	12.0					
	19	400	100	15.0	100	14.3					
	20	200	70	10.5	80	12.0					
	21	400	70	10.5	120	13.5					
	22	900	70	10.5	90	10.2					
	23	400	70	10.5	100	11.3	4.10				
	24	300	70	10.5	200	16.5					
	25	350	70	10.5	200	6.5					
	26	400	80	12.0	70	2.3					
	27	300	90	13.5	250	6.8					
	28	350	70	10.5	150	4.9					
	29	350	80	12.0	150	5.5	4.00				
	30	270	70	10.5	100	2.5					
Dec.	1	450	90	13.5	80	2.0					
	2	400	80	12.0	100	2.5					
	3	400	70	10.5	90	2.3					
	4	410	70	10.5	150	3.8					
	5	260	80	12.0	110	2.8	2.95				
	6	400	80	12.0	140	11.9					
	7	420	80	12.0	160	13.6					
	8	520	80	12.0	150	12.7					
	9	380	80	12.0	140	11.9					
	10	420	80	12.0	150	12.7					
	11	440	80	12.0	80	6.8					
	12	420	120	18.0	100	8.5					
	13	430	110	16.5	80	5.4	4.20				
	14	280	120	18.0	90	6.1					
	15	460	120	18.0	100	6.7					
	16	440	120	18.0	110	7.4					
	17	420	120	18.0	80	5.4					
	18	480	240	36.0	150	10.2					
	19	500	Ringers	2.0	230	15.4	3.70				
	20	500	Ringers	2.0	250	16.7					OPERATION
	21	500	Ringers	2.0	130	8.7	2.80				
	22	300	33	5.0	80	8.3					
	23	420	120	18.0	90	9.3					
	24	340	80	15.0	70	7.2		43	1.15	0.42	
	25	300	120	18.0	100	7.2		100	1.12	0.97	BLEEDING
	26	320	160	24.0	50	5.2		88	1.73	0.80	BLEEDING
	27	350	80	12.0	70	7.3	3.50	117	2.03	1.13	BLEEDING
	28	350	70	10.5	90	10.6		27	1.70	0.26	BLEEDING
	29	300	60	9.0	90	10.6		20	2.12	0.19	BLEEDING
	30	360	60	9.0	60	7.1		27	1.32	0.26	BLEEDING
	31	480	60	9.0	100	11.8		77	2.03	0.74	BLEEDING
Jan.	1	250	90	13.5	60	7.1		39	1.72	0.38	BLEEDING
	2	380	70	10.5	70	8.3		65	0.82	0.63	
	3	320	70	10.5	60	7.1		58	1.08	0.56	
	4	380	70	10.5	80	9.5	2.90	34	1.17	0.33	
	5	280	60	9.0	60	7.1		62	1.18	0.63	

Illustration 23. TABLE OF RESULTS - Dog #8

DOG # 8 - JUNIOR

Date 1950		Water c.c.	Diet gm.	K in Diet meq.	Urine c.c.	K in Urine meq.	Serum K meq/l	c.c.	pH	meq	
Jan.	6	320	70	10.5	60	7.7		46	1.08	0.44	
	7	260	50	7.5	60	7.7		48	1.08	0.46	
	8	430	80	12.0	100	12.8		45	1.05	0.43	
	9	360	90	13.5	100	12.8		40	1.12	0.39	
	10	320	110	15.5	90	13.9	3.20	Food			BREAKDOWN
	11	300	120	18.0	80	12.4		Food			
	12	280	120	18.0	100	15.5		Food			
	13	260	120	18.0	110	17.1		Food			
	14	420	120	18.0	100	15.5		Food			
	15	360	120	18.0	110	17.1		Food			
	16	400	120	18.0	100	15.5		Food			
	17	0	0	0	120	14.2	4.30				
	18	0	0	0	110	13.4					REPAIR
	19	0	0	0	90	11.7		20	4.72	-	
	20	40	0	0	60	7.1		20	5.10	-	
	21	530	90	13.5	80	9.2		25	-	-	
	22	220	90	13.5	90	11.6		21	-	-	
	23	440	90	13.5	180	14.6		15	-	-	
	24	320	90	13.5	120	11.9	4.50	10	-	-	
	25	260	110	16.5	120	11.9		PUS	-	-	
	26	420	110	16.5	130	13.8		-	-	-	
	27	220	120	18.0	100	14.2		-	-	-	
	28	420	130	19.5	130	14.8		-	-	-	
	29	300	110	16.5	130	14.8		-	-	-	
	30	240	120	18.0	120	11.9		-	-	-	
	31	330	120	18.0	110	11.4	4.55	-	-	-	
Feb.	1	200	120	18.0	90	9.6		-	-	-	
	2	180	120	18.0	140	13.3		-	-	-	
	3	180	130	19.5	120	12.5		-	-	-	
	4	320	110	16.5	130	12.8		-	-	-	
	5	480	120	18.0	130	12.8		-	-	-	
	6	240	120	18.0	90	9.6		-	-	-	
	7	320	40	6.0	90	9.6	4.40	-	-	-	
	8	300	0	0	80	6.2		-	-	-	EXCISION
	9	240	0	0	40	4.4		-	-	-	
	10	-	-	-							DIED

Illustration 23. TABLE OF RESULTS - Dog #8

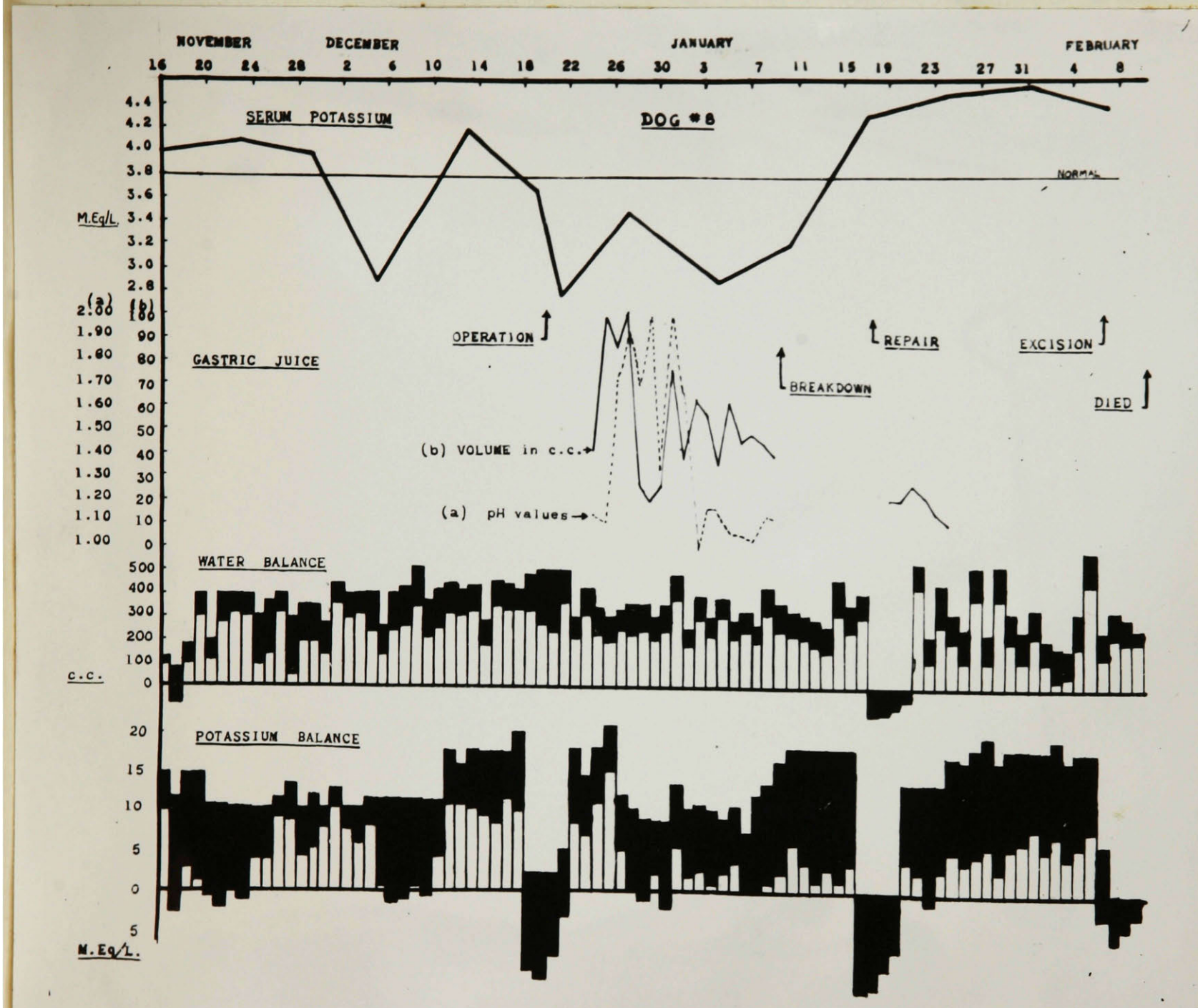


Illustration 24. GRAPH OF RESULTS - Dog #8

serum proteins 7.5 gms. per 100 c.c. CO_2 capacity was 44.94 volumes per 100 c.c., chlorides 418 mg. per 100 c.c. and electrocardiograms on November 23 and 30 were normal.

The bleeding from the pouch from the 25th to 31st of December forwarned of the mucosal partition perforation which was found on January 10/50. During this period the level of potassium in the serum dropped for reasons unknown; the drop occurred before operation. Following the liberation of the gastric pouch and the excision of the communicating intra-abdominal abscess, pus only drained from the stoma of the pouch. Apparently the blood supply to these new gastric pouches is adequate but insufficient when these pouches have to be liberated from the stomach to repair a perforation of the mucosal partition. At the time of excision of the pouch on February 8/50 many adhesions were found and actually by lifting up the pouch after it was liberated from the anterior abdominal wall, attachments were found to almost all of the abdominal organs. With some difficulty it was freed but oozing was not controlled as a haemorrhagic peritonitis was the major finding at autopsy.

Dog #9. The study on this dog began on November

16/49. Water and potassium balance studies showed normal values up to the time of operation. Illustration #25 shows the collected results of the study. These results are also shown in illustration #26. Illustration #26 shows the drop of the serum potassium level on the potassium deficient diet and the small rise when potassium was refed. There is practically no increase in the volume of gastric juice secreted except for seven days after the refeeding of potassium. There is a significant increase in the volume of water exchange in the potassium deficient state and this is well shown in the bar graphs. The dog remained in positive potassium balance except for a short period following operation until the time when the dog was given a potassium deficient diet. After this time there was a negative potassium balance which gradually lessened as the deficiency progressed. The refeeding of potassium caused a positive balance as is shown.

The second graph shows the more acid reaction and decreased concentration of pepsin in the gastric juice of this animal in potassium deficiency. The daily secretion of potassium in the gastric juice remained about the same during the potassium depletion but this level was much lower than the control level. An attempt to show

DOG # 9 - TOPSY

Date 1949		Water c.c.	Diet gm.	K in Diet meq.	Urine c.c.	K in Urine meq.	Serum K meq/l	Gastric Juice c.c.	pH	Pepsin	Meq	
Nov.	16	350	100	15.0	50	0.05	3.70					
	17	100	100	15.0	20	2.5						
	18	180	100	15.0	20	2.5						
	19	330	90	13.5	70	8.8						
	20	200	100	15.0	100	12.6						
	21	250	80	12.0	50	6.3						
	22	400	80	12.0	100	12.6						
	23	400	80	12.0	80	10.1	4.60					
	24	370	110	16.5	160	12.5						
	25	450	120	18.0	140	16.9						
	26	380	100	15.0	20	1.3						
	27	400	80	12.0	120	7.5						
	28	420	90	13.5	140	12.5						
	29	390	80	12.0	110	7.5	4.40					
	30	400	100	15.0	130	19.2						
Dec.	1	440	90	13.5	120	8.2						
	2	410	80	12.0	150	13.7						
	3	380	80	12.0	100	6.9						
	4	400	100	15.0	130	8.9						
	5	360	100	15.0	120	8.2						
	6	350	100	15.0	130	13.0	4.30					
	7	390	100	15.0	120	12.0						
	8	410	100	15.0	130	13.0						
	9	360	100	15.0	160	16.0						
	10	360	100	15.0	130	13.0						
	11	400	100	15.0	150	15.0						
	12	380	100	15.0	100	10.0						
	13	500	Ringers	2.0	120	10.4	4.25					
	14	500	Ringers	2.0	180	3.2						OPERATION
	15	500	Ringers	2.0	120	4.8						
	16	200	33	5.0	80	3.6		20			0.22	
	17	300	120	18.0	90	3.2		27	1.46		0.29	
	18	430	120	18.0	80	4.0		65	0.91	0.090	0.17	
	19	320	120	18.0	100	5.9	3.30	50	1.03		0.50	
	20	340	120	18.0	70	6.7		40	1.16	0.031	0.44	
	21	380	120	18.0	80	5.9		52	1.16	0.051	0.57	
	22	400	80	12.0	70	6.7		22	1.40		0.24	
	23	370	90	13.5	90	5.0		30	1.23		0.33	
	24	320	120	18.0	60	6.3		62	1.01		0.68	
	25	300	120	18.0	75	8.4		90	1.14		0.79	
	26	390	120	18.0	100	5.0		78	1.40		0.69	
	27	420	120	18.0	60	5.0	3.80	61	1.24	0.055	0.54	
	28	400	120	18.0	70	7.0		123	1.06		0.84	
	29	380	120	18.0	90	9.0		119	1.07	0.128	0.81	
	30	400	120	18.0	60	6.0		128	1.14		0.87	
	31	420	120	18.0	140	14.0		131	1.40		0.95	
Jan.	1	400	120	18.0	130	13.0		87	1.26		0.59	
	2	360	120	18.0	130	13.0		79	1.06		0.53	
	3	380	120	18.0	70	7.0		58	1.08		0.39	
	4	400	130	19.5	100	10.0	3.7	60	1.06		0.38	
	5	450	120	18.0	100	15.2		110	1.42		0.67	
	6	450	110	16.5	110	16.7		96	1.12		0.60	
	7	420	110	16.5	125	19.0		115	1.09		0.74	

Illustration 25. TABLE OF RESULTS - Dog #9

DOG # 9 - TOPSY

Date 1950		Water c.c.	Diet gm.	K in Diet meq.	Urine c.c.	K in Urine meq.	Serum K meq/l	Gastric Juice c.c.	pH	Pepsin	Meq	
Jan.	8	380	110	16.5	120	18.2		90	1.03		0.58	
	9	390	110	16.5	140	12.3		88	1.07		0.56	
	10	400	120	18.0	130	4.8	3.80	78	1.04		0.19	DEFICIENCY
	11	420	120	0	100	3.7		63	1.43		0.16	DIET
	12	380	100		90	3.3		58	1.76		0.15	
	13	400	100		100	3.7		53	1.75	0.108	0.13	
	14	320	100		130	4.8		60	1.68		0.15	
	15	400	120		120	4.4		66	1.36		0.17	
	16	360	110		130	4.8		56	1.38	0.140	0.14	
	17	330	120		120	1.1	3.10	60	1.24		0.26	
	18	380	120		140	1.3		62	1.42		0.27	
	19	410	120		130	1.4		56	1.40		0.24	
	20	330	120		120	1.1		52	1.36		0.22	
	21	660	120		160	1.4		67	1.24		0.29	
	22	440	110		240	1.8		87	1.29		0.37	
	23	480	120		120	1.1		75	1.30		0.32	
	24	620	120		120	1.0	2.80	105	1.25		0.35	
	25	520	130		100	0.9		83	1.34		0.27	
	26	620	130		100	0.9		98	1.26		0.32	
	27	480	130		120	1.0		91	1.29		0.30	
	28	580	140		140	1.2		95	1.32		0.31	
	29	460	130		120	1.0		68	1.34		0.22	
	30	600	130		120	1.0		99	1.24		0.33	
	31	540	130		130	0.8		67	1.32		0.20	
Feb.	1	520	130		110	0.7	2.60	58	1.28		0.17	
	2	660	130		180	1.0		63	1.26		0.19	
	3	580	130		160	1.0		83	1.30		0.25	
	4	620	130		120	0.7		76	1.27		0.23	
	5	660	130		160	1.0		68	1.30		0.20	
	6	680	130		200	1.2		57	1.32		0.17	
	7	780	130		210	0.9	2.10	78	1.24		0.29	
	8	580	130		120	0.5		74	1.30		0.28	
	9	640	100		150	0.6		78	1.24		0.29	
	10	560	110		180	0.8		76	1.24		0.29	
	11	540	120		140	0.6		71	1.22		0.27	
	12	480	110		130	0.6		68	1.24		0.26	
	13	580	100		130	0.6		70	1.14		0.27	
	14	560	100		120	0.6	2.65	79	0.98	0.107	0.24	
	15	400	100		130	0.6		74	1.08		0.22	
	16	580	110		120	0.5		74	1.10		0.22	
	17	460	110		150	0.7		64	1.12		0.19	
	18	480	90		140	0.6		42	1.08		0.13	
	19	560	90		120	0.6		50	1.10		0.15	
	20	530	90		130	0.6		47	1.06		0.14	
	21	640	80		130	0.4	2.50	93	1.12		0.31	
	22	660	90		150	0.5		91	1.36		0.30	
	23	620	100		140	0.5		102	1.08		0.40	
	24	640	120		150	0.5		82	1.14		0.27	
	25	880	120		240	0.8		96	0.96		0.32	
	26	540	120		180	0.6		106	0.90		0.35	
	27	520	110		160	0.5		84	1.02		0.28	
	28	660	120		180	1.1	2.50	87	1.08		0.24	

Illustration 25. TABLE OF RESULTS - Dog #9

DOG # 9 - TOPSY

Date 1950		Water c.c.	Diet gm.	K in Diet meq.	Urine c.c.	K in Urine meq.	Serum K meq/l	Gastric Juice c.c.	pH	Pepsin	Meq	
Mar.	1	760	110		170	1.1		85	1.06		0.23	
	2	820	110		180	1.1		74	1.04		0.20	PARALYSIS
	3	740	90		180	1.1		65	1.00		0.18	
	4	650	80		130	0.8		76	1.01	0.056	0.21	
	5	540	50		120	0.7		46	1.03		0.12	
	6	430	90		130	0.8	2.50	45	1.00		0.12	
	7	440	40		150	1.0		40	0.90		0.22	
	8	720	90	15.0	140	0.9		82	1.00		0.67	REFED K
	9	480	80	12.0	130	0.8		66	0.94		0.52	
	10	500	80	12.0	150	0.9		96	1.04		0.46	
	11	780	90	13.5	210	1.5		116	0.98		0.62	
	12	820	90	13.5	220	1.6		98	1.02		0.48	
	13	520	90	13.5	200	1.4	3.10	157			0.62	
	14	630	90	0	170	1.6		158		0.027	0.64	
	15	560	90		150	1.5		146	1.00		0.60	
	16	720	90		180	1.7		109			0.51	
	17	640	100		190	1.8		110			0.51	
	18	750	100		130	1.2	2.80	127	1.04		0.62	
	19	700	90		200	1.8		103			0.41	
	20	840	100		250	2.3		105	1.02		0.38	
	21	820	100		200	1.8		102		0.022	0.37	
	22	760	80		200	0.8		96	0.98		0.19	
	23	660	80		180	0.7	2.15	136	0.96		0.22	
	24	690	80		210	0.8		84			0.17	
	25	630	90		190	0.7		76	1.04		0.16	
	26	500	80		140	0.6		42	1.02		0.10	
	27	620	70		130	0.5		56			0.11	
	28	480	50		120	0.5	1.90	43			0.10	
	29	450	35		120	0.5		40			0.10	
	30	230	20	10.0	100	0.4		24			0.05	
	31	500	Ringers	5.0	230	0.9						
Apr.	1	400	Ringers	7.0	120	0.5	2.70					
	2		- - - Found Dead- - -									

Illustration 25. TABLE OF RESULTS - Dog #9

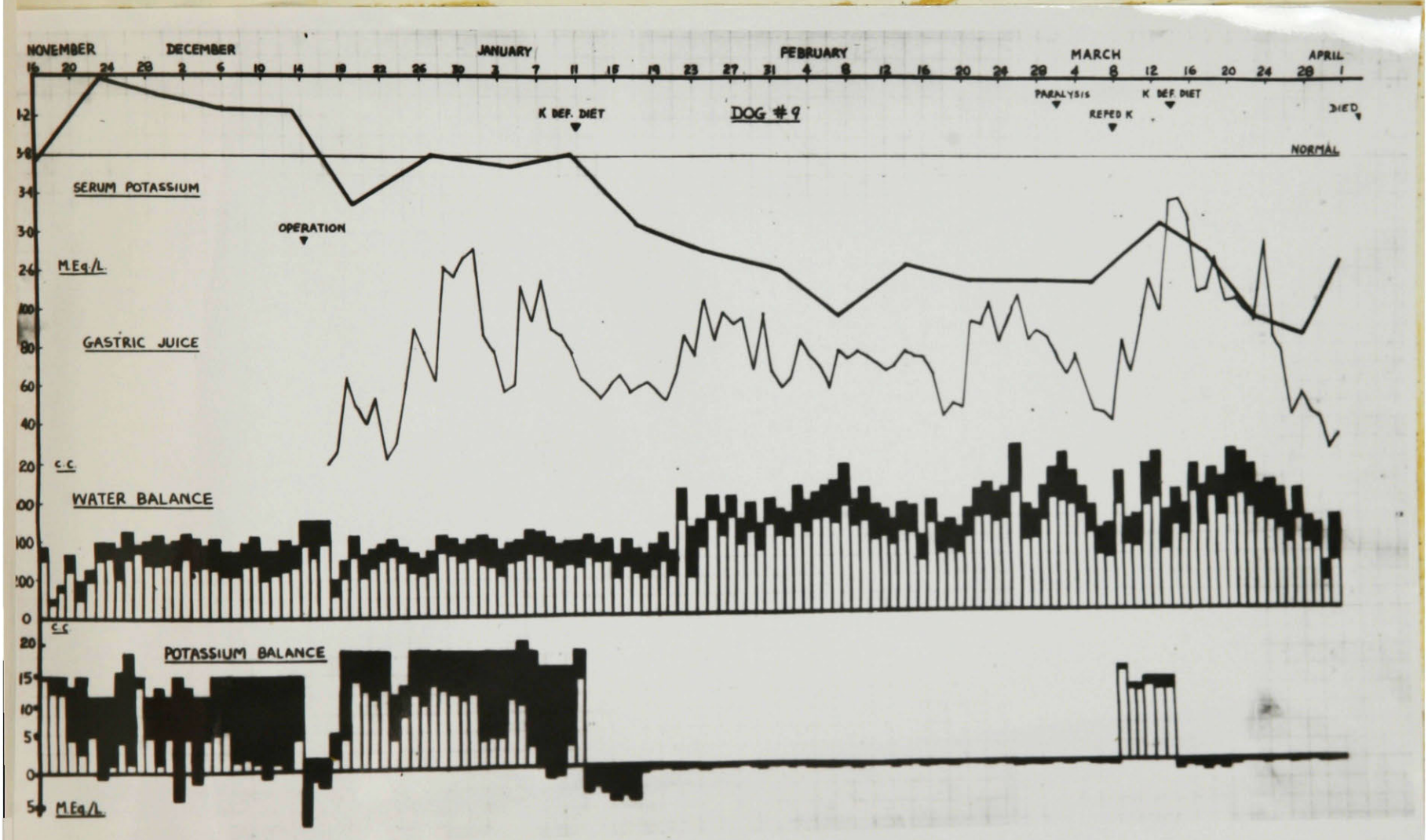


Illustration 26. GRAPH OF RESULTS - Dog #9

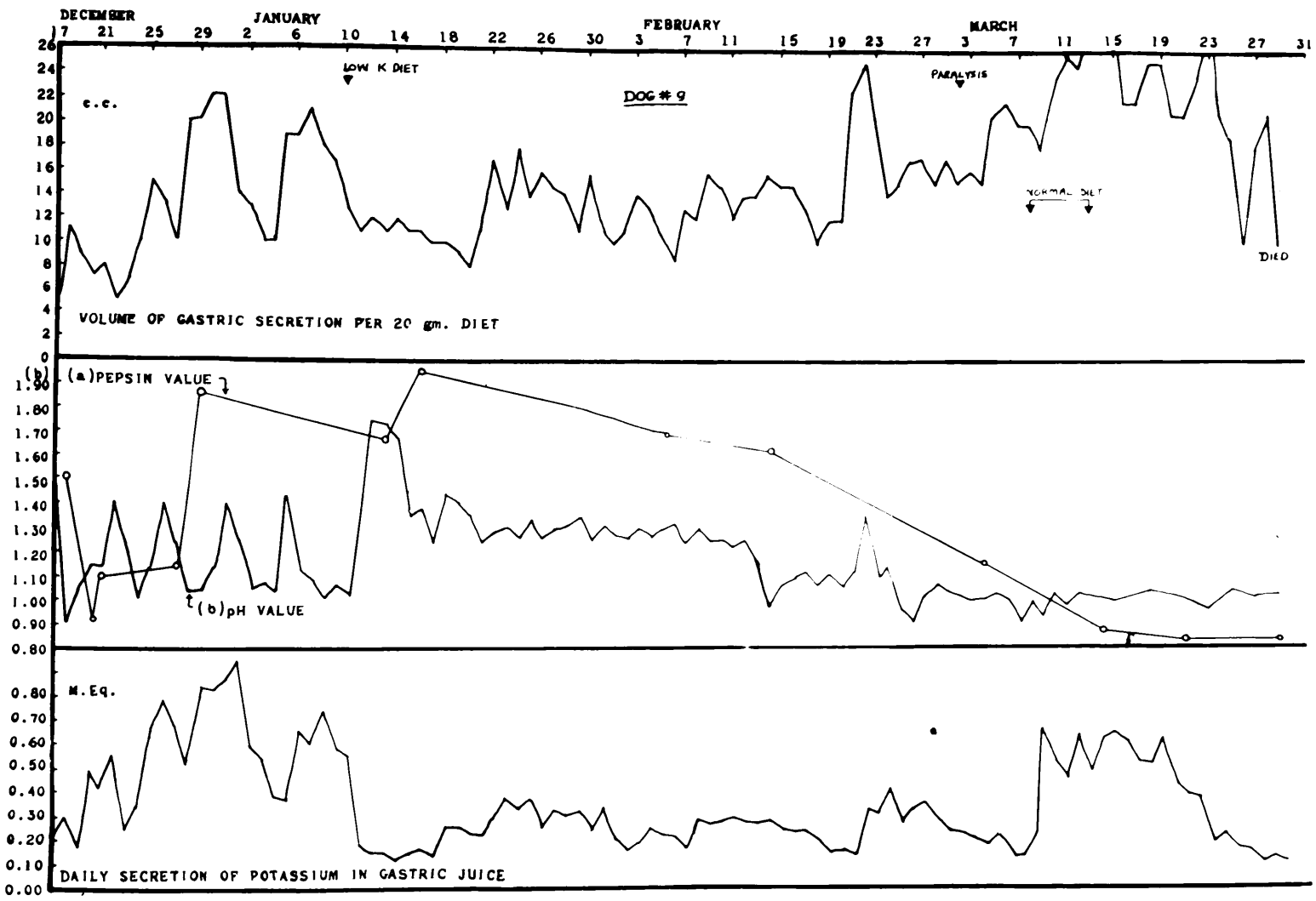


Illustration 26. GRAPH OF RESULTS - Dog #9

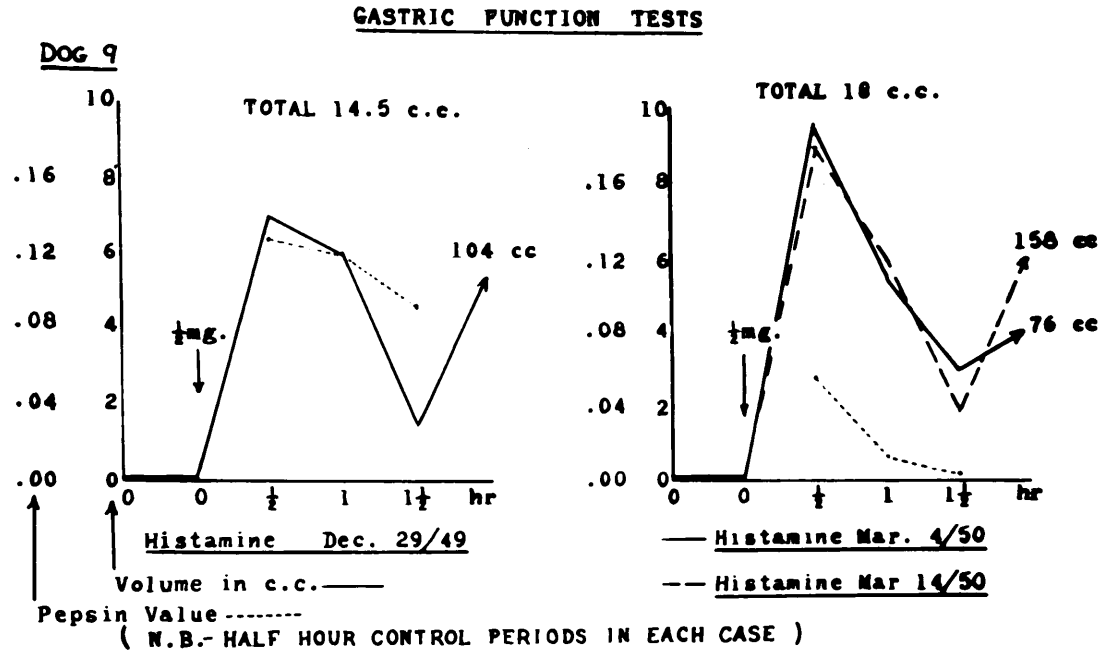


Illustration 26. GRAPH OF RESULTS - Dog #9

the amount of gastric secretion per unit of diet was made and shown at the top of this graph. The curve of volume of gastric juice secreted per 20 gm. of diet almost parallels the curve of the daily secretion of gastric juice as shown in the previous graph.

Because Dog #10 died on the intravenous administration of potassium, no insulin tests were performed on this dog in the potassium deficient state. Results of histamine and teasing tests are shown in graph #26 and show a change only in the chemical phase of secretion but even this is not marked. Note that in the histamine tests, the pepsin values are much lower in the potassium deficient state. Seven days after intermittent (periodic) paralysis appeared, the dog was refed potassium for one week. He was then again placed on a potassium deficient diet but unfortunately became very weak after two weeks. He was found dead in his cage one morning and complete autopsy revealed no gross abnormalities apart from emaciation and bilateral bronchopneumonia which apparently was the cause of death. Discussion of the histological examination of the autopsy material will be given at the end of this section.

Biochemical studies were performed in the control period and during the stage of periodic paraylsis due to potassium deficiency. The plasma NPN was 26.9 mg. per 100 c.c. (Nov.24) and 21.0 mg.per 100 c.c.

(Mar. 7), proteins 6.78 gms. per 100 c.c. (Nov.24) and 5.18 mg. per 100 c.c. (Mar. 7), serum sodium 144 M.Eq./L. (Nov.29) and 14.3 M.Eq./L. (Mar.7), serum chlorides 416.mg. per 100 c.c. (Nov.28) and 373. mg. per 100 c.c. (Mar.7), and the CO_2 C.P. 36.58 vol. per 100 c.c. (Nov.28) and 37.75 vol. per 100 c.c. (Mar.8). Again, complete blood counts were well within the limits considered normal for humans and dogs.

Electrocardiograms were taken four times. One was taken in the control period and another during the stage of periodic paralysis on March 2. The latter set of electrocardiograms show a slurring of the ST segment, most marked in lead 2, but little else characteristic of potassium deficiency at least in human electrocardiograms.

Dog #10. Results are shown in illustrations #27 and #28. As in the case of the previous dog, each operative procedure was accompanied by a drop in the serum potassium and negative potassium balance. The second drop in serum potassium level on December 20 and the negative potassium balance which accompanied this, occurred for no known reason. The reason for the break in the mucosal partition in the late postoperative period is also unknown. Very fortunately it was easily repaired and no adequate cause for the break was found at operation on February 10/50. Signs of paralysis were thought

DOG #10 - SHORTY

Date 1949		Water c.c.	Diet gm.	K in Diet meq.	Urine c.c.	K in Urine meq.	Serum K meq/l	Gastric Juice c.c.	pH	Pepsin	Meq	
Nov.	21	400	80	12.0	40	3.7						
	22	350	80	12.0	70	6.1						
	23	350	80	12.0	60	5.3	4.20					
	24	450	80	12.0	30	4.1						
	25	400	80	12.0	100	13.5						
	26	350	90	13.5	50	6.8	4.20					
	27	200	90	13.5	50	6.8						
	28	400	90	13.5	150	20.2						
	29	400	90	13.5	110	14.9	4.40					
	30	150	80	12.0	120	5.7						
Dec.	1	500	Ringers	2.0	360	17.1						
	2	500	Ringers	2.0	170	12.6	3.20					OPERATION
	3	500	Ringers	2.0	140	10.4		10			0.08	
	4	250	Salt Mix.	15.0	130	16.7	3.45	20	1.42		0.15	
	5	150	20	3.0	60	7.7		59	1.20	0.050	0.45	
	6	460	15	2.3	85	9.3	3.90	29	1.86	0.040	0.19	
	7	280	25	3.8	100	10.9		36	1.60		0.23	
	8	400	70	10.5	120	13.1		38	1.86		0.24	
	9	300	50	7.5	70	7.7		32	1.90		0.21	
	10	250	70	10.5	90	9.8		35	1.84		0.36	
	11	500	65	9.8	60	6.7		44	1.46		0.45	
	12	350	50	7.5	70	7.7		36	1.47		0.37	
	13	420	80	12.0	100	6.7	4.55	34	1.43	0.067	0.35	
	14	400	90	13.5	50	3.4		33	1.46		0.34	
	15	450	90	13.5	70	4.7		56	1.42		0.58	
	16	350	110	16.5	80	5.4		61	1.18		0.57	
	17	320	110	16.5	90	6.0		45	1.22		0.42	
	18	450	120	18.0	70	4.7		98	0.91	0.049	0.91	
	19	400	120	18.0	70	4.7	3.40	69	0.91		0.64	
	20	450	120	18.0	100	21.4		70	1.03	0.064	0.65	
	21	380	110	16.5	90	19.2		84	1.02	0.055	0.78	
	22	450	120	18.0	70	15.0		38	1.01		0.35	
	23	420	110	16.5	80	17.1		75	1.30		0.61	
	24	320	110	16.5	60	12.8		96	1.14		0.78	
	25	300	120	18.0	50	10.1		87	1.20		0.71	
	26	400	120	18.0	60	12.8		66	1.22		0.54	
	27	320	120	18.0	70	15.0	4.60	44	1.52	0.049	0.36	
	28	420	120	18.0	80	4.6		55	1.14		0.45	
	29	330	120	18.0	90	5.2		110	1.06	0.055	1.28	
	30	300	120	18.0	60	3.5		59	1.06		0.69	
	31	300	80	12.0	70	4.1		46	1.12		0.53	
Jan.	1	400	110	16.5	60	3.5		31	1.10		0.36	
	2	360	110	16.5	90	5.2		43	1.15		0.51	
	3	320	120	18.0	70	4.1		72	1.06		0.83	
	4	400	120	18.0	90	11.8	4.3	32	1.12		0.31	
	5	280	110	16.5	60	7.9		71	1.10		0.70	
	6	320	110	16.5	100	13.1		56	1.06		0.55	
	7	450	110	16.5	80	10.5		54	1.12		0.53	
	8	480	110	16.5	90	11.8		43	1.06		0.42	
	9	370	110	16.5	110	14.4		45	1.08		0.44	
	10	420	120	0	100	8.0	3.85	34	1.06	0	0.32	DEFICIENT
	11	400	120		100	3.0		50	1.18		0.47	DIET

Illustration 27. TABLE OF RESULTS - Dog #10

DOG #10 - SHORTY

Date 1950		Water c.c.	Diet gm.	K in Diet meq.	Urine c.c.	K in Urine meq.	Serum K meq/l	c.c.	pH	Pepsin	Meq	
Jan.	12	380	120		90	3.7		59	1.58		0.56	
	13	320	110		110	3.3		62	1.94	0.079	0.59	
	14	280	110		100	3.0		40	1.88		0.38	
	15	580	120		110	3.3		46	1.88		0.44	
	16	340	110		100	3.8		43	1.70	0.130	0.41	
	17	360	120		110	3.0	3.10	76	1.16		0.48	
	18	440	40		100	2.9		60	1.33		0.38	
	19	480	40		130	3.5		40	1.65		0.25	
	20	380	80		120	3.2		42	1.28		0.26	
	21	330	100		100	2.7		48	1.30		0.30	
	22	520	110		70	1.9		63	1.34		0.39	
	23	420	100		120	3.2		66	1.28		0.42	
	24	640	100		200	2.7	3.20	60	1.30		0.35	
	25	330	90		120	2.6		34	1.26		0.20	
	26	520	90		100	2.2		77	1.31		0.45	
	27	340	100		110	2.4		53	1.24		0.31	
	28	380	110		100	2.2		88	1.28		0.52	
	29	240	90		130	2.9		63	1.22		0.37	
	30	420	90		120	2.8		93	1.34		0.55	
	31	380	100		130	1.7	2.70	87	1.46		0.31	
Feb.	1	420	110		120	1.6		92	1.48		0.33	
	2	480	110		140	1.8		54	1.24		0.19	
	3	460	120		130	1.7		71	1.32		0.26	
	4	420	120		100	1.3		60	1.28		0.22	
	5	440	120		120	1.6		48	1.26		0.17	
	6	480	120		100	1.3		63	1.34		0.23	
	7	440	120		100	1.4	2.30	78	1.26		0.37	
	8	370	120		130	1.8		-	-		-	BREAKDOWN
	9	200	0		80	1.1		-	-		-	
	10	0	0		80	1.1		-	-		-	REPAIR
	11	20	0		80	1.1		20	-		0.17	
	12	310	100		100	1.4		30	-		0.25	
	13	260	120		90	1.3		56	1.24		0.36	
	14	200	120		100	0.9	2.65	64	0.92	0.057	0.47	
	15	260	120		120	1.1		65	0.98		0.48	
	16	580	130		130	1.1		55	0.98		0.41	
	17	330	130		110	0.9		84	1.00		0.64	
	18	400	120		100	0.9		76	1.02		0.56	
	19	440	110		130	1.1		85	0.98		0.64	
	20	520	110		140	1.2		86	1.08		0.65	
	21	600	120		140	1.0	2.40	134	0.96	0.052	0.52	
	22	540	110		130	0.9		95	1.02		0.37	
	23	500	120		130	0.9		86	0.98		0.34	
	24	620	120		150	1.0		89	1.00		0.35	
	25	520	110		160	1.1		84	1.02		0.33	
	26	420	110		140	1.0		76	1.04		0.30	
	27	440	110		140	1.0		66	0.98		0.26	
	28	480	120		160	1.1	2.20	50	1.02	0.047	0.19	10 mg.
Mar.	1	520	110		150	1.0		58	0.98		0.23	Cortate
	2	540	100		180	1.2	2.6	54	0.96		0.21	Neck Paralysis
	3	-	-	- - -	DIED	- - -						

Illustration 27. TABLE OF RESULTS - Dog #10

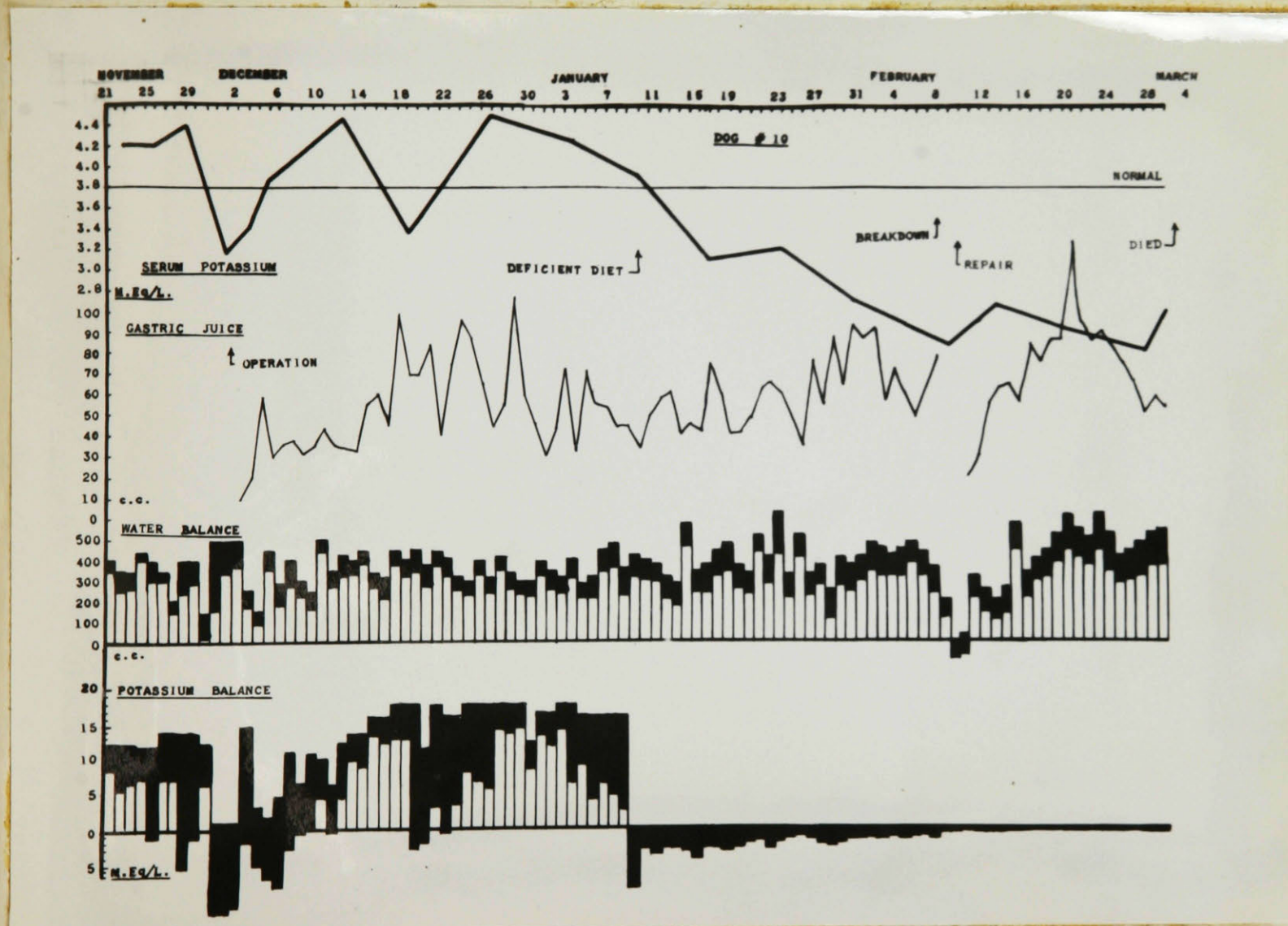


Illustration 28. GRAPH OF RESULTS - Dog #10

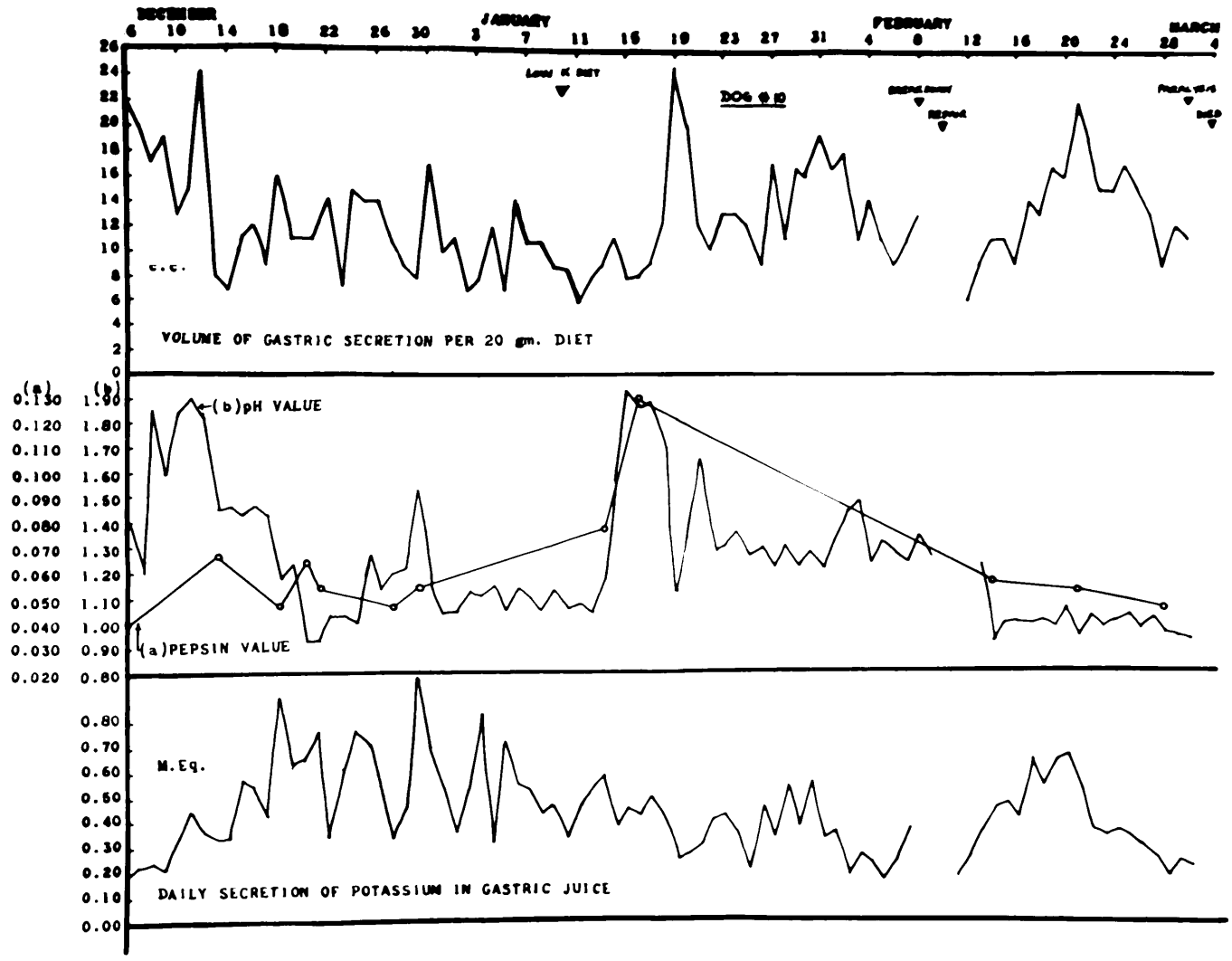


Illustration 28. GRAPH OF RESULTS - Dog #10

to be rather slow in appearing so 10 mg. of "cortate" (desoxycorticosterone acetate - Shering) was given on February 28/50 and March 1/50. Neck weakness appeared on March 2/50 with generalized paralysis on the following day. An insulin test was attempted on March 3/50. Immediately after the intravenous injection of half of the previously used quantity of insulin the dog became cyanosed, frothed at the mouth and stopped breathing. In spite of artificial respiration coramine injection and intravenous dextrose solution the animal died. Blood was immediately taken for the various biochemical determinations and are compared with similar determinations in the preoperative control period. Plasma NPN 21.5 mg. per 100 c.c. (Nov. 24) 32.0 mg.per 100 c.c. (Mar.3); total proteins 6.74 gm. per 100 c.c. (Nov.24) 6.22 gm. per 100 c.c. (Mar. 3); chlorides 382 mg. per 100 c.c. (Nov.28) 388 mg. per 100 c.c. (Mar.3); serum sodium 140 M.Eq./L. (Nov.29) 140 M.Eq./L. (Mar.3); CO_2 capacity 46.32 volumes per 100 c.c. (Dec.14 - postoperative) blood sugar 118 mg. per 100 c.c. (Nov.30) 129.0 mg. per 100 c.c. (Mar.3) were the values found.

As seen in illustration #28 there is a tendency to an increase in the volume of gastric

juice secreted as the potassium deficiency progressed and this was more or less parallel to the decrease in level of serum potassium and increase in water exchange. Graph #28 shows a tendency of the pouch to secrete a more acid juice of lowered pepsin content and a decrease in the total content of potassium in the daily volume. The volume of gastric juice secreted per unit of diet almost parallels the total volume of gastric juice secreted as shown in the previous graph. Electrocardiograms in the control period (Nov.30) and during the period in which the dog showed intermittent paralysis (Mar.2) show a lowering of the ST segment and an inversion of the T waves. These are believed to be changes due to potassium deficiency. Autopsy revealed no gross lesions and the microscopic findings will be discussed later.

Dog #11. The results of the observations on dog #11 are shown in illustrations #29 and #30. Studies were begun on this dog on March 30/50 and on April 5 a large Heindenhain pouch was made. The dog did well postoperatively and by April 17/50 was standardized to various stimulants of gastric secretion and started on a low potassium diet. Next day this dog was started on the daily injection of 25 mg. of desoxycorticosterone acetate

PAVLOV - Dog #11

DATE	WATER c.c.	DIET gm.	K in DIET M.Eq/L.	K in URINE M.Eq/L.	SERUM K M.Eq/L.	GASTRIC JUICE Vol.	pH	Pepsin	K	DOCA mg.
Mar. 30	280	90	13.5		3.80					
31	300	130	19.5							
Apr. 1	300	140	21.0							
2	300	120	18.0							
3	250	110	16.5		3.80					
4	0	0								
5	460	40	2.0							
6	400	60	6.0							
7	200	80	12.0			15			0.13	
8	300	90	13.5			20			0.17	
9	300	80	12.0			24			0.20	
10	200	50	7.5			22			0.18	
11	260	60	9.0	92.0	4.20	28			0.23	
12	250	80	12.0			18			0.15	
13	200	60	9.0			26	1.22		0.22	
14	250	70	10.5			17			0.14	
15	260	80	12.0			20			0.17	
16	350	175	26.5			25			0.22	
17	350	180		165.0	4.30	22	1.10	0.049	0.19	
18	250	180				24			0.21	
19	250	170				23			0.19	15
20	280	160				25			0.14	25
21	220	160				22		0.052	0.12	25
22	260	160				26			0.15	25
23	500	200				24			0.13	25
24	400	190				25	1.08		0.15	25
25	400	190			4.10	42			0.23	25
26	500	180				45			0.25	25
27	400	180				47			0.26	25
28	500	170				34			0.19	25
29	550	170				44			0.24	25
30	700	150				42			0.23	25
31	400	190		81.0		35			0.19	25
May 1	700	150				24			0.13	25
2	500	170			3.80	23			0.13	25
3	400	160				25			0.14	25.
4	450	120				38			0.19	25
5	500	80				38		0.030	0.21	26
6	400	120				8			0.04	25
7	550	120				5			0.04	25
8	500	100				6			0.03	25
9	500	150				10			0.05	25
10	450	100		30.0	3.70	20			0.10	25
11	650	120				19			0.10	25
12	600	120				30	1.00		0.15	25

Illustration 29. TABLE OF RESULTS - Dog #11

PAVLOV - Dog #11

DATE	WATER c.c.	DIET gm.	K in Diet M.Eq/L.	K in Urine M.Eq/L.	SERUM K M.Eq/L.	GASTRIC JUICE Vol.	pH	Pepsin	K	DOCA mg.
May 13	650	100				30			0.15	25
14	550	120				30			0.15	25
15	600	160				28			0.14	25
16	650	200				28			0.14	25
17	600	180		10.5		22			0.11	25
18	700	180				15			0.06	25
19	650	100				10			0.04	25
20	800	100				20			0.08	0
21	800	140				23			0.09	0
22	990	140				18		0.026	0.08	0
23	700	140				12			0.05	0
24	800	200				15			0.07	0
25	700	140		.3	2.60	20			0.09	25
26	650	150				28			0.12	25
27	600	170				20			0.09	25
28	650	150				0			0.09	25
29	650	150				18			0.08	25
30	400	200				23			0.11	25
31	600	150		6.2	.5	18			0.08	25
June 1	625	160				29			0.14	25
2	750	150			3.70	15			0.07	25
3	800	150				18	1.01		0.08	25
4	350	150				10			0.05	25
5	700	150				11			0.05	25
6	700	150				15			0.07	25
7	600	140				18			0.09	25
8	900	200				25			0.12	25
9	750	200				17			0.08	25
10	700	150				16			0.08	25
11	950	120				13			0.06	25
12	800	120	4.7	.10		15			0.07	25
13	900	80				5			0.02	25
14	550	50				5	1.03		0.01	25
15	600	120	4.5	.20		5			0.01	25
16	900	150				5			0.01	25
17	900	200				5			0.01	25
18	700	200				5			0.01	25
19	750	200				16			0.04	25
20	700	140		.10		13			0.03	25
21	700	120				3	1.30		0.01	25
22	850	130		1.35		3			0.01	25
23	Died suddenly									

Illustration 29. TABLE OF RESULTS - Dog #11

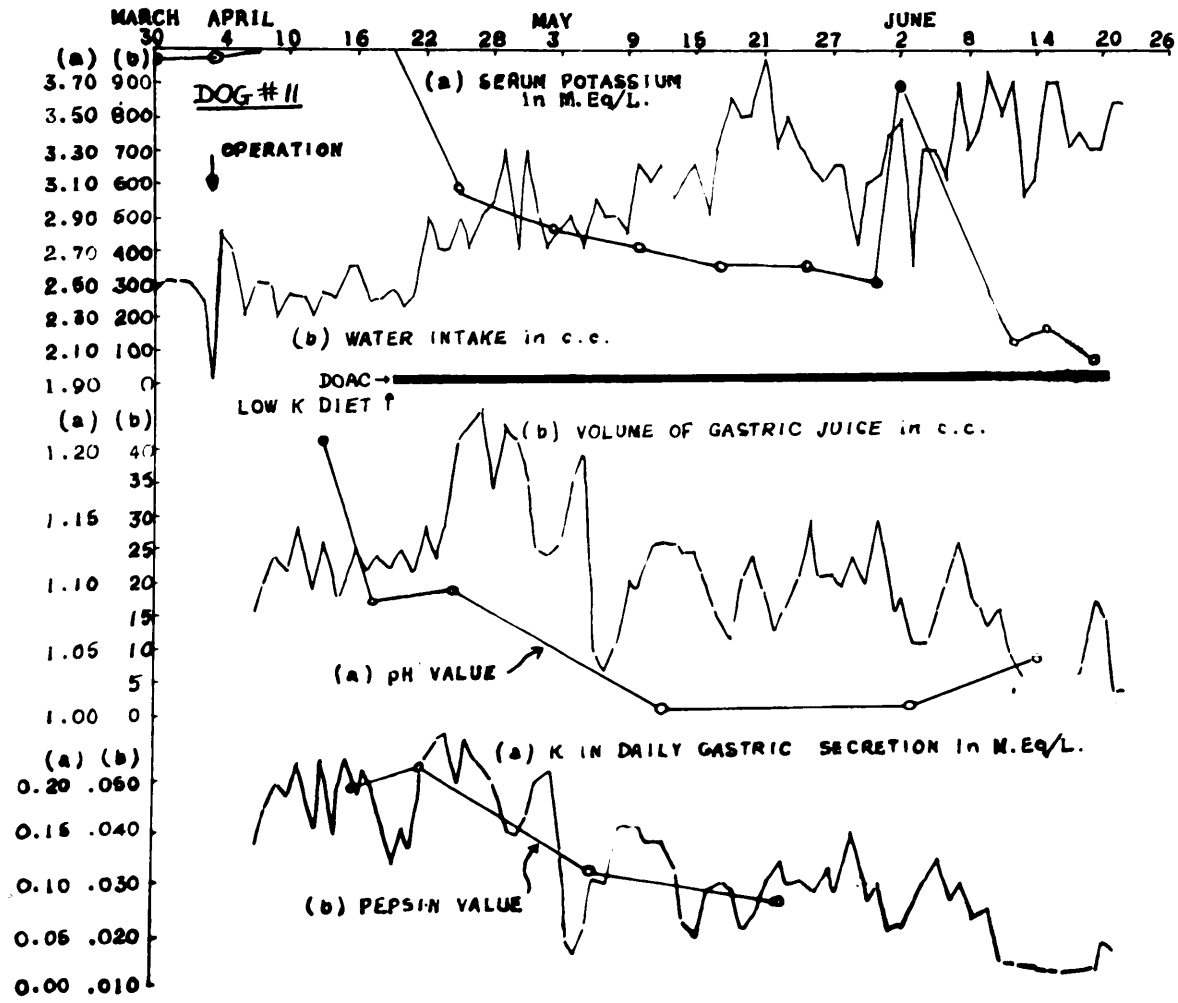


Illustration 30. GRAPH OF RESULTS - Dog #11

As one can see from illustrations 29 and 30 the dog slowly became depleted of potassium to the extent that periodic paralysis developed sixty days later on June 15/50. The volumes of gastric juice secreted daily were at first increased but later during this period they became less and remained small until the dog died. The periodic paralysis assumed again the characteristic form but became worse day by day until June 20/50 at which time it was severe and persisting. The dog died suddenly while eating on the morning of June 23. Gross examination at autopsy revealed no changes which could be ascribed to potassium deficiency. The graphs show the typical changes as the dog became depleted of potassium - the negative potassium balance, the increased fluid intake, the decreased excretion of potassium in both urine and gastric juice and the lowering of serum potassium.

Histamine tests and feeding tests repeated during the stage of periodic paralysis simply reflected what is shown in the curve of daily excretion of gastric juice. In the histamine test, the total secretion was 11 c.c. on April 19/50, only 11.5 c.c. on June 14 and only 5 c.c. on June 21/50. Electrocardiographic changes were not marked and simply showed a lowering of the T wave with a slight depression of the ST segment.

Unfortunately blood samples taken at the time of death were allowed to stand too long to be of any value. However, a plasma pH was done and was 7.52 as compared with the plasma pH value of 7.54 on April 16. There was no evidence of acid-base imbalance.

Microscopic sections were made of nine different tissues from dogs #9 and #10 and from the pancreas, kidney and liver of dog #11. Careful study confirmed by Dr. T.R. Waugh of the Department of Surgical Pathology revealed no changes apart from parenchymal degeneration of a mild extent in the kidney and liver of each animal. To prove that this was a postmortem change rather than an antemortem degeneration, frozen sections with fat stains were made. No fat was found in these slides so that these changes were presumed to be postmortem degeneration.

CHAPTER V111

DISCUSSION

Because of the epidemic of lower respiratory infection in the kennels of the laboratory animals during the months of October and November, the dogs used early in this study contributed very little. Dogs 1, 2, 3, 4 and 5 died of pneumonitis during this epidemic and all procedures had to be started afresh.

An attempt was made to construct a gastric pouch which would be more effectively innervated than the Pavlov pouch. A modification of the Cope operation was used and this type was found the most satisfactory. The advantages, method of construction and management have been described in detail.

The synthetic diet used was found to be adequate as the younger dogs grew normally and adult dogs maintained their weight and health. The only evidence of inadequacy was the common finding of a patchy loss of hair after three or more months on this diet. Dogs in other series developed cutaneous ulcers, but these may have been slowly healing acute traumatic ulcers. The deficiency was not identified.

Potassium deficiency has been produced by the

loss of gastric juice alone ("Bevin", Dogs 2,3 & 4) by potassium deficient diet alone (Dogs 9 & 10) and by potassium deficient diet, loss of gastric juice and the administration of desoxycorticosterone (Dog #11). Potassium deficient diet alone produced signs of depletion in 50 days in small dogs whereas a larger, well nourished dog did not show signs of deficiency until the 60th day in spite of desoxycorticosterone, loss of gastric juice and potassium deficient diet. Why the latter dog (#11) did not develop potassium deficiency much sooner than the other animals remains unexplained.

The paralysis the dogs developed in the potassium deficient state was similar to the paralysis seen in humans suffering from periodic familial paralysis. Both are flaccid and the defect seems to be in transmission of the motor impulse across the myoneural junction. At first, both are intermittent. In humans, the paralysis occurs usually 2 hours after a heavy meal and so is usually observed in the evening because of the habit of taking the heaviest meal at suppertime. The dogs were fed once daily always in the morning. As one would expect, their paralysis developed several hours after this feeding and usually lasted until the evening. Later the paralysis in the dogs became more severe and was observed throughout

the whole day, even immediately before feedings. It is felt that in the period of intermittent paralysis the animal must be in a critical state of potassium balance. The suggested explanation is that the feeding causes a secretion of gastric juice which contains a considerable amount of potassium even in potassium depleted animals and that this small amount is enough to temporarily deplete the animal so that flaccid paralysis develops. Later however, readjustment occurs probably by the reabsorption of potassium from the gastrointestinal tract and/or potassium given up by other organs such as the liver or kidney and the flaccid paralysis disappears. To support this, on March 6/50 using Dog #9 several potassium determinations were performed. The fasting level was 2.50 M.Eq./L. and the dog was not paralized. Four hours later, one hour after the head drop appeared, the level was 2.15 M.Eq./L. and seven hours after feeding when the paralysis was well developed the level was 3.10 M.Eq./L. There was no paralysis next morning before feeding when the level was found to be 2.60 M.Eq./L.

At one time the paralysis these dogs showed was thought to be of the spastic type because the head dropped and the dog was unable to raise its head. However when the dog was held by his legs upside down the

head flopped loosely in extension; it was not a spastic paralysis of the flexors in the neck but rather a flaccid paralysis of the extensor muscles in the neck.

In humans, the paralysis usually affects the legs whereas in dogs the paralysis affects the extensor muscles in the neck. The only suggested explanation is that the paralysis due to potassium deficiency affects those skeletal muscles which are most continuously used in the body - in humans, the muscles of the legs are required continuously to maintain balance and in the dog the extensor muscles of the neck are required continuously to support the head because of the horizontal position of the dogs body. No experimental evidence is known to support this hypothesis.

Proof that the intermittent paralysis in the animal is due to potassium deficiency was shown by the immediate relief of paralysis on the refeeding potassium to Dog #9.

The electrocardiograms were used only as a check on the potassium deficiency. The prolonged ST interval, the low T waves and the depressed ST segments are proof of potassium deficiency (a low level of serum potassium).

There is an increase in the fluid exchange (water intake and output of urine) in potassium deficient

animals as shown by the graphs (illustrations 26, 28 and 30). The reason for this is not known. It has been suggested that it is due to an imbalance between the diuretic hormone of the adrenal cortex and the anti-diuretic principle of the posterior lobe of the pituitary (126, 127). The suggestion that it is due to elevation of serum sodium level is apparently untrue because this was not observed in any of the dogs in this study. The increase in fluid exchange in these animals was between 50 - 60% of their normal exchange.

Potassium balance studies on the whole revealed little that was not expected. The animals all remained in positive potassium balance while on a normal diet except for the operative and several postoperative days. This happened in spite of the use of Ringer' s solution for intravenous therapy during this period. Ringer's solution contains 2.003 M.Eq. per 500 c.c. The animals showed a negative balance while on the potassium deficient diet as one would expect. As the animal became depleted less and less potassium was excreted by the kidneys. Apparently there was some attempt by the kidneys to conserve potassium when the intake and internal stores of potassium were low.

The main aim of this work was to try to re-

demonstrate the increase in the volume of gastric juice in a potassium depleted animal which was observed in these laboratories two years ago. On reviewing all of the charts, the increase in volume is not marked. It apparently paralleled the increase in fluid exchange which these animals demonstrated and amounted to an increase of no more than 50% whereas two years ago an increase of 300% was noted. Curiously the increase was usually found fairly early in the deficiency and disappeared as the deficiency became more marked. Another interesting and unexpected observation is in marked increase in the volume of secretion in Dog #9 after the refeeding of potassium (illustration 26). A certain amount of potassium in the diet may be necessary for the increase in the volume of gastric secretion. Two years ago, the potassium deficient dog was fed a normal diet. The studies of the concentration of potassium in the gastric juice show that in spite of the depleted state of the animal, the stomach continues to secrete a juice which contains considerable amounts of potassium. Apparently there is little attempt on the part of the stomach to conserve potassium when the intake and body stores of potassium were low.

As the potassium deficiency progressed in each case the concentration of active pepsin in the gastric juice decreased. The explanation remains obscure. The gastric juice became more acidic as the deficiency became more marked. This may have been due to a decreased concentration of mucinous substances in the juice so that the proportion of free acid was greater, the total acidity may have remained unchanged. Unfortunately, this was not expected and was not checked.

Why, then, the difference between the observations on these dogs and the dog under observation two years ago? None of the dogs in this series showed evidence of alkalosis whereas the other dog had a CO_2 combining power of 85.1 volumes per 100 c.c. in the state of potassium deficiency. This series shows that alkalosis is not invariably associated with potassium deficiency as was once thought. If this is the reason for the difference in results, what is the underlying biochemical explanation for the increase in gastric secretion? I can suggest no reasonable explanation. This aspect is at present under investigation in these laboratories.

One other possibility requires consideration. The dog under observation two years ago was made deficient by the loss of gastric juice and consequently may have been deficient in other substances. Because of the

development of tetany it has been suggested that the dog was also depleted of magnesium. Perhaps the changes in the volume of gastric juice were due to or at least influenced by these other deficiencies.

Then again, perhaps the dog is unsuitable for studies on potassium deficiency. Most of the work on potassium deficiency has been performed using rats and in these laboratories certain observations on potassium depleted rats have not been confirmed by experiments using potassium depleted dogs.

Another unexplained observation is the apparent fact that these animals in the potassium deficient state are more sensitive to insulin. It is known that humans requiring insulin for the treatment of diabetes require less insulin if the intake of sodium chloride is increased. The sodium content of these deficient animals is undoubtedly increased but whether this association is significant or not remains unknown.

After a careful study of gross and microscopic tissues from potassium depleted dogs, no changes have been found which may be ascribed to potassium deficiency.

CHAPTER 1X

SUMMARY

In an attempt to confirm the observation of an increase in the volume of gastric juice secreted by a dog in potassium deficiency, which was made in these laboratories two years ago, dogs were prepared with gastric pouches and were depleted of potassium. Some animals were depleted by the loss of gastric juice alone, others by low potassium diet alone and one dog by a combination of low potassium diet, loss of gastric juice and the administration of desoxycorticosterone acetate.

Potassium depletion was followed by the lowering of the level of serum potassium, the decreased excretion of potassium in the urine and gastric juice and the signs of periodic or continuous flaccid paralysis. A study of the fluid exchange, potassium balance and character of gastric juice secreted from gastric pouches was made. The volume, acidity, pepsin content and potassium content of the gastric juice was followed. In addition, electrocardiograms were used to confirm the potassium deficient state and tissues from postmortem examination were studied grossly and microscopically.

Complete observations have been recorded. The

changes have been discussed in some detail. The previously made observations have not been confirmed and possible explanations of this have been suggested and discussed. Further work on this problem is in progress at the time of writing and will not be included in this thesis.

CHAPTER X

CONCLUSIONS.

(1) The fact that there is an increase in the fluid exchange in potassium depleted dogs has been confirmed.

(2) Potassium deficiency in dogs may be produced by loss of gastric juice, low potassium diet on the administration of desoxycorticosterone acetate.

(3) Early in potassium deficiency there is a tendency to an increased volume of gastric juice but the previously made observation of a threefold increase in volume has not been confirmed.

(4) In potassium deficiency there is a tendency to secrete a more acid gastric juice.

(5) In potassium deficiency there is a tendency to secrete a gastric juice of lowered pepsin content.

(6) In potassium deficiency a characteristic periodic flaccid paralysis of the extensor muscles in the neck appears and progresses to involve all skeletal muscles continuously.

(7) Typical electrocardiographic changes of potassium deficiency have been redemonstrated.

(8) No gross or microscopic pathological changes whichmay be ascribed to potassium deficiency have been found.

(9) A new method for the more efficient construction of gastric pouches in dogs was devised.

(10) The synthetic diet used was found adequate to support growth and maintain weight in healthy dogs.

(11) The mechanism whereby there is an increased volume of gastric secretion in a dog after prolonged loss of gastric juice remains unexplained and the observation remains unconfirmed.

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THE EFFECT OF BILE AND PANCREATIC JUICE ON THE COLON

Part B

THE EFFECT OF BILE AND PANCREATIC JUICE ON THE COLON

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A McGill University thesis submitted in partial fulfillment of the requirements for the degree of Master of Science in Experimental Surgery.

August, 1950

ACKNOWLEDGEMENTS

To Dr. D.R. Webster I wish to express my sincere gratitude for his constant encouragement, interest and advice and for the provision of facilities for this extra work. I am indebted to Dr. J.E. Pritchard for assistance in the interpretation of the microscopic sections.

I wish to thank again Mrs. K. Wright for the typing of this thesis, Miss Carol Philip for secretarial assistance, and Miss Hope Thompson for the various biochemical determinations. The majority of the photographic work was performed by Mr. Paul Roustan. Special thanks is also due Mr. James Byers for the supply and care of the animals and Mr. Leo Groulx for other duties in the animal rooms. The microscopic sections were made by Mr. Hans Torunski, and the Department of Pathology of the Montreal General Hospital.

It has been a real pleasure to work in the same laboratory with Dr. Andrew Chau, Dr. W.D. Miller, Dr. Stan Skoryna, Dr. Helen Henrikson, Dr. R.A. Forse and Drs. Toovey and Rutis. I wish to thank them in particular for operative assistance. The high degree of cooperation and companionship which exists in these laboratories has made this past year a most enjoyable one.

D.J.C.

Experimental Ulcerative Colitis: The Effect of Bile and Pancreatic Juice on the Colon.

Part D. Experimental Work.

ILLUSTRATIONS

Figures

CHAPTER 1 - INTRODUCTION

Certain clinical characteristics of patients with peptic ulcers were also recognized clinically in cases of chronic ulcerative colitis. In patients with peptic ulcers there are certain abnormal characteristics in the psychological background, there are remissions and exacerbations remarkably influenced by psychological disturbances, there is a local physiological disturbance (gastric hypersecretion) which can be almost wholly attributed to the psychological upset and there is a local necrotizing agent (pepsin in hydrochloric acid) which precipitates mucosal ulceration. It was felt that these characteristics may also be found in patients with chronic ulcerative colitis. The abnormal psychological background and remissions and exacerbations influenced by psychological disturbances are well known. What could be the upset physiological process and the local necrotizing agent to cause colonic ulceration in chronic ulcerative colitis?

Perianal excoriation in persons with diarrhea is well known. It was thought that this might be due to the proteolytic activity of digestive enzymes. On reading it was learned that trypsin was found in the stool of adults only if diarrhea was present - as it is after purgatives are taken (38) and in cases of chronic

ulcerative colitis (84). It has been found that living tissue can be digested by trypsin solution (76). It has long been known that psychological disturbances may cause intestinal hypermotility. Perhaps then in chronic ulcerative colitis patients, psychological disturbances cause intestinal hypermotility so that potent trypsin reaches the colon and that perhaps the colonic mucosa is susceptible to the proteolytic effect of these enzymes. This work was designed to find out if undiluted potent pancreatic secretion would digest and so ulcerate the mucosa of the colon and to this might be an initiating or at lease an aggravating factor in the etiology of ulcerative colitis. Infection of the ulcerated mucosa may follow this to cause the toxemia, fever, leucocytosis and pus cells in the stool.

CHAPTER 11

CHRONIC (IDIOPATHIC) ULCERATIVE COLITIS.

Ulceration of the wall of the large bowel is a characteristic of many diseases. The more common conditions include bacillary dysentery, amoebiasis, tuberculosis, lymphogranuloma venereum and uremia. However, in a fairly large number of cases, the specific etiological agent cannot be determined and of these, in cases which run a typical course to be described, the diagnosis of chronic (or idiopathic) ulcerative colitis is made. It is believed that Sir William Wilks, in 1875, first segregated these cases and described their characteristics in some detail (45).

Clinical Picture

This condition is characterized by periodic attacks of diarrhea in which the stool is fluid or semi-fluid, with mucus and blood showing in almost all cases at some stage of the disease. The diarrhea is associated with crampy abdominal pains and weight loss and the accompanying general signs and symptoms include anorexia anemia, asthenia and general lassitude. Fever is occasionally found presumably due to bacterial infection in the colonic ulcerations. Remissions and exacerbations of the disease, which are so characteristic, are often

frequent and unpredictable and are prolonged in the more severe cases. During exacerbations, sigmoidoscopic examination will show the mucosal ulcerations in over 95% of cases.

It was once believed that the disease was inevitably progressive involving first the rectum and spreading thereafter to involve the rest of the large bowel but recently it has been observed that in the majority of patients the disease attacks the colon either partially or wholly during the initial episode and usually remains relatively confined to these portions subsequently.

The extent of the disease as shown radiologically is not related directly to the type of onset, duration or severity of symptoms. The radiographic appearance may be practically normal in a patient with marked symptoms and again, symptoms may be very mild with X-ray evidence of extensive changes in the colon. The clinical course is far more closely related to the stool examination and the sigmoidoscopic picture of the colonic mucosa.

The personality type deserves consideration. Immaturity, childishness, emotional instability, dependence, sensitiveness, over-conscientiousness,

fussiness, anxiety and fear of failure may be present singly or in combination. It is obvious that social, economic, or domestic difficulties will have profound effects on such individuals, and so aggrevate any existing disturbances. These changes are found to such a degree that many clinicians actually believe that the disease is psychogenic; all agree that the mental disturbances contribute to a greater or lesser extent the severity and course of the disease; yet outright claims of so-called "colon neurosis" progressing to idiopathic ulcerative colitis are rare indeed.

Toxemia is always present and causes intermittent fever, sweats, tachycardia, loss of weight, malaise, anorexia, headache, and probably gives rise to lesions remote from the colon such as arthritis, ocular symptoms, liver and renal lesions, thromboses, inflammation of serous membranes and splenomegaly.

Emaciation may be very marked and not only due to anorexia and decreased food intake but also to loss of blood and protein, disordered digestion, and increased catabolism. It is obvious that one cannot reduce the caloric intake in order to provide a bland diet. Hypochromic anemia and low serum proteins (especially serum albumin fraction) are often found.

Leucocytosis and fever is taken to indicate infection presumably in the colonic ulcerations. Anorexia and deficient absorption may give rise to avitaminoses and excessive loss of essential minerals.

Signs and symptoms directly related to the colonic changes are seen in the exacerbations. There is clinical and radiographic evidence of increased motility, defective absorption, and either a serous or purulent exudation from the colonic ulcers depending upon the severity of the infection. Vague discomfort colicky lower abdominal pains and diarrhea are present with small, liquid, offensive stools which contain small amounts of fecal material mixed with blood occasionally, pus often and varying amounts of mucus always. Although defecation may be painless, frequent evacuations cause anal symptoms such as soreness and tenderness with excoriation and may predispose to the formation of haemorrhoids or prolapse of the rectal mucosa.

Abdominal examination may reveal nothing more than tenderness over the large bowel and absence of gaseous distension. It is said that occasionally one can feel a firm fibrosed colon in a long standing case. Rectal examination may reveal only edema and

fibrotic firmness, but may determine the presence of polyps, carcinoma or other local complications. Sigmoidoscopic and radiographic changes are described elsewhere.

Stool examination shows nothing more than has been described. The presence of mucus in the stool is of no special significance other than a possible indication of irritation of the colon. Florey and Webb (29) produced emptying of the globlet cells of the colon and massive secretion of mucus by the instillation of mustard oil and other irritants per rectum. Hypoproteinemia and especially hypoalbuminemia are often found along with hypoprothrombinemia in the severely affected patients. Secondary hypochromic anemia, varying increase in the leucocyte count with often a mild eosiniphilia and increased sedimentation rate may be observed. In severe cases, other biochemical studies including liver function tests show varying "changes due to toxemia".

Medical Management

The principles of medical management are designed to (i) put the colon at rest

(ii) provide a nonirritating adequate diet,

(iii) correct existing deficiencies,

(iv) treat symptoms, including mental unrest.

There is no specific treatment; the cause of the condition is not known. The features of medical therapy may be outlined as follows

(i) Diet - smooth, low residue, high in proteins, reasonably high in carbohydrates, and so arranged to provide a high caloric intake. Often a diet high in fat is not well tolerated. Vitamin supplements are desirable and should be given in divided doses. The possibility of mineral deficiencies must be kept in mind because many essential minerals are lost in considerable quantity in the diarrhia fluid.

(ii) Antispasmotics are indicated in the treatment of crampy lower abdominal pains.

(iii) Psychotherapy may be very important depending upon the individual and the circumstances in which the exacerbation occurred and this therapy should include explanation, reassurance and suggestion.

(iv) Sedation for sleeplessness and for over-anxiety.

(v) Adsorbants are of benefit in patients carefully chosen by competant practitioners.

(vi) Other drugs - for the treatment of symptoms or the correction of deficiencies such as aspirin compound and ferrous sulphate.

(vii) Antibiotics - commonly used only when there is evidence of infection in the ulcerated colon as shown by fever, leucocytosis, and massive numbers of pus cells in the stool. Antibiotics are also indicated in the treatment of complications due to the spread of infection. Choice of the drug depends upon the organism believed responsible and these drugs may be given by mouth as well as by injection. Sulphaguanidine, penicillin streptomycin and aureomycin are the antibiotics usually employed.

In acute exacerbations strong supportive measures are necessary to carry the patient through the emergency. These measures may include

(i) Blood transfusion for gross bleeding

(ii) Intravenous therapy amounting, on occasion, to complete parenteral feedings.

(iii) Complete bed rest

(iv) Medical ileostomy may be carried out by continuous (suction) emptying of the terminal ileum through a Miller-Abbott tube. This is designed to put the colon at complete rest by removing the upper gastro-intestinal contents and this proceedure is combined with total intravenous alimentation.

(v) Surgical Measures to be outlined later.

Many other forms of therapy have been tried and usually reported to be of definite benefit originally but have not been generally accepted. They may be of value in well chosen cases but apparently are not specific for ulcerative colitis.

These measures include vaccines of streptococci and colon bacilli, polyvalent dysentery serum, bacteriophage, oxygen inhalations, fever therapy, colonic irrigations, rectal instillations of various bacteriostatics and bacteriocides and exposure of the body to ultraviolet light.

Kertesz, Walker and McCay (52) found that pectins relieve diarrhea induced in rats by a lactose-milk mixture. Pectins form the basis for many compounds used today for the relief of frequent bowel movements. Xetzel, Banks and Sagall (101) believed that amino acids by mouth improved the clinical condition of patients with chronic ulcerative colitis and enero-colitis. Gill (32 (33) (34) believed that chronic ulcerative colitis was a deficiency disease and so fed his patients cleaned but uncooked pigs small intestine and made three reports on the beneficial effects of such feedings. Following this work Friedman, Haskell and Waldron (30) reported favourable results in treating patients having

chronic ulcerative colitis with an extract of hogs intestine, and more recently Steitcher, Grossman and Ivy (91) used dessicated, defatted hog duodena and reported mild but definite decreases in frequency of exacerbations in the majority of patients. Ehrlich (26) (27) postulated that ulcerative colitis was due to the premature presence of upper gastrointestinal proteolytic enzymes in the colon. Under normal conditions he believed that an antiproteolytic substance was present in the walls of gastrointestinal tract in decreasing concentration from the stomach analward and that chronic ulcerative colitis was actually due to a deficiency of this substance in the lower bowel. Consequently he has reported the favourable effects of the oral administration of an extract of hog stomach. A careful analysis of his reported results does not lend evidence to support his hypothesis.

The polyvalent dysentery serum first devised and used by Hurst (45) in 1921 has not cured the disease or relieved a significant number of patients.

Complications of Ulcerative Colitis

(i) Local Complications

Infection of the colon is believed to be a complication because it does not necessarily accompany each exacerbation. Signs of infection during an exacerbation are fever, leucocytosis and numerous pus cells in the stool. If it can be considered a complication rather than an essential factor in the disease, it certainly is the most common complication.

Pseudopolyps are actually swollen islands of mucosa butting into the lumen and cannot be distinguished radiologically from true polyps. Incidence 10 - 60%.

Polyps are often seen and are believed to arise from these mucosal islands as local exaggerations of the regenerative process. Incidence 2 - 5%.

Carcinoma of the colon in association with ulcerative colitis is more common than in the general population and probably arise from polyps. Incidence 1 - 2.5%

Pericolitis with adhesions, loss of colonic mobility and shortening of the mesentery are often seen in severe cases. Shortening of the colon is also seen but whether or not this is due to pericolitis is not established.

Abscesses and fistulae develope when the infection spreads from the colon to neighbouring structures.

Haemorrhage in small amounts is very common and is bright red due to the rapid transit of the fecal stream. Massive haemorrhages are seen later in the disease and are due to deep ulcerations with erosion of large vessels.

Perforation and general peritonitis are seen in fulminating cases. Perforations are often multiple.

Stenosis may be due to fibrosis or edema and and in either case the colon may become obstructed.

(ii) Remote Complications

Remote complications are not specific for chronic ulcerative colitis but may be seen in many debilitating diseases. They are believed due to "toxemia" and nutritional deficiencies. They include polyarthritis, pleuritis, pericarditis, nephrotic syndrome, splenomegaly, hepatic damage, septic mesenteric thrombophlebitis and septicaemia.

Surgical Treatment

Surgical treatment is reserved for patients who do not respond to medical management and for complications requiring operative treatment. Under medical treatment about 20% return to good health, 60% improve and 20% (4) to 26% (18) fail and require surgical therapy.

Indications for surgical treatment may be listed as follows (18)

(1) Failure of Medical Management - toxemia, impending perforation, incapacitated more than 3 months yearly, fecal incontinence, uncontrolled diarrhea or weight loss.

(2) Perforation, subacute perforation, abscesses and fistulae (73)

(3) Obstruction - contracture or stenosis

(4) Haemorrhage - usually limited to ileostomy and only in well chosen cases - massive bleeding is rare (73)

(5) Infections, Polyarthritis - to remove focus of infection.

(6) Polyposis which occurs in 10% of cases (73)

(7) Carcinoma

(8) Segmental colitis - in rare cases resection may be performed.

In failure of medical therapy the usual management is to perform an ileostomy only. After six months, if the symptoms remain absent, the ileostomy is left alone. If the symptoms return or continue one must do a colectomy in a second proceedure and if the disease continues in the rectum (ulceration or haemorrhage) the rectum must be removed at a third stage by an abdomino-perineal method. One third require colectomy alone but

the other two-thirds require colectomy and abdomin-operineal resection of the rectum (18). Bacon and Vaughan (4) recommend resection of the rectum because in 90% of cases it is involved whereas Cave (19) believes it should not be removed because of the possibility of reestablishing the bowel, except when badly deseased or bleeding. Ileostomy as an emergency proceedure for haemorrhage, uncontrolled diarrhea, impending perforation or sepsis carried a 53% to 75% mortality whereas if ileostomy is performed as an elective proceedure the mortality is 6 - 9% (4).

Miller, Ripstein and Tabah (73) have described the surgical management recommending a new approach to the problem. Because an ileostomy alone is not ideal and because there is considerable absorption of toxic substances from the right half of the colon, they believe an ileostomy with a right colon resection is the proceedure of choice in the first instance. Then, later if indicated as above, the remaining colon and possibly the rectum may be resected.

Prognosis of Patients with Ulcerative Colitis

The prognosis of the patient with chronic ulcerative colitis must be judged in each case. However, certain factors do influence the prognosis generally and these will be briefly outlined.

(a) Adequate therapy Bockus (12) states that "I know of no disease in which the results are so dependent upon the patience, ingenuity, experience and interest of the attending physician".

(b) Age - The more acute fulminating types tend to occur in the younger age groups and the prognosis is particularly poor when the disease begins in childhood. A comparison of the disease in 95 children has been made with the disease in 871 adults by Jackman Bargen and Helmholz (48) and figures are copied below:-

Types of Ulcerative Colitis	Children	Adults
Ordinary form	23%	50.9%
Severe form	77%	49.1%
Results of treatment		
Symptom-free or Improved	49.3%	53.9%
Worse or Died	54.8%	37%

(c) Duration - The longer the symptoms have been present the better the immediate and ultimate prognosis.

(d) Type of Onset - The milder the onset the better the prognosis for the tendency is to lapse into the chronic or subacute form whereas the prognosis is much worse following an acute onset.

(e) Clinical Progress - The prognosis is better in cases that follow a benign mild course with definite

remissions. Patients in whom the disease is less extensive have a better prognosis and in those cases which fare well, the lesion is often confined to the rectum and the lower sigmoid. The prognosis is very serious in cases with complications difficult to control.

(f) General Statistics - The results obtained by various clinicians vary widely. Bockus (12) found that the overall mortality of the disease in numerous reports varied from 3 - 40%, the good results from 19 - 80% and the poor results from 13% to 81%.

Radiological Diagnosis

The essential radiographic findings have been stated by Buckstein (14) and are:

(1) Absence of normal haustral configuration

(2) Shortening of the colon

(3) Rigidity with loss of distensibility of the colonic wall (hypomotility)

(4) Hypermotility of the colon

(5) Narrowing of the colon.

(6) Irregular obliteration of the mucosal pattern

(7) Irregular dense areas due to polypi.

(8) Changes may be localized.

(9) Retrogressive or progressive changes.

These are in general agreement with the reports

of other radiographers (99). Golden (36) adds that in cases of diarrhea if the barium enema shows none of the above signs, the diagnosis is extremely doubtful and the small bowel should be checked by barium meal for tuberculosis, lymphosarcoma, neoplasms, deficiency states, nonspecific granulomata or psychogenic hypermotility.

CHAPTER 111

THE PATHOLOGICAL CHANGES IN CHRONIC ULCERATIVE COLITIS

Ulcerative colitis is a chronic disease of unknown cause in which there is a diffuse inflammatory reaction involving all coats of the colon and rectum either in whole or in part. Keifer and Jordan (53) state that in 56% of cases the whole colon is involved, in 17% the disease is limited to the rectum and in 21% all or part of the left colon and rectum are affected. It is notoriously subject to unexplained exacerbations and remissions. It is complicated by varying degrees of sepsis, ulceration and necrosis of the mucosa which often results in extensive fibrosis of the intestinal wall.

Ulcerative colitis apparently starts as an acute inflammation of the colonic wall followed at times by necrosis and sloughing leading to ulcerations of varying size and depth. The mucosa and submucosa are involved and in later stages hyperplasia of isolated areas of mucosa leads to the formation of adenomatous changes resulting in polypi (54).

Grossly, the lining of the bowel is deep red or purple in colour due to hyperemia and congestion and is wet and shiny due to mucus and free blood, and

petechial haemorrhages may be observed. Ulcers vary in size, shape, number, extent and distribution. Ulcers may be so large and coalesce so that only small irregularly shaped elevated patches of epithelial lining remain. Ulcers may be long, narrow and gutter-like, and do not often overlie the taeniae (96) contrary to the descriptions of Lium (47). Characteristically the submucosa is exposed but not penetrated but may be covered by pus and other necrotic material. Soft bulbous edematous pseudopolypoid nodules may be seen in areas of remaining epithelium. Externally, the serosal surface is relatively unchanged except that it may be edematous or congested and later in the disease the colon may be shortened and thickened by fibrosis. Soft, slightly enlarged lymphatic nodules may be found in the mesentery.

Microscopically, the epithelial continuity is irregularly interrupted by multiple, shallow ulcers. In the base of these ulcers, there is a heavy infiltration of lymphocytes, plasma cells, eosiniphils, and macrophages, with very vascular granulation tissue. Often the inflammatory reaction extends into the inner half of the muscularis mucosae.

Shields Warren (96) describes two types of

microscopic change. In one, the essential change is a vasculitis with necrosis of the vascular wall, thrombosis, arteritis, phlebitis and/or periarteritis. In the other the essential feature is the appearance of crypt abscesses which apparently arise from the rupture of infected, distended, blocked crypts. This purulent material extends through the submucosa undermining the epithelial lining causing spread of ulcerated areas. These two types account for the changes in half of the cases of ulcerative colitis and Warren states that these changes may cause the condition in these instances. No abnormalities in the lymph follicles are seen in marked contrast to the characteristic changes in cases of bacillary dysentery. Regenerative changes, such as epithelial hyperplasia, hypertrophy of the muscularis mucosae, subserosal and submucosal fibrosis follow the expected histological appearance. Pseudopolyps are edematous, infiltrated tags of epithelium with little or no hyperplasia.

McCready, Bargen, Dockerty and Waugh (62) have reported ileal involvement in 28% of 103 cases. The changes are similar pathologically except that there is no thickening of the ileal wall with no

stenosis, hypertrophy, or malignant change. Clinically 72% of the cases involving the colon alone perforate whereas they report ileal perforation in 24% of cases with this involvement, and further, haemorrhage is more common from the ilium in cases with this involvement than from the colon with colonic involvement only.

Pathologically, cases of chronic ulcerative colitis must be distinguished from cases of dysentery (bacillary and amoebic) and from simple ulcer of the colon. This latter condition is rare (8) (9) (51) as only about 60 cases have been reported. There is a report (5) of the experimental production of a simple ulcer of the colon by the subcutaneous injection of mercurochrome but this required confirmation.

CHAPTER lV

THEORIES OF THE ETIOLOGY AND THE ATTEMPTED EXPERIMENTAL PRODUCTION OF CHRONIC ULCERATIVE COLITIS

Many attempts to produce chronic ulcerative colitis experimentally have been made and each has been attended by no success except for the production of acute ulcerations. Such studies usually stimulate the formation of a new theory of the etiology of the disease. The number of such studies reported is very great and numerous analytic reviews of these reports have been made. A brief summary only can be attempted here and most of the details are taken from the reviews of Martinez (68), Winklestein (100), Smith (90), Gunsberg and Ivy (35) and Bokus (11).

Causes postulated for this condition may be grouped as follows:

(1) Infectious agents

(2) Allergy

(3) Mechanical Trauma

(4) Vascular Changes

(5) Obstruction of Lymphatic Supply

(6) Vitamin Deficiencies

(7) Excretion of Toxic Substances

(8) Autonomic Nervous System Instability.

Acute lesions of the colonic mucosa have been produced by the intravenous injection of diplostreptococci (Bargen), B. coli, B. dysenteriae, and presumably a virus. Cook is reported to be the only investigator to produce a persisting ulceration with relapses using Bargen's diplostreptococci which was once believed the specific etiologic agent for chronic ulcerative colitis. B. necrophorum may contribute to the persistance of acute ulcers already produced.

Mechanical trauma of the mucosa or vascular injuries caused by a contraction of the muscularis (57) or vascular injuries caused by vascular poisons may cause acute lesions of the colon. Lymphatic obstruction alone will cause the same effect (82). However, such acute lesions heal rapidly. Similarly, acute ulcerations may be attributed to allergic reactions but these ulcers are never chronic.

Irritation of acute ulcers by pancreatic juice may constitute a chronicity factor but this theory remains unproven. Vitamin deficiencies, especially of vitamin A, have been thought to be the chronicity factor but this is again unproven.

Clinically ulcers of the colonic mucosa may be due to amoebae hystolytica, B. dysenteriae, severe dietary deficiency, tuberculosis and in the early stages

of lymphogranuloma venereum. It is accepted that either bacillary or amoebic dysentery may preceed chronic ulcerative colitis but are not believed to be the cause of this disease. Local allergy has been stated to be the precipitating cause or the chronicity-producing factor. It appears that nutritional deficiency is a secondary rather than a primary causative factor. There is no evidence to support the thought that the disease may be due to a disturbance of the excretory function or of some metabolic disorder.

Though emotional disturbances, such as anxiety, resentment and guilt, are concerned in the exacerbation of symptoms and in many cases related to the onset of relapses of the disease, there is little evidence to show that this disease follows mucous colitis, functional dyskinesia of the colon or of some subtle vascular or neurotropic disturbance. If such emotional disturbances are etiologically concerned, they cannot be the sole factor since they are also thought to be concerned in the genesis of other diseases with large psychogenic elements such as peptic ulcer.

In more recent years, autonomic nervous system instability has been thought to be the etiologic factor. Lium produced foul diarrhea with blood and mucus in the stool in dogs by the removal of

sympathetic ganglia but again these changes were not persistant and did not resemble the pathological changes of chronic ulcerative colitis. Wener, Hoff and Simon (98) (McGill) produced acute and subacute ulcerating colitis in dogs by the prolonged administration of mecholyl. Here again, erosions and general inflammatory reaction persisted as long as the drug was given but soon cleared when discontinued for no chronic lesions were produced.

Very recently, detailed study has been made on the variations in concentration of lysozyme in the stool in relation to chronic ulcerative colitis. Lysozyme is a mucolytic enzyme found in the normal stool and was discovered by Fleming in 1918 (39). The mechanism of lysozyme activity is explained in terms of the hydrolysis of a mucoid substance contained in the walls of a certain bacterium, micrococcus lysodeikticus. This mucoid substance has been isolated in a high polymer form and Meyer and Hahnel (71) have described a visciometric method for the estimation of lysozyme activity using this extracted substance. The concentration of lysozyme was previously determined by the rate of clearing of a standard suspension of micrococcus lysodeikticus and con- the hydrolysis of the mucoid substances by determining

the amounts of nonprotein nitrogen and phosphate which are liberated in the reaction. No substrate for this enzyme has yet been found in the normal or diseased gastrointestinal tract (49) (95) (69).

The sources of lysozyme are outlined in the following table (69) (71):

Egg white 12,500 units per gram

Human tears 950 units per c.c.

Human saliva 1.3 units per c.c.

Human rib cartilage 36.3 units per gm.

Highest in normal stool 528 units per 24 hours

Highest in chronic ulcerative colitis stool 44,400 units per 24 hours

Mean titre, normal stool 2.7 units per gm.

Mean titre, purge stool 1.6 units per gm.

Mean titre, chronic ulcerative colitis stool 56.0 units per gm.

Mean titre, mucus from chronic ulcerative colitis 158.1 units per gm.

The enzyme is found in high concentration in the gastric juice of patients with peptic ulcer as well as in the stool of patients with chronic ulcerative colitis. In spite of the fact that neither gastric or colonic mucus is a substrate for lysozyme whether

specimens be from normal persons or from cases of peptic ulcer or ulcerative colitis (49) (95), still various groups of workers (69) (70) (72) (83) (85) believe that lysozyme removes a protective mucous layer from the gastroduodenal or colonic mucosa and so predisposes to these ulcerative diseases.

The concentration of lysozyme is lower in stools from ileostomies than in rectal stools so that it is believed to be produced in the colon (69). Wetting agents such as sodium hexadecyl sulphate have been shown to inactivate lysozyme and have been recommended for the treatment of cases of peptic ulcer and chronic ulcerative colitis, (72) (83). Vagotomy has no effect on either the motility, mucus or lysozyme secretion in chronic ulcerative colitis (38). Grace, Seton, Wolf and Wolf (39) found that when any individual meets a threat to his security with feelings of humiliation, guilt, anger, or hostility but was repressing them to present a serene, non-aggressive exterior, an excess of colonic lysozyme was likely to be elaborated. The concentration of lysozyme increased markedly and was maintained at a higher level longer in the stool of patients with chronic ulcerative colitis than in the stool of normal persons. Prudden,

Lane and Meyer (85) produced acute sloughing of a portion of the thickness of the mucosal layer by the intra-arterial injection of massive doses of lysozyme and Wang, Grant, Janowitz and Grossman (95) produced mild acute lesions of the gastrointestinal tract by the feeding of lysozyme in moderately large doses. Here again, acute lesions have been produced but the typical chronic pathological changes seen in chronic ulcerative colitis have not been produced.

In review, there is evidence that lysozyme in large doses can produce acute lesions of the gastrointestinal tract in vivo and in vitro but as yet there has never been found a substrate for lysozyme in the normal or diseased gastrointestinal tract of animals or humans. The theory that lysozyme predisposes to chronic ulcerative colitis or peptic ulcer by removing the protective mucus lining of the colon or stomach is therefore unreasonable. Other experimental proceedures have often produced an acute ulcerative colitis but pathological changes similar to those seen in chronic ulcerative colitis have not been produced and a chronic ulcerative colitis has never been produced.

PART B - THE HYPOTHESIS AND PROBLEM

CHAPTER V

THE HYPOTHESIS

The hypothesis upon which this problem is based is that bile and/or pancreatic juice will initiate or at least aggravate the lesions found in chronic ulcerative colitis. It was thought that this effect would be brought about by the proteolytic effect of the pancreatic juice and perhaps also by the detergent action of bile. Should the presence of bile and/or pancreatic juice in the colon be the cause of such lesions, certain questions must be answered.

(1) Is trypsin present in the normal stool and does it appear in the stool in chronic ulcerative colitis and in other conditions associated with diarrhea?

It will be shown in the next chapter that trypsin, the active proteolytic ferment of the pancreatic juice, is not normally present in the stool of adults except after purgatives but is found in the stools of patients with chronic ulcerative colitis, in fairly high concentration.

(2) Why is bile and/or pancreatic juice present

in the colon in cases of diarrhea?

There may be an increased secretion of bile and/or pancreatic juice or there may be hypermotility of the small bowel. Hypersecretion has never been demonstrated in cases of simple diarrhea or in cases of chronic ulcerative colitis. For the time, it seems more likely that the principal reason for the presence of bile and/or pancreatic juice in the colon is a state of hypermotility of the small bowel. It has been shown that hypermotility can result from psychic disturbances and the psychic disturbances in chronic ulcerative colitis are well recognised. This theory then presupposes a primary psychogenic hypermotility of the small bowel and if so, it can be seen easily how exacerbations and remissions may result from changes in the emotional status of the patient, a fact which is frequently observed clinically. Evidence from the literature will be presented shortly.

(3) Does bile and/or pancreatic juice produce lesions in the colon similar to the changes seen in chronic ulcerative colitis?

This is the object of the experimental proceedures in this problem and are presented in Parts C and D.

(4) What explanation may be presented to account for the fever, leucocytosis, pus in the stool and toxemia?

These are believed to be manifestations of invading bacteria which infect the denuded, damaged colon and give rise to toxemia by the liberation and consequent absorption of "toxic substances". It is thought that these bacteria are not specific but are actually normal inhabitants of the large bowel.

CHAPTER VI

SUPPORTING EVIDENCE FROM THE LITERATURE

The volume of pancreatic juice is about 500 c.c. per 24 hours. It is alkaline with pH of about 8. Trypsin is the most potent proteolytic enzyme and is excreted in the zymogen form as trypsinogen, which is changed into trypsin by enterokinase which is secreted by the duodenal mucosa. This enzyme attacks peptide linkages not adjacent to the terminal group. The net result of trypsin activity is to break down the products of peptic digestion still further and to digest those proteins which cannot be digested by pepsin. Its optimum pH is in the neighborhood of 8 and 9 (55).

The proteolytic activity of stools may come from foods, drugs, pepsin (?), pancreatic and intestinal proteolytic enzymes, intestinal bacteria or from combinations of these. In certain diseases, proteolytic activity may come from parasites, protozoa or even leucocytes.

Not many foods have proteolytic activity in the normal pH of stools but apparently fresh pineapples and honeydew mellon do (89). Gastric pepsin is enzymatically inactive at the normal pH of stools.

Certain bacteria do possess a mild proteolytic effect in the stool such as Pr. vulgaris, staphylococcus, some B. coli, C. Aerogenes, Bacteriodes and certain Clostridia.

In 1913, Hahn and Lust (42) reviewed the then controversial subject of the presence of trypsin in the stool. They studied infants and children and demonstrated the presence of trypsin in the stool, using casein as the substrate and showed that trypsin is normally present in the stool of children regardless of the pH of the stool or of the presence of constipation or diarrhea. Incidentally, they showed that sucklings excrete trypsinogen only, as they have no activating enterokinase and so no trypsin.

Schlecht (88) found that by the administration of a strong laxative to an adult, a stool was excreted which exhibited tryptic activity. This was explained by the fact that the laxative speeded the passage of the upper intestinal enzymes into the colon and so the natural inactivation, absorption or destruction that takes place is decreased. The formation of a pancreatic fistula in dogs would cause the disappearance from the stool of this enzyme. Because he found that the diet of adults does not change the

trypsin content of the stool, he suggested stool trypsin determination after a laxative be used as a test for diseased pancreas or blockage of the pancreatic ducts. Hecht (44) found trypsin present in the stools of children with acute and chronic nutritional disturbances but, since quantitative studies were not made the report adds little because Hahn & Lust found trypsin was normally present in the stools of children. Budde (15) added the observation that stool trypsin concentration in children did not depend on either the age of the child or on their nutritional status, whereas Lukacs (59) found a decreased concentration of trypsin in the stool in children with nutritional disturbances and curiously in the stools of rachitic children there is 4 to 10 times the concentration of trypsin found in normal children's stools. The significance of these latter observations has never been elucidated. It is clear, however, from the foregoing that trypsin is present in the stool of normal children but not of adults unless a laxative has been given and a fluid movement is examined.

Food has little effect on the concentration of proteolytic enzymes in the stool. Only drugs which have a laxative effect have any effect on this concen-

tration. Bettoni (10) showed that any measurable proteolytic activity in the stools of humans is not due to bacterial action but only to the activity of pancreatic enzymes.

Necheles, Levitsky and Maskin (76) studied the digestion of living tissues by enzymes and concluded that the most complete digestion resulted from the repeated exposure of the tissue alternately to acid pepsin solution and alkaline trypsin solution. It is hard to see that such repeated exposure could possibly have any effect on the colon but this repeated exposure may be the necrotizing agent in duodenal ulceration. They also showed that living tissues can be digested by Trypsin alone under appropriate conditions.

Portis, Block and Necheles (84) studied the content of trypsin in the stool of patients with chronic ulcerative colitis and also the effect on the stool following the feeding of a detergent. They found that the stool of patients with chronic ulcerative colitis contain large amounts of trypsin. Ileostomy stools also have high tryptic content but after a time there is an apparent accommodation because the tryptic concentration falls. In 19 acute experiments, they irrigated the large bowel of dogs with acid pepsin and 2% trypsin solutions alternately.

They were able to produce superficial mucosal necrosis in 7 out of 9 experiments using the 2% trypsin solution alone. In 7 chronic experiments with three dogs they were able to produce hyperemia, small haemorrhages, blood clots and friability of the mucosa. Irrigations were made through a caecostomy and observations by sigmoidoscope. There was also a large increase in the mucus secretion. This series of experiments is closely related to the problem herein presented and actually stimulated the only other study (47) of this type, designed to produce colonic lesions by the proteolytic action of bile and pancreatic juice. Portis (83) has since reviewed new concepts in the etiology of ulcerative colitis - he stated that lysozyme was the precipitating factor and the secretion of lysozyme is dependent upon the sacropelvic outflow of the parasympathetic nervous system and that is why the disease starts in the rectosigmoid. The onrush of upper intestinal enzymes causes the lesions produced by lysozyme to persist. There was no experimental work reported in this case to confirm his beliefs.

Driver (24) has studied the production of ulcers and perforations in intestinal loops filled with enzyme solutions under a hydrostatic pressure of 90 cm. of water. Pepsin was found to be the most

potent in causing perforation whereas trypsin solutions did not cause perforations but varying degrees of surface necrosis in half of the cases.

Ham and Sandsdedt (43) have made an extract from unheated soy beans which will retard tryptic activity by approximately 66%. Mirsky (74) found that Ham and Sandsdedt's trypsin inhibitor has reasonably potent antibiotic properties. Chernick, Lepkovsky and Chaikoff (21) found that soy bean failed to support maximal growth, that the pancreases of such animals were enlarged and had an increased proteolytic enzyme content. They believed that this was due to the antitrypsin substance in soy bean which stimulated the pancreas to increased activity. These observations are only of interest in passing, and are mentioned in view of the possibility of feeding animals soy bean to decrease the trypsin activity in the bowel and to study the effect of the inhibition of trypsin on the bowel. For similar reasons, a short review of the problem of the response of the pancreas to various types of foods will be presented. Babkin, Mellanby and many others have pointed out that the enzyme content of the pancreatic juice is regulated largely by the vagus nerve whereas the secretion of fluid and bicarbonate is influenced mainly by secretin.

Atropine inhibits the flow of pancreatic juice in the cephalic phase but has no effect on the secretion of juice in the gastrointestinal phase. In 1897 Walter and again Pavlov (12) suggested that for each type of food ingested the pancreas secretes the juice best adapted to its digestion. However, McClure (60) presented evidence that the degree of concentration of all enzymes, rather than varying degrees of particular enzymes, is governed by the type of foodstuffs ingested. This again is not quite accurate because the concentration of enzymes in the pancreatic juice depends upon the volume and rate of secretion (Babkin). According to Lagerlof (56) substances formed from fat in the intestine stimulate the secretory nerves (vagus) of the pancreas and so fats are considered stimulants of pancreatic secretion. Thomas and Crider (92) (93) found that the introduction of various products of protein digestion into the intestine stimulates the flow of pancreatic juice. Greengard, Grossman, Roback and Ivy (40) and Grossman, Greengard and Ivy (41) found that a high protein, high carbohydrate diet provoked an increase in the trypsin and amylase content of the pancreatic juice whereas a high fat diet or high fat, high protein diet did not. Comfort and Priestly (22) noted a greater stimulation of pancreatic juice in regard to all components from a low fat,

high protein, high carbohydrate diet in a patient with an external pancreatic fistula.

Conclusions are difficult to draw from these observations. Apparently proteins and carbohydrates by mouth stimulate the secretion of all components of the pancreatic juice. The stimulating effect of fat varies from one experiment to another. Casein and cane sugar when introduced into the duodenum do not stimulate the pancreas (22) but if these same substances are introduced into the stomach an effect is produced similar to that obtained following the injection of secretin.

The psychiatric characteristics of patients with chronic ulcerative colitis have been frequently studied and widely reported. Because of the close correlation between the exacerbations and remissions of the disease and the emotional status of the patient, psychiatrists have gone as far as to claim that the disease is wholly psychogenic. Most clinicians will agree that tremendous emotional reactions accompany various phases of the disease and whether these are causative or merely coincidental findings remains to be proven. According to the hypothesis at hand, the gastrointestinal hypermotility is probably caused by the emotional upset in a susceptible individual.

The characteristic personality type, according to Brown, Pren and Sullivan (13), is characterized by low energy endowment, emotional lability, anxiety and a tendency to give up in the face of difficulties. They state clearly that in these personality types, emotional disturbances are important factors in precipitating exacerbations of chronic ulcerative colitis. Mahoney, Bockus, Ingram, Hundley and Yaskin (63) studied 20 patients with proven chronic ulcerative colitis and found that all had definite neurotic traits, tension inability to assert oneself, anxiety, and sensitivity, 19 were hostile and immature, 18 showed guilt and indecision, 16 passivity, 15 dependency and conscientiousness, 12 aggression and perfectionism, 6 aestheticism and one showed rigidity.

Almy and Fulin (1) made prolonged sigmoidscopic examinations on patients with chronic ulcerative colitis and found that when under stress by induced cold or headache an emotional conflict resulted and there was increased motor activity of the lower sigmoid in all cases and most showed hyperemia and congestion. These changes were not directly related to the quality of the emotional reaction.

In chronic ulcerative colitis, the

radiological finding of hypermotility of the upper intestinal tract with consequent rapid passage of a barium meal has been stated numerous times but usually passed over lightly. For example, White (99) in Nelson's Loose Leaf Medicine states that more information may be obtained about chronic colitis by enema than by barium by mouth, "for the latter passes along rapidly and does not fill the colon". Or, Weber (97) states that the barium meal shows "nothing more than rapid emptying". Again, "nothing more than rapid emptying is shown by the barium meal" has been written by Bargen and Weber (7). Carman and Moore (16) believe the barium enema is best for study and state "the ingested meal merely shows rapid emptying as in all conditions accompanied by diarrhea". Kantor (50) found one other sign by the barium meal. He has described ileal stasis in cases of chronic ulcerative colitis and states that this is due to colonic irritability due to colitis. Although Mackie (61) has reported hypomotility in the proximal half of the colon, no mention is made of small bowel hypomotility and, in fact, states that there is occasionally seen a complete evacuation of a barium meal in 24 hours in cases of chronic ulcerative colitis. It appears then

that small bowel hypermotility exists but because no particular importance has been realized, this phenomenon has never been accurately or fully investigated in this condition.

PART C - METHODOLOGY

CHAPTER VII

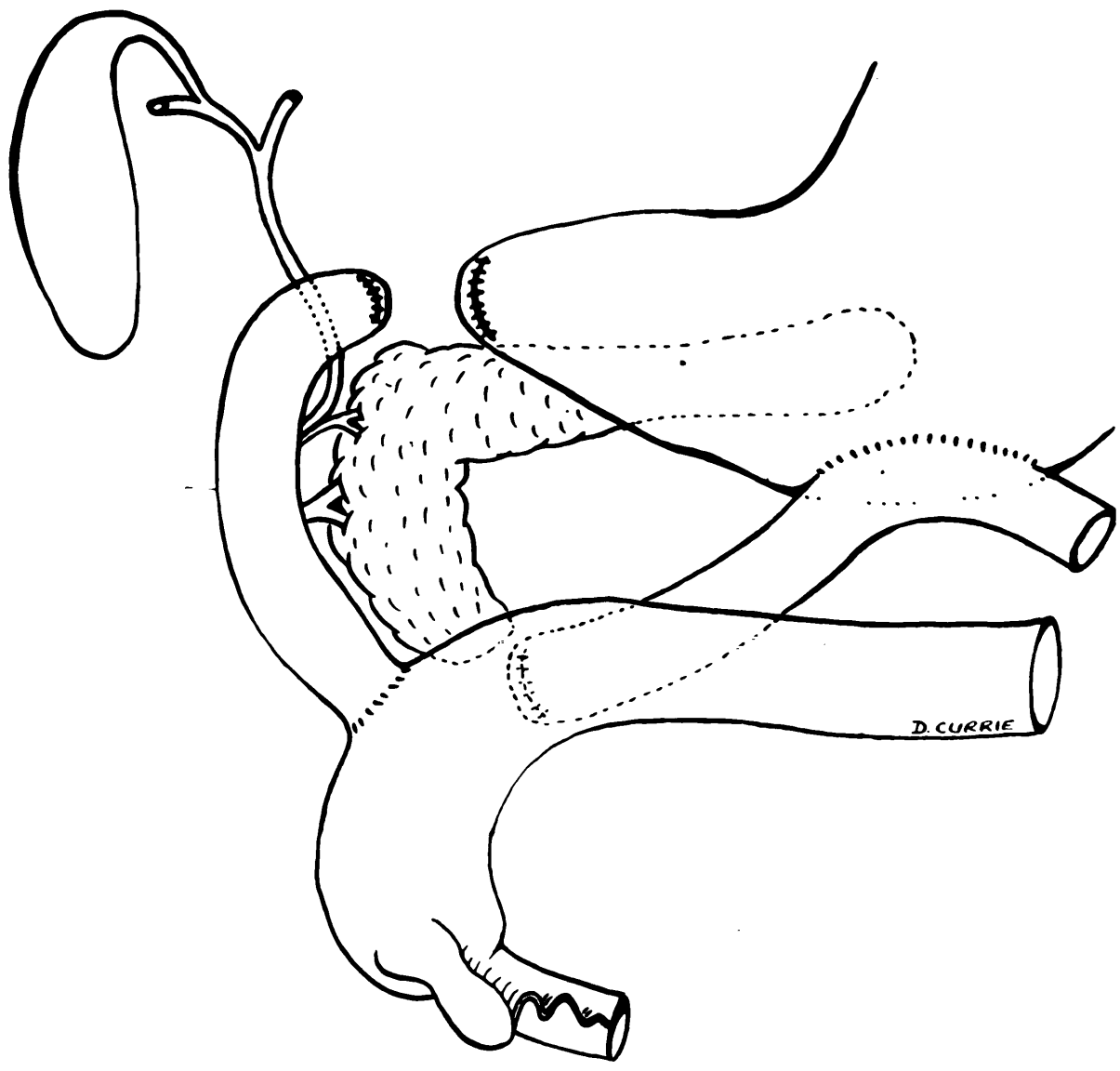
THE OPERATIVE PROCEEDURES

The method of carrying out this investigation in brief is as follows. Two operative proceedures have been designed. In one all of the bile and pancreatic juice, uncontaminated by food, is shunted into the ascending colon and bowel continuity is restored by a gastrojejunostomy. In the other, all of the external secretion of the pancreas through the major pancreatic duct is shunted into the ascending colon via a duodenal pouch and bowel continuity is maintained by an end to end duodenal anastomosis. Postoperatively, the dogs were studied by barium enemata, gross stool examination and stool trypsin determination. Complete autopsies were performed and special pathological examinations of the colon were made.

Dogs were prepared for three days preoperatively by sulphathiazole two grains per pound of body weight twice a day. On the second day before operation, a strong laxative was given such as 2 oz. of magnesium sulphate. The dogs were starved the day before operation except for one drink of water or milk

in the morning and the sulphathiazole tablets. During operation many of the dogs were given intravenously 500 c.c. of 5% glucose in normal saline and these dogs withstood the proceedure better and awoke from the anaesthetic sooner than the other dogs. The anaesthetic was always intravenous nembutal, one grain for every 5 pounds of body weight.

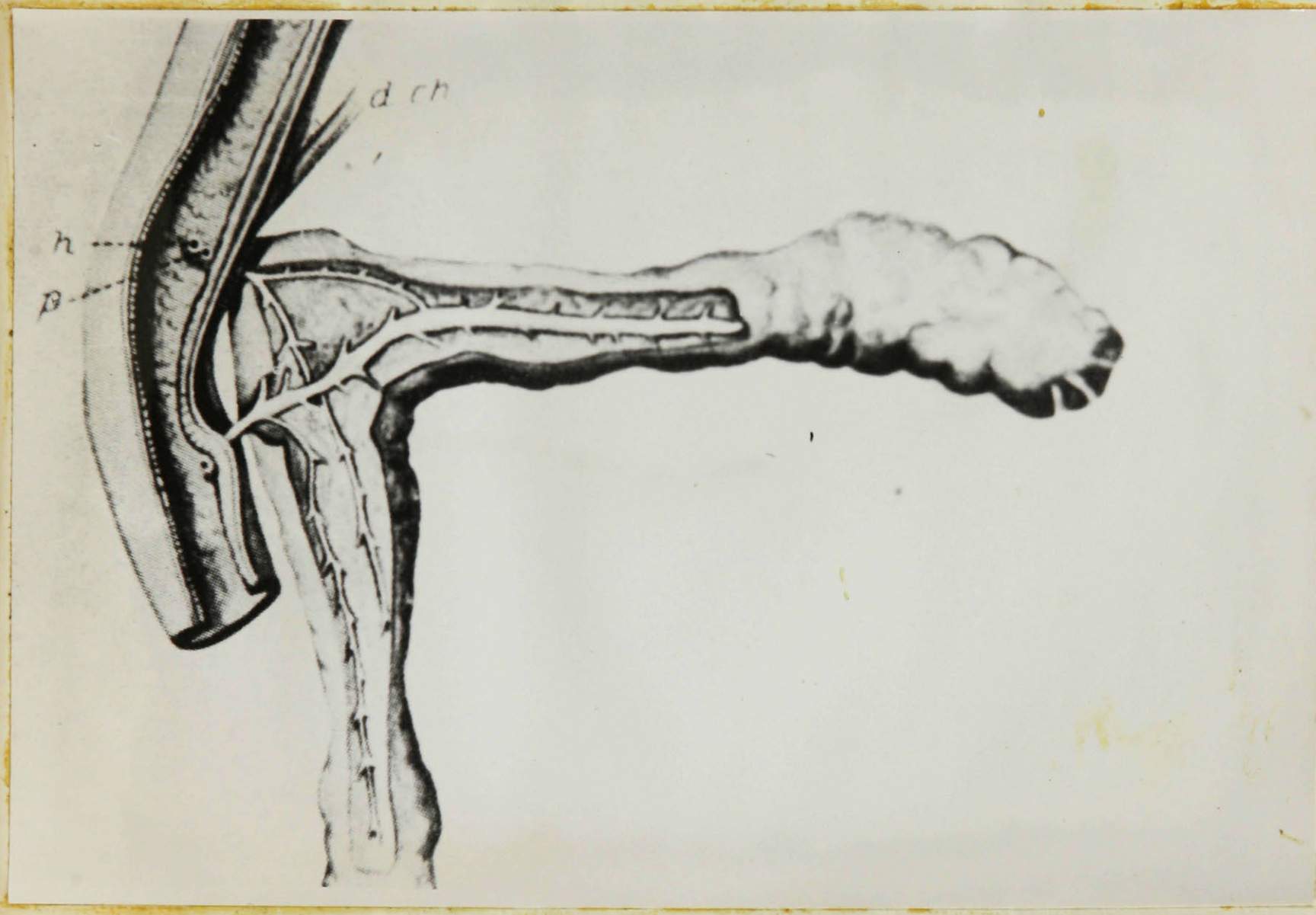
Aseptic surgical technique was used throughout all operative proceedures.. The abdomen was opened through either a midline or right rectus-splitting epigastric incision. In the first type of operation all of the bile and pancreatic juice was shunted into the colon and it was performed as follows. (Figure 1). The pylorus was divided and both ends were closed by purse-string sutures and oversewn. An anterior antiperistaltic gastrojejunostomy was performed in the accepted technique, the resulting stoma was usually $1\frac{1}{2}$ - $1\frac{1}{2}$" in diameter. The inner sutures were continuous locking posteriorly and continuous baseball or inverting Connell suture anteriorly of 00 or 000 chromic intestinal catgut reinforced by an outer ring of interrupted #40 cotton sutures. The site of anastomosis was within 3 inches of the ligament of Treitz. The duodenum was then completely divided



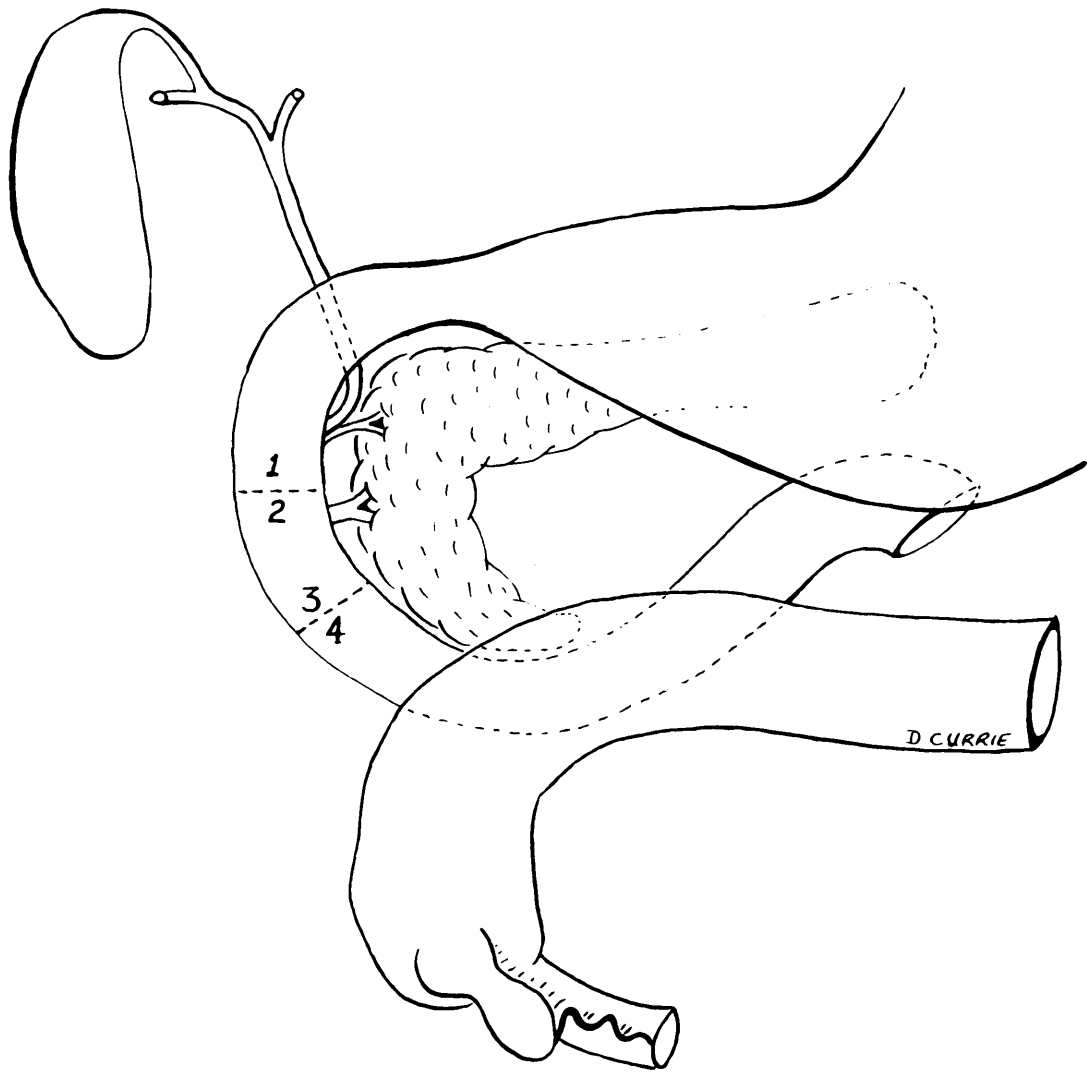
(1) DRAWING OF OPERATION I

about 5" below the pylorus at a convenient place distal to the major pancreatic duct and the distal end was closed and oversewn. The proximal end was joined to the ascending colon in an end to side anastomosis using the same technique but in addition using absorbable sutures throughout and taking special precautions against contaminating the operative field with large bowel contents and bile.

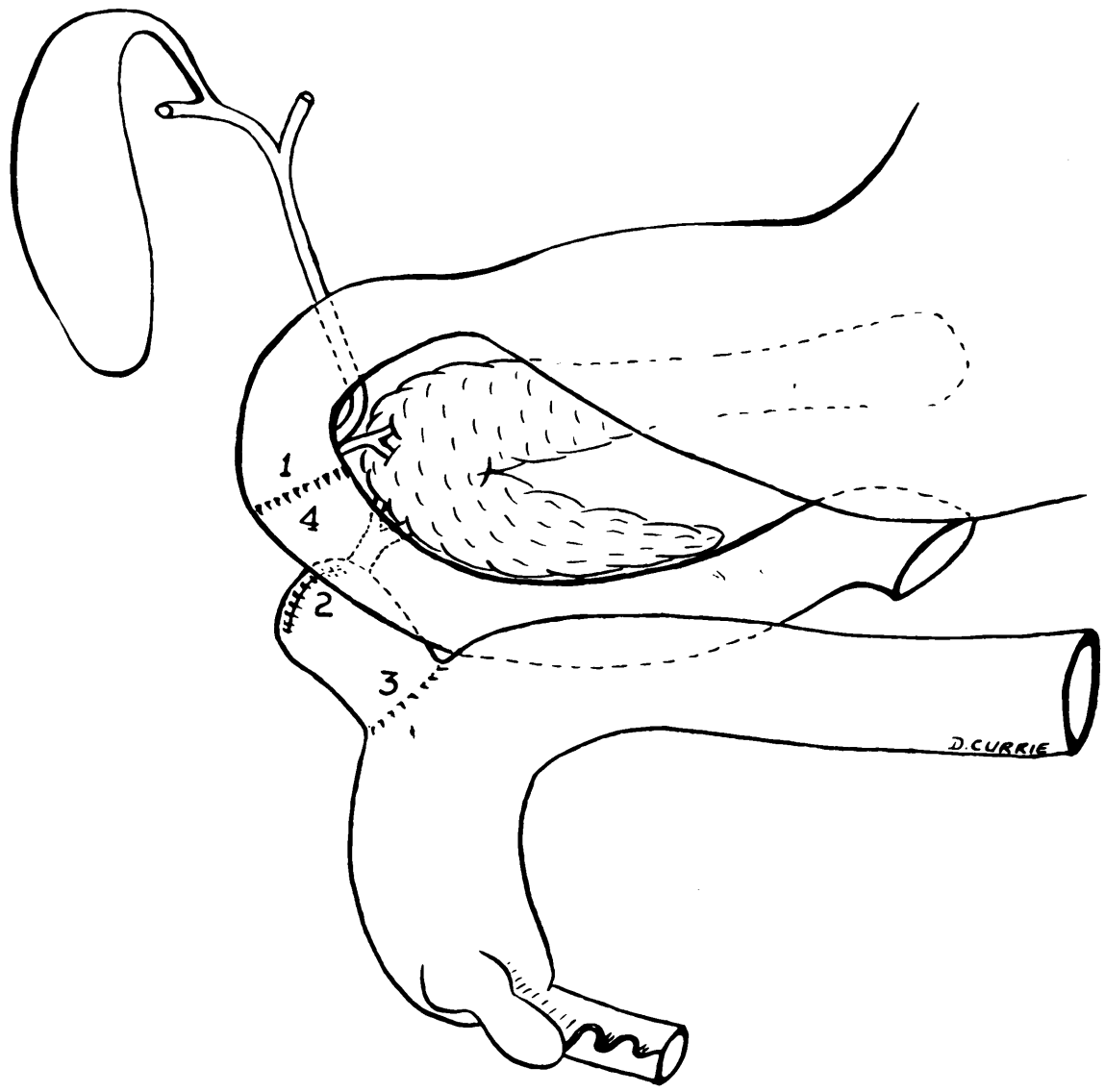
In the second type of operation, only the pancreatic juice from the major pancreatic duct was shunted to the colon via a duodenal pouch and the operation was performed as follows. Both the (upper) minor and (lower) major pancreatic ducts were found by careful dissection. These ducts are shown in Figure 11 which was reproduced from a text by Professor Babkin (3). The duodenum was then divided between these ducts about $\frac{1}{2}$ inch proximal to the major duct and the distal end was closed (Figures III and IV.) The duodenum was again divided $1\frac{1}{2}$ to 2 inches distal to the major pancreatic duct, and, leaving a rubber-shod intestinal clamp on the proximal end, the distal end was then anastomosed to the proximal end of the first duodenal division in the usual intestinal anastomosis technique. Finally,



(2) THE PANCREATIC DUCTS IN DOGS



(3) DRAWING OF OPERATION II



(4) DRAWING OF OPERATION II

removing the intestinal clamp, the duodenal pouch so formed was anastomosed to the ascending colon 3" from the appendix in the same fashion as used in the other operation and taking the same precautions. No drainage tubes were used.

Postoperatively, all dogs were starved until the second day when small volumes of milk and water were given. Feedings were gradually increased until on the fourth day the dogs were given the normal diet ad libitum. Penicillin was given on the operative and first postoperative days. About 5 gm. of sulphathiazole crystals was smeared over the various anastomoses before closing the abdomen.

These operative proceedures are original. The first proceedure, however, is a modification of the Mann-Williamson operation (65) for producing experimental peptic (jejunal) ulcers in that the duodenum, instead of the jejunum was anastomosed to the colon rather than to the terminal ileum as Mann and Williamson originally described. Incidentally Mann and Williamson reported a mild diarrhea in their dogs in the early postoperative period which was believed to be due to jejunitis. Saltzstein, Sandweiss, Hammer, Hill and Vandenberg (87) in studying the effect of vagotomy on Mann-Williamson ulcers in dogs found

diarrhea in 60% of these dogs and again attributed this to jejunitis rather than either the vagotomy or the possibility of a colitis.

In 1945 Ivy and Clarke (47),in investigating the previously mentioned work of Portis, Block and Necheles (84) on the effect of 2% trypsin solution on the colon, performed a modified Mann-Williamson operation on six dogs. Instead of anastomosing jejunum to ileum they anastomosed the jejunum, 15 cm. distal to the ligament of Treitz, to the appendix and studied the large bowel of these dogs after they died from either perforation or haemorrhage from a gastrojejunal ulcer. They reported no changes in the large bowel of these animals in spite of a moderately severe diarrhea through the whole postoperative period. There was no evidence of any blockage of the flow of any of the secretions so the probable explanation of the lack of change is that there was too great a length of intestine from the second portion of the duodenum to the rectosigmoid colon where changes take place. During intestinal transit, the pancreatic enzymes are utilitzed, absorbed, inactivated or metabolized and apparently the speed of transit was not great enough to allow active proteolytic enzymes to reach the susceptible part of the large bowel.

CHAPTER VIII

OTHER STUDIES USED

In the postoperative periods several repeated determinations were made of the activity of the trypsin in the fluid stool of each dog. Fresh specimens were obtained and suitably diluted. Assays were made according to the method of Schwachman, Patterson and Laguna (89) in which the gelatin digesting activity of varying dilutions of the stool was determined under standard conditions. The more potent specimens have the standard degree of proteolytic activity in greater dilutions, and so results are expressed in terms of the greatest dilution in which the unknown solution can show this activity.

Radiological studies following barium enemata were carried out on several dogs. After a dog passed a fluid movement, a barium suspension was slowly instilled under a pressure of 18" of the solution until the suspension ceased to flow. Pre-evacuation and post-evacuation radiographs were taken.

Several complete haematological studies were made but as several showed little change, studies were not made on each dog.

Complete autopsies were performed except for

the opening of the cranium and bacterological studies. Microscopic examination was made of all abnormal tissues found and of all of the large bowel of dogs who lived at least three days after operation. Slides for histological study were made by Mr. Torunski of the Department of Histology, Mr. Tomlinson of the Pathological Institute and the Department of Pathology of the Montreal General Hospital.

PART D: EXPERIMENTAL WORK

CHAPTER IX - METHOD

The dogs used in this investigation were divided into two series. In Series A (figure 5) eight dogs were used. The first operative proceedure was carried out on these dogs so that all of the bile and pancreatic juice was shunted into the ascending colon three inches from the appendix. Each dog received the same care, as previously described, and the dates of operation and death are shown in figure 5.

In Series B (figure 6) eleven dogs were used. The second operative proceedure was carried out on each dog so that all of the pancreatic secretion from the major pancreatic duct, about 2/3 of the total external pancreatic secretion, was shunted into the ascending colon about three inches from the appendix and the duodenum was reunited by an end to end anastomosis. The dates of operation and of death are shown in figure 6.

Stool trypsin determinations and barium enemata were carried out on certain surviving dogs and the results will be given in the following chapter.

Series A — OPERATION I

Number	Operation	Death	Findings	Studied
1.	Dec. 16	Dec. 28	Died 12th P.O. day with acute diarrhea	Yes
2.	Jan. 4	Jan. 8	Peritonitis due to leaking anastomosis	No
3.	Apr. 3	Apr. 4	Massive pulmonary infarction	No
4.	Apr. 18	Apr. 21	Eventration and anaesthetic death on attempted repair	No
5.	Apr. 18	Apr. 28	Died 9th P.O. day with acute diarrhea	Yes
6.	Apr. 19	Apr. 21	Peritonitis due to leaking anastomosis	No
7.	Apr. 28	May 10	Died 12th P.O. day with acute diarrhea	Yes
8.	Apr. 28	May 12	Died 14th P.O. day with acute diarrhea	Yes

- - - - - - - - - - -

Early postoperative deaths . . . . . 4 dogs

Survival with death due to acute diarrhea in the first two weeks . . 4 dogs

(5) SUMMARY OF SERIES A

Series B **OPERATION II**

Number	Operation	Death	Findings	Studied
1.	Jan. 10	Mar. 8	Died 58th P.O. day with suppurative pneumonitis and diarrhea	Yes
2.	Jan 16	Jan.30	Died 14th P.O. day with acute diarrhea	Yes
3.	Jan. 23	July 24	Sacrificed 182nd P.O. day with diarrhea persisting	Yes
4.	Jan. 27	July 24	Sacrificed 179th P.O. day with diarrhea persisting	Yes
5.	Feb. 3	Feb. 5	Gas gangrene septicaemia	No
6.	Feb. 10	Feb. 11	Failed to recover from anaesthetic	No
7.	Feb. 17	Feb. 18	Failed to recover from anaesthetic	No
8.	Feb. 17	July 24	Sacrificed 158th P.O. day with diarrhea persisting	Yes
9.	Feb. 23	Feb. 27	Gas gangrene septicaemia	No
10.	Feb. 27	Feb. 28	Aseptic peritonitis with fat necrosis	No
11.	Feb. 27	Feb. 28	Failed to recover from anaesthetic	No

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Early postoperative deaths . . . . . 6 dogs

Survival with death due to acute diarrhea . . . . 2 dogs

Sacrificed after prolonged survival with diarrhea . . . . 3 dogs

(6) SUMMARY OF SERIES B

CHAPTER X - RESULTS

The results of every dog used in series A and B in the investigation of this problem are outlined in tabular form in figures (5) and (6).

In series A half of the dogs did not survive the immediate effects of the operation. The remaining four dogs experienced acute persisting diarrhea until they died of the effects of acute diarrhea up to fourteen days after operation. Death was probably a combination of electrolyte loss, acidosis and starvation. Some dogs passed fluid stools flecked with blood several times during the few days before death. Since all of the bile and pancreatic juice was shunted into the colon one could not expect these dogs to remain in a normal metabolic state.

In each case the most marked changes were found in the rectum and rectosigmoid whereas the proximal half of the large bowel remained relatively normal. In the following pages a photograph from the large bowel of one of these dogs is shown (figure 7) and typical microscopical changes are shown in photomicrographs (figures 8, 9, 10 and 11). In each dog that survived three days or longer after operation the large bowel showed minute rectal haemorrhages and ulcerations, submucosal collections of chronic inflammatory cells

and in most in some areas showed superficial necrosis of the mucosa with an infiltration of inflammatory cells into the deeper portions of the mucosa between the remaining gland units.

In series B six out of eleven dogs died of the early effects of the anaesthetic or operative proceedure. Two dogs survived the early period but died subsequently of the effects of acute diarrhea. The remaining three survived and were sacrificed at the conclusion of this investigative work. The dogs apparently remained in a normal metabolic state and this might be expected in spite of the severe persisting diarrhea because only about 2/3 of the external secretion of the pancreas was shunted into the colon and the bile and remaining portion of the pancreatic juice entered the reconstituted upper gastrointestinal tract as under normal circumstances.

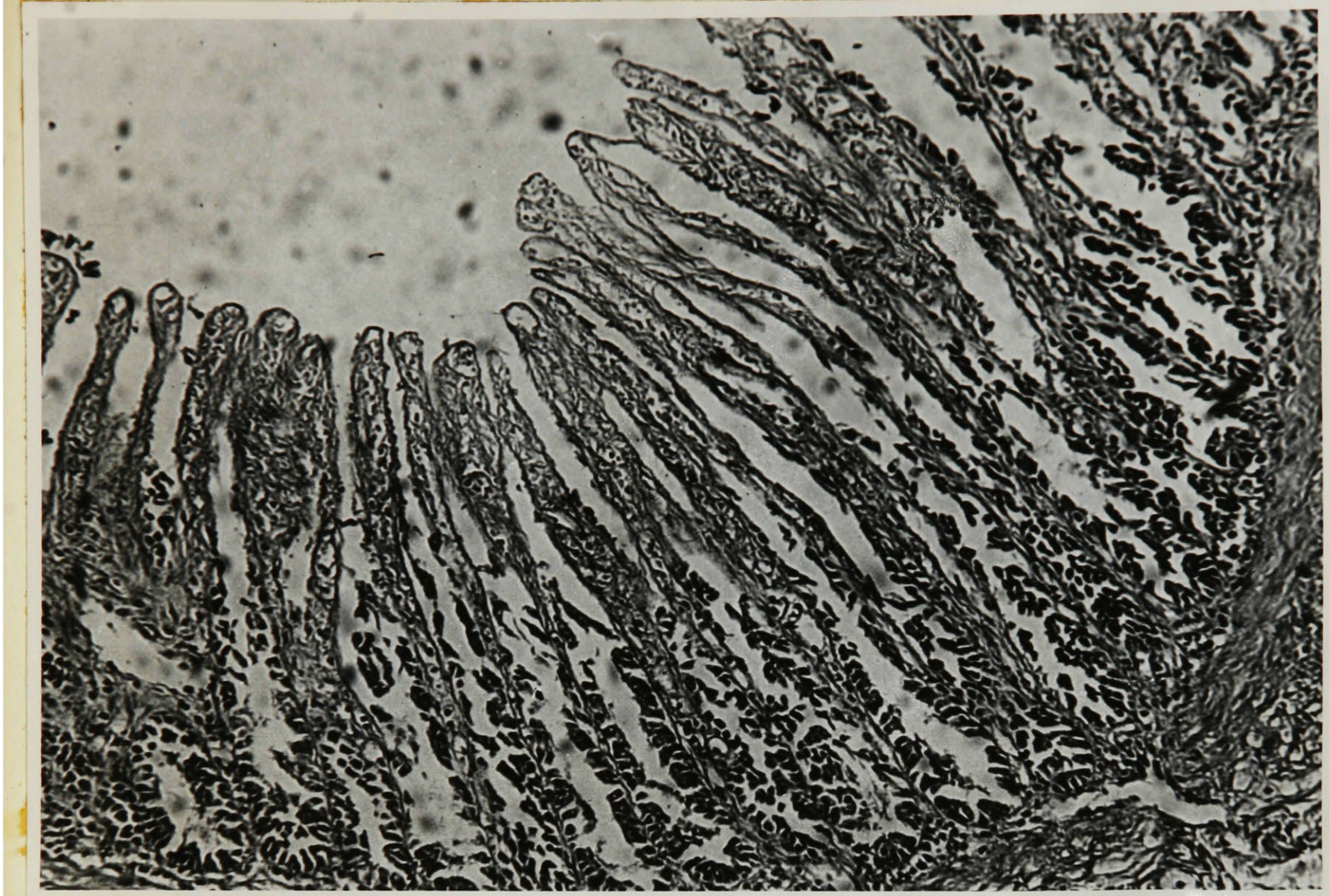
In following pages a typical gross specimen is shown (figure 12) and typical histological changes are shown in photomicrographs figures (13, 14, 15, 16 and 17). Again, all dogs had a severe persisting diarrhea from the time of operation. Occasionally flecks of blood were seen in the fluid stools. At autopsy the large bowel was always found shortened, after the haustral markings were lost. On examining the mucosal

surfaces, small rectal ulcers and small haemorrhages were found in all specimens. Many specimens showed loss of the mucosal pattern and these areas usually showed the typical superficial mucosal necrosis. In all, the most marked changes were found in the recto-sigmoid and rectum and the proximal half of the colon was relatively free of any pathological changes. Microscopically, the changes were almost identical with the changes found in series A except that in the dogs that survived for prolonged periods, the submucosal abscesses and infiltration by chronic inflammatory cells was more marked but ulcers were neither more numerous nor much larger.

Repeated analysis of the fluid stools from dogs in both series showed the active trypsin content was from ten to twenty five times the active trypsin content of the stools of normal dogs. There was no change in the white blood cell, red blood cell, or or platelet count or in the differential count of leucocytes in stained blood smears. Repeated barium enemata (8 in all) showed variable changes - the only constant findings were shortening of the colon after operation and loss of the mucosal pattern in the recto-sigmoid region in several animals (B3 and B4).

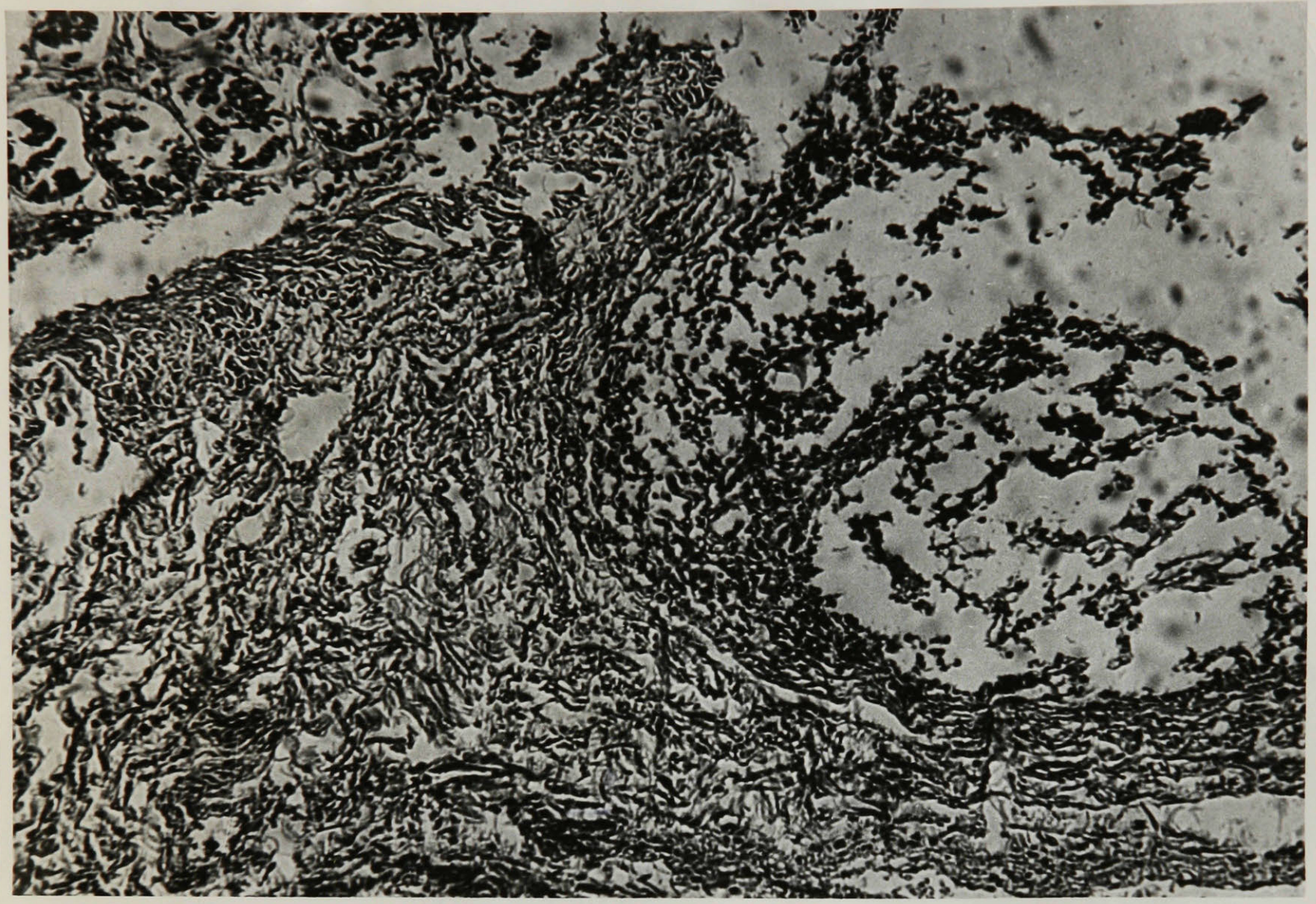
(7) Photograph 1. - Large Bowel of Dog A1

This is the bowel of a dog on which operation 1 was performed twelve days before death due to acute diarrhea. The second and third portions of the duodenum have been fashioned into a pouch - the proximal end receives the pancreatic excretion through the major pancreatic duct and the distal end empties into the colon (marker). Small rectal ulcers are shown on the left side of the photograph along with mucosal haemorrhages. In the middle portion, more haemorrhages are seen with areas of loss of the mucosal pattern. The upper half of the large bowel appeared normal.



(8) Photomicrograph 1 - Rectosigmoid of Dog A1.

Typical appearance of the lower half of the large bowel of a dog which died on the 12th postoperative day with acute diarrhea. The bile and/or pancreatic juice caused a superficial mucosal necrosis. Note the disappearance in the upper half of the mucosa of gland and stromal cells leaving only a dead "framework" of connective tissue. Gland cells in the deeper half of the crypts have survived and the stromal regions is infiltrated by chromic inflammatory cells.

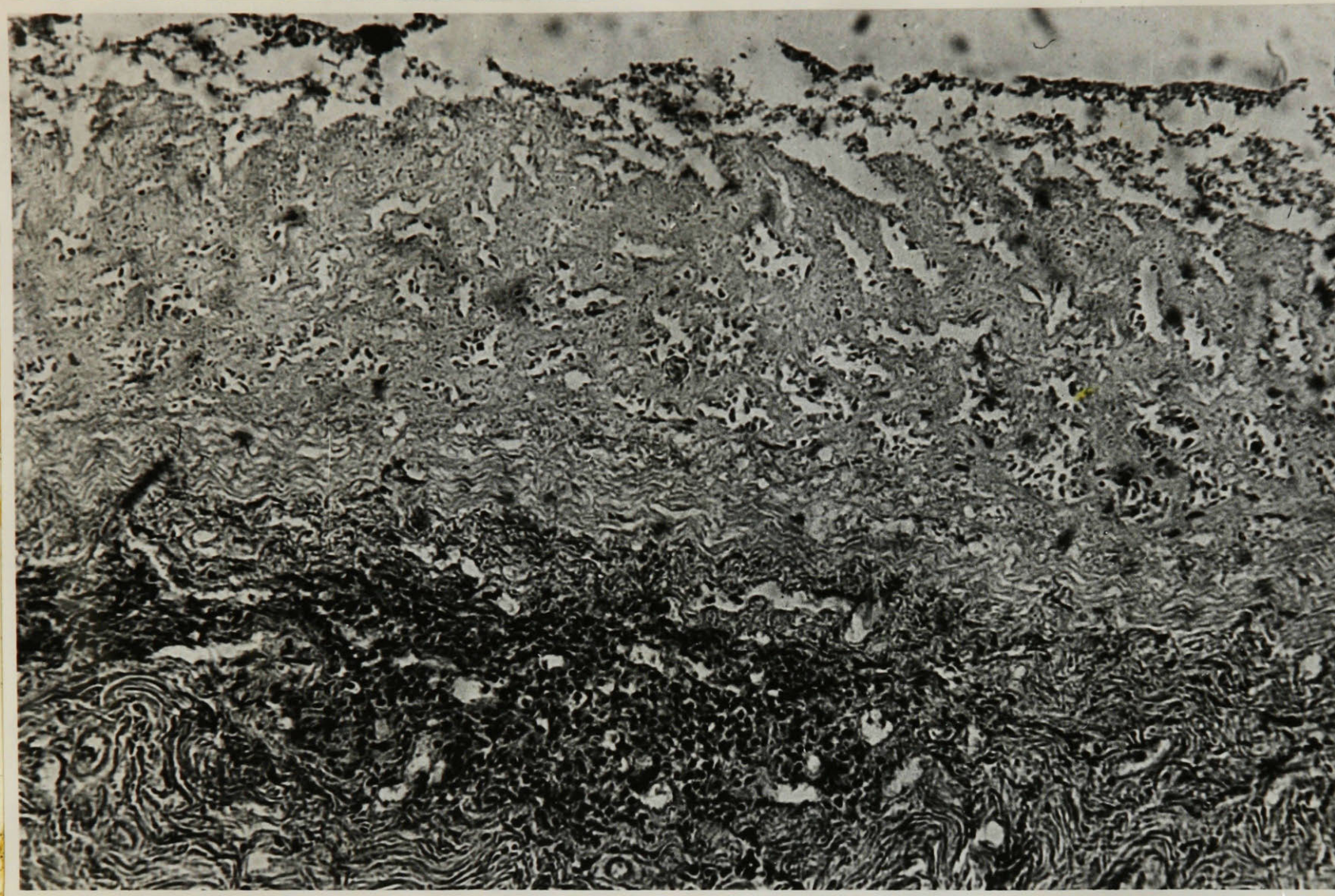


(9) Photomicrograph 2 - Rectum of Dog A1.

This shows the typical appearance of the edge of one of the small ulcers in the rectum. The lower portion of the mucous membrane is shown in the upper left corner, the edge of the ulcer in the centre and almost the whole of the right half of the photograph is the floor and base of the ulcer showing lymphocytes, plasma cells, a few leucocytes and numerous dead cells. The base of the ulcer is infiltrated by these same chronic inflammatory cells.

(10) Photomicrograph 3 - Rectosigmoid of Dog A5

This dog died 10 days after operation 1 was carried out and had a severe diarrhea continuously after operation. The photograph shows the extreme disruption and death of both gland and stromal cells of the mucosa with the connective tissue stroma remaining. Some of the gland cells deep in the crypts have survived. Some chronic inflammatory cells may be found between the glandular units of the mucosa and in the submucosa. Numerous erythrocytes were found extravascularly in the mucosa in other sections from the same bowel in the rectum along with numerous small ulcers.

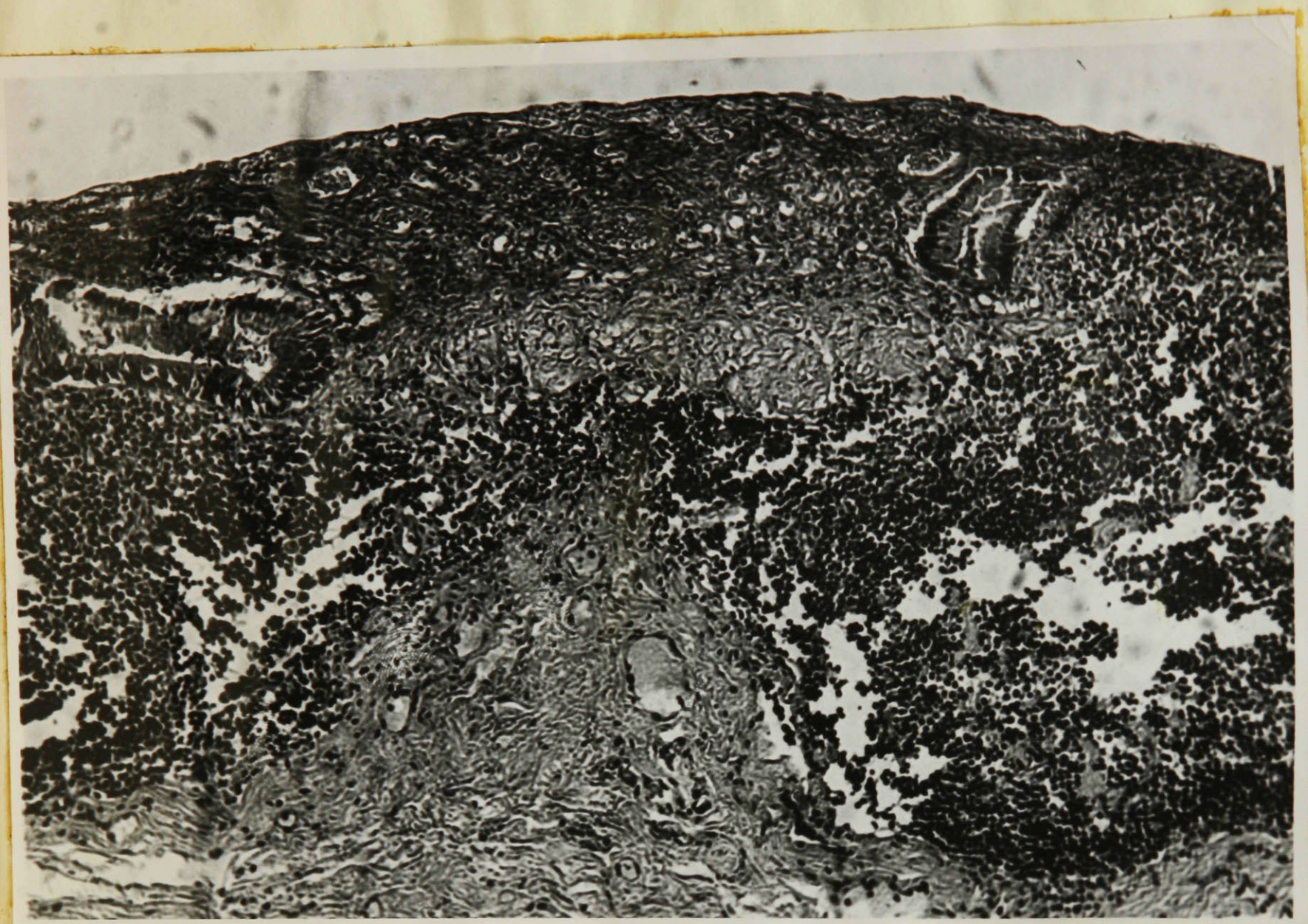


(11) Photomicrograph 4 - Rectosigmoid of Dog A8

This dog died of acute diarrhea fifteen days following operation 1. Note the similarity in the appearance of this picture with that shown in photomicrograph 3. However, the submucosal infiltration in this case is far more marked and actual abscesses are numerous. Some had ruptured through the necrotic mucosa to produce ulcers as shown in photomicrograph 2. Submucosal vessels are engorged and numerous haemorrhages are seen in other sections from this specimen.

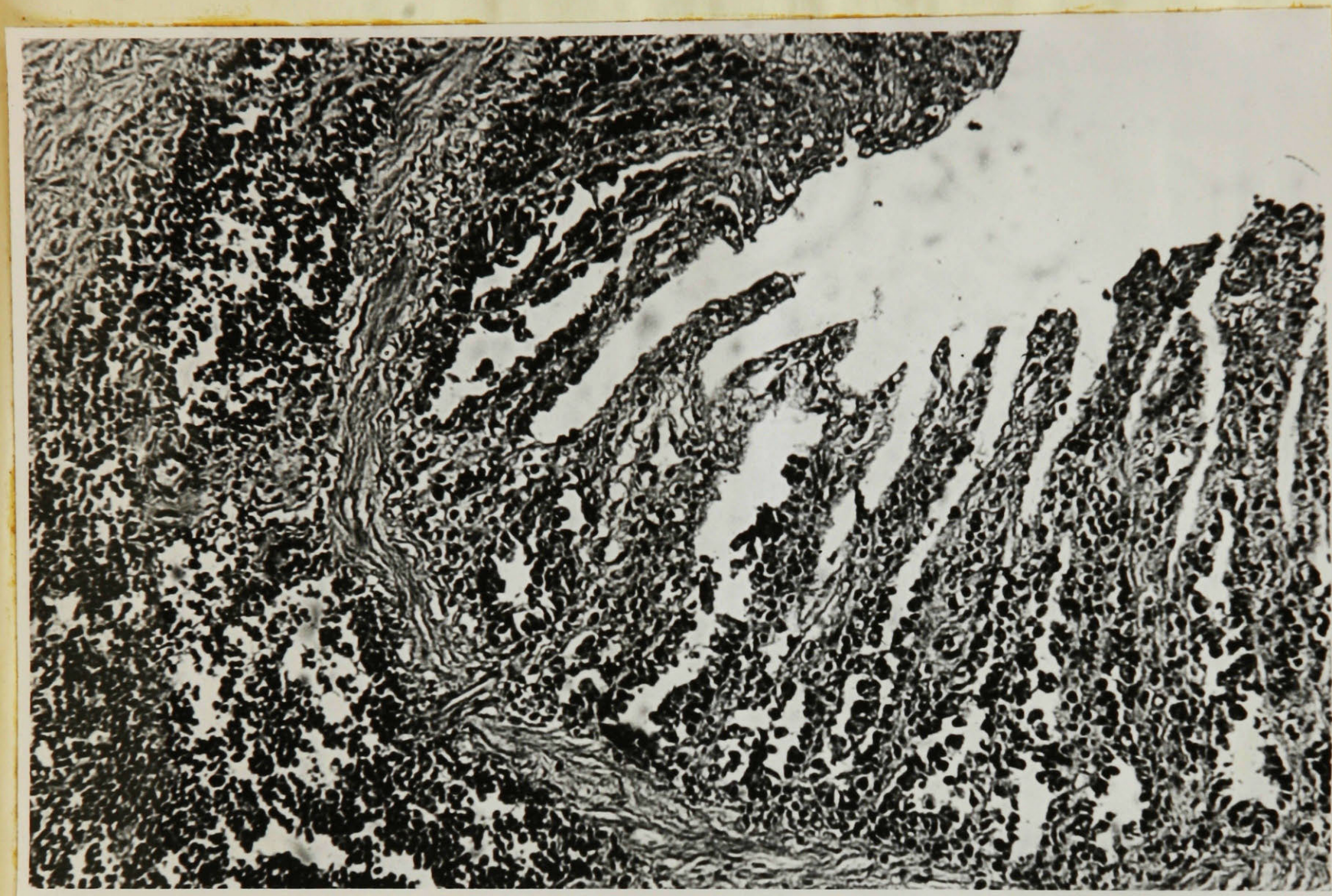
(12) Photograph - Large Bowel of Dog B8.

Gross specimen from dog which was sacrificed 158 days after operation 11 was performed. Note the short pouch of duodenum, into which the major pancreatic duct drains and which is anastomosed to the colon about three inches from the appendix. Colour photographs have recorded the congested reddended appearance of the lower rectosigmoid and rectum. Although the colon is shortened, the haustral and mucosal pattern are normal. Microscopically the changes are confined to the lower sigmoid and rectum (see photomicrograph 8).



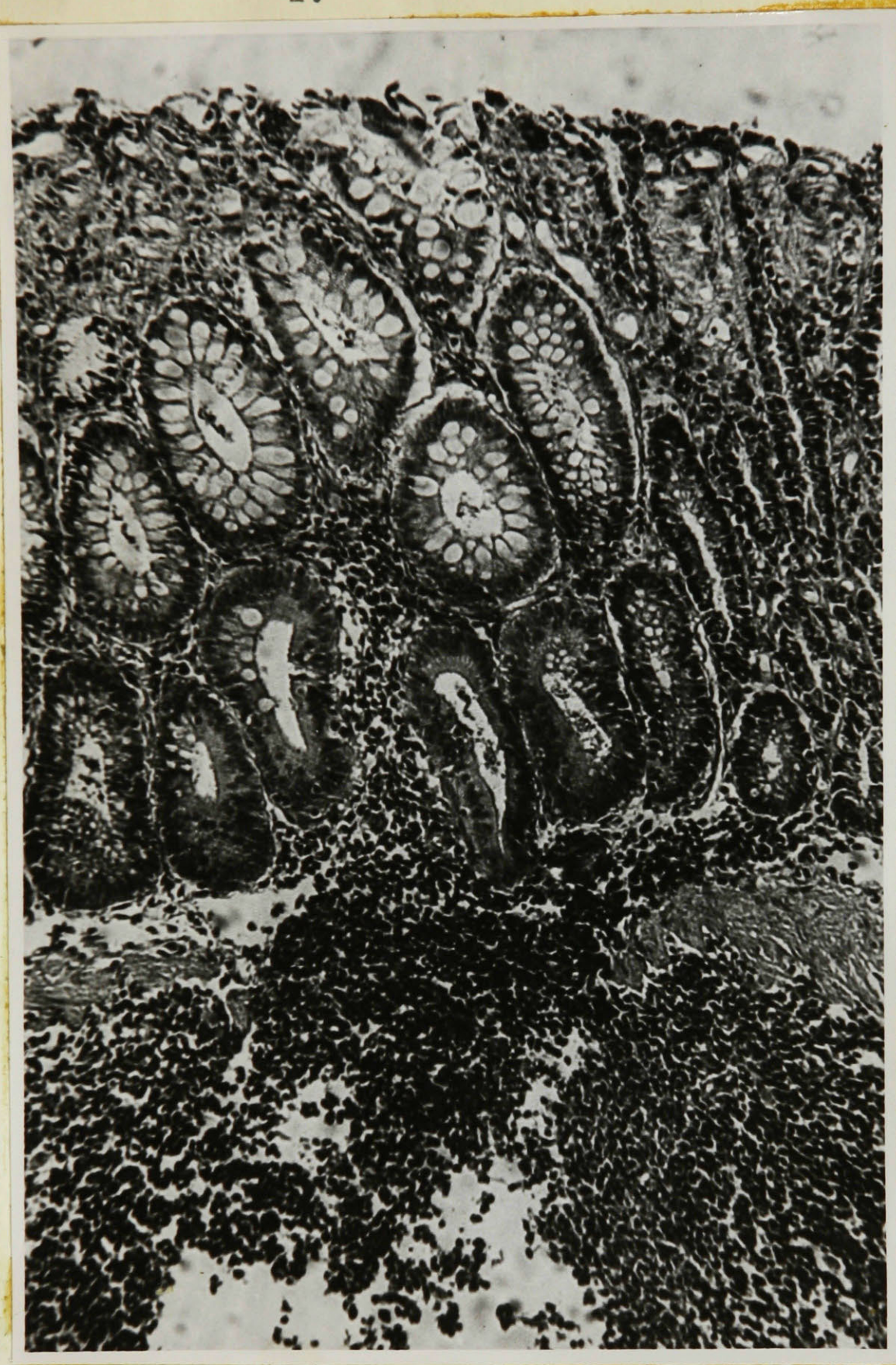
(13) Photomicrograph 5 - Rectosigmoid of Dog B2.

This dog died 15 days after operation 11 was performed. The whole of the sigmoid and rectum was red and congested. The extreme atrophy of the mucous membrane is well shown above with only a few gland crypts remaining and several small haemorrhages are shown in the mucosa. The submucosa is extensively infiltrated by chronic inflammatory cells producing numerous abscesses. Two of these areas are shown in this photomicrograph. The abscess on the right has almost ulcerated through the mucosa to the lumen of the bowel.



(14) Photomicrograph 6 - Sigmoid colon of Dog B2

This specimen is taken from the same bowel as that shown in the previous photomicrograph only farther from the rectum. It shows the superficial mucosal necrosis, the mucosal infiltration of chronic inflammatory cells and the submucous abscess formed by collections of these same cells. The photograph is taken in the depth of a mucosal fold which persisted in this region but the mucosal pattern was obliterated in the recto-sigmoid area (photomicrograph 5).

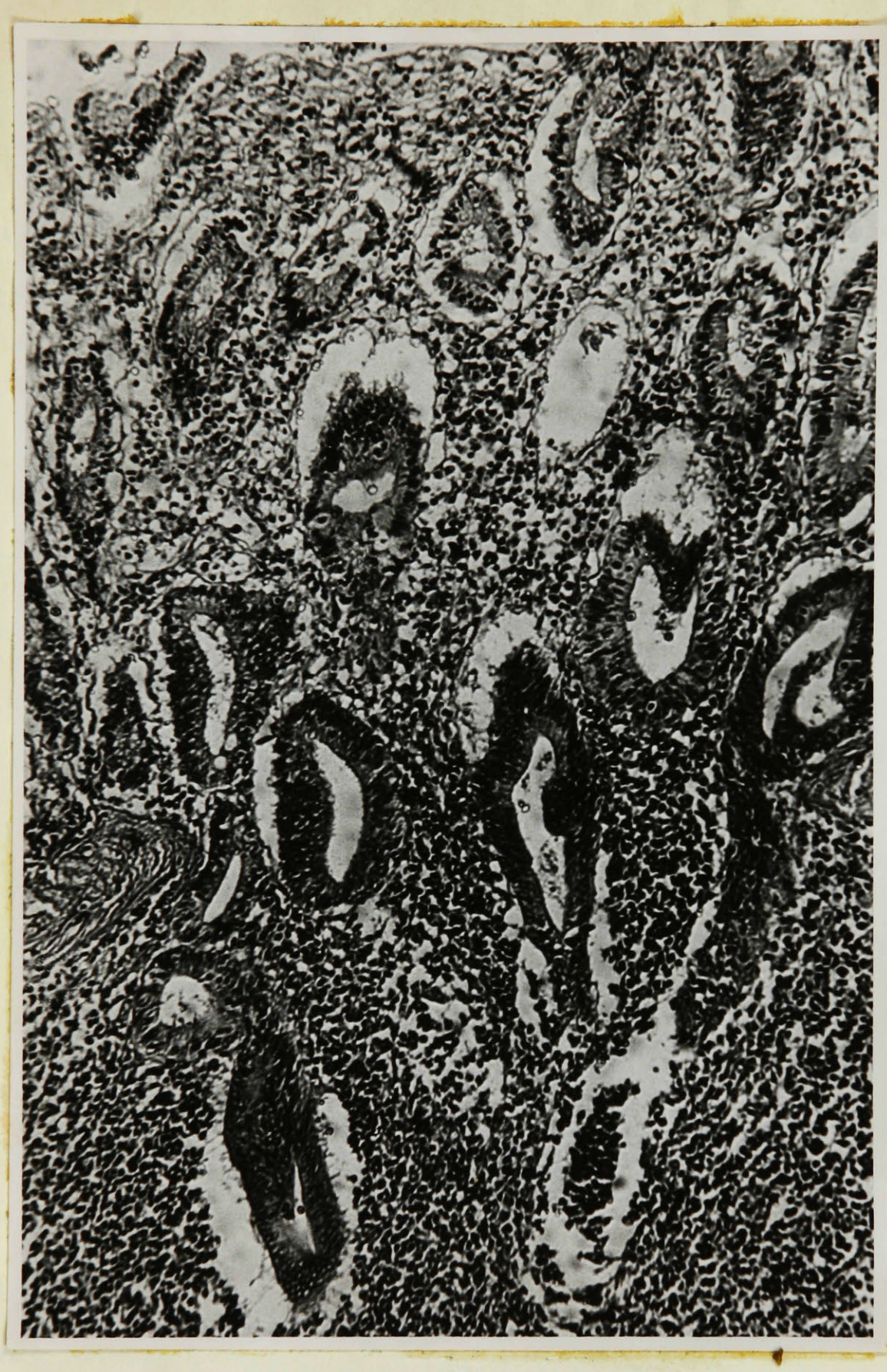


(15) Photomicrograph 7 - Rectosigmoid of Dog B4.

This dog was sacrificed 179 days after operation 11 was performed. Note the large submucosal abscess breaking through into the stroma of the mucous membrane. There is some superficial mucosal necrosis but this was more marked in other areas. Ulcers were found in other sections.

(16) Photomicrograph 8 - Sigmoid of Dog B4.

This photograph is similar to the previous photograph and is taken from the sigmoid colon of the same dog. Notice again the submucosal abscess and infiltration by inflammatory cells. There is some necrosis of the superficial half of the mucosa but the gland cells in the deeper half of the gland crypts appear normal.



(17) Photomicrograph 9 - Rectosigmoid of Dog B8.

This dog was sacrificed 158 days after operation 11 was performed. The lumen of the bowel is just off the top of the photograph. The dividing line between mucosa and submucosa is in the centre of the photograph. Note the dense infiltration of inflammatory cells in both layers and the widely separated gland units. Apparently gland units have extended into the submucosal abscess.

CHAPTER XI - DISCUSSION

The purpose of this work was to find the effect on the large bowel of undiluted bile or pancreatic juice in the living dog. Two operative proceedures were designed as described and a series of dogs were operated upon and studied until they died or were sacrificed. The cause of deaths in the immediate postoperative period (within 3 days) are outlined in figures 5 and 6. Although the mortality rate in the series is just over 50% this cannot be considered too high because of technical difficulties, of the frequent use of poor risk animals, and because of the usually high anaesthetic death rate in such animals.

Certain findings were common to all animals studied - a severe persisting diarrhea followed both operations, at autopsy the large bowels were always found shortened, the gross and microscopic changes were always most marked in the rectosigmoid and rectum and all showed small rectal ulcerations and the submucosal infiltration of chronic inflammatory cells. In many areas, superficial mucosal necrosis was found along with in inflammatory infiltration of the stroma of the mucous membrane. In some, the mucosa was very thin and atrophic with numerous haemorrhages and loss of gland units. It should

be noted that all dogs had fluid foul smelling stools but only two or three movements a day so that the normal function of the sigmoid and rectum in storing faeces so that periodic evacuation is possible, was retained and so the fecal stream with its potent proteolytic enzymes remains in contact with these portions of the large bowel for considerable length of time. Perhaps this is the reason why the changes were most marked in the lower half of the large bowel.

Few differences were found in these two series. This would indicate that bile was not necessary to cause these changes in the large bowel. Whether the detergent action or irritating action of bile has any effect on the colon was not shown because no dogs were operated upon in such a way that bile only was shunted into the colon.

The important feature of this work is the possibility that bile and/or pancreatic juice may initiate or at least aggravate the lesions found in chronic ulcerative colitis in the large bowel in humans. Other workers have shown that trypsin is present in the stool of humans with chronic ulcerative colitis so it would seem reasonable to assume that in such patients the rapid passage of potent upper intestinal enzymes into the colon will aggravate or even initiate the disease process.

The stools of these dogs contained fragments of digested food in a fluid medium. Very few pus cells were found but often the fluid stool showed a positive test for blood. It would have been interesting if a fresh fluid stool from a case of chronic ulcerative colitis could have been instilled into the large bowel of one of these dogs in the postoperative period. Perhaps then the theoretical second factor of infection could have been introduced and so experimental ulcerative colitis may have been produced.

CHAPTER XII - SUMMARY

A theory of the etiology of chronic ulcerative colitis was advanced in which psychogenic small bowel hypermotility caused the rapid transit of potent proteolytic upper intestinal enzymes into the large bowel where these juices might digest the mucosa and allow secondary infection and so cause the typical lesions in the large bowel.

Two operative proceedures were designed to study the effect of bile and/or pancreatic juice on the colon. These proceedures were carried out upon a small series of dogs and the results have been analyzed.

All dogs suffered from severe persisting diarrhea, changes were found in the large bowel of all animals and were always most marked in the rectum and rectosigmoid. Superficial mucosal necrosis, mucosal haemorrhages and ulcerations, submucosal abscesses and infiltrations by chronic inflammatory cells were found microscopically. Other studies revealed little except the fact that all trypsin determinations showed at least a tenfold increase in trypsin content following operation.

The possible significance of these findings was discussed.

CHAPTER XIII - CONCLUSIONS

(1) Both bile and pancreatic juice and pancreatic juice alone, when shunted undiluted into the colon in dogs, causes an inflammatory reaction with marked changes in the mucous membrane.

(2) These changes are always most marked in the rectum and rectosigmoid regions.

(3) Dogs suffer an acute persisting diarrhea following either operative proceedure.

(4) The large bowel is shortened in all cases as seen by barium enemata and at autopsy.

(5) In the mucosa, superficial mucosal necrosis, infiltration by inflammatory cells, small haemorrhages and ulcerations are produced.

(6) In the submucosa, abscess and marked infiltration by inflammatory cells are produced.

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CHAPTER X111

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