A STUDY OF SEVERAL FACTORS AFFECTING THE INTESTINAL ABSORPTION OF WATER, SODIUM AND POTASSIUM.

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requirements for the Degree of
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by

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"A physician, jealous of the title in its scientific sense, must go into his laboratory; and there, by experiments on animals, he will seek to account for what he has observed in his patients, whether about the action of drugs or about the origin of morbid lesions in organs or tissues. There, in a word, he will achieve true medical science."

Claude Bernard

An introduction to the study of experimental medicine, 1865.

OUTLINE OF THESIS

This thesis presents several related studies of the intestinal absorption and secretion of water, sodium and potassium in the dog and in man. The aim of the experimental work has been to characterise and explain the alterations in the handling of fluids and electrolytes by the bowel when it is obstructed.

The obstructed bowel will be shown to be incapable of absorbing water and electrolytes, and, by secreting these substances in large quantity, to contribute greatly to the fluid accumulating in its lumen. Several reasons for such disturbances are advanced.

Of the several local and systemic consequences of obstruction, which may affect the absorption and secretion of water and electrolytes, two have been selected for further study, namely, the effect of mesenteric venous congestion and the action of the adrenal mineral-corticoid, aldosterone. The latter has been studied not only to evaluate its contribution to the disturbances observed in obstruction, but also to assess its role in the normal physiology of the intestinal absorption of fluid and electrolytes.

The experimental section of the thesis begins with a description of the methods which have been used to measure the simultaneous movement of water and electrolytes into and out of the intestinal lumen.

ARRANGEMENT OF THE THESIS

This thesis is presented in two volumes.

The first volume contains the main text of the thesis including a review of the literature. The experimental studies are presented in four parts. Each experimental section contains a discussion of the results, which have been presented in the section, and ends with a summary of the main conclusions which have been drawn. The last part of the thesis (Part VI) is a brief account of the general conclusions, integrating the different parts of the thesis. The first volume ends with a list of the literature which has been cited in the text.

The second volume is divided into two parts. In the first part are the tables and illustrations set out in the order encountered in the text. The second part of this volume contains all the appendices, detailing the specifications of the chemical and radioactive substances used, and the detailed records of individual experiments, etc.

VOLUME I

CONTENTS OF VOLUME I

Page

STATISTICS

The experimental data have been analysed using conventional statistical methods (Moroney, 1956). The levels of significance for values of t and F were determined from Fisher and Yates (1963).

The following abbreviations have been employed:-

n	=	number of items in a sample.
mean	=	arithmetic mean, unless otherwise stated.
s	=	standard deviation.
S.E.M.	=	standard error of mean.
S.E.M. difference	=	standard error of mean difference.
v	=	coefficient of variation.
d	=	difference between duplicates.
d. of f	=	degrees of freedom.
σ^2	=	variance estimate.
F	=	Snedecor's F ratio
	=	$\frac{\text{greater estimate of variance of population}}{\text{lesser estimate of variance of population}}$
t	=	$\frac{\text{Difference of means}}{\text{Standard error of difference}}$
P	=	probability
r	=	correlation coefficient
z	=	Fisher's z transformation
	=	$1.15 \log_{10} \left(\frac{1 + r}{1 - r}\right)$

INTRODUCTION

INTRODUCTION

Water and electrolytes are continually being exchanged between man and his external environment. Since life can continue only if the fluid composition of the body is maintained within narrow limits, this exchange must be equal. Fluids which are lost from the body must, in the long run, be replaced. Whatever the environmental source of water and electrolytes may be, they have only one portal of entry - the intestinal mucosa.

The dietary intake of fluids and electrolytes, the amount and composition of which are variable, represents only a small proportion of the total daily load of water and salt presented to the bowel for absorption. Into the upper reaches of the intestinal tract are poured 7 - 9 litres of fluid of relatively constant composition from the liver, pancreas and gastro-intestinal glands (Carter et al., 1959). Since less than 100 ml of fluid are lost in the faeces daily, absorption is almost complete.

The absorption of the dietary and glandular fluid, however, is incorporated in a much larger exchange of fluid between the body and the lumen of the intestine. Water and electrolytes are simultaneously transferred across the intestinal mucosa in both directions at such a rate that a volume of fluid, equal to the plasma volume, enters and leaves the lumen of the bowel every 90 minutes (Visscher et al., 1944b). The process of absorption, by which the

body obtains water and electrolytes from the intestinal lumen, is the resultant of two opposing fast-flowing streams of fluid, adjusted so that more fluid leaves the lumen and enters the body than proceeds in the opposite direction.

The intestinal contribution to the maintenance of fluid and electrolyte balance is therefore considerable. However, as far as water and electrolytes are concerned, the gut absorbs what is presented to it, irrespective of the homeostatic requirements. Any control of fluid intake is exercised remotely at higher centres of nervous activity in response to the sensations of appetite and thirst. The rate of water absorption appears to be limited by the ability of the body to bear a water load rather than by the capacity of the bowel to transfer water molecules into the blood stream. On the other hand, the absorption of electrolytes may not be so indiscriminate and evidence will be presented subsequently that a degree of control may be imposed by the intestine in response to the body's needs. Nevertheless, the gut does not possess the precise homeostatic mechanisms of the kidney.

The clinical importance of the absorption of fluids and electrolytes springs from the ease with which the orderly sequence of secretion and reabsorption within the intestinal tract can be upset, leading to serious and

perhaps fatal losses of fluid from the body. Not surprisingly, the commonest causes of disorders of fluid balance are found in the gastro-intestinal tract (Black, 1957).

The surgeon most frequently encounters severe losses of salt and water in intestinal obstruction. The dilated coils of fluid-filled bowel stand as mute evidence of the disturbances in the normal pattern of secretion and absorption in the intestinal tract. The intestinal contents, unable to pass the obstruction, accumulate above it, and their volume is progressively augmented by the continued addition of biliary, pancreatic and gastro-intestinal juices. In addition, it has often been assumed that the obstructed bowel becomes incapable of absorbing fluids, and indeed may aggravate the situation by beginning to secrete into its own lumen. The altered capacity of the bowel to absorb and secrete, when it is obstructed, has received little systematic study in the past, and certainly no investigations, based on the recent concepts of water and electrolyte absorption, have been reported.

Such an investigation forms the central theme of this thesis. As a preliminary to such a study, it was necessary to investigate and develop the existing ways of measuring the rates of movement of water and electrolytes into and

out of the intestinal lumen and, in particular, to validate several of the assumptions implicit in the methods.

The various observed alterations in the intestinal handling of fluids by the obstructed bowel required explanation. Obstruction of the intestinal lumen produces a number of effects, both locally upon the bowel and generally upon the body, which individually can alter the absorption and secretion of fluids by the bowel. The influence of some of them can be deduced from the literature. However, two effects of obstruction were selected for further study.

A feature common to almost all types of intestinal obstruction is congestion of the mesenteric veins as a result of which the wall of the obstructed bowel becomes heavy with fluid and blood. Such congestion may easily contribute to the fluid accumulating within the lumen. Yet the role of increased venous pressure in influencing water and electrolyte transport has not been adequately studied in the past, despite good evidence from in vitro preparations that the hydrostatic pressure upon both sides of the intestinal mucosa may be of importance.

Obstruction of the intestine, together with the losses of fluid and the surgery often entailed, could presumably act as a powerful stimulus to adrenal-cortical activity. The hormones, produced in response, may very well influence the handling of water and electrolytes by the

bowel, in the same way that they affect electrolyte transport in other tissues. The evidence for such an assumption is good, but most of the previous work has been concerned with the concentration of electrolytes in the intestinal lumen. There have been few studies in which the rates, at which these substances are exchanged across the intestinal mucosa, have been measured following the administration of adrenal steroids, and no study has been undertaken employing the powerful, naturally-occurring mineral-corticoid, aldosterone. For its possible influence in intestinal obstruction, and because of its undoubted role in electrolyte metabolism, the action of aldosterone upon the intestinal transport of water and electrolytes was therefore investigated.

In the preliminary approaches to this work a number of deficiencies in the existing reviews became apparent. Much discussion had rightly been directed to the mechanisms of water and electrolyte transport; less consideration was usually given to the various factors affecting the absorption and secretion of these substances, and to the advantages and disadvantages of the methods of study. As a result in the review of the literature, with which this thesis begins, these aspects have been treated more fully.

PART I

A REVIEW OF THE LITERATURE ON THE ABSORPTION AND SECRETION OF WATER AND ELECTROLYTES IN THE INTESTINE.

Chapter 1 THE PHYSIOLOGICAL ASPECTS OF THE INTESTINAL ABSORPTION OF WATER AND ELECTROLYTES

HISTORY

The absorption of fluid and electrolytes by the intestine has attracted the attention of physiologists for over a century. Progress, however, has been slow (Bucher, Anderson and Robinson, 1950), due to fundamental differences in the interpretation of experimental observations and to the difficulty in designing experiments in which the many inter-related factors affecting absorption are controlled. Even yet a complete description of the means by which water and electrolytes are absorbed cannot be given.

The beginning of the century saw a protracted controversy over the forces which move fluids across the intestinal mucosa. Some believed that the transport of water and electrolytes could be explained entirely by the physical forces of diffusion and osmosis. Others argued that the participation of a "vital force" was necessary - that work had to be done by the intestinal cells themselves. That such a debate was so protracted seems strange, for at the time several experiments clearly demonstrated that physical forces alone could not account for the absorption of fluids from the

intestinal lumen.

A Scottish Professor of Physiology, Waymouth Reid, of Dundee, was perhaps the first to point out the "vital" nature of intestinal absorption. He demonstrated that, when both sides of the isolated intestine of the rabbit were bathed with identical solutions, fluid moved from the mucosal to the serosal side of the bowel (Reid, 1892).

These observations were confirmed *in vitro* by Cohnheim (1899, 1902), and, *in vivo*, by Heidenhain (1894).

Those who refuted the "vital force" theory of absorption were neither united nor consistent in their opposition. Thus, Goldschmidt and Dayton (1919*a*, *b*, *c*, *d* and *e*) described the movement of salt from the lumen of the colon to the blood against a concentration difference; yet Goldschmidt (1921) later denied the existence of forces other than those of simple diffusion. Hamburger (1908) claimed that he obtained results in a dead animal similar to those of Reid, Cohnheim and Heidenhain. This was not the case, for he described only the movement of water and not of electrolytes; in fact his observations could not be confirmed by Goldschmidt

and Dayton (1919a). Finally Höber, who at first believed that physical factors alone were concerned with absorption (Höber, 1899), later accepted the view that a special driving force was required (Höber, 1926).

Nevertheless, it was strongly argued that the active participation of intestinal cells was unnecessary for the absorption of simple saline solution. The influence of non-electrolytes, of diffusible and non-diffusible anions, and of proteins, was invoked as a reason for disregarding a "vital force". However, the critical experiment was the demonstration that sodium chloride and water were absorbed from autogenous serum instilled into the gut (Voit and Bauer, 1869; Visscher, Roepke and Lifson, 1945). Simple diffusion and osmosis, therefore, are not the only forces bringing about the absorption of water and electrolytes from the intestine.

The metabolic energy, required to absorb a saline solution, obviously need not be expended in moving all the constituents of the solution. Only one component may be transported actively, the rest following in accordance with simple physical laws. Thus the intestinal mucosa may actively transport both sodium chloride and water, or only one of them. Indeed, in the

case of sodium chloride, either the cation or the anion, or both, may be actively absorbed. To decide which substances are actively transported, the mechanisms available for absorption need to be considered briefly.

ACTIVE AND PASSIVE TRANSPORT.

The transport of materials across the intestinal mucosa, as through any biological membrane, may be regarded as active or passive. Transport is called passive if the process can be accounted for by physical forces; active transport involves the expenditure of energy from metabolic sources. These definitions are too simple and do not remove the ambiguities which surround the use of these terms and which have been partly responsible for the protraction of the mechanist - vitalist controversy.

An exhaustive description of the characteristics of active and passive transport is beyond the scope of this thesis, and is not strictly required since the experimental work described does not seek to modify present concepts of the transport mechanisms in the bowel. The discussion of active and passive transport will be limited to what is relevant to intestinal absorption. The general problems of transport across biological membranes have been discussed by others.

(Rosenberg, 1948, 1954; Ussing, 1949a, 1952, 1954, 1957, and 1960; Koefoed-Johnsen and Ussing, 1960).

Passive Transport.

The simplest type of passive transport is free diffusion in which the substance moves across the membrane from a region of high concentration into one of low concentration, and is brought about by the thermal energy of the particles. Such movement is governed by the quantitative laws, formulated by Fick (1855), which unfortunately cannot be applied directly to the intestinal transport of electrolytes.

There are three main reasons for this:

(a) The mucosa across which transfer takes place is not a simple uniform membrane but in fact presents three barriers to diffusion - the membranes on the luminal and serosal aspects of the cell and the basement membrane. Each are constructed differently and so have different permeability characteristics.

(b) Electrolytes are acted upon by forces other than simple diffusion. As charged particles, they will be influenced by electrical forces, tending to be attracted into fields of opposite charge

and repelled from those of similar charge. Obviously, if an ion is carried through a membrane because of differences in electrical potential across the membrane, such transport must be regarded as passive. Using the analogy of the Fick equation, Ussing (1949b) was able to express mathematically the movement of ions under the influence of electrical and chemical forces. Many assumptions had to be made (Koefoed-Johnsen and Ussing, 1960): the membrane was regarded as uniform, and the effect of solvent drag was ignored.

(c) When water is moving through a membrane, a force is exerted upon the diffusing particles so that those moving in the direction of flow are speeded up whereas those moving against the stream are slowed down. To such interference has been applied the term 'solvent drag' (Koefoed-Johnsen and Ussing, 1953; Ussing and Andersen, 1956). The influence of solvent drag on ion transport becomes considerable in any system where hydrostatic and osmotic gradients occur. The existence of solvent drag has been

described in the intestine (Fisher, 1955; Cooperstein and Brockman, 1959).

The description of the passive transport of electrolytes is therefore complicated by the fact that several forces act upon them simultaneously - diffusion force, electrical force and solvent drag. The several assumptions which have been introduced to simplify the mathematical treatment may introduce errors of considerable magnitude even for a single membrane (Ussing, 1960). Their application to a complex epithelial surface such as the intestinal mucosa is probably not justified.

Much useful information, however, can be obtained, avoiding many of the assumptions, if the ratio between the rates of unidirectional movement of the substance across the membrane is considered, rather than the absolute rates themselves (Ussing, 1949b). This ratio, the flux ratio, depends upon the electro-chemical differences across the membrane. Thus,

$$\frac{M_{in}}{M_{out}} = \frac{a_o}{a_i} \cdot e^{zFE/RT} \qquad (1)$$

where M_{in} is the influx, i.e. amount of ion moving into the cell in unit time; M_{out} is the efflux, i.e. amount of ion moving out of the cell; a_o and a_i are the electro-chemical activities of the ion outside and inside the cell; z, the number of charges; F, the Faraday number; R, the gas constant; T, the absolute temperature; E, the potential difference across the membrane.

This equation (Equation 1) is valid for an ion moving passively under the influence of electrical and chemical forces but does not take solvent drag into account. However, when a transfer system is being examined for active or passive behaviour, solvent drag can be safely ignored (Ussing, 1960).

The value of this equation lies in its ability to distinguish between active and passive transport and to demonstrate the type of passive transport. Thus the flux ratio M_{in}/M_{out} can be obtained experimentally by determining the individual fluxes with isotope tracers. The flux ratio can also be calculated if the ratio of the electrochemical activities, a_o and a_i, is determined from the internal and external concentrations of the ion and the measured electrical potential. Where the two

estimates of flux ratio agree, the ion in question is considered to have moved by free diffusion.

If the observed flux ratio M_{in}/M_{out} is less than the calculated ratio, then exchange diffusion is said to have occurred (Ussing, 1947), in which considerable exchange takes place across the membrane but little net transfer occurs (Levi and Ussing, 1949). Such exchange diffusion resembles active transport in that it seems to be carrier-mediated, but differs in that work does not need to be performed. This type of passive transport has been described in the stomach (Hogben, 1955) and the large intestine (Cooperstein and Hogben, 1959) of the frog.

When the observed flux ratio is greater than the calculated ratio the transport is considered to be active. The only exception to this is the unusual type of passive transport described by Hodgkin and Keynes (1955) in the squid axon and termed "single file diffusion".

Active Transport.

Probably the only safe way of deciding that transport is active is to exclude the possibility that the transfer process is passive in nature (Ussing, 1960). Active transport has been defined as

movement against a chemical gradient for uncharged substances and an electrochemical gradient for charged substances (Rosenberg, 1948 and 1954; Ussing, 1957).

To decide whether an electrolyte has been actively transported, its concentration on either side of the membrane, and electrical potential across the membrane, must be known. The use of the isotopically-determined flux ratios, M_{in}/M_{out} has already been described. To establish active transport of water it would be necessary to demonstrate movement into a region of similar or greater activity of water, i.e. net movement without or against an osmotic gradient - or the maintenance of a difference in osmotic pressure across a membrane freely permeable to water.

Active transport is, by definition, dependent on continuing metabolic processes and so will possess certain characteristics (Robinson, 1960; Wilson, 1962). Active transport can be inhibited by metabolic poisons. Competitive inhibition between chemically-related substances may be seen; in addition the transport system often exhibits a degree of

structural specificity. The facts that the rate of transport is not a linear function of concentration and that the process can be "saturated", suggest that a carrier is required to assist in the transport of the substance through the membrane. The possession of such features by a transfer system does not necessarily imply that the transport is active, because certain types of passive transport have these properties.

Active transport, therefore, means that the substance is moved uphill against the electrochemical gradient and that the required energy is derived from metabolic sources. The actual vehicle used and the way in which the energy is transferred to the moving substance are quite unknown. The several theoretical systems, that have been described, are reviewed by Ussing (1957 and 1960). These will be briefly outlined and their relevance to intestinal transport considered.

(a) Simple membrane carrier transport (Osterhout, 1940).

The substance to be transported reacts with a component of the cell membrane to form a complex which then diffuses across the membrane. On the inner surface of the membrane, the carrier

releases the substance, chemically unchanged. Despite the attractions of this theory, no specific ion-binding substrates have been demonstrated in cell membranes.

(b) Pinocytosis (Lewis, 1931).

Minute droplets of the fluid surrounding the cell are taken up or ingested by the cell, transported across the cytoplasm and given up by the cell at its other side. This is an unlikely method for electrolyte and water transport for it obviously implies the movement of equivalent amounts of sodium, chloride and water; this does not occur (Koefoed-Johnsen, Ussing and Zerahn, 1952).

(c) Fluid-circuit hypothesis (Ingraham, Peters and Visscher, 1938).

The basis of this theory, which was proposed to explain salt absorption in the gut, is that electrolytes and water are carried through pores in the cell membrane, and that subsequently water is returned to the intestinal lumen through narrower pores. This theory will be considered in detail later.

(d) Electron-linked transport.

In this theory, the energy for ion transport is considered to be derived from the electron-transferring reactions of respiration. Such a system has been used to explain acid secretion (Conway, 1953). It seems likely, however, that the energy for ion transport is derived from energy-rich phosphate bonds rather than respiratory electron transfer (Zerahn, 1956).

The popular theory of active transport is that of carrier-mediated transfer across the cell membranes. No such hypothetical mechanisms have been isolated nor have they ever been described in the terms of chemical substances. However, the high degree of specificity, the expenditure of energy, the type of saturation kinetics and competitive inhibition make the likelihood of their participation very great.

INTESTINAL TRANSPORT OF ELECTROLYTES.

Although many electrolytes - all more or less dissociated into their constituent ions - are found in the body, only a few of them play an important part in controlling the volume and distribution of water and

maintaining the tonicity of body fluids. These chief electrolytes are the cations, sodium and potassium, and the anions, chloride and bicarbonate. Their intestinal transport will now be described.

The absorption of other electrolytes, e.g. calcium, phosphate, iodine, magnesium and iron, will not be discussed since their function is highly specific, since their contribution to the ionic composition of the body is slight, and since their intestinal absorption is relatively slow and individual.

Cations.

(i) Sodium

Sodium, it is generally agreed, is actively transported across the intestinal mucosa. This conclusion, however, has been reached only after considerable dispute, and required the design of several ingenious experiments satisfactorily to control the various changes which occur in salt solutions during the process of absorption.

The evidence, so far presented in this review, has suggested that the absorption of fluid and electrolytes required the active participation of the intestinal cells. To prove that sodium chloride, rather than water,

was actively transported, absorption against concentration differences would have to be demonstrated. Such evidence was difficult to obtain for the gut does not easily allow anisotonic fluid to dwell in its lumen and will quickly attempt to render it isotonic by adding or subtracting water (Goldschmidt and Dayton, 1919b; McDougall and Verzar, 1935). Such a trend to isotonicity quickly abolishes any differences in concentration between both sides of the intestinal mucosa. The use of osmotically-active but poorly-absorbed substances provided an answer to the problem. When a solution containing a low concentration of sodium chloride was brought to isotonicity with mannitol (Katzenellenbogen, 1906), magnesium chloride or sodium sulphate (Cobet, 1913) and then instilled into the gut, there was no immediate flow of water to adjust osmotic relations. Absorption of sodium chloride against a concentration difference was demonstrated.

With the acceptance of the active transport of salt, the next step was clearly to decide whether sodium ions, or chloride ions, or both, were actively absorbed. Obviously the situation could exist in which one ion only was being actively transported and the other was being

moved to maintain electrochemical neutrality. For this decision, the electrical potential differences across the membrane must be measured.

Electrical potentials.

The measurement of the electrical parameters of absorption experiments was simplified by Ussing and Zerahn (1951), who, in isolated preparations, passed a current equal to the physiological one but opposite in direction to "short circuit" the membrane.

With such a technique Ussing and Andersen (1956) showed that the positive charge, which developed on the serosal surface of the large intestine of the toad, was caused almost entirely by the net movement of sodium cations towards the serosa. Indeed all the current came from sodium transport, suggesting that sodium ions were the only ones being actively transferred. Similar results were obtained by these authors with the caecum of the guinea-pig.

In the isolated colon of the bull-frog sodium moved toward the serosal side against the electrical gradient (Chalfin, Cooperstein and Hogben, 1958; Cooperstein and Hogben, 1959). The passive nature of chloride transport was obvious - indeed exchange diffusion was demonstrated. However, the current

required to "short-circuit" the membrane was greater than the amount of sodium moving: the active transport of another cation in the same direction or of an anion in the opposite direction seemed to be taking place.

With the measurement of electrical potentials in vivo, the active transport of sodium and the passive movement of chloride have been demonstrated in the colon of the rat (Curran and Schwartz, 1960) and of dog (Cooperstein and Brockman, 1959).

In the small intestine, on the other hand, potential differences are extremely small. One reason may be that both sodium and chloride are actively absorbed so that their transport potentials neutralize one another (Curran and Solomon, 1957; Curran, 1960). Any decision concerning the nature of the transport of ions in the small intestine is made difficult by such low electrical resistance of the tissues.

Bi-directional movement of sodium.

When salt-free solutions are introduced into the bowel, sodium can be detected in the intra-luminal solution within a short time (Hober, 1899; Cobet, 1913; Rabinovitch, 1927; Burns and Visscher, 1935). Sodium had entered the intestinal lumen from the body. Therefore a two-way traffic of sodium ions into and out

of the lumen was feasible during the absorption of salt solutions from the gut.

Such bi-directional flux of sodium was first convincingly demonstrated by Visscher et al.(1944b) using radio-isotopic techniques which were then in their infancy. The net movement of sodium across the intestinal mucosa is therefore the difference between the amounts simultaneously moved into and out of the lumen of the bowel. If the rates of movement in opposite directions were equal, no net movement would occur despite a large turnover of sodium. The rates of such bi-directional exchange vary in different parts of the intestine.

(ii) Potassium

Potassium, like sodium, moves in both directions across the intestinal mucosa (Katzenellenbogen, 1906; Hober, 1926). No definite opinions can be given whether potassium transport is mainly active or passive.

Large amounts of potassium are secreted into the bowel lumen with the digestive juices but yet only about 9 mEq per day are lost in the faeces, (Dempsey et al., 1958). The amount of potassium absorbed must be considerable but little is known about the site or

mechanism involved.

Potassium has been shown to be more rapidly absorbed than sodium from equimolar isotonic solutions in the intestine of the dog (Ingraham and Visscher, 1936a). However, since the extra-cellular concentration of potassium is much less than that of sodium, a steeper concentration gradient existed for potassium. Indeed, if this concentration gradient were steep enough, active transport processes would not be required. Under normal circumstances in man with an average concentration of potassium in the gut of 16 mEq per litre (Spencer, 1960) and with an extra-cellular concentration of 5 mEq per litre, an adequate gradient exists.

Potassium may be secreted passively into the colonic lumen to neutralize the potential difference induced by the active movement of sodium in the opposite direction. Or a coupled sodium-potassium pump may exist - actively transferring sodium from lumen to blood, and potassium in the opposite direction (Ussing, 1960).

While little is known of the mechanism of potassium absorption there is no doubt that the ion plays an important part in alimentary physiology. Gastro-

intestinal secretions contain large quantities of potassium whose concentrations in the lumen of the stomach, duodenum, and colon are greater than that in the plasma. Most of this potassium is absorbed. If such re-absorption is prevented by disease potassium depletion will quickly develop.

Anions

The movements of sodium and potassium are closely linked to those of the anions, the principal two of which are chloride and bicarbonate.

(i) Chloride

Early workers suggested that chloride was actively absorbed. When isotonic mixtures of sodium chloride and sodium sulphate were introduced into the colon (Goldschmidt and Dayton, 1919d) or ileum (Ingraham and Visscher, 1936a) of the dog, the chloride concentration diminished rapidly. The term "chloride impoverishment" of the luminal solution was applied to this phenomenon which was thought to demonstrate active transport since it could not be observed in the presence of metabolic poisons such as fluorides and cyanides

(Ingraham and Visscher, 1936b).

When an isotonic solution of sodium chloride is presented to the gut, a concentration gradient for chloride will exist even although there will be none for sodium, since the extra-cellular concentration of chloride is much less than that of sodium. Chloride ions have been shown to move against a concentration gradient (Curran and Solomon, 1957; McHardy and Parsons, 1957), but, since this movement was down the electrical gradient, the transport of chloride ions seems to be passive, particularly in the large intestine (Cooperstein and Hogben, 1959; Curran and Schwartz, 1960). The active transport of both chloride anions and sodium cations in the small intestine is probably the reason that electrical potential differences cannot be easily detected at that site (Curran and Solomon, 1957).

(ii) Bicarbonate

While chloride is being absorbed from the colon, the anionic concentration remains constant because of the entry of bicarbonate ions into the lumen (d'Agostino, Leadbetter and Schwartz, 1953). Indeed a reciprocal relationship between bicarbonate and chloride movement

has been demonstrated not only in the dog (Bucher et al., 1950) but also in the rat (Parsons, 1956) and in man (Bucher, Flynn and Robinson, 1944). Bicarbonate may be exchanged for chloride.

Solutions introduced into the jejunum become slightly acid (de Beer, Johnston and Wilson, 1935; Ingraham and Visscher, 1938); in the ileum, on the other hand, there is a tendency to alkalinity, pH 7.5. The level at which the reaction of the gut content changes from acid to alkali varies with the species (Wilson and Kazyak, 1957). The ability of the jejunum to render its contents slightly acid and of the ileum its contents slightly alkaline has been observed in the dog (Ingraham and Visscher, 1936a; Robinson, Luckey and Mills, 1943; Bucher et al., 1950) and in man (McGee and Hastings, 1942; Bucher et al., 1944).

With everted sacs of ileum, Wilson and Kazyak (1957) showed that the pH and concentration of bicarbonate fell on the serosal side of the mucosa with a corresponding gain on the mucosal side. They suggested that the ileum secreted an isotonic solution of sodium or potassium bicarbonate. Since the carbon dioxide tension (PCO_2) of the serosal solution rose they proposed

that hydrogen ion was being added in exchange for another cation. Parsons (1956) suggested that hydrogen ions may be exchanged for sodium during sodium absorption. Wilson (1962) has studied in detail the pH changes across the gut wall.

INTESTINAL TRANSPORT OF WATER.

The prompt diuresis which follows a high fluid intake must be brought about by a rapid rate of water absorption in the first place. In some species the rate of water absorption may be fast enough to cause intravascular haemolysis (Lee, 1954). Following its intra-gastric instillation, deuterium oxide appears in the portal blood within 2 - 4 minutes (Benson et al., 1956). The movement of water across the intestinal mucosa, like that of sodium and potassium, is bi-directional (Visscher et al., 1944a).

The facility with which water and electrolytes can enter and leave the lumen of the intestine ensures that markedly anisotonic fluids are quickly rendered isotonic. When introduced into the gastro-intestinal tract, tap water, which is damaging to the mucosa of the intestine (Dennis, 1940; Blickenstaff, 1954b), becomes isotonic in the stomach and duodenum due to

the entry of electrolytes and rapid removal of water (Burns and Visscher, 1935; Follansbee, 1945; McHardy and Parsons, 1957). Water will enter hypertonic solutions (Goldschmidt and Dayton, 1919c). Under normal conditions most of the intestinal mucosa is therefore presented with isotonic fluid for absorption.

From this fluid, water and solute are absorbed at approximately equal rates (Peters and Visscher, 1939; Wilson, 1956a; Curran and Solomon, 1957; Smyth and Taylor, 1957). In this way the bowel content remains isotonic or nearly so (Visscher and Roepke, 1945; Visscher et al., 1945).

Active or passive transport

The type of transport system employed in the absorption of water has not been completely elucidated. One widely-held view is that water transport is passive and secondary to the transfer of solute. Solute is absorbed, and water follows in response to the osmotic gradient set up (Curran and Solomon, 1957; Curran, 1960; Curran and Schwartz, 1960).

This concept of passive transport for water absorption is strengthened by several observations on the effect of hydrostatic pressure. Water absorption

was found, within limits, to be enhanced by applying pressure to the intra-luminal solution (Blickenstaff et al., 1952) and water transfer from the mucosal to serosal side of isolated intestine can be brought to a halt by the application of even quite a low pressure on the serosal surface (Wilson, 1956b).

The passive nature of water transport has been challenged by several groups on four main counts:-

(a) Absorption of water from a hypertonic solution, against the osmotic gradient, has been observed both in vivo (Goldschmidt and Dayton, 1919b; Tidball and Tidball, 1956; McHardy and Parsons, 1957) and in vitro (Fisher, 1955; Parsons and Wingate, 1961). Any theory of water transport has to explain these observations.

(b) Some studies in vitro have not confirmed the marked influence of hydrostatic pressure upon water transport (Smyth and Taylor, 1954; Fisher, 1955). Such lack of agreement with other work may spring from the basic unsuitability of in vitro preparations for the investigation of water transport, since water has to traverse the

entire thickness of the intestinal wall rather than only mucosa in the intact state.

(c) The transport of water appeared to require the expenditure of energy, for the presence of glucose in the bathing solutions seemed to be essential for the absorption of water by the isolated bowel (Smyth and Taylor, 1954 and 1957; Fisher, 1955; Lifson and Parsons, 1957; Parsons and Wingate, 1961). Such apparent glucose-dependent transport was easily arrested by mucosal poisons (Smyth and Taylor, 1955). On the other hand, the isolated hamster intestine does not seem to require glucose for water absorption (Wilson, 1956a), and, of course, the absence of glucose from the luminal solution in the intact animal will not affect absorption (McHardy and Parsons, 1957) since the mucosal cells are nourished by the blood. The relationship between water movement and the expenditure of energy, however, may not be direct. Passive water movement secondary to the active transfer of solute could be an equally acceptable explanation.

The relationship between the absorption of water and sugars has been comprehensively reviewed by Crane (1960).

(d) Since water movement did not comply with the classical theory of osmosis, the transport of water was considered to be active (Visscher et al., 1944a). However, when water flows through a porous membrane, simple osmosis does not take place and the disparity observed by Visscher and his colleagues can be explained on the laws of laminar flow which apply to this circumstance (Koefoed-Johnsen and Ussing, 1953; Ussing and Andersen, 1956).

To clarify the relationship between solute and water transport, Curran and Solomon (1957) used a solution, with a low concentration of salt, made isotonic with poorly-absorbed mannitol. Under these conditions, the absorption of both salt and water was diminished. These findings have been confirmed (McHardy and Parsons, 1957). Indeed when no salt was absorbed, no water was absorbed. Since the activities of water on both sides of the membrane were identical, these findings

suggested that water transport was not an independent process but passive and controlled by the movement of solute.

This concept would explain the apparent paradox of absorption of water from a hypertonic sodium chloride solution. From a sodium chloride solution, sodium, and hence, water, would be rapidly absorbed. From a hypertonic sodium sulphate solution, on the other hand, sodium and water were poorly absorbed (Goldschmidt and Dayton, 1919d; Burns and Visscher, 1935). Water will be absorbed from isotonic saline solution and from plasma so long as active solute transport is taking place.

To explain the various apparently-conflicting observations described above a model of water transport has been proposed by Curran (1960). The observation that a solution will emerge on the serosal surface of the isolated gut even if there is no solution bathing that surface (Smyth and Taylor, 1957) suggested to him that the driving force for water transport may be not only an osmotic gradient but also a hydrostatic pressure developing within the tissue itself. Across the mucosal surface, which is thin and porous, solute is

actively transported, with water following by osmosis. The increased hydrostatic pressure within the tissue will extrude water through a membrane which is thicker and has larger pores. Such a membrane may be the submucosal and muscular layers. The transport of large volumes of water across the membrane would hinder diffusion in the opposite direction.

However, it can not be too readily concluded that the absorption of water is entirely passive. The concept of the active transport of water, suggested by several *in vitro* experiments (Fisher, 1955; Smyth and Taylor, 1957; Parsons and Wingate, 1961), has had further support from Vaughan (1960) and Ullman *et al.*, (1960) who showed, in the dog and the cat respectively, that water can leave the intestinal lumen against an activity gradient. There may therefore be several mechanisms available for water transport.

Fluid-circuit theory

Although not now generally held, the *fluid circuit theory* will be considered further since its advocates propounded the theory from their observations on intestinal absorption (Ingraham *et al.*, 1938; Ingraham and Visscher, 1938). The theory postulated

that water was actively absorbed and that solute was dragged along in its wake. This movement was thought to take place through a membrane which possessed a mosaic-like structure in which thicker pores allowed the passage of water and solute into the cell and thin pores, relatively impermeable to solute, allowed water to leak out of the cell back into the intestinal lumen. This theory was first advanced to explain the fall in chloride concentration in a solution containing a mixture of sodium chloride and sodium sulphate; however more acceptable explanations for this phenomenon are available, (Curran and Solomon, 1957). Despite the many objections the fluid circuit theory still has its supporters (Vaughan, 1960; Grim, 1962).

Chapter 2 THE ANATOMICAL ASPECTS OF THE INTESTINAL ABSORPTION OF WATER AND ELECTROLYTES.

The description of the mechanisms of absorption hinted at the complex surface across which water and electrolytes are transported. It is necessary now to describe more fully the morphology of the intestinal mucosa, with particular reference to fluid and electrolyte absorption.

I - THE SITES OF ABSORPTION OF WATER AND ELECTROLYTES.

Strict comparison of the absorptive ability of different segments of gut requires that the rates of transport are related to the mucosal surface area. Although the intestinal epithelium is arranged as a tube, the mucosal surface area cannot be calculated from the length and radius of this tube because the mucous membrane has undergone several modifications to increase its area. Because of the valvulae conniventes, the villi and the microvilli, the surface area of the bowel is about 600 times greater than the area of a simple tube of similar gross dimensions (Wilson, 1962). The various attempts to estimate surface area from mucosal outlines neglect the microvilli (Warren, 1939; Wood, 1944; Fisher and Parsons, 1950; Grim, 1962). Although the number of microvilli per columnar cell

and per unit area of intestine have been calculated (Granger and Baker, 1950; Zetterqvist, 1956), microvilli vary in size and shape with the site of cell in which they are contained (Dalton, 1951; Palay and Karlin, 1959). There is therefore no valid method for calculating the total surface area available for absorption. Any attempt to compare the absorptive abilities of various segments of bowel on such a basis will have a low level of accuracy.

(a) Stomach.

The stomach is not an important site of absorption (Karel, 1948). Although exchange between gastric content and blood occurs (Scholer and Code, 1954), only small quantities of sodium (Reitemeier, Code and Orvis, 1957b) and of water (Lee, Code and Scholer, 1955) are in fact absorbed. Sodium leaves the cavity of the stomach at a slower rate than that of potassium and water, particularly in the presence of acid, whose hydrogen ions may compete with sodium for the absorptive mechanisms (Code et al., 1963).

(b) Small intestine.

(i) Duodenum.

Despite large exchanges of water and sodium across the duodenal mucosa, little net movement

occurs (Visscher et al., 1944a and b; Code et al., 1960; Grim, 1962). The duodenum has been regarded as the equilibrator of the intestinal tract (Hindle and Code, 1962). Sodium enters the duodenum to raise the luminal concentration to that of plasma. Water will enter the duodenum when hypertonic solutions are introduced. Thus, under physiological conditions, the mucosa of the rest of the intestinal tract encounters only isotonic fluid.

(ii) Jejunum and ileum.

The rest of the small bowel seems to be designed for absorption. Even when an anisotonic solution is introduced directly into the ileal lumen no great attempt is made to render these solutions isotonic - absorption is quickly and effectively begun (Hindle and Code, 1962). Many of the differences among the published rates of transport in the ileum and jejunum can be attributed to the gross inaccuracies in measuring surface area of the mucosa. Thus, Visscher et al., (1944a and b) and Code et al., (1960) described that, in the dog, the rates of exchange of water and electrolytes in

the jejunum were higher than those in the ileum; whereas the opposite situation was observed by Grim (1962). However, all three groups of workers agreed that greater net absorption was found in the ileum because more sodium and water left the lumen than entered at any given time. In the rat, (Parsons, 1956), and in the hamster (Wilson, 1956a), twice as much sodium was absorbed by the jejunum as by the ileum.

(c) Large intestine.

Attempts to compare the absorptive ability of the colon with that of the small bowel have led to confusion because of the afore-mentioned inaccuracies in measuring the surface areas. Thus the rates of sodium and water transport in the large bowel have been said to be greater (Grim, 1962) and smaller (Visscher et al., 1944a and b) than those in the small intestine. There is general agreement, however, that the mechanisms for the absorption of sodium are more efficient in the colon (Visscher et al., 1944b) and that hardly any sodium "leaks" back into the colonic lumen. Nevertheless more sodium is probably absorbed in the small intestine since it presents a larger total

surface area.

When isotonic solutions containing potassium at a concentration identical to that of plasma are instilled into the small bowel, there is practically no absorption of potassium - indeed slight secretion of potassium may occur (Berger, Kanzaki and Steele, 1959b; Code et al., 1960). Under similar circumstances, potassium is secreted into the colon in greater quantity for more potassium ions enter the lumen of the colon than that of the small bowel.

In summary, then, while comparison of the rates of transport between ileum and jejunum cannot easily be made, the distal jejunum and ileum absorb more fluid and electrolytes than the proximal duodenum whose function is to secrete fluid into the hypertonic solutions which enter from the stomach. In the colon, into which potassium is secreted, sodium absorption is efficient, but the small bowel, having a greater total area, absorbs more sodium and water than the colon.

II - THE INTESTINAL MUCOUS MEMBRANE.

The morphology of the surface epithelium which is composed chiefly of columnar cells, whose function is probably absorption, and of goblet cells, which

secrete mucus, has been well reviewed by Laster and Ingelfinger (1961). The functions of the argentaffin cells and of the Paneth cells are obscure but probably not related directly to intestinal absorption.

The mucous membrane presents complex barriers to absorption. The first obstruction to be negotiated is the surface of the cell facing the lumen. Using a variety of drugs Hogben and his group (Hogben et al., 1957 and 1959; Schanker et al., 1958; Hogben, 1960) have shown that the rate of absorption was directly related to the lipoid-solubility of the drug. This finding suggested to them that the luminal surface of the intestinal cell was predominantly lipoid in character. A much smaller portion of the cell surface is thought to be composed of a trellis-work of water-filled pores through which water and small ions can pass. These pores (which have not been detected by electron microscopy) seem to be impermeable to the passage of particles of molecular weight greater than 100. The diameter of these pores has been deduced as 36A (Durbin, Curran and Solomon, 1958) an estimate which has been rejected as too large (Hogben, 1960).

Although the nature of the barrier offered by the mucosal surface of the intestinal cell and the

vehicle for traversing it (possibly a carrier mechanism), are entirely theoretical, the concepts described above correspond to the classical views of cell membranes (Collander, 1937; Höber, 1945; Davson and Danielli, 1952; Ussing, 1954).

Having penetrated the luminal membrane of the cell, water and electrolytes have to traverse the cell cytoplasm. Probably simple diffusion is the main mechanism although the participation of cytoplasmic organelles such as the mitochondria (Green, 1959) or endoplasmic reticulum (Palade and Porter, 1954) is possible. From the observation of Grim, Lee and Visscher (1955), that the intestinal mucosa was slower than the muscle coat and venous blood in reaching equilibrium during the absorption of deuterium oxide, Berger (1960) suggested that water may pass through or around the intestinal cell in channels and undergo little mixing with the cytoplasm.

When water and electrolytes reach the basal surface of the cell, there is another membrane to be penetrated. No mechanism for crossing this barrier has been suggested. The infolded double membranes, which are particularly noticeable in the kidney (Pease, 1955) and are said to be associated with water transport

(Pease, 1956), have not been described in the intestine.

III - ROUTES OF INITIAL DISTRIBUTION OF ABSORBED WATER AND ELECTROLYTES

Extruded from the basal surfaces of the intestinal cells, water and electrolytes concentrate locally in the extra-cellular spaces. The main route for water and electrolytes from the intestinal tract is the blood stream; 99 per cent of absorbed water and electrolytes appear in the portal circulation (Benson et al., 1956). Although local equilibrium of water and electrolytes may be established between the extra-cellular fluid and the lymphatic circulation (Lee, 1961), negligible quantities of these substances are transported from the gut in the large lymphatic vessels. The increased sodium and water content of lymph, observed during the absorption of saline, is derived from the arterial circulation (Grim et al., 1955) which is augmented after a meal (Herrick et al., 1934).

The further distribution of absorbed water and electrolytes is beyond the scope of this review and has been fully discussed elsewhere (Edelman, 1962; Ginsberg, 1962).

IV - GASTRO-INTESTINAL COMPARTMENT

A proportion of the fluid of the body can always be found within the lumen of the gastro-intestinal tract. In rabbits, and other herbivorae, as much as 12 per cent of the total body water may be sequestrated in the intestines (Gotch, Nadell and Edelman, 1957); in carnivores and omnivores, the proportion is less (Cizek, 1954). Autopsy studies indicate that, in man, 1.5 per cent of the total body water and body sodium lie within the gastro-intestinal tract (Gotch et al., 1957). This is probably a gross underestimate of the situation as it exists in life.

The gastro-intestinal fluid is that part of the extra-cellular space which has been divided into several pools separated from one another by cellular structures. To such pools, the term transcellular has been applied to indicate their association with specific physiological functions, e.g. the cerebrospinal fluid, the aqueous humor (Edelman and Leibman, 1959).

The gastro-intestinal compartment is in a state of dynamic equilibrium with the rest of the extra-cellular fluid on account of the rapid exchange of water and electrolytes across the intestinal mucosa. An amount

of sodium, equivalent to the total sodium in the plasma, moves into and out of the gastro-intestinal lumen every 90 minutes (Visscher et al., 1944b). Heavy water, instilled into the gut, quickly reaches equilibrium with the body fluids (McDougall et al., 1934), and conversely, when injected intravenously, is rapidly detected in the gut (Gotch et al., 1957).

The important aspect of this compartment is that although the fluid which it contains is in equilibrium with the rest of the body fluids, the cells of the intestinal mucosa can transfer water and solute out of the compartment to replenish the fluid and electrolyte content of the body. Also, continuous withdrawal of fluids from this compartment by vomiting, diarrhoea, etc., will lead to a shrinkage of all body compartments and death ultimately from gross fluid and electrolyte depletion.

Chapter 3 FACTORS AFFECTING WATER AND ELECTROLYTE ABSORPTION.

Many inter-related factors influence the absorption of water and electrolytes. They will be discussed under the following headings:-

Local Factors.

1. Mucosal.
2. Forces of absorption.
3. Local circulation.

General Factors.

1. Drugs.
2. Body composition.
3. Endocrine secretion.

LOCAL FACTORS.

1. MUCOSA.

(a) Metabolic poisons.

The active transport of sodium chloride is abolished by a number of metabolic poisons, e.g. sodium arsenite, sodium fluoride, sodium cyanide, mercuric chloride and hydrogen sulphide (Ingraham and Visscher, 1936b). The effects produced by these poisons are non-specific: metabolic activity is abolished so that the intestine absorbs material passively and becomes freely

permeable to plurivalent ions, e.g. sodium sulphate.

(b) Ionising irradiations

Excessive whole-body irradiation has a marked effect upon the gastro-intestinal tract (Conrad, 1956; Quastler, 1956). Radiation sickness may in origin be either central (Wang, Renzi and Chinn, 1958) or local (Baker and Hunter, 1958). In addition, structural changes in the intestinal mucosa follow irradiation particularly in those areas with the highest rate of regeneration (Lesher, 1957).

Studies of the effect of irradiation upon intestinal absorption in the intact individual are complicated by the associated delay in gastric emptying (Goodman, Lewis and Schuck, 1952) and altered intestinal motility (Conrad, 1951). After irradiation, sodium absorption was found to be reduced and, indeed, secretion frequently occurred (Curran, Webster and Housepian, 1960). This observation may explain the apparently preferential loss of sodium, compared to that of potassium, in post-irradiational diarrhoea (Jackson, Rhodes and Entenman, 1958). The longer period of survival in some species after irradiation has been ascribed to a larger colon providing greater opportunity for reabsorption of fluids and electrolytes

(Conrad, 1956).

Local irradiation of the colonic mucosa reduces the rate of transport of sodium and chloride from the lumen to blood (Irvine et al., 1960).

(c) Avitaminosis

Alterations in epithelial surfaces are common in vitamin deficiencies. It is not surprising, therefore, that the intestinal absorption of water and electrolytes is affected by niacin deficiency, and that the rates return toward normal with correction of the deficiency (Nelson, Code and Brown, 1962).

(d) Hydrogen ion concentration.

Within physiological limits, the intestinal absorption of fluids and electrolytes is not affected by change in the hydrogen ion concentration of the solution within the lumen of the bowel. Thus Budolfsen (1952) did not observe any alteration in the absorption of sodium or of chloride in the small or large intestine at a pH of 6.0, 7.0, or of 8.3. However, in the jejunum of rats, net sodium transfer was slowed by increasing the hydrogen ion concentration (McHardy and Parsons, 1957): the absorption of saline solution at pH 5 was found to be one-sixth of that obtained at pH 7. In dogs acidification of the

duodenal and ileal contents slowed the transfer of sodium, potassium and water from lumen to blood (Code et al., 1960); the increased flow of electrolytes, in the opposite direction, observed by these workers, may be related to the increased secretion of mucus caused by acid irritation of the intestine.

2. FORCES OF ABSORPTION.

(a) Hydrostatic pressure.

The influence of hydrostatic pressure on water absorption has already been mentioned. Increase in the pressure of the fluid in the intestinal lumen was shown to enhance water absorption (Blickenstaff et al., 1952). At higher intra-luminal pressures, absorption is inhibited (Wells, 1931; Dobyns and Dragstedt, 1932-33), and secretion stimulated (Burget et al., 1930; Herrin and Meek, 1933).

(b) Motility.

The motility of the gut has always been assumed to influence the rate of intestinal absorption by producing a local, transient increase in intra-luminal pressure, by distributing the bowel content over a wider area, or by facilitating diffusion of solute within

the luminal fluid (Hogben, 1960). No definitive proof of these assumptions is available.

Attempts to provide this proof have made use of drugs. Conflicting results have been obtained using atropine (Rabinovitch, 1927; Blickenstaff and Lewis, 1952; Tidball and Tidball, 1958) and its analogues, methaneline bromide, "Banthine" (Higgins, Code and Orvis, 1956) and propaneline bromide, "Probanthine", (Groisser and Farrar, 1960). Sodium transport was observed to be increased after atropine but reduced following methaneline and propaneline. The difficulty in using drugs to study the effect of motility upon absorption was well demonstrated by Groisser and Farrar (1962) who observed that the absorption of sodium was reduced following propaneline despite increased motility of the gut and wider dispersion of the solution over the mucosa. Indeed the use of drugs to alter intestinal motility is particularly open to criticism since they may directly affect the permeability of cells (Kirschner, 1955).

Since sympathectomy and vagotomy do not produce predictable effects upon intestinal movements, section of the extrinsic nerves cannot be used in a controlled

study of the effect of motility on absorption. Examining the clinical effects of vagotomy in man, rather than claiming any particular change in motility, Cox (1962) found a slight reduction in the absorption of iodine, labelled with ^{131}I; this returned to normal within a week.

(c) Glucose.

Some degree of coupling apparently exists between sodium and glucose absorption (Ussing, 1960). Thus phlorhizin inhibits the absorption of both glucose and sodium by the small intestine, the inhibition of glucose transport being greater.

Budolfsen (1952) observed that potassium added to saline solutions reduced the rate of absorption of sodium, but not of chloride, from the small intestine. The addition of potassium chloride to glucose solutions reduced the rate of glucose absorption in the bowel. These inhibitory actions of potassium, neither of which has been observed in the large intestine, have been ascribed either to a direct action of potassium on the mucosa or to a specific effect of potassium on sodium transport upon which glucose absorption is dependent (Ussing, 1960).

3. LOCAL CIRCULATION.

Absorption is probably not affected by the normal variations in blood flow (Schanker et al., 1957). There is little doubt, on the other hand, that gross alterations in the intestinal circulation may affect the absorption of water and electrolytes.

(a) Mesenteric vein congestion.

By applying a clamp across the mesentery of the dog, Wells (1940) compressed mainly the venous and lymphatic return from the intestine. Initially the rate of absorption of isotonic saline was reduced; with greater compression, absorption ceased; and then, ultimately, secretion occurred. The effect of such mesenteric compression would obviously be composite - and arterial inflow would also be partially occluded. Venous occlusion by itself reduces the mesenteric blood flow (Turner, Neely and Barnett, 1959) and produces engorgement of the intestine (Johnson and Hamson, 1963).

Using an in vitro preparation, Lee (1961) inhibited the absorption of water by occlusion of the venous and lymphatic drainage of the intestine.

(b) Arterial blood pressure and oligaemic shock.

Variations in the arterial blood pressure, by

carotid sinus stimulation, did not alter the rate of saline absorption within the range, 71 - 137 mm Hg. Pressures above this range were accompanied by increased absorption (Stickney, Northup and van Liere, 1947).

The effect of oligaemic shock upon the intestinal absorption of fluids and electrolytes is of great interest to the clinician. Experiments in dogs have shown little change in absorption with systemic arterial pressures as low as 50 mm Hg; only in advanced shock was the intestinal absorption of saline diminished (Goldberg and Fine, 1945; Cordier and Touze, 1948). It is difficult to produce an explanation for these observations since opposing views are held as to whether oligaemic shock causes splanchnic venous congestion (Selkurt, Alexander and Paterson, 1947), or vasoconstriction (Freidman, Frank and Fine, 1951; Reynell et al., 1955) with reduction in portal blood flow (Blalock and Levy, 1937) and increase in portal blood pressure (Wiggers, Opdyke and Johnson, 1946).

The accumulation of fluid within the lumen of the bowel of dogs in irreversible shock has been prevented by atropine (Porciuncula and Crowell, 1963).

The significance of this finding is not clear and the work requires confirmation. However, it must be stressed that the response of the dog's intestine to oligaemic shock - mucosal congestion, blood-stained extravasations into the lumen - are specific to the species and are not seen in man.

GENERAL FACTORS

1. DRUGS

(a) Anaesthesia

It is necessary to know the effect of anaesthesia upon absorption since many acute experiments are done under anaesthesia. If an unaesthethetised dog becomes greatly excited or distressed, intestinal absorption is impaired and the intestinal mucosa becomes pale (Dennis and Visscher, 1940). When such an excited animal is anaesthetised, absorption returns to normal.

Barbiturates do not affect the rates of absorption to any great extent (Code *et al.*, 1960).

(b) Anticholingeric drugs

The effect of atropine and its analogues have already been described.

(c) Mercurials

Inorganic mercurials affect absorption since they

are metabolic poisons (see above). The organic mercurial diuretics reduce the rate of absorption of sodium from the jejunum of dogs (Blickenstaff, 1954a) and of man (Groisser and Farrar, 1960). This reduction is apparently brought about by an increased rate of entry of sodium ions into the bowel (Berger, 1960).

2. BODY COMPOSITION

The extent to which the intestinal absorption of water and electrolytes may be modified by changes in body composition seems to be minimal. However, the lack of sufficient observation in this field is an invitation to further study.

(a) Plasma concentration of electrolytes

Although the part which physical forces play in the absorption of water and electrolytes is not defined, a change in the composition of the extracellular fluid, and consequent change in the chemical gradient, might be expected to alter the rates of absorption. Thus reduction of the plasma osmolality by intravenous infusions of hypotonic solutions was shown to produce an increase in the rate of sodium movement into the body (Lind, Code and Orvis, 1959).

Conversely, increase in the plasma osmolality by hypertonic overloading was accompanied by an increase in the osmolality of the jejunal and ileal contents (de Beer et al., 1935), although the colon, where sodium transport is active, did not show this change. However such alterations in electrolyte transport, following changes in plasma concentration, should not be ascribed entirely to physical factors. The electrolyte content of the active secretion of exocrine glands can be altered by a change in the plasma concentration of sodium and potassium (Gilman and Cowgill, 1933).

(b) Fluid and electrolyte balance

The faecal loss of sodium is small in man. The amount of salt eaten does not alter the faecal excretion of sodium since the dietary intake represents only a small part of the electrolyte load which the gut has to absorb. Therefore, although the concentration of sodium in the small bowel can be increased by a high salt diet, this excess is absorbed by the colon (Dole et al., 1950; Henneman and Dempsey, 1956).

The bowel seems able to respond, at least partially, to the needs of the body. In salt depletion, the rate of sodium absorption is increased and the

sodium content of the bowel reduced (Field et al., 1954 and 1955; Gallagher, Harrison and Skyring, 1962). Such conservation of sodium is achieved by a reduction in the rate at which sodium ions enter the intestinal lumen (Clarke and Shields, 1963). Inasmuch as sodium depletion is a powerful stimulus to aldosterone secretion (Mills, 1962), the possibility exists that the adrenal cortex is responsible for the increased capacity of the intestine to absorb sodium, especially since potassium secretion is increased at the same time. The adrenal-cortical control of electrolyte transport in the gut will be discussed subsequently.

On the other hand, the intestine is apparently unable to prevent overloading of the body with salt. The rate of sodium absorption from an isolated segment of intestine is not reduced when the dietary intake of sodium is raised and a positive sodium balance established (Berger et al., 1959a).

3. ENDOCRINE SECRETION.

(a) Adrenal cortex

The adrenal cortex has long been known to play an important role in electrolyte metabolism (for reviews, see Kruhøffer, Thaysen and Thorn, 1960; Edelman, 1961;

Beck and McGarry, 1962; Currie, Symington and Grant, 1962; Ross, 1962). While much attention has been paid to the effect of the adrenal steroids upon the body distribution and renal excretion of electrolyes, much less work has been done to clarify the action of these hormones on the intestinal absorption of electrolytes.

The effects of the removal or destruction of the adrenal cortex have been studied in several species. After adrenalectomy in rats (Clark, 1939) and in dogs (Dennis and Wood, 1940) the absorption of sodium and chloride is impaired but can be restored, at least in the rat, by the administration of deoxycorticosterone (Stein and Wertheimer, 1941). The increased loss of sodium in the faeces of patients with Addison's disease can be reduced also by deoxycorticosterone (Emerson, Kahn and Jenkins, 1953).

Much of the work defining the influence of the adrenal cortex on intestinal absorption has been done by measuring the faecal excretion of electrolytes. An inverse relationship has been demonstrated between the faecal loss of sodium and the urinary excretion of aldosterone (Duncan, Liddle and Bartter, 1956). Sodium

is excreted only in small quantity in the faeces of oedematous patients (Berger and Steele, 1952), in whom there is often a secondary aldosteronism (Luetscher and Johnston, 1954; Dyrenfurth et al., 1957).

The transport of potassium in the colon is influenced by the adrenal cortex. Aldosterone causes an increased loss of potassium in the faeces of man (August, Nelson and Thorn, 1958). In the dog the administration of 9-α-fluorohydrocortisone was followed by a decrease in the concentration of sodium and an increase in that of potassium in the faeces (Poutsiaka, Thomas and Linegar, 1957). In the dog, made ascitic by constriction of the thoracic inferior vena cava, the increased urinary excretion of aldosterone was associated with an increased faecal loss of potassium (Davis et al., 1959).

The action of the mineral corticoids is not confined to the large bowel. Sodium restriction, which stimulates aldosterone secretion, is accompanied by a fall in the concentration of sodium and a rise in that of potassium in the ileum of dogs (Field et al., 1955) and in the ileostomy dejecta of man (Gallagher et al., 1962). In patients who had undergone total

colectomy for ulcerative colitis, administration of steroids was usually followed by an increase in the potassium concentration (Smiddy et al., 1960) and a reduction in the sodium/potassium ratio (Goulston, Harrison and Skyring, 1963) of the ileostomy discharge. Brooke (1958) did not observe an increased loss of potassium from the ileostomy with the administration of cortisone; his patients may have been depleted of potassium.

The glucocorticoids, adrenocorticotrophic hormone (ACTH) and cortisone have little effect on sodium absorption in man (Danowski and Greenman, 1953) and in dogs (Barnett, Turner and Hardy, 1958). There is no evidence that water transport is greatly influenced by adrenocortical hormones.

These alterations in the absorption and secretion of sodium and potassium are brought about by changes in the rates at which these electrolytes are transported into and out of the intestinal lumen. The changes in unidirectional movements have received, until lately, scant attention. Berger, Kanzaki and Steele (1960) found that, following the administration of deoxycorticosterone, the rate of sodium absorption from the colon of dogs was increased because of an increase in the rate

at which sodium ions left the colonic lumen. Potassium secretion into the colon was enhanced by an increase in the rates of transport in both directions, movement into the colon being affected to a greater extent. In the small gut, the movements of sodium and potassium were not affected.

(b) Hypophysis

(i) Adenohypophysis

In normal dogs, and in those rendered ascitic by constriction of the thoracic inferior vena cava, hypophysectomy is followed by increased loss of sodium and potassium in the faeces (Davis et al., 1959). Any effect, which the adeno-hypophysis may have on the intestinal absorption of electrolytes, is probably mediated by the adrenal cortex.

(ii) Neurohypophysis

The stimulating effect of the various neurohypophysial hormones on the transport of water and sodium across different membranes has been reviewed by Diamond (1962). The intestinal transport of sodium and water has been observed, in vitro, to be increased by the neurohypophysial hormones (Ussing, 1960). The absorption of

isotonic saline solution *in vivo* was enhanced by pitressin (Blickenstaff, 1954c).

The influence of the endocrine system on the absorption of sodium and potassium has been considered in some detail. The conclusion must not be reached that the hormonal control over electrolyte transport in the bowel is as complete and precise as that in the kidney. The action of the mineral corticoids on the intestinal mucosa, as on the sweat and salivary glands, may only be part of the general action of these steroids on cell membranes.

Emerson and his colleagues (1953) have suggested that, under normal conditions, adrenal corticosteroids are not necessary for the absorption of electrolytes, which is probably an obligatory autonomous function of the intestine. However, in conditions of stress, where the need to conserve electrolyte is great, there may be an additional facultative absorption under hormonal control.

INTESTINAL MUCOSA AND RENAL TUBULAR EPITHELIUM.

The action of the adrenal mineral-corticoids on the gut, in conserving sodium and enhancing potassium loss, is reminiscent of their effect upon the kidney (Ross *et al.*, 1959). In addition, the intestinal actions

of the mercurial diuretics and the neurohypophysial hormones are qualitatively similar to their influence on renal function. However, the effect of these substances on the kidney is much more powerful than on the intestine.

The possibility of a close relationship between renal and intestinal function has been strengthened by the recent demonstration, in the gut, of disorders of metabolism first detected in the kidney. In particular, in disorders of amino-acid metabolism, such as cystinuria and Hartnup disease, the defect in amino-acid transport in the renal tubules has been identified in the intestine (Asatoor et al., 1962, 1963).

In gastro-intestinal physiology, there is a need for a quantitative approach to intestinal absorption employing the concept of clearance, which has been exploited with such success in renal physiology (Hogben, 1962). This has been attempted, but not to any advantage (Spencer, 1956).

Chapter 4 THE METHODS FOR THE STUDY OF INTESTINAL ABSORPTION OF WATER AND ELECTROLYTES.

The information that can be obtained, and the conclusions drawn, from any experiment on intestinal absorption will depend largely upon the method of study selected. In this chapter the usefulness of the various techniques for studying the absorption of water and electrolytes will be discussed, with particular reference to those requiring isolation of a loop of bowel, as this type of preparation has been used in the present studies. Detailed descriptions of the other methods available will be avoided since there are many excellent reviews to which reference can be made (Goldschmidt, 1921; Magee, 1930; Verzar and McDougall, 1936; Korelitz and Janowitz, 1957; Berger, 1960; Quastel, 1961; Wilson, 1962; Smyth, 1963).

TECHNIQUES IN VITRO.

In these techniques, the intestine is removed from the animal and receives its oxygen and other nutrients from the solution in which it is suspended. The early methods, in which the bowel was opened up and, as a membrane, used to separate two solutions, were limited by inadequate oxygenation of the mucosa (Wilson, 1962). The last two decades have seen a

"methodological revolution" (Janowitz, 1961), with the development of well-oxygenated *in vitro* preparations (Fisher and Parsons, 1949; Darlington and Quastel, 1953; Wiseman, 1953; Wilson, 1956b; Smyth and Taylor, 1957), culminating in the "everted-sac" technique (Wilson and Wiseman, 1954; Wiseman, 1961). These methods, which are ideally suited for demonstrating active transport and the specificity of absorption, have been used most successfully in the investigation of amino-acid and sugar absorption.

In vitro preparations have been employed for the study of the intestinal transport of water and electrolytes (Smyth and Taylor, 1954, 1955 and 1957; Fisher, 1955; Ussing and Anderson, 1956; Wilson, 1956a and b; Lifson and Parsons, 1957; Cooperstein and Hogben, 1959; Curran, 1960; Gilman and Koelle, 1960; Parsons and Wingate, 1961). The useful information which has been obtained by such methods has already been described in the earlier chapters of this review. A disadvantage of these preparations is that they tend to become abnormally permeable to water-soluble solutes (Chalfin *et al.*, 1958) and, because of the early loss of adenosine triphosphate, may lose

their capacity for active transport (Parsons, 1959).

Nevertheless the differences between *in vitro* and *in vivo* preparations may not be so great as formerly supposed (Smyth, 1963).

Vessel cannulation.

Several excellent preparations both *in vivo* and *in vitro* have been devised in which the artery supplying, and the vein draining, a segment of gut are cannulated, and the arterio-venous difference of a test substance determined (Garry, Holmes and Wishart, 1957; Collings, Swann and Stegall, 1958; Varro *et al.*, 1964). Such techniques, however, have been used infrequently for the study of water and electrolyte absorption (Lee, 1961).

TECHNIQUES IN VIVO.

In these preparations the intestine receives oxygen and nutrients through its blood vessels. The following methods will be described:

(A) *INTACT INDIVIDUAL.*

(1) Balance studies.

(2) Concentration within body.

(3) Intestinal intubation.

(B) ISOLATION OF INTESTINAL SEGMENT.

(1) 'Acute' preparation.

(2) 'Chronic' preparation.

It will be appreciated that such a classification is arbitrary and the procedures overlap the different categories.

(A) INTACT INDIVIDUAL.

(1) Balance study.

In this type of study, the absorption of a substance is taken as the difference between the dietary intake and excretion in the faeces. Occasionally the substance under test is given parenterally and is subsequently estimated in the faeces. Frequently, unabsorbed indicators are administered along with the test meal, and, by comparing the concentration of the indicator with that of the test substance, estimates can be made of the amount absorbed.

Certain disadvantages are inherent in these techniques, particularly when used to study water and electrolyte absorption:-

(a) Bidirectional movement across the intestinal mucosa cannot be measured.

(b) The indicator is assumed to be inert and unabsorbed, and to move along the bowel at the

same rate as the test substance.

(c) If faecal excretion of the substance is measured, several difficulties may arise:-

(i) the substance may be metabolised by intestinal bacteria and parasites,

(ii) the substance may be synthetized by intestinal bacteria,

(iii) the substance may be involved in an enterohepatic circulation

(iv) the substance may be added to the bowel content by desquamation of intestinal cells.

(2) Concentration within body.

The principle of this method is that the test substance is fed by mouth and its concentration within the body subsequently measured, either in the blood or in an organ, which has an affinity for the substance. Occasionally, the urinary excretion of an orally-administered substance is used as an index of absorption.

Such techniques cannot be employed for the study of water and electrolyte transport for the following reasons:-

(a) the movement of water and electrolyte

into and out of the intestinal lumen cannot be measured,

(b) there is no organ which preferentially takes up most of the absorbed water and electrolyte,

(c) as an index of absorption the blood level is unreliable, because it will depend not only on the rate of absorption but also on the rates of distribution, metabolism and excretion.

Such criticism has in part been answered by the use of a double-isotope technique (Scholer et al., 1955). One isotope, e.g. ^{24}Na, is injected intravenously and its disappearance from the blood measured; at the same time, another isotope of the same element, e.g. ^{22}Na, is instilled into the gut and the rate of its appearance in the blood determined. By integrating the curves of appearance and disappearance, an estimate of the rate of transfer of sodium from the gut into the body can be obtained. Such a technique does not allow measurement of net absorption nor of the movement of sodium in the opposite direction - out of the body into the lumen of the bowel. A second defect of this

sophisticated technique is that, since the activities of the isotopes are determined in the peripheral arteries, no account is taken of the hepatic uptake of the absorbed water and electrolyte. Recent work suggests, however, that the effect of the liver may be ignored in the calculation of the rates of water and electrolyte transfer (Code, Moll and Orvis, 1963).

(d) the absorptive capacity of different parts of the intestinal tract cannot be compared.

(3) Intestinal intubation.

The balance technique may be elaborated by passing a tube orally into various parts of the intestine. In this way solutions can be instilled (Reitemeier, Code and Orvis, 1957a) or intestinal content withdrawn (Abbott and Miller, 1936; Borgström et al., 1957), and estimates of the absorptive ability of different parts of the intestine can be made. However, calculation of the bidirectional transport cannot readily be accomplished because the test solution will tend either to be contaminated by biliary, pancreatic and gastric secretion or to be carried

further down the intestinal tract so that it cannot be withdrawn for accurate analysis.

To this end, attempts have been made temporarily to "isolate" a segment of bowel by inflating balloons carried on the shaft of a multi-lumen tube, inserted into the intestinal lumen orally, rectally, or through a fistula. Personal observations have shown that inflation of the balloon to prevent leakage of solution or entry of alimentary secretions usually evokes abdominal discomfort and colic.

To overcome this difficulty, perfusion techniques have been devised. With a multi-lumen tube lying in the lumen of the intestine, test solution is instilled into the small bowel through one hole in the tube and withdrawn through another hole, more caudally placed (Fordtran et al., 1961). A criticism of this technique is that, while a constant length of gut may be tested, there is no guarantee that the same segment of gut is studied throughout the test, for intestine may move up and down over the length of the tube. To study absorption in the colon, solutions can be perfused through the large bowel from a tube which has been swallowed and whose tip lies at the caecum, to another tube, inserted through the anus, and whose tip lies in

the rectum (Levitan et al., 1962). This latter method has been used to study the colonic absorption of water and electrolytes in several patients (Part V of the thesis). These new techniques, which offer great promise for the future, allow only a limited number of studies in individual patients because the oral (or nasal) tube cannot be tolerated for a long period.

(B) ISOLATION OF INTESTINAL SEGMENT.

The isolation of a length of bowel from the rest of the intestinal tract is necessary if the absorptive capacities of different parts of the gut are to be compared, or if movement of material into and out of the intestine is to be measured accurately. Obviously such techniques can be carried out in man only under exceptional circumstances.

(1) 'Acute' preparations.

In acute experiments, ligatures are tied round the bowel to occlude the lumen and the intestine is studied in situ with the animal anaesthetized. Solutions may be instilled into, and, after a time withdrawn from, the isolated bowel (Code et al., 1960; Ullman et al., 1960); alternatively solutions can be continuously perfused through the bowel (Clarke and Smyth, 1950; Sheff and Smyth, 1955; Curran and Solomon, 1957;

Jacobs and Luper, 1957; McHardy and Parsons, 1957). Although such methods have the advantage that the blood supply to the bowel is intact, and that permeability characteristics of the mucosa are preserved, mixing of the intestinal content is suppressed in the anaesthetized animal so that intra-luminal diffusion becomes the limiting factor of absorption. Although anaesthetic agents do not greatly affect intestinal absorption, particularly if barbiturates are used, there remains the possibility that the surgery to prepare the intestinal segment may alter the rates of transport. Experimental work, to be described later (Part III), suggests that this criticism may be valid.

(2) 'Chronic' preparations.

Many types of preparation have been described in which a segment of bowel is permanently isolated from the rest of the intestine, and continuity of the gastro-intestinal tract re-established by anastomosis. The isolated lengths of bowel, whose blood supply has been preserved, may have one end closed, and the other end opening on to the skin surface - Thiry fistula (Thiry, 1864) - or both ends may open to the exterior - Thiry-Vella fistula (Vella, 1888).

Types of chronic preparation.

With the permanently-isolated intestine, two methods of study can be used:-

(a) continuous perfusion of a solution through the lumen (Pearson, 1958; Vaughan, 1960),

(b) instillation of a solution into the isolated intestine and subsequent withdrawal. In some methods (Berger et al., 1959a; Code et al., 1960), the fluid was retained within the bowel for an hour with frequent sampling to measure changes in volume and in electrolyte concentration. It would seem more desirable to keep the solution in the bowel for a shorter time, e.g. 10 - 15 minutes, for the following reasons:-

(i) under normal conditions, fluid probably does not remain in contact with the same area of mucosa for much longer than 10 minutes,

(ii) changes in volume can be more accurately measured,

(iii) alterations in the specific activity of isotopes will not be great. This point will be discussed more fully later (Part II, Chapter 2).

Advantages

Such chronic preparations possess certain advantages over the acute preparations:-

(a) Repeated experiments can be performed in the same animal over the same area of intestinal mucosa.

(b) In the well-trained, placid animal, the effects of emotion, of anaesthesia and of recent surgery are avoided.

(c) In such preparations, the influence of changes in metabolism upon intestinal absorption can be studied.

Disadvantages

Several unfavourable criticisms have been levelled against such preparations:-

(a) Some workers have claimed that absorption rates will change with time so that only experiments performed in successive days can be compared (Magee, 1930). However, Berger et al., (1959a) did not observe any alteration in the rates of water and electrolyte transport nor any histological change in the intestinal mucosa over a 7-year period.

(b) Another defect of such preparations is that the instilled solution may leak out of the

isolated bowel. Various techniques to overcome this have been suggested (Johnston, 1932; Clarke and Smyth, 1950; Gregory, 1950; Berger, 1960). The most acceptable method, which has been adopted for the experimental work described in this thesis, has been the sealing of the open ends of a Thiry-Vella fistula with modified Foley catheters (Code et al., 1960).

(c) One difficulty in using a technique in which fluid is instilled into and then withdrawn from the bowel, is that it is impossible completely to aspirate all the fluid lying in the lumen. The volumes of the residual solutions can be calculated with accuracy if volume indicators are used. Such substances should ideally be inert, neither absorbed, nor adsorbed on to the mucosa, and should not be osmotically active; nor should they interfere with the function of the intestinal mucosa. Obviously they must be capable of easy and accurate estimation in low concentration.

Various substances have been described (see Smyth, 1961); none, however, is ideal. Bromosulphalein (Hendrix, 1957) and phenol red (Reynell and Spray, 1956; Cooperstein and Brockman, 1959) are both absorbed to a certain extent. Although haemoglobin has been used (Curran and Solomon, 1957) slight bleeding into the

bowel will invalidate the results. Succinysulphathiazole (Pearson, 1958) has the theoretical objection that, being a chemotherapeutic agent, it may alter absorption by affecting the metabolism of the mucosal cells, or, if used frequently, alter mucosal surface area by influencing bacterial growth (Gordon and Bruckner-Kardoss, 1961). The estimation of methylcellulose (Berger et al., 1959a) becomes inaccurate in the presence of contaminants. The most useful volume indicator would seem to be polyethylene glycol (molecular weight, 4000) which has been widely used (Borgström et al., 1957). Another useful technique is that used by Code et al., (1960) who, after withdrawal of the test solution which contained radio-active isotopes, washed the segment with non-radioactive solution. The residual volume could then be calculated from the radio-activity acquired by the rinsing solution. Provided that there is little delay between the withdrawal of the test solution and rinsing of the bowel no great error will accrue. This last method of estimating residual volume is used in the experiments described later.

(d) The electrical potential differences across the mucosa cannot be easily measured.

TERMINOLOGY

Since water and electrolytes are exchanged simultaneously in both directions across the intestinal mucosa, a precise nomenclature is needed unambiguously to describe both movements, and, at the same time, denote the net or resultant movement.

For unidirectional movement, various terms have been employed. For transport of materials out of the lumen of the bowel into the blood, the following terms have been suggested:- "gut-to-blood" (Visscher et al., 1944b), "out-flux" (Berger, 1960), "secretory-to-nutrient" (Hogben, 1955), "flux-rate (lumen to blood)" (Davenport, 1961). Appropriate converse terms have been used for movement in the opposite direction. Objections to such terminology are clumsiness (which deters the frequent use of the term), ambiguity (for "out-flux" could equally well apply to movement out of the body into the bowel), and potential inaccuracy (because "flux" implies flow and it may very well be that water does not follow the same route as ions across the intestinal mucosa).

A useful nomenclature has been suggested by Code (1960). The term "insorption" denotes movement from gut to blood, and "exsorption", movement in the

opposite direction. The advantage of this terminology is that the body is regarded as the point of reference, and movement of substances is either into the body (insorption) or out of the body (exsorption).

Under most circumstances the rates of insorption and exsorption are not equal. When movement into the body (insorption) is more rapid than movement out of the body (exsorption), obviously material will be gained by the body: absorption will have occurred. Conversely, when the rate of exsorption exceeds that of insorption there will be a net loss of material from the body. Code has suggested the term "entero-sorption" to describe this net movement, but there seems no particular advantage to be gained in using this word and it has been suggested that the term "secretion" be retained for net movement into the gastro-intestinal lumen (Hogben, 1962). Since absorption is given a specific meaning in this nomen-clature, the word "sorption" has been coined, as a generic term, to describe the whole process of intestinal transport.

This nomenclature, which is illustrated in Figure 1, has been adopted in this thesis.

Chapter 5 THE ABSORPTION AND SECRETION OF WATER AND ELECTROLYTES IN INTESTINAL OBSTRUCTION.

INTRODUCTION.

Few problems in surgical physiology have commanded greater attention than those associated with intestinal obstruction. Although the principles of operative treatment were established in the 19th century, the mortality from this condition was hardly affected (Ashhurst, 1886). Death was attributed to the absorption of toxins from the obstructed bowel (Wangensteen, 1947). The work of Hartwell and Houget (1912), who prolonged the lives of dogs, with high intestinal obstruction, by infusing saline solutions subcutaneously, stimulated research into the fluid and electrolyte losses in obstruction and led to the classical studies of Gamble and his associates (Gamble, 1951). The "toxic factor" in intestinal obstruction was shown to be largely depletion of water and salt.

Fluid and electrolytes are lost because the orderly sequence of secretion and re-absorption in the gastro-intestinal tract is disrupted. First, the pancreatic, biliary and gastro-intestinal secretions, whose volumes are probably increased in obstruction (Wangensteen, 1947), cannot pass beyond the occlusion

and as a result accumulate in the bowel above. Secondly, the loss of these secretions may be aggravated by the inability of the obstructed bowel to absorb water and salt at the usual rate; indeed there is some evidence that the bowel above the obstruction may secrete water and electrolytes and so augment the volume of fluid collecting within its own lumen. It is with this latter aspect that this thesis is concerned.

Only the literature relating to absorption and secretion by the obstructed bowel will be reviewed. The other aspects of intestinal obstruction are considered in the monographs of Wangensteen (1947), Cantor and Reynolds (1957) and Welch (1958). Strangulation obstruction, in which the circulation of the gut is impeded, has not been considered since the many factors which act simultaneously - obstruction, reduced blood flow, ischaemia, gangrene, production of toxins - cannot be separated easily.

THE ALTERATIONS IN INTESTINAL ABSORPTION AND SECRETION IN OBSTRUCTION.

The passage of material through the bowel wall is, without doubt, altered in obstruction. Vital dyes, e.g. trypan blue, are more rapidly absorbed by the

lymphatics, (Sperling and Wangensteen, 1935c), probably because the flow of lymph is increased when the mesenteric veins are congested. When the viability of the gut becomes compromised, transperitoneal absorption may occur (Sperling and Wangensteen, 1935b).

In contrast, absorption by the blood stream seems to be retarded in obstruction. The absorption rates of strychnine (Braun and Boruttau, 1908), of calcium (Clairmont and Ranzi, 1904), and of tap water (Sperling, 1938) from the obstructed bowel of dogs have been found to be reduced. In addition, the secretion of fluid by the intestine may be stimulated, for, in the late stages of obstruction, fluid was found to be extravasated into the intestinal lumen (Enderlen and Hotz, 1911).

Such experiments, however, reveal only the gross changes in the ability of the obstructed bowel to absorb substances to which it is not usually exposed. The effect of obstruction upon the intestinal handling of fluids with which it has normally to deal has not been investigated; nor have there been any fully-documented reports of the alterations, if any, in the fluid shifts into and out of the obstructed gut. Thus the changes in net movement, i.e. diminished absorption and increased

secretion, which are suggested from the literature reviewed above, could be brought about by an increase in the rate at which fluid enters the gut or a reduction in the rate at which it leaves, or both. Davenport (1961) stated that, in intestinal obstruction, movement of fluid out of the intestinal lumen was reduced but movement in the opposite direction, unaltered. However, no experimental details were given in his report nor was the duration and method of production of the obstruction described.

More recently, Derblom, Johansson and Nylander (1963a) claimed that absorption was impaired in rats with intestinal obstruction. They measured absorption by the disappearance of radio-active iodide from the lumen of isolated bowel and its appearance in the tail vein. Increase in the weight of the obstructed segment was said to measure the volume of fluid accumulating in the lumen of the obstructed bowel. These observations, at the most, can convey only a qualitative impression of the disturbances in the fluid and electrolyte exchanges in intestinal obstruction. Precise information on electrolyte absorption cannot be obtained using radio-active iodide, for the intestinal

transport of iodine differs from that of other electrolytes: it is secreted into the lumen of certain parts of the bowel (Davenport, 1943; Honour, Myant and Rowlands, 1952; Pastan, 1957; Acland and Illman, 1959). Also, the appearance of an isotope in a peripheral vein or its disappearance from the lumen of the bowel provides only a rough measurement of movement in one direction, i.e. from gut to blood; neither movement in the opposite direction nor net movement can be calculated. Nor can secretion be deduced from the increase in weight of a segment of bowel because fluid and blood collects within the interstitial spaces of the intestinal wall as well as within the lumen (Sperling and Wangensteen, 1935a).

Obstruction of the intestine brings about a number of changes, each of which may affect the intestinal handling of water and electrolytes. Locally, the pressure within the lumen of the obstructed bowel is increased and the gut distends; intestinal motility and circulation are altered. Generally, there may be considerable losses of fluid and electrolyte from the body. A discussion of the individual effect of these various pathological changes on absorption and secretion will be more appropriate and meaningful after the

alterations in the intestinal transport of water and electrolytes have been characterised (Part III).

Chapter 6 CONCLUSIONS FROM THE LITERATURE ON THE ABSORPTION AND SECRETION OF WATER AND ELECTROLYTES, WITH PARTICULAR REFERENCE TO INTESTINAL OBSTRUCTION.

PHYSIOLOGY

The dietary intake of fluid and electrolytes, usually in excess of what is required to replace the obligatory losses from the skin, lungs and kidney, represents only a small proportion of the water and salt load presented to the gut for absorption. Considerably greater quantities of these substances are discharged into the lumen of the bowel by the alimentary glands and the intestinal mucosa itself and require to be re-absorbed.

Participating in the absorption of this fluid are several transport mechanisms whose individual contribution is ill-defined. Active transport implies that energy from metabolic sources is used to drive the substance uphill against an electro-chemical gradient. In the gut the clearest example of active transport is the absorption of sodium by the colon. Where the movement of a substance can be accounted for by physical forces, passive transport is said to occur. The movement of chloride ions in the colon seems to be by passive transport.

However, great difficulty is experienced in characterizing the types of transport system employed, because (1) several different forces, viz., chemical and electrical forces and solvent drag, can all act on electrolytes, (2) the intestinal mucosa has a complex structure, (3) the route taken through the epithelium, and the vehicle used, (perhaps a carrier), are entirely hypothetical, (4) concentration gradients are difficult to maintain and, in the small intestine, an electrical gradient is absent.

The first change which occurs to fluid entering the gastro-intestinal tract is that water enters or leaves to render it isosmotic with plasma. Little is absorbed in the stomach in which sodium transport is inhibited by acid. In the duodenum, despite a high rate of exchange of water and electrolytes across the mucosa, little net movement takes place other than what is required to bring the activities of these substances in the luminal solution close to those in plasma. In the jejunum and ileum, most of the fluid is absorbed: both sodium and chloride ions are actively absorbed, although passive movement of these ions also occurs; the absorption of water is probably secondary to the

movement of solute. In the large bowel where absorption is completed, sodium is actively transported and the other ions move, mainly passively, to maintain electrochemical neutrality.

The absorbed water and electrolytes accumulate locally in the intestinal extracellular spaces and are then carried off almost exclusively in the portal blood.

As a result of the shift of water and ions into and out of the bowel, there will always be, at any time, a part of the total body fluid within the intestinal lumen. Although this gastro-intestinal fluid is in a state of dynamic equilibrium with the rest of the body fluids, certain parts of the intestine, viz., colon, seem particularly adapted for the efficient transfer of water and electrolytes out of the bowel into the body with little "leakage" of these substances back into the lumen.

The efficient, and almost total, absorption of the large fluid load presented to the intestine can be influenced by several factors. Absorption is inhibited by metabolic poisons, ionising radiations, vitamin deficiency, and severe oligaemic shock. These are all powerful factors, damaging to tissues; their effect is probably quite non-specific.

Few physiological factors seem to control the absorption of sodium and water. Gross alteration in the plasma concentration of electrolytes, outside the ranges normally found in health, will influence the intestinal transport of water and electrolytes. Depletion of sodium enhances the absorption of sodium and increases the secretion of potassium. It is likely that this response is mediated through the adrenal cortex whose secretion of mineral corticoids can modify the movement of electrolytes across the intestinal mucosa.

METHODOLOGY

Of the various techniques used to study the intestinal absorption of water and electrolytes, *in vitro* preparations are suitable when the characteristics of the transport process are being investigated - active or passive transport, competitive inhibition, specificity, etc. Their use is limited by their abnormal permeability to water and, of course, they cannot be employed to relate alterations in intestinal absorption with changes in body metabolism.

The study of intestinal absorption in the intact individual is hampered by the inability of the available methods - balance studies, etc., - to provide accurate measurement of the unidirectional movements of water

and electrolytes; nor can the rates of transport in different parts of the gastro-intestinal tract be calculated. Attempts to obtain this information by intestinal intubation are usually frustrated by the contamination of the test substance with other secretions or by the low rate of its recovery from the lumen.

The most suitable methods available at present involve the isolation of a segment of intestine. When such experiments are performed in the anaesthetized animal, frequent mixing of the intestinal contents are necessary. With permanently isolated segments, anaesthesia is not required and the intestinal response to various general factors, e.g. hormones, etc., can be investigated. The methods will be most accurate when solutions are left in the lumen for a short time only - 10 - 15 minutes - provided that the residual volume of solution can be calculated. There is no evidence that these segments undergo any functional or morphological deterioration over a period of time if they are washed frequently with isotonic solutions.

INTESTINAL OBSTRUCTION

The assumption that the obstructed bowel cannot handle water and electrolytes in a normal manner is not

supported by extensive, irrefutable proof of an experimental nature. The value of observations on the altered absorption of iodine, calcium and tap water is limited. Apart from the brief, undocumented report of Davenport (1961), no work has been done to characterise the alterations in the absorption and secretion of water and electrolytes in the presence of obstruction.

STATEMENT OF THE PROBLEM

1. To develop and validate methods for measuring the simultaneous exchange of water, sodium and potassium across the intestinal mucosa.

2. To characterise the effects of obstruction upon the intestinal transport of water and electrolytes.

3. To describe the various changes, locally in the intestine and generally in the body, which are found in obstruction, and to discuss their influence on the intestinal handling of fluids and electrolytes.

4. To investigate the extent to which congestion of the mesenteric veins and adrenal-cortical activity can affect the absorption of water and electrolytes in the intestine.

PART II

THE MEASUREMENT OF THE INTESTINAL TRANSPORT OF WATER, SODIUM AND POTASSIUM

Chapter 1 THE METHODS OF MEASURING THE INTESTINAL TRANSPORT OF WATER, SODIUM AND POTASSIUM.

In the review of the literature were described the various methods by which water and electrolyte absorption may be studied. Particular attention was paid to those techniques involving the isolation of a segment of bowel, for such a manoeuvre is required if the simultaneous movement of these substances into and out of the intestinal lumen is to be measured.

Two types of experimental preparation have been used:-

(a) An 'acute preparation' in which segments of intestine were tied off from one another in the anaesthetized animal.

(b) A 'chronic preparation' in which a measured segment of intestine was removed from the intestinal tract without disturbing its blood supply, and its ends allowed to open on to the skin surface. Absorption studies were performed in the unanaesthetized animal.

PRINCIPLE OF THE METHOD

The rates at which sodium, potassium and water enter and leave the intestinal lumen are obtained by

presenting to the bowel a physiological solution containing these three substances and their isotopes. A change in the volume of the solution indicates the net movement of water - a decrease indicating absorption, and an increase, secretion of water. Similarly, a decrease (or increase) in the total quantity of electrolyte (labelled and unlabelled) indicates absorption (or secretion) of the electrolyte. The disappearance rates of the isotopic tracers give a measure of the rates at which sodium, potassium and water leave the intestinal lumen (insorption).

The rates of exsorption can then be obtained from the equation

rate of absorption (secretion)

= rate of insorption - rate of exsorption _____(2)

A positive value for the right-hand side of the equation indicates that absorption has occurred; a negative value, secretion.

In this thesis, if a rate of net movement is preceded by a plus sign, then the rate is one of absorption; if the rate is preceded by a minus sign, then secretion is indicated.

MATERIALS.

DOGS.

Healthy mongrels, weighing 9 - 20 kg, were quarantined for three weeks during which time they were immunised against distemper and given trichlorethylene as a vermicide. All animals were fed a standard kennel diet but, for the 24 hours preceding an experiment, were allowed water only.

ACUTE PREPARATION.

The technique was essentially similar to that of Code et al., (1960). Anaesthesia was induced by the intravenous injection of sodium pentobarbitone, 25 mg per kg body-weight and, maintained at a light level by supplementary injections of the same agent. An endotracheal tube was inserted and respirations were spontaneous.

The anaesthetised dog was laid on an electric blanket. With aseptic precautions, the abdomen was opened in the midline and, through a small incision on the antimesenteric side of the ileum, 30 cm from the ileo-caecal junction, a specially-constructed tube (Fig. 2) was inserted into the lumen and threaded in a caudal direction, carefully to avoid

mucosal damage. The intestine was tied by tape to the bobbins of the absorption tube and a rubber catheter was inserted through the same intestinal incision but threaded cranially to drain off any accumulating secretion. The incision in the bowel was closed round the emerging tubes by continuous inverting sutures of catgut. The isolated segment, whose serosal area was approximately 100 cm^2, was replaced within the abdominal cavity and the abdomen closed in layers round the tubes. The completed preparation is shown diagrammatically in Figure 3. The temperature of the dog was maintained throughout the experiment between 37°C and 39°C by covering the animal with sheets. External heating was rarely required for the ambient temperature was usually 23°C - 26°C.

CHRONIC PREPARATION.

Females were preferred because they tend to be more placid and because the urinary bladder is more easily catheterised. In each animal, a Thiry-Vella fistula of colon or of ileum was fashioned by separating a length of intestine and opening its ends on to the skin of the anterior abdominal wall as a Brookes-type ileostomy (Fig. 4). Continuity of the intestinal tract

was re-established by end-to-end anastomosis (Dennis, 1939).

The ileal fistulas, approximately 22 cm long, were prepared from bowel 10 cm cranial to the ileo-caecal junction. Colonic fistulas consisted of the cranial 16 cm of large bowel. These lengths of bowel provided a serosal surface area of 100 cm^2. At least three weeks were allowed to elapse before beginning absorption experiments, all of which were performed within six months of the construction of the fistula. All fistulas were rinsed at least 3 times each week with isotonic saline solution.

Solutions were instilled or withdrawn through a Foley catheter (French gauge, no. 16), modified by placing a balloon 16 or 22 cm from the tip (Code et al., 1960). The portion of catheter between the tip and the balloon had several perforations. A second Foley catheter was inserted into the other end of the fistula and the balloons on each catheter inflated. By withdrawing the catheters, the balloons were pressed against the inside of the stoma to obtain a water tight seal.

TEST SOLUTION.

The test solution was freshly-prepared Tyrode's solution (Code and McIntire, 1956), containing the

radioactive isotopes of sodium (^{24}Na) and of potassium (^{42}K) and the stable isotope of water, deuterium oxide (D_2O). (The composition of the test solution is detailed in Appendix 1; the radioactive isotopes are specified in Appendix 2). The reaction of the test solution, measured by a glass electrode pH meter, was brought to a pH 7 with 0.1 N hydrochloric acid. The test solution was kept in a stoppered flask and maintained at a temperature of 37°C in a water bath. In a few experiments, indicated in the text, ^{22}Na was substituted for ^{24}Na.

GLASS WARE.

Before use, all glass-ware was washed twice in tap water, steeped overnight in dilute hydrochloric acid, and then washed twice in triple-distilled water. All solutions containing D_2O were kept in firmly-stoppered flasks, or, where possible, in sealed ampoules.

EXPERIMENTAL PROCEDURE.

An experiment was begun by rinsing the lumen of the intestinal segment with Tyrode's solution at 37°C, until the returning fluid was clear. The segment was emptied and left for 30 minutes. Twenty-five millilitres of test solution were pipetted into a syringe and

injected into the isolated segment. To encourage intraluminal mixing, the solution was rapidly withdrawn and re-instilled 3 and 6 minutes after the beginning of the test. Throughout a test, the syringe was held in a clamp just above the isolated segment, and fluid was allowed to rise and fall in the catheter. At 10 minutes, as much as possible of the fluid within the intestine was aspirated. The volume of this aspirate was noted. The segment was immediately washed with 100 ml Tyrode's solution and the volume of the rinse noted. The bowel was allowed to drain freely for at least 30 minutes before the next test. Tests in which solution leaked from the isolated segment were abandoned.

At the end of an acute experiment the animal was killed. The intestine was opened longitudinally. If infestation with Echinococcus granulosus was discovered, the data from that dog were discarded, since the damage, which these parasites inflict, alters the rates of absorption (unpublished observations). The opened segment was then pinned on cork under uniform tension and its serosal surface measured. Similarly, the surface area of a Thiry-Vella fistula was measured at the end of a series of experiments. In both cases the calculated

rates of absorption etc., were expressed in terms of 100 cm^2 serosal surface area. The intestinal segments were then fixed for histological examination.

ESTIMATIONS.

Sodium and potassium.

The chemical concentrations of sodium and potassium in the test solution were obtained, in duplicate, using a flame photometer with appropriate filters (Evans Electroselenium, Limited). A calibration curve was drawn on each occasion from three standards for each electrolyte.

Radioactive sodium and potassium.

Aliquots of the test solution, before and after instillation, and of the rinse, were counted simultaneously in beta and gamma counters. Beta counting was performed in a Geiger-Muller liquid tube, Type M 6, with wall, 1 mm thick (20th Century Electronics, Ltd.). The tube was contained in a lead castle and connected to an automatic scaler (Panax Equipment, Ltd., Type AC-300-6). At each counting session, the mid point of the plateau of the voltage characteristic curve was established, usually around 1100 volts, and all subsequent counts made at this working voltage. All counts were corrected for 'dead-time' (Appendix 3).

From these corrected counts was subtracted the background count, obtained before each sample count by counting the empty Geiger tube for 100 seconds.

Gamma counting was performed in a shielded well-type scintillation counter (Isotope Development, Ltd. (I.D.L.), no. 663) with a thallium-activated sodium-iodide crystal (I.D.L., no. 2003A) and attached to an automatic scaler (I.D.L., no. 1700). From each count was subtracted the mean background count, determined from three counts, each of 1000 seconds, made before, during and after a counting session.

In both instruments, all counts were more than 10,000 except for the rinse when at least 4000 counts were obtained. The aspirate from each test was counted in duplicate. The test solution itself, and two counting standards, one containing ^{24}Na (2 μc per litre Tyrode's solution), the other ^{42}K (4 μc per litre Tyrode's solution), were counted on three occasions during the course of a counting session.

Deuterium oxide.

In most of the experiments, the concentration of deuterium oxide in the test solution was estimated by infra-red spectrophotometry, using a modification of the method described by Berglund-Larsen (1956). The measure-

ments were carried out in a Perkin-Elmer infra-red spectrometer, model 237. The home-made cells were constructed by cementing two quartz crystalline slides (Vickers Instruments Ltd., M8588) on either side of lead spacers, 0.08 mm thick, using the black wax cement "picene" to form a thin even seal. The exact thickness of a cell was determined by weighing it empty and then full of water. Suitable metal holders for the cells were also constructed so that the cell was always held in exactly the same position in the beam.

A calibration curve was prepared by plotting optical density at a wave-length of 2490 cm^{-1} against four standard samples of deuterium oxide over the range 0.5 - 2 per cent with an upper limit of 6 per cent. Ordinary distilled water was used as a reference standard.

The cells were filled rapidly when the tip was broken from an ampoule containing the sample and the open end held against the cell end. Care was taken to exclude minute air bubbles in the cells which, after each recording, were emptied from the opposite end and dried by sucking air through the cell. The absorption of ordinary distilled water in the same cell was checked between analyses. All measurements were made rapidly to

minimise the exchange of water while the sample was in the cell.

In a few experiments, indicated in the text, the concentration of deuterium oxide in the test solution was estimated by mass spectrometry (Code et al., 1954). Water was distilled from the samples, vaporised and passed over hot zinc to reduce it to hydrogen and deuterium whose ratios were then determined in the mass spectrometer.

In both cases the concentration of deuterium oxide was expressed as atoms per cent excess.

A diagram summarising the method is drawn in Figure 5.

CALCULATIONS.

In Appendix 4 are given the formulae for the calculation of the rates of movement of water, sodium and potassium.

The several steps in the calculations are as follows:-

1. The individual counts due to radiosodium and radiopotassium in the isotope mixtures were derived by

simultaneous differential counting (Veall and Vetter, 1958). The detailed formulae are given by Equations (4) and (5) in Chapter 2 of this Part of the thesis. Allowance was then made for the decay of both short-lived isotopes during the course of the experiment from standard decay tables.

2. The volume of the residual fluid remaining in the lumen, after most of the test solution had been withdrawn, was obtained by washing the intestinal segment immediately with the non-radioactive rinse. The acquired radio-activity of a sample of this rinse was then counted. To obtain the residual volume, the total activity of the rinse was divided by the counts per millilitre of the test solution aspirated at 10 minutes.

3. The actual volume of test solution unabsorbed at the end of 10 minutes was obtained by adding the residual volume to the volume of aspirated test solution. Finally, the net movement of water was calculated by subtracting the volume of test solution unabsorbed from the volume of test solution instilled. A positive value indicated absorption; a negative value, secretion (Equation 1, Appendix 4).

4. The net movements of sodium and potassium were obtained by subtracting the total amount of each

electrolyte left in the lumen after 10 minutes from the total quantity of each electrolyte introduced (Equation 2, Appendix 4).

5. The rates of insorption of sodium, potassium and water were calculated from the formulae of Visscher et al., (1944a and b) (Equations 5 and 7, Appendix 4).

6. The rates of exsorption were calculated by substitution in the equation

rate of net movement = rate of insorption - rate of exsorption.

7. All rates were then expressed as per 100 cm^2 surface area.

In Appendix 5 is set out the protocol of a single 10-minute absorption test with the calculation of the rates of movement of water, sodium and potassium.

TERMINOLOGY.

The nomenclature to describe directions of movement has been discussed in Part I, Chapter 4, and is shown diagrammatically in Figure 1.

Chapter 2 THE ASSUMPTIONS AND THE ERRORS OF THE METHOD.

The assumptions of the methods will now be considered, and where possible, validated. Also in this section will be described the errors of the various components of the method so that some estimate of the cumulative error may be obtained.

(1) The intestine was assumed to be incapable of discriminating between the labelled and unlabelled electrolyte and water.

(2) The rates of insorption of water, sodium and potassium were calculated from the rates of disappearance of their tracer nuclides from the luminal solution (Equations 5 and 7, Appendix 4). A necessary assumption of the calculations was that the tracer, once having left the intestinal lumen, would not later re-enter the bowel in any significant quantity.

(a) It was necessary to prove that tracers were not adsorbed on to the mucosa, or on to the sides of absorption tubes to become detached later. Direct counting of all containers and tubes, and of excised bowel at the end of an experiment, did not reveal any significant permanent attachment of radioactive material, probably because of the large quantity of carrier sodium and

potassium present.

(b) It was also assumed that tracers, which had been absorbed, would be so diluted in the extra-cellular fluid, that only negligible quantities of tracer would re-enter the lumen subsequently. For example, from 25 ml test solution instilled, approximately 20 ml water would be insorbed; this volume of water would become diluted in the blood and in the extra-cellular space which have, in a dog of medium size, volumes of 1.3 and 9 litres respectively (Moore et al., 1962). These compartments are very large compared to the quantity of fluid within the bowel lumen.

The actual error produced by the re-entry of insorbed tracer into the bowel was measured by the following experiments. Eight absorption tests were performed at 30-minute intervals using ^{22}Na as the radioactive label. Its long half-life (2.6 years) would exaggerate any error caused by re-entry. Then 25 ml of non-radioactive Tyrode's solution were instilled into the intestinal lumen and withdrawn after 10 minutes. Six experiments were performed in this manner. The mean radio-activity detected in the Tyrode's solution which was initially non-radioactive

was 15 counts per second (c p s) and represented only 0.6 per cent of the mean activity of the radioactive test solutions after 10 minutes in the bowel (Table 1), despite significant increase in the radio-activity of the arterial blood (Table 2). The error due to re-entry was shown to be of little significance, and in most of the experimental work reported in this thesis, even less, because usually fewer than eight tests were performed, over a longer period of time, employing short-lived radioactive isotopes in less concentration. In this way accumulation of radioactivity in the dog was minimized.

(3) In the derivation of the mathematical formulae for calculating rates of movement (Appendix 4), certain assumptions were made:

(a) The specific activities of the electrolytes in the test solution decrease during their stay in the intestinal lumen. This reduction is brought about by the entry of unlabelled material into the lumen (exsorption) because it is assumed (i) that labelled and unlabelled material will move out of the lumen in the proportion that they bear to one another in the lumen (see 1 above), and (ii) negligible quantity of isotope will re-enter the lumen (see 2 above).

In the calculation of the rates of insorption (Equation 6, Appendix 4) the arithmetic mean of the specific activity at the beginning and at the end of the test period has been used to estimate the mean specific activity. Although many workers have employed the arithmetic mean (Visscher et al., 1944b; Cooperstein and Brockman, 1959; Code et al., 1960; Grim, 1962), its use has been rightly criticized by Berger and Steele (1958). However, these last authors pointed out that the difference between the mean specific activity, as calculated by them, and that obtained from the arithmetic mean can be neglected if the change in specific activity during the experiment is less than 40 per cent. This was achieved in the present experiments by restricting the test period to 10 minutes.

(b) Visscher's formula (Equation 3, Appendix 4) does not allow for the fact that frequently the movement of sodium and water into and out of the bowel may be exponential (Code et al., 1960). However, the form of the exponential curve is such that the rates of movement are, for practical purposes, linear with time until about 50 per cent of the isotope has been absorbed.

During a 10-minute test period, usually less than 20 per cent of isotope has been absorbed. The rates calculated from the Visscher formula and from an exponential curve should therefore be similar. This similarity has been confirmed experimentally (Code et al., 1960). However, it was felt to be more accurate to express all rates as per 10 minutes rather than as per minute.

(c) The Visscher formulae have the virtue that only a single compartment is considered in the calculation - the intestinal lumen. Water and electrolytes, which leave this compartment, are considered to enter the body, which forms, in fact, the second compartment. A third compartment, the intestinal mucosa, intervenes between the other two. However, as far as water and sodium are concerned, this third compartment does not affect appreciably the kinetics of the transport system, either by retaining or altering these materials, because (i) this third compartment comes into rapid equilibrium with the second: Benson et al., (1956) have shown that 99 per cent of absorbed water and sodium appear within a short time in the portal blood; (ii) direct counting of the mucosa (Curran and Solomon, 1957) and

estimations of D_2O in the mucosa (Visscher et al., 1944a) have shown retention of less than 5 per cent of the absorbed sodium and water.

Visscher and his co-workers (1944a and b) have demonstrated the applicability of their formulae for water and sodium to a number of experimental situations. It may very well be that absorbed radioactive potassium will be retained for a time within the intestinal cell. However, direct counting of the excised mucosa has not revealed this. It is probably safe to say that the rates of movement of water, sodium and potassium out of and into the intestinal lumen, as calculated from the Visscher formulae, truly represent movement into and out of the body proper.

(4) An important measurement is that of the residual volume of test solution which could not be aspirated from the intestinal lumen at the end of the test period, for, from this calculated volume, is obtained the volume of unabsorbed fluid on which all subsequent calculations are based. The calculation of the residual volume was made from the radioactivity acquired by a rinsing solution at the end of the test period. Since two radioactive-isotopes have been employed, two estimates of the residual volume can be

obtained. In most cases these estimates were similar (Fig. 6), so that in subsequent calculations their mean was used.

The assumption in estimating residual volume in this way is that no isotope was insorbed during the interval of 25-30 seconds between the end of a test and the instillation of the rinse. Since less than 2 per cent of the isotope was absorbed each minute, on most occasions the error of estimating the residual volumes was less than 1 per cent.

Nevertheless, it was decided to compare the isotopic method of estimating residual volume with a method based on a different principle - the recovery of an unabsorbed reference substance introduced with the test solution (Part I, Chapter 4). On 12 occasions, 1 per cent w/v polyethylene glycol (PEG) of molecular weight 4,000 (Light and Co.) was added to the test solution and the residual volume calculated from the equation;

$$RV_{peg} = \frac{\text{Amount of PEG instilled - Amount of PEG aspirated}}{\text{Concentration of PEG in aspirate.}} \quad (3)$$

The concentration of PEG was estimated by the turbidimetric method of Hyden (1955). The residual

volume was also calculated from the mean of the isotopic data (RV_{isot}). RV_{peg} and RV_{isot} had closely similar values (Fig. 7) but RV_{peg} tended to be slightly higher than RV_{isot}. This discrepancy can be attributed to two factors (a) RV_{peg} tended to over-estimate the true residual volume since only 95 per cent of the PEG added to intestinal content could subsequently be recovered by Hyden's method; (b) RV_{isot} under-estimated the residual volume because of the slight insorption of isotope between test and rinse.

Since the two entirely different methods of estimating residual volume gave closely similar results, the calculation of residual volume by the isotopic method seemed justified.

(5) The accuracy of the method is also dependent upon satisfactory discrimination of ^{24}Na and ^{42}K in a mixed sample. The technique of discrimination (Veall and Vetter, 1958) is based on the difference between the irradiations emitted by the isotopes. While both emit fairly high beta radiation, ^{24}Na emits much more gamma radiation than ^{42}K (Appendix 2). If a mixed sample is counted in a scintillation counter most of the observed counts will be due to ^{24}Na, particularly when the discriminator is adjusted in favour of the

higher energy gamma-rays of this isotope. If the same sample is counted in a thick-walled beta counter the high energy beta-rays of ^{42}K are only slightly affected but the transmission of the beta particles from ^{24}Na is substantially reduced.

Therefore if a mixed sample has a count rate of $\underline{R}_s$ in the scintillation (gamma) counter, and of $\underline{R}_g$ in the Geiger (beta) counter, then the number of counts in the sample due to ^{42}K ($\underline{A}_k$) is given by

$$A_k = \frac{R_g - qR_s}{1 - pq} \quad \text{---------- (4)}$$

and the number of counts in the sample due to ^{24}Na ($\underline{A}_{na}$) is given by

$$A_{na} = \frac{R_s - pR_g}{1 - pq} \quad \text{---------- (5)}$$

where p = $\frac{\text{count rate of } ^{42}K \text{ standard in gamma counter}}{\text{count rate of } ^{42}K \text{ standard in beta counter}}$ ---(6)

and q = $\frac{\text{count rate of } ^{24}Na \text{ standard in beta counter}}{\text{count rate of } ^{24}Na \text{ standard in gamma counter}}$ ---(7)

The ratios $\underline{p}$ and $\underline{q}$ should be as small as possible, the ideal case being $p = q = 0$. Since over all the experiments, the mean value for the ratio $\underline{p}$ was 0.78,

and, for q, was 0.23, discrimination was acceptable although the gamma counter was rather sensitive to emissions from ^{42}K.

For practical purposes, however, discrimination was satisfactory as shown by the following experiment. A sample from a solution containing ^{24}Na was counted in a gamma counter, and a sample from a solution containing ^{42}K, in a beta counter. The two solutions were mixed, and samples from the mixture counted simultaneously in both counters. The activities due to ^{24}Na and ^{42}K were calculated, using the formulae above, and compared to their known activities (Table 3). The calculated activities did not differ significantly from the known activities, with a mean recovery of 97 per cent for ^{24}Na and of 101 per cent for ^{42}K.

This method of discrimination will be valid only if simultaneous counting is performed since exact correction for decay cannot be applied to the mixtures owing to the differences of the half-lives of the two isotopes.

The total error of the radioactivity measurements is composed of (a) the errors due to counting and (b) the error in deriving the separate activities of ^{24}Na and ^{42}K in a mixture.

(a) The error of a single radioactive count is easily obtained since the distribution of observed counts of a sample about a 'true' value is described by a Poisson curve (Veall and Vetter, 1958). The standard error (S.E.) of a single determination of n counts is therefore the square root of n and the coefficient of variation in counting is given by $100/\sqrt{n}$. Therefore to obtain a coefficient of variation of 1 per cent in counts each sample was counted for at least 10,000 counts. All counts were at least 50 times background so that the statistical fluctuation in background did not contribute to the error of counting the samples.

(b) The error in deriving the activities of ^{24}Na and ^{42}K in a mixture can be calculated in the following way. A mixture of ^{24}Na and ^{42}K was counted in beta and gamma counters. The coefficient of variation of these counts was considered to be 1 per cent. The separate activities in the mixture due to ^{24}Na and ^{42}K were derived in the manner described above. The error produced in deriving the counts was calculated according to the formulae of Robinson, Arons and Solomon (1955). The results (Table 4) show that the error in deriving the ^{24}Na activity was 3 per cent

and is obviously caused partly by the tendency of the scintillation counter to count gamma rays emitted from ^{42}K. The error in deriving ^{42}K activity in a mixture was 1 per cent, no greater than the error produced by the counting alone.

(6) The errors in estimating sodium and potassium by flame photometry were found to be 1.3 per cent for sodium and 2.5 per cent for potassium (Appendix 6). These errors are within acceptable limits (Henry, 1964).

(7) The error in estimating deuterium oxide by infra-red spectrophotometry was calculated to be 0.86 per cent (Appendix 7). The error in carrying out the determination by mass spectrometry is 0.004 per cent (Code et al., 1954).

The contribution of the following errors to the total error of the method is probably negligible:- the measurement of the volumes of the test solution; errors in dilution of standards for flame photometry and for radioactive counting.

Since there are still several unknown errors it is difficult to estimate the total error in the measure-

ment of the rates of transport of water, sodium and potassium; also the effect of an error of one determination upon an error of another determination is unknown. The various separate errors are detailed in Table 5.

It is probably safe to say that the total error of the method is not less than 10 per cent. Such errors must contribute, to a certain extent, to the variation in transport rates which are observed and will be described later.

CONCLUSION.

The two methods selected for studying the intestinal absorption of sodium, potassium and water, namely an acute preparation with the intestine *in situ*, and a permanent Thiry-Vella fistula, are well suited to the problem and have no major disadvantages. The assumptions, on which the procedure and calculations of results are based, are valid. The total error of the method is probably not greater than 10 per cent.

Chapter 3 RATES OF MOVEMENT OF WATER, SODIUM AND POTASSIUM INTO AND OUT OF THE INTESTINAL LUMEN

1. ACUTE PREPARATION.

The rates of transport were measured in 17 anaesthetized dogs in each of whom two tests of absorption were performed, on a segment of ileum isolated in continuity. In 12 dogs the movements of sodium and water were measured; in 5 dogs, the movement of potassium.

All of these dogs were part of the investigation into the effect of increase in mesenteric venous pressure upon water and electrolyte absorption (Part IV). The data reported in this section are drawn from the two initial tests performed to establish the baseline rate before the mesenteric vein was compressed.

Rates of transport of sodium, potassium and water. (Table 6).

In all experiments both sodium and water were absorbed and potassium secreted. During the ten minutes that the test solution lay in the ileal lumen the bowel absorbed 680 µEq sodium and 4.6 ml water, and secreted 14 µEq potassium. Sodium moved at a rate of 1151 µEq per 10 minutes out of the lumen and, at a rate of 471 µEq per 10 minutes, into the lumen. At the same time

16.9 ml water were insorbed into the body while 12.3 ml moved in the opposite direction. The rate of potassium exsorption (38 µEq per 10 minutes) was greater than the rate of insorption (24 µEq per 10 minutes).

Variability in rates of movement. (Table 6).

The variability of the rates of movement of each substance into and out of the bowel was expressed as a coefficient variation of the mean rates. The variability was greatest for sodium, being 24 per cent and 33 per cent for insorption and exsorption respectively, compared to 21 per cent and 14 per cent for potassium and 18 per cent and 26 per cent for water.

Relationship between sodium and water movement.

The rates of water movement were plotted against those of sodium movement determined at the same time (Figs. 8 - 10). Water and sodium movement were closely correlated, particularly net movement ($r = 0.98$, Fig. 8), and extrapolation of the regression line for sodium to the y-axis shows that when there was no sodium absorption there would be little water absorption. By calculating the amount of sodium which would theoretically move with each litre of water, it was found that, during insorption, 68.2 $\pm$ 2.9 mEq sodium

left the intestinal lumen with each litre of water, and for each litre of water exsorbed, 38.5 ± 1.8 mEq sodium entered the intestinal lumen. The net result was that for each litre of water absorbed, 145.9 ± 4.2 mEq sodium were also absorbed from the test solution whose initial concentration was 142 ± 0.4 mEq per litre.

Luminal concentration of sodium and potassium. (Table 7).

During the absorption of sodium and water in the ileum, the concentration of sodium in the test solution, initially 142 mEq per litre, fell by 2 mEq, a significant decrease ($P < 0.01$). Over the same period of time, but in other dogs, the concentration of potassium in the test solution rose from 4.0 mEq per litre to 4.8 mEq per litre ($P < 0.001$).

2. CHRONIC PREPARATION.

The rates of movement of sodium, potassium and water were determined in five dogs, each with a single Thiry-Vella fistula. Two dogs had a fistula of ileum, and three dogs, of colon.

All of these dogs were part of the study to investigate the effect of aldosterone upon water and electrolyte absorption (Part V). The data reported in

this section are drawn from 107 ten-minute tests performed under control conditions when no aldosterone had been given.

In each dog no fewer than two, and as many as eight, tests were performed in a single day so that the hour-to-hour and the day-to-day variability in rates of movement could be calculated.

Rates of movement of sodium, potassium and water.

(a) Net movement.

All three substances were secreted into the Thiry-Vella fistula of ileum:- sodium, at a mean rate of 307 μEq per 10 minutes; potassium, at 21.5 μEq per 10 minutes; and water, at 1.8 ml per 10 minutes (Table 8). In the colon, on the other hand, only potassium was secreted, at a rate of 14.9 μEq per 10 minutes; both sodium and water were absorbed at rates of 109 μEq and 0.9 ml per 10 minutes respectively (Table 9).

(b) Unidirectional movement.

(i) Ileum (Table 8): the mean rates of insorption of sodium, potassium and water were all less than those of exsorption. These mean rates for sodium and water, however, conceal the fact that, on occasions, the rate of insorption exceeded that of exsorption so that these

substances were absorbed. This phenomenon was not confined to any particular experiment nor to any particular dog, but occurred seemingly in a random fashion. At no time, however, was potassium insorbed at a greater rate than it was exsorbed so that, in the ileum, potassium was always being secreted.

The rates of insorption in one dog (no. 34) were, in general, less than those of insorption in the other dog (no. 33) so that the rates of secretion of sodium and water in the first dog were relatively greater.

(ii) Colon (Table 9): potassium entered the intestinal lumen at a greater rate (28 μEq per 10 minutes) than that in which it left (13 μEq per 10 minutes). Secretion of potassium was invariable in the colon. For sodium and water the rates of insorption were usually greater than those of exsorption; only occasionally was the reverse situation encountered. This phenomenon seemed to occur randomly as in ileum. When the rates of movement of sodium and water in all 3 dogs were considered together the rates of insorption of water and sodium were greater than those of exsorption. However, in one of the dogs (no. 37) both sodium and water were secreted in small quantity;

secretion was brought about by a relative increase in the rate of exsorption of sodium and water, compared to the other dogs.

Variability in the rates of movement.

The variability in the rates of movement of each substance was compared by calculating the coefficient of variation of the mean rates. With few exceptions the variability in rates from dog to dog was much greater than the variability in rates among several tests performed in the same dog. When the variability in rates in each individual dog were compared, it was found that the mean coefficient of variation was greatest for sodium (37%) and least for water (21%), potassium occupying an intermediate position with a mean coefficient of 26 per cent.

To see if the variability in the rates could be further reduced, the variation from day to day in each dog was compared with that from hour to hour in the same dog. Analysis of the variance in the rates of transport in three dogs (Table 10) indicated that in all cases the variability between the rates of sodium movement was significantly reduced when tests were performed over several hours rather than over several days. Analysis of variance in the other two

dogs could not be undertaken because of insufficient data.

Relationship between net movement of water and electrolytes.

The net movement of water absorbed or secreted in the ileum and colon was plotted against the net movement of sodium alone, and of sodium plus potassium (Na + K) (Figs. 11 and 12). In both ileum and colon the mass of sodium movement was so great compared to that of potassium that the regression lines of water movement on sodium (Na) and on sodium plus potassium (Na + K) were similar.

In the ileum (Fig. 11) the relationships between water movement, on the one hand, and the movements of sodium (Na) and of sodium plus potassium (Na + K), on the other, were found to be similar and close ($r = 0.91$). In the colon (Fig. 12) water movement seemed at first more closely related to the combined cation movement (Na + K) ($r = 0.87$) than to the movement of sodium alone ($r = 0.82$) but the difference between these correlation coefficients was not significant.

In both segments of intestine, cation and water were at times absorbed, and at other times secreted. Absorption was more common than secretion in the colon

and was rare in the ileum. With only one exception (in the ileum), the net movement of cation and water proceeded in the same direction: when cation was absorbed, water was absorbed; when cation was secreted, water was secreted. In addition, by extrapolation, when no cation was absorbed or secreted, then neither was any water absorbed or secreted (the y-intercepts of the regression lines would obviously pass through the origin by chance).

The ratio of net moving cation (Na + K) to net moving water was found to be 186 $\pm$ 11 mEq per litre in the ileum, and to be 150 $\pm$ 19 mEq per litre in the colon.

Relationship between the unidirectional movement of water and electrolytes.

For both ileum and colon the rates of movement of water in one direction were plotted against the rates of movement of sodium alone (Na) and of cation (Na + K), in the same direction (Figs. 13 to 16). From all the graphs it is immediately apparent that there was a linear relationship between water movement and cation movement in the same direction. Also it is clear that the amount of potassium transported was always such a small fraction of the total cation

movement that the regression lines of water on sodium alone (Na) were almost identical to those of water on sodium plus potassium (Na + K). For reasons given later, in the subsequent discussions, only the ratio of water movement to the movement of cation (Na + K) will be considered; (Na + K) is designated cation movement.

(i) Insorption.

When the relationship between cation and water insorption in the ileum is compared to that in the colon, the two regression lines are found to differ only in their y-intercepts, for the slopes of the lines do not differ significantly ($P < 0.2$). Also the relationship between the rates of insorption of cation and water in the ileum was not significantly closer than that in the colon, because the difference between the correlation coefficients ($r = 0.68$ and $r = 0.5$) was less than one standard error of the difference when Fisher's z transformation was used (Moroney, 1956).

For each litre of water insorbed, 56 mEq of cation were insorbed in the ileum and 49 mEq in the colon. Thus both ileum and colon seem to insorb water and cations in similar proportions so that in both cases

a hypotonic solution entered the body.

(ii) Exsorption

The relationship between the exsorption of cation and the exsorption of water in the ileum is similar to that in colon, the only difference lying in the y-intercepts of both regression lines. The slope of the regression lines did not differ significantly ($P < 0.4$). Nor is the higher degree of correlation between water and cation movement in the ileum of any significance, since the difference between the z transformations of the coefficients was only slightly greater (1.2) than one standard error of the difference between the correlation coefficients.

For each litre of water exsorbed, 78 mEq of cation entered the ileal lumen and 44 mEq of cation entered the colonic lumen.

Luminal concentration of sodium and potassium (Table 7).

The concentration of sodium in the test solution in ileum and in colon did not alter during the 10 minute period. On the other hand, the concentration of potassium rose slightly, but nevertheless significantly: in the ileum the concentration of potassium rose by 0.5 mEq per litre ($P < 0.001$), and in the colon the

increase in potassium concentration was 0.6 mEq per litre ($P < 0.001$).

Age of fistula.

No alteration in transport rates was observed over a six month period.

Histology of a Thiry-Vella fistula.

The histological appearances (on light microscopy) of normal canine ileum and colon were preserved if the fistula was washed frequently with isotonic solutions (Appendix 8).

DISCUSSION.

The accurate measurement of the simultaneous movement of water and electrolytes in both directions across the intestinal mucosa demands an isolated segment of bowel. Acute experiments carry the advantage that many tests may be performed simultaneously on several segments of bowel in a single dog. They are particularly applicable to the present study for such absorption tests can be performed upon segments of intestine which have been previously obstructed. However, in these short-term experiments, only factors which have a rapid effect on intestinal absorption can be studied. A disadvantage of such preparation is that the surgery performed upon the animal may affect the rates of absorption. Anaesthesia with sodium pentobarbitone alters the rate of absorption only slightly (Code et al., 1960). The other effects of surgery have not been specifically studied hitherto. Observations to be detailed later suggest that the rate of secretion of potassium into the lumen of the bowel is increased within an hour or so of the beginning of the operation.

Chronic experiments in a trained placid dog allow tests to be repeated over many weeks in the same

segment so that metabolic and hormonal studies can be undertaken. Such permanent separation of a length of bowel from the frequent stimulation of food and other secretions may lead to the loss of its normal characteristics and acquisition of those associated with disuse. We have sought to avoid this complication by frequent rinsing of the segment. However, sodium and water were frequently secreted into the isolated ileum, a situation which differs from that observed in the acute preparation and from what would normally be anticipated. Others have observed this phenomenon in both acute and chronic preparations (Berger et al., 1959a and b; Duthie and Atwell, 1964). Code et al., (1960) have attributed such secretion to ageing of the segment; however, all the segments used in this present study were prepared in the previous six months. We have confirmed Berger's observation that, on light microscopy, there is no histological change in the isolated segments. Our own experience is that secretion occurs randomly and can not be associated with any particular dog or any particular solution. In particular it is emphasised that an isolated ileal segment which is secreting responds to various stimuli e.g. sodium depletion, in a similar manner to a segment

which is absorbing (Clarke and Shields, 1963). Secretion of water and sodium in the isolated ileum may be regarded as an artefact but does not prevent the ileum from being influenced in the same way as normal bowel.

There is good agreement between the results of the present study and those obtained by other workers, who used dogs, if all observations are expressed according to the serosal surface area of bowel (Tables 11 and 12). Attempts to relate results to total mucosal area are futile since no accurate allowance can be made for the microvilli. These rates are also closely similar to those found in the intestinal tract of other species (Curran and Solomon, 1957) and, with the exception of the erythrocyte, are of the same order of magnitude as the unidirectional fluxes across other tissues for which data are available (Berger, 1960).

A feature of the intestinal absorption of water and electrolytes remarked upon by most workers, and confirmed in this study, is the marked variability in the rates of movement (Visscher et al., 1944a and b; Bucher et al., 1950; Curran and Solomon, 1957; Berger et al., 1959a). Such variability requires that repeated observations are performed for adequate

statistical analysis and implies that the action of any factor on intestinal absorption will become manifest only if its effect upon the intestine is gross. The complicated nature of the experiments and the errors in measurement, already outlined, must contribute to the observed variability. In addition, variation among dogs can be attributed to the unsatisfactory reference base - surface area - that is used. However, the present work confirms the observations of Berger et al., (1959a) that the rates of sodium movement show the greatest variability. It is difficult to understand how this could come about unless the variability were real. This tenet is supported by another observation, confirmed by the present study, that the variability in sodium movement was related to the part of intestine under study - being least in the colon (Visscher et al., 1944b). The causes of such variation are unknown. Berger and his colleagues (1959a) sought unsuccessfully to minimise it by removing the adrenal glands. The present study demonstrates that variation in sodium movement can be reduced if experiments are performed within a few hours of one another.

In these experiments isotonic solutions with an

electrolyte composition similar to that of plasma were instilled into the bowel. The movement of water and cation, particularly sodium, into and out of the intestinal lumen were closely related. The net movement of water and electrolyte took place in the same direction: when no net movement of cation was observed, no net movement of water could be detected. The cause of this close relationship cannot be deduced from this present study. Curran and Solomon (1957) have suggested that water movement is passive and controlled by the transport of solute. If this is so, the driving force for water will be mainly, but not exclusively, the osmotic gradients set up by solute movement. For this reason, in this study, water transport has been related to total cation movement rather than to the movement of sodium alone. When such isotonic solutions are instilled, an approximately isotonic fluid is absorbed or secreted. However, such net movement is the resultant of two opposing, fast flowing streams:- the amount of cation moving along with water into and out of the intestinal lumen is such that markedly hypotonic solutions are insorbed and exsorbed. Such solutions are, of course, hypothetical for there is no evidence that cation and water share the same path through the intestinal mucosa.

CONCLUSIONS.

1. Methods for the study of the intestinal transport of water, sodium and potassium in isolated segments of bowel in anaesthetized and unanaesthetized dogs have been established.

2. The two preparations, acute and chronic, are well suited to the problem and carry no major disadvantages.

3. The assumptions, upon which the procedure and calculations are based, are valid.

4. The total error of the method was probably not greater than 10 per cent.

5. When physiological isotonic solutions were introduced into the ileum and colon, potassium was then secreted into the intra-luminal solution. In the colon, sodium and water were usually absorbed; in the ileum sodium and water were frequently secreted.

6. In both preparations, and in both ileum and colon, absorption and secretion of water and cations were the results of a simultaneous two-way traffic of these substances across the intestinal mucosa. The observed rates in the present study did not differ significantly from those obtained by other workers.

7. Because the movements of water and sodium were closely related to one another, the concentration of sodium in the ileum remained constant; on the other hand, potassium concentration tended to rise.

8. The variability in the rates of movement, greatest for sodium, can only be attributed partly to experimental error - biological variation for undefined reasons must remain an important cause but can be minimized by comparing results obtained within a few hours of one another.

PART III

THE INTESTINAL TRANSPORT OF WATER, SODIUM AND POTASSIUM IN EXPERIMENTAL OBSTRUCTION

THE INTESTINAL TRANSPORT OF WATER, SODIUM AND POTASSIUM IN EXPERIMENTAL OBSTRUCTION.

INTRODUCTION.

Investigations in patients with intestinal obstruction were not undertaken for the following reasons:-

(1) The prolongation of the operation for absorption studies would not be acceptable in ill patients nor could opening into the intestinal lumen to insert tubes be invariably justified.

(2) The short-lived isotopes were not always available.

(3) Clinical material did not provide a standard preparation, in which the type and site of obstruction, the degree of fluid loss, and the extent of previous treatment were all uniform.

For these reasons absorption studies were undertaken in dogs in whom intestinal obstruction was experimentally produced.

MATERIALS AND METHODS.

In twelve dogs, weighing 8 - 15 kg, simple

intestinal obstruction was produced, under aseptic conditions, by transecting the ileum, 30 cm from the ileocaecal junction, and closing the cut ends of the bowel with a double inverting layer of interrupted non-absorbable sutures.

In two dogs absorption tests were performed immediately after the ileum had been transected and closed. The remaining dogs were allowed to recover. On these animals, absorption tests were performed at 12, 24, 36, 48 and 60 hours after the formation of the obstruction, two dogs being studied on each occasion.

Under general anaesthesia (intravenous pentobarbitone, 25 mg per kg body weight), the abdomen was reopened. The absorption tests were performed in a similar way to the acute preparation described in Part II of the thesis. Multiperforate catheters were inserted into the intestinal lumen, cranial and caudal to the obstruction, through small anti-mesenteric incisions placed at silk sutures inserted at the first operation (Fig. 17). These small sutures had been tied to the serosal surface of the ileum, 21 cm cranial and caudal to the obstruction, to mark a length of ileum whose initial serosal surface area would be approximately

100 cm^2. The wall of the bowel was tied to the bobbin carried on the catheter. The holes in the intestine and the abdominal wound were closed round the emerging catheters.

Fluid lying in the lumen of the isolated segment was removed as far as possible. Thirty millilitres of modified Tyrode's solution, containing ^{24}Na (2 μc per litre solution), ^{42}K (4 μc per litre solution) and D_2O (1 per cent, v/v), were instilled into both segments by means of a syringe, and allowed to mix with the intestinal content. Five millilitres of the intraluminal fluid was then withdrawn, and, by counting its radioactivity, allowance was made for the volume of fluid which was not removed by the preliminary aspiration. At the end of 10 minutes as much as possible of the test solution was removed and the segments rinsed with 100 ml non-radioactive Tyrode's solution.

In each segment three tests were performed at 30 minute intervals. Therefore, in the 12 dogs, 72 tests were undertaken.

In three of these dogs, in addition to these tests performed on the ileum adjacent to the obstruction, three absorption tests were also performed, at the same time, in the upper ileum. A multiperforate catheter

carrying two bobbins was inserted into the lumen and absorption tests performed as in the acute preparation (Part II). These tests, three in each dog, were performed 15 minutes (Dog no. 19), 36 hours (Dog no. 25) and 48 hours (Dog no. 27) after the formation of the obstruction.

For control experiments, a sham operation was performed in three additional dogs (nos. 30 to 32) some time before absorption tests were carried out. In these dogs the abdomen was opened, and then immediately closed. Some time later (24, 36 and 48 hours respectively) the abdomen was reopened and a multiperforate catheter inserted into the lumen of the terminal ileum. Three tests of absorption were performed upon the isolated ileum in the usual manner.

In all cases body temperature was maintained and anaesthesia continued during the course of the tests.

The technique of performing the tests, the composition of the test solution and the methods of calculating the sorption of water, sodium and potassium did not differ from the method already described.

The concentration of sodium and potassium in the peripheral blood of each dog was estimated, by flame photometry, on two occasions - before the obstruction

was formed, and during the absorption tests. At these times the concentration of urea in the blood was estimated by the method of Varley (1962).

At the end of the third absorption test, the dog was killed and a post-mortem examination carried out. Particular attention was paid to the intestinal tract the volume of whose content, cranial and caudal to the obstruction, was measured. The surface area of the isolated segment was also determined. All rates of movement were expressed as per 100 cm^2 serosal surface area. The bowel was then fixed for subsequent histological examination.

RESULTS.

I. CLINICAL EFFECTS OF OBSTRUCTION.

Recovery from anaesthesia was invariably rapid. For the first 24 hours the dogs showed the lethargy and disinclination to eat which are usual after intestinal surgery. Then the abdomen became slightly swollen but vomiting was rare except in those dogs which were allowed to survive for 60 hours. Water was offered to, and taken by, all dogs. No intravenous infusions were required.

Findings at second operation.

After 24 hours of obstruction, about half of the small intestine was distended, mainly with gas, and 5 - 10 ml brown faeculent fluid had collected in the lumen of the bowel cranial to the obstruction. By 36 to 60 hours, almost all the bowel was dilated with gas, and fluid had accumulated in the length of bowel extending cranially from the obstruction for 30 to 50 cm.

The wall of the fluid-filled segment of gut was reddened, congested, thick and flaccid. The veins in the adjacent mesentery were dilated and engorged. Although the upper coils of bowel were dilated with gas, they presented an otherwise normal appearance.

There was no evidence of perforation of the intestinal wall, nor of ulceration of the mucous membrane.

Post-mortem appearances.

The above findings were confirmed. No abnormality of other organs or tissues was found. The ileum above the obstruction shortened (Fig. 18); but, since its circumference increased at the same time, the surface area did not alter except in those dogs whose bowel had been obstructed for 60 hours, in whom the surface area of bowel had increased (Table 13). The dimensions of the bowel caudal to the obstruction did not change appreciably.

Histologically the gut above the obstruction showed capillary dilatation and engorgement of the small venules (Fig. 19). The tissue spaces were oedematous and wider than usual. Occasional bleeding under the mucosa was evident and in those dogs whose bowel was obstructed for 48 and 60 hours mononuclear infiltration into all layers of the intestinal wall could be seen.

II. INTESTINAL TRANSPORT OF WATER AND CATIONS IN THE PRESENCE OF LOW ILEAL OBSTRUCTION.

The effect of an ileal obstruction upon the

exchange of fluid and electrolytes across the intestinal mucosa will be described in the following order:-

(1) Movement of water and cations in ileum cranial to obstruction:-

(a) immediately adjacent to obstructing lesion

(b) remote from obstruction, in the proximal ileum.

(2) Movement of water and cations in ileum caudal to obstruction.

(3) A comparison in water and cation movement between ileal segments cranial and caudal to obstruction.

(4) The relationship between water and cation transport in obstructed bowel.

(5) The concentration of cations in the lumen of the bowel in obstruction.

(1) MOVEMENT OF WATER AND CATIONS IN ILEUM CRANIAL TO OBSTRUCTION.

The exchange of water, sodium and potassium across the mucosa of intestine cranial to the obstruction was greatly altered.

(a) Ileum immediately cranial to an obstruction.

(i) Water transport (Fig. 20: Table 14)

Within 12 hours the ileum cranial to the

obstruction ceased to absorb and began to secrete fluid at a steadily increasing rate until, after 60 hours, 13 ml water collected in the lumen of the ileal segment every 10 minutes.

Such a change resulted, in the first place, from an abrupt and significant decrease in the rate at which water was leaving the intestinal lumen. Water continued to enter the obstructed bowel at a normal rate at first, but, after 48 hours, the rate of exsorption of water increased rapidly and significantly, so that in the later stages of obstruction, the accumulation of fluid in the obstructed bowel was augmented.

(ii) Sodium transport (Fig. 21: Table 15).

A similar response was observed in the handling of sodium by the obstructed ileum. Within 12 hours, the ileum was observed to secrete, rather than to absorb, sodium, and thereafter the rate of secretion increased until, at 60 hours, 1.8 mEq sodium accumulated in the lumen of the ileal segment above the obstruction every 10 minutes.

The rates of both insorption and exsorption were affected within 12 hours. The rate of insorption fell abruptly and, indeed, after 24 hours hardly any sodium

left the lumen of the obstructed bowel. The rate of entry of sodium into the ileum increased in the later stages of obstruction, particularly after 36 hours.

(iii) Potassium transport (Fig. 22; Table 16).

The obstructed ileum secreted potassium at an increasing rate; the longer the duration of the obstruction, the greater the rate of potassium secretion so that after 60 hours potassium secretion had increased sixfold.

This altered behaviour was attributable to a rapid and early fall in the rate of potassium insorption (after 24 hours hardly any potassium ions left the obstructed ileum) and a simultaneous, but greater rise, in exsorption so that, at 60 hours, more than twice the usual amount of potassium entered the ileal lumen.

(b) Proximal ileum - cranial to, and distant from, the obstruction.

In three dogs the movement of water and cations across the mucosa of the upper ileum was measured at the same time as the rates in the lower ileum (Fig. 23; Table 17). In general, the changes in rates were similar in direction but much less in extent to those in the lower ileum immediately above the obstruction.

In the absence of obstruction the rate of

absorption of water in the upper ileum was less than in the lower ileum. In the presence of obstruction both parts of ileum were observed to secrete water: the upper ileum to a lesser extent than the lower ileum, adjacent to the obstruction. The marked decrease in insorption and increase in exsorption noted in the lower ileum did not occur in the upper ileum. A similar situation obtained for sodium transport - indeed the upper ileum secreted sodium only after 48 hours of obstruction. The marked increase in potassium secretion, evident in the lower ileum, was not observed more proximally.

(2) MOVEMENT OF WATER AND CATIONS IN ILEUM CAUDAL TO OBSTRUCTION.

The exchange of water and electrolytes across the mucosa of the ileum, distal to the obstruction, was not affected greatly.

(i) Water transport (Fig. 20: Table 18).

The volume of water absorbed by the ileum distal to the obstruction was reduced to less than one-third of its original rate after 60 hours of obstruction. At no time, however, was water secreted by this part of intestine. Since insorption did not vary, the fall in the rate of absorption was caused by a slight rise

in the rate of exsorption.

(ii) Sodium transport (Fig. 21; Table 19).

Likewise the rate of sodium absorption was reduced in the ileum distal to the obstruction. At no time was sodium secretion observed.

The reduction in sodium absorption was caused by a slight fall in insorption and rise in exsorption but these changes in the rates of unidirectional movement were hardly significant.

(iii) Potassium transport (Fig. 22; Table 20).

The rate of secretion of potassium in the ileum distal to the obstruction steadily increased, ultimately becoming twice the rate observed initially. The increased secretion can be ascribed almost entirely to an increased rate of entry of potassium ions into the ileal lumen - after 60 hours, at a rate twice that observed under normal conditions. Insorption of potassium was little affected.

(3) A COMPARISON IN WATER AND CATION MOVEMENT BETWEEN ILEAL SEGMENTS CRANIAL AND CAUDAL TO OBSTRUCTION.

Although some allowance must be made for the slight differences in the rates of ion and water transport between segments of ileum, in obstruction the handling of fluid and electrolytes by the ileum

immediately above the obstruction was profoundly altered compared to the ileum immediately below the obstruction.

As far as the transport of water (Fig. 20; Table 21), and of sodium (Fig. 21; Table 22) are concerned, the ileum above the obstruction ceased to absorb and began to secrete fluid, whereas the ileum on the other side of the obstruction continued to absorb although at a reduced rate. Significant differences in insorption of sodium and water between the two segments were noted early in obstruction whereas differences in the rates of exsorption were observed only after 24 - 36 hours.

Both ileal segments secreted potassium at a greater rate after the obstruction had been formed but at all times the rate of secretion was greater in the cranial segment (Fig. 22; Table 23). The cranial segment originally insorbed potassium at a greater rate than the caudal segment, but this situation was reversed significantly when the obstruction had been present for 12 hours and thereafter. The slightly greater rate of potassium exsorption in the cranial segment became significantly greater than that in the caudal segment after 36 hours.

(4) THE RELATIONSHIP BETWEEN WATER AND CATION MOVEMENT IN OBSTRUCTED BOWEL.

The net cation movement was derived from the algebraic sum of sodium and potassium net movement - where absorption was regarded as positive and secretion as negative. The net cation movement was then plotted against net water movement (Fig. 24).

When cation was absorbed, water was absorbed; when cation was secreted, water was secreted. At no time was water being secreted when cation was absorbed, or vice versa.

In the caudal segment a close correlation ($r = 0.90$) existed between the rates of absorption of water and of cation. For each litre of water absorbed 142 ± 5.1 mEq cation ($n = 42$) were absorbed.

In the segment above the obstruction both water and cation were secreted into the gut, with a close relationship ($r = 0.95$) between their rates. For each litre of water secreted, the obstructed bowel also secreted 162 ± 4.6 mEq cation ($n = 36$).

Unobstructed ileum insorbs from 56 to 77 mEq cation along with each litre of water insorbed (Table 24). This relationship is lost in the segment of ileum cranial to an obstruction when quite high volumes of water (8 ml)

can be insorbed with hardly any cation moving in the same direction (Fig. 25). On the other hand, the correlation between water and sodium insorption remains high (r = 0.9) in the segment caudal to the obstruction.

Unobstructed ileum exsorbs about 40 mEq cation with each litre of water (Table 24). Although the amount of cation exsorbed with each litre of water increased in both segments with the duration of the obstruction, ultimately the fluid entering the lumen of the cranial segment had twice the concentration of cation as that entering the caudal segment (Fig. 26; Table 24).

(5) THE CONCENTRATION OF CATIONS IN THE LUMEN OF THE BOWEL IN OBSTRUCTION.

(a) Sodium (Table 25)

When the test solution was instilled into the unobstructed bowel there was no significant change in the concentration of sodium after ten minutes.

In the presence of obstruction the concentration of sodium rose in the cranial segment and fell in the caudal segment, the changes in both cases being significant.

No relationship was observed between the changes in concentration and the duration of the obstruction.

(b) Potassium (Table 26)

When test solution, containing 3.9 mEq potassium per litre, was instilled into unobstructed bowel, the concentration of potassium increased in both cranial and caudal segments.

When obstruction was present, the concentration of potassium in the test solution rose in both segments, the rise in the caudal segment being significantly greater than the rise in the cranial segment ($t = 9.7$; $P < 0.001$).

The changes in potassium concentration were related neither to the duration of the obstruction nor to the changes in sodium concentration.

III. THE CONCENTRATION OF ELECTROLYTES AND UREA IN THE BLOOD.

In the twelve dogs, before any operative procedures were carried out, the concentrations of sodium and potassium in the serum were found to be 142 ± 0.8 mEq per litre and 4.0 ± 0.1 mEq per litre respectively. The mean concentration of urea at the same time was observed to be 30.5 ± 0.9 mg per 100 ml blood. (The $\pm$ precedes the S.E. of the mean).

The longer the duration of the obstruction, the

higher did the concentrations of potassium and urea become (Fig. 27), significant increases in both being found at 48 and 60 hours. There was a tendency for the serum sodium concentrations to fall but the mean values observed after 60 hours of obstruction were only just outside the normal range.

IV. CONTROL EXPERIMENT.

EFFECT OF PREVIOUS 'SHAM' OPERATION UPON TRANSPORT OF WATER AND CATIONS.

The ileum caudal to the obstruction did not absorb sodium and water as well as normal bowel but potassium secretion doubled. Such changes could be attributed to the previous surgery (to form the obstruction) rather than the local influences of the obstruction itself. To test this hypothesis, and to determine the effect of operations upon the intestinal handling of fluids and electrolytes, a 'sham' operation was performed in three dogs 24, 36 and 48 hours previous to absorption tests in the terminal ileum.

If surgery had been performed previously the rates of absorption of sodium and water were less than in the unoperated animal (Table 27). Within the two-day period of study the fall in absorption of sodium and water was directly related to the interval between the 'sham'

operation and the absorption tests. The reduction in absorption of both water and sodium was produced largely by an increase in the rates of exsorption; a fall in insorption contributed to a lesser extent.

Potassium secretion into the ileum increased after surgery and was almost double its usual rate, 48 hours after a 'sham' operation (Table 27). Increase in exsorption was responsible for this increase in secretion, for the rate at which potassium ions left the ileum was not greatly affected.

The altered rates in water and cation movement after surgery were then compared to the changes in the rates, at corresponding times, observed in the segments of ileum caudal to the obstruction. The close similarity in the changes was striking (Figs. 28, 29 and 30). In addition, in both circumstances the relationships between water and cation movements were similar and the changes in the concentration of electrolyte in the intestinal lumen were almost identical (Table 28).

No significant change in the concentrations of sodium and potassium in the serum, nor of urea in the blood, was observed in these dogs who had undergone a previous 'sham' operation.

DISCUSSION.

Experiments on intestinal obstruction were restricted to 60 hours. During that time the dogs remained well, external fluid losses were small, abdominal distension was not pronounced, and parenteral replacement of fluids was not required. Thereafter vomiting became frequent and distressing, and lost fluids had to be replaced. More prolonged observations therefore were considered unjustified, on humane grounds, and impracticable since the replacement of lost fluids would modify the response to obstruction (Parkkulainen, 1962).

The obstructed ileum shortened to three-quarters of its original length. Such decrease in length has been attributed to contraction of the longitudinal muscle (Sperling and Wangensteen, 1935a). These authors also observed that the obstructed gut became heavier, partly due to oedema, more so due to stasis and congestion in the vessels of the bowel wall. In the present experiments, the distension of the gut above the obstruction compensated for its shortening, so that the area of mucous membrane did not alter appreciably until late in obstruction. The area of gut distal to the obstruction decreased slightly because of a

reduction in its calibre.

Distension of the bowel is an invariable feature of gastrointestinal obstruction. Although the degree of distension may vary greatly (Kader, 1892; Brandenburg, 1940), the extent to which gas and fluid separately contribute to the distension depends mainly on the duration of the obstruction, gaseous accumulation occurring earlier (Cantor and Reynolds, 1957; Welch, 1958). In these experiments fluid accumulation predominated in the later stages of obstruction.

The paucity of changes in the gross and microscopic appearances of obstructed bowel, apart from distension and venous engorgment, has been pointed out by others (Gage and Hosoi, 1935; Sperling, 1938; Parkkulainen, 1962). Only when there was strangulation did these authors observe destruction of the normal architecture of the gut.

TRANSPORT OF WATER AND ELECTROLYTES IN THE ILEUM.

1. In the absence of obstruction.

In the two dogs in whom absorption tests were performed after the ileum had been transected, but before the obstruction had developed, the rates of transport of sodium, potassium and water were similar to those already observed in other acute preparations

(Table 6). In these dogs, the adjacent ileal segments, separated only by the transection, showed a similar capacity to absorb sodium and water, and to secrete potassium.

The unidirectional fluxes of sodium did not differ significantly between the two segments. In the cranial segment, however, the rates of entry and exit of water and of the insorption of potassium were more rapid. Such observations are consistent with the higher flux-rates found in the more cranial parts of the intestine. Despite these slight differences, a comparison of the rates of transport between the segments cranial and caudal to the obstruction seems valid.

The absorption experiments, performed in the dogs which had undergone previously a 'sham' operation, will be discussed subsequently (in the section entitled 'Possible mechanisms of the altered transport of water and electrolytes in obstruction').

2. Ileum cranial to the obstruction.

(a) Adjacent to obstruction.

The brunt of an intestinal obstruction is borne by the bowel immediately above the occlusion. This part of the gut becomes the most distended, its

circulation is the most obviously impaired and it stands the greatest risk of becoming gangrenous and perforating. The results of these experiments show that, in addition, its capacity to handle fluid and electrolytes is the most seriously disturbed.

The ileum above an obstruction ceased to absorb sodium and water: these substances accumulated in the lumen, and, as time passed, the rates of their secretion increased. Potassium, normally secreted by the ileum, was secreted at an even greater rate after the gut had been obstructed.

These changes in net water and electrolyte movement were produced by marked alterations in the two-way exchange of water and cations across the mucosa of the obstructed bowel. These alterations can be described in two phases. First, during the initial 24 hours, the rate of insorption of water, sodium and potassium fell to almost negligible values. Thus, in early obstruction, water, sodium and potassium accumulated in the lumen of the bowel because, although they were still able to enter the bowel at a normal rate, they were unable to leave. Similar changes have been reported by Davenport (1961), who claimed that the rate of exsorption was unaltered in obstruction.

The second phase began 24 to 36 hours after the formation of the obstruction: fluid and electrolytes entered the gut above the obstructing lesion at an increasing rate so that the rates of their secretion were accelerated. After 60 hours, ileum, of surface area 100 cm^2, immediately above the obstruction, was secreting 13 ml of water, 1.88 mEq sodium and 0.09 mEq of potassium every ten minutes.

(b) Upper ileum, cranial to the obstruction.

These rates of secretion in the obstructed lower ileum are considerable. If the entire small intestine responded in a like manner, 1.4 litres of fluid would be lost into the intestinal lumen every hour. (This calculation is based on the assumption that a serosal surface area of 2000 cm^2 would lie above an obstructing lesion in the terminal ileum of the dog). Since these dogs vomited rarely, since intestinal distension was not gross, and since the concentration of electrolytes and urea in the blood changed only moderately, the rest of the small intestine obviously did not share in this increased secretion.

Such behaviour could be anticipated from clinical observation, for, in low ileal obstruction, copious vomiting is not frequently encountered and gross

alteration in the fluid and electrolyte constituents of the body is not a feature (Schnohr, 1934; Aird, 1941).

In three dogs the absorption of water and electrolytes by the bowel at some distance above the obstruction was studied. In the absence of obstruction the upper ileum absorbed sodium and water at rates lower than those of the terminal ileum - the increasing aboral rate of sodium and water absorption has already been described (Part I, Chapter 2). Potassium secretion was similar in both parts of the ileum. When the terminal ileum was obstructed, the upper ileum maintained its normal absorptive activity for a considerable time: sodium was absorbed in the upper ileum even after 36 hours of obstruction, and the increase in potassium secretion was only one third of that found more distally. The rates of insorption in the upper ileum became affected by the obstruction earlier than those of exsorption; even then the fall in the rates of insorption in the upper ileum was not so marked as that in the distal ileum.

It can be speculated that initially only the ileum immediately above the obstruction is affected and fluids and electrolytes accumulate in its lumen. With increasing intra-luminal pressure, the fluid is dispersed in an oral direction until it meets bowel still capable of absorbing.

In this way excessive accumulation of fluids is avoided. Such retrograde spread of intestinal content has been observed through a transparent plastic window sutured into the abdominal wall (Parkkulainen, 1962). Also the absorption of intestinal content at a higher level in obstruction has been suggested by the work of Redfern, Close and Ellison (1961) who described that water and electrolyte depletion in experimental obstruction was greater if an enterostomy was made to allow the intestinal secretions to escape. Where such dispersion is prevented, e.g. in closed loop obstruction, the accumulation of fluid is more rapid.

When obstruction has been present for a longer time, the upper reaches of the gut began to show alterations in their ability to deal with water and electrolytes; and secretion, albeit at a lower rate and occurring later, was observed. As in the lower ileum, insorptive ability was impaired earlier than exsorptive capacity.

3. Ileum caudal to obstruction.

In contrast to these marked alterations in the function of the bowel cranial to the obstruction, the caudal ileum showed only moderate changes in its absorptive and secretory ability. Absorption of sodium

and water was maintained although at a reduced rate; secretion did not occur.

The most striking change observed in the caudal ileum was a two-fold increase in the rate of potassium secretion, entirely due to an increase in the rate at which potassium ions entered the gut. This increase in potassium secretion will be discussed subsequently.

RELATIONSHIP BETWEEN WATER AND CATION MOVEMENT.

In the unobstructed ileum, and in the ileum caudal to the obstruction, a close relationship ($r = 0.9$) existed between the amount of cation and the volume of water absorbed - indeed the theoretical concentration of the absorbed solution was 142 mEq (Na + K) per litre water. Although the concentration of sodium in the luminal solution fell slightly, the total cation concentration was maintained by an increase in the concentration of potassium. The fluids which entered and left the gut were hypotonic, the cation concentration of the insorbed fluid being 70 mEq per litre, and of the exsorbed fluid, 50 mEq per litre. These theoretical concentrations were similar to those found in other preparations (Part II, Chapter 3).

Water, sodium and potassium were secreted into the lumen of the ileum above the obstruction. The

relationship between cation and water secretion was close (r = 0.95). The secreted fluid was slightly hypertonic, 162 mEq cation in each litre of water. As a result the cation concentration within the lumen increased, chiefly due to the increased amount of potassium entering the lumen of the obstructed gut. This preservation of the relationship between cation and water movement when, in disease states, the gut begins to secrete, has been observed by others (Visscher et al., 1944a and b; Code et al., 1960; Nelson et al., 1962). The clinical importance of this observation is that the obstructed gut secretes into its lumen a solution having a cation concentration slightly greater than that of plasma.

In advanced obstruction, the obstructed gut was exsorbing a solution which was almost isotonic, 124 mEq of cation per litre of water.

SERUM ELECTROLYTE CONCENTRATIONS.

The concentration of sodium and potassium in the serum of the dogs with obstruction altered only slightly. A fall in the concentration of sodium, and a rise in that of potassium, can be expected as a result of the metabolic response to surgery (Moore, 1959). In low ileal obstruction, in which marked external losses of

water and salt are unusual, gross changes in serum sodium and potassium concentrations are not found (Aird, 1941). Increased loss of fluid into the gastro-intestinal compartment occurred in these dogs, but, since the fluid lost had a sodium and potassium concentration similar to that of plasma, no marked change in the plasma concentrations need be anticipated in early obstruction. However, the loss of isotonic fluid into the gastro-intestinal tract severely depletes the extracellular compartment. This pre-renal deviation of fluid partly explains the rising blood urea; the increased protein catabolism consequent upon surgical trauma would also have been contributory. This latter factor is obviously not of great importance for little alteration in the urea concentration in the blood was observed in dogs previously subjected to a 'sham' operation.

The changes in body fluids in intestinal obstruction have been reviewed by Cantor and Reynolds (1957) and Welch (1958). Gross disruption in water and electrolyte balance, and acid-base status, is found only in late ileal obstruction. Since such depletions would greatly alter the osmolality of the extracellular fluid, the present experiments were confined to the first 60 hours

of obstruction during which time the water and electrolyte composition of the body fluids would not be greatly altered.

SUMMARY OF THE EFFECT OF OBSTRUCTION UPON THE INTESTINAL TRANSPORT OF WATER AND ELECTROLYTES.

A simple obstruction of the intestine was produced in dogs by transecting the ileum near the ileo-caecal valve. Measurements were made of the movement of water, sodium and potassium into and out of isolated segments of bowel immediately cranial and caudal to the obstruction as well as in segments more distant. The manner in which the absorption and secretion of fluids were disturbed by the obstruction can be described in two phases. During the first 36 hours water and electrolytes accumulated in the lumen of the bowel above the obstruction because the rate at which fluids left the lumen was reduced although they continued to enter at the same rate. After 36 hours the rate of fluid accumulation was accelarated because the speed at which fluid entered the lumen increased while hardly any fluid could leave the bowel. The fluid collecting in the intestinal lumen had a cation composition similar to that of plasma. The rate of secretion into the obstructed bowel was ultimately 13 ml fluid every 10 minutes per 30 cm length of ileum.

The upper reaches of the bowel were not at first affected by the low ileal obstruction. Fluid collecting

in the bowel immediately above the obstruction could therefore be absorbed more proximally. There is good evidence for such retrograde dispersion, which is probably caused by increasing intra-enteric pressure rather than by retrograde peristalsis. Fluid losses would not therefore be great in low ileal obstruction except when retrograde dispersion is prevented, e.g. closed loop obstruction, or when the absorptive ability of the upper small intestine becomes impaired.

The gut below the obstruction showed less marked changes in water and electrolyte absorption. The absorption of water and sodium was reduced and the secretion of potassium enhanced. Almost identical changes were observed in unobstructed bowel of dogs after a 'sham' operation. Changes in the gut caudal to the obstruction may be caused less by local factors than the response of the intestine to the general effects of trauma.

POSSIBLE MECHANISMS OF THE ALTERED INTESTINAL TRANSPORT OF WATER AND ELECTROLYTES IN OBSTRUCTION.

These experiments have characterised the alterations in the handling of water and electrolytes by the bowel when it is obstructed. Mere occlusion of the intestinal lumen will not *per se* affect the exchange of fluids across the mucosa. However, such an occlusion sets in motion a train of events which, individually, can influence the absorption and secretion of fluids - the gut becomes distended because of an increase in intra-enteric pressure, intestinal motility and vascularity are altered, etc.

The relationship between these events, i.e., the effects of obstruction upon the structure and function of the bowel, and the alterations in water and electrolyte transport will now be discussed, with a view to defining the possible causes of the changes in absorption and secretion which have been observed.

LOCAL FACTORS.

Since the disturbances in intestinal transport of fluid and electrolytes are particularly marked in that part of the bowel immediately above the obstruction, the causes of such disorders must be chiefly local.

1. Increased intra-enteric pressure.

In small bowel obstruction, the intra-enteric pressure may reach 8 cm water, in contrast to a normal intra-luminal pressure of 2 to 4 cm (Owings et al., 1928; Sperling, Paine and Wangensteen, 1935). Higher pressures have been recorded in obstructed large bowel (Wangensteen, 1947), in closed loop obstruction (Burget et al., 1930) but, only rarely, in small gut obstruction (Stone and Firor, 1924).

Such increase in the pressure within the lumen of the obstructed bowel, whether it is produced by gas or fluid, produces a number of changes, each of which can influence fluid transfer.

(a) Both in vitro and in vivo experiments have shown that, within limits, increased pressure within the bowel enhances the absorption of water, either because the hydrostatic pressure at one end of the diffusion gradient is increased, or because the mucosa is unfolded, so increasing the surface area (Goldschmidt, 1921). However, the pressures employed in those physiological experiments were not great. Others (Elman and Aird, 1935; Sperling, 1938) have described a critical intra-luminal pressure of 40 to 50 cm saline above which absorption of water ceases, presumably

because of interference with the mucosal blood flow (Dragstedt, Lang and Millet, 1929). Such high pressures are rarely seen in obstruction of the small bowel. However, it has been suggested that the continuous application of even small pressures may, over a period of time, produce gross structural changes (Sperling, 1938). Certainly distension of a segment of small bowel with a balloon will evoke secretion (Herrin and Meek, 1933).

(b) Some workers (Molnar, 1909; Herrin and Meek, 1933; Antoncic and Lawson, 1941) have suggested that distension may evoke secretion by increasing the number of afferent nerve impulses. Much of this work is unconfirmed and contradictory (Fine, Rosenfeld and Gendel, 1939). In any case, water and electrolyte absorption does not seem greatly to be affected by nervous influences.

(c) Distension does not appear to increase the surface area available for absorption since the increase in circumference is compensated for by shortening.

2. Blood Flow.

The obstructed bowel becomes greatly congested (Elman and Hartman, 1931; Sperling, 1938); indeed the sequestration of blood within its walls is almost

entirely responsible for its increase in weight (Sperling and Wangensteen, 1935a). The blood collects within distended vessels for interstitial haemorrhage is uncommon in early obstruction and the veins in the intestinal villi become greatly dilated (Derblom, Johansson and Nylander, 1963b).

The effect of mesenteric vein congestion upon intestinal absorption has not been completely studied. Wells (1940) observed that, under control conditions, the volume of an isotonic saline solution diminished when it was placed into an isolated loop of bowel; but, when the mesentery was compressed, the absorption of this solution diminished and, with a rising pressure within the mesenteric vein, absorption ceased; ultimately, the volume of fluid within the intestine increased. These observations were confined to the net transfer of water. The absorption and secretion of electrolytes were not studied; nor were the exchanges of water and electrolytes across the intestinal mucosa measured. Since the increase in venous pressure was produced by compressing the mesentery between two metal plates, the accompanying obstruction of the arterial and lymphatic flows may have contributed partly to the changes that Wells observed.

There would thus seem to be a place for studying further the effect of mesenteric venous congestion upon the intestinal transport of water and electrolytes. Such an investigation would not only assess the contribution of raised venous pressure to the disturbed absorptive and secretory pattern in the obstructed bowel, but also define, *in vivo*, the influence of raised hydrostatic pressure on the serosal side of the intestinal mucous membrane. Recent *in vitro* experiments (Wilson, 1956b) have demonstrated that the transfer of water from the mucosal to the serosal side of everted intestine can be brought to a halt by the application of pressure to the serosal surface.

The results of a separate study of the effect of increased venous pressure upon the intestinal sorption of water and electrolytes are given in Part IV of this thesis.

3. *Motility*.

The increased activity of the bowel to overcome an obstruction is well known. However, there is considerable doubt concerning the effects of obstruction upon the motility of that part of the bowel immediately above the obstruction. Paralysis of the obstructed segment *rapidly* supervening on a brief initial period

of increased activity has been described by some (Kader, 1892; Hotz, 1909; Masuda, 1932). Others have considered that hyper-motility was more usual (Antoncic and Lawson, 1941). The current view (Wangensteen, 1947; Cantor and Reynolds, 1957) is that the increased small bowel activity that occurs early in mechanical obstruction gradually develops into atonic ileus depending on the type and nature of the obstruction. Antiperistalsis does not seem to occur in the obstructed bowel (Brandenburg, 1940; Parkkulainen, 1962).

The position is therefore confusing. Not only is the type of intestinal motility in obstruction uncertain, but also the effect of intestinal motility upon the intestinal transport of water and electrolytes is in doubt. The major impediment to further progress is the difficulty in producing changes in motility alone without affecting other factors which in themselves influence absorption, e.g. surface area, mucosal blood flow, cell permeability.

4. Toxic factors (Winfield and Mersheimer, 1958).

The role of toxins and endotoxins in intestinal obstruction is obscure. The mortality of intestinal obstruction was formerly attributed to toxins formed in

the obstructed bowel. In the absence of strangulation, toxic factors are probably not of great importance. The content of obstructed intestine may be instilled into the gut of a normal dog without serious effect. Also the transfusion into normal dogs of blood taken from veins draining obstructed bowel will not cause toxic effects (Carlson, Lynch and Wangensteen, 1930). In the presence of strangulation, however, are elaborated toxins to which the gut may become abnormally permeable (Barnett, 1960).

It is conceivable that in simple intestinal obstruction the intestinal mucosa may be damaged by locally-produced toxins so that its absorptive capacity is impaired. Metabolic poisons, it will be recalled, inhibit the active transport of sodium chloride. No experimental work in this field has been reported.

GENERAL FACTORS

The ileum below the obstruction secreted more potassium, and absorbed less sodium and water, than normally. Similar changes in water and electrolyte movement were observed in dogs which had undergone a 'sham' operation previously and whose intestine was not obstructed. The common factor in both these experiments was injury which seemed to influence the intestinal

handling of water and electrolytes. It may be speculated that the bowel responds to injury in a manner similar to the kidney, by conserving sodium and water and by losing potassium.

The fact that intestinal obstruction itself must constitute a powerful stress to the body cannot be ignored. It is conceivable that the alterations in absorption and secretion, which are produced largely by the local factors already considered, may be modified by the systemic response to the obstruction.

1. The trauma of intestinal obstruction

Like any other form of trauma, obstruction may be expected to elicit a neuro-endocrine response, in which various biochemical and physiological adjustments occur as the consequence of, or at least accompanied by, alterations in the level of activity of the endocrine glands. The nature of these metabolic changes and the evidence that the ductless glands participate have been presented by Moore (1959) and will not be further considered. The adrenal cortex and the posterior lobe of the pituitary gland are particularly concerned in the alterations in water and electrolyte metabolism after injury. The hormones elaborated by these glands may

affect the transport of water and electrolytes across the intestinal mucosa.

The increased secretion of antidiuretic hormone in response to injury affects the metabolism of water (Ariel and Miller, 1950; Le Quesne and Lewis, 1953). In most tissues the neurohypophysial hormones stimulate water transport (Diamond, 1962), and in the gut, the absorption of isotonic saline is enhanced following the administration of pitressin (Blickenstaff, 1954c). A priori then, the impaired absorption of water in intestinal obstruction cannot readily be attributed to the secretions of the posterior lobe of the pituitary gland.

There is little doubt that the adrenal cortex exhibits increased activity after injury, although its actual role - direct or permissive - in mediating the changes in electrolyte metabolism is still undefined. Increased production of the salt-active hormone, aldosterone, has been described (Llaurado, 1955; Zimmerman et al., 1956). The reduction in the absorption of sodium and the increase in the secretion of potassium, observed in the ileum below the obstruction and in the intestine of dogs subjected to a 'sham' operation, are closely similar to the changes found in the intestine in

states of increased adrenal-cortical activity (Part I, Chapter 3). Most previous studies, however, have been concerned with the electrolyte composition of the intestinal content and the only recent work in which the rates of exchange of electrolytes across the intestinal mucosa have been measured, following the administration of the adrenal-cortical hormones, is that of Berger et al., (1960). These workers, who used DOC, found that electrolyte transport in the small bowel was unaffected. However, there would seem to be good grounds, both from the present studies and from the literature, to suggest that the small intestine can indeed respond to adrenal-cortical hormones. The role of the adrenal cortex in influencing the intestinal transport of electrolytes in both small and large intestines was therefore re-examined, using the more powerful, naturally-occurring mineral-corticoid, aldosterone, which has recently been synthetized (Schmidlin et al., 1955). The results of this part of the study are reported in Part V of the thesis.

2. Plasma osmolality.

Loss of sodium in obstruction, particularly if fluid replacement has been mainly with dextrose solutions, not infrequently leads to reduction in the osmotic

pressure of the plasma. Such hypotonicity, often aggravated by the entry, into the extra-cellular compartment, of sodium-free water from the cells, is frequently observed in intestinal obstruction, particularly when the obstruction is placed at a high level or has been present for some time (Moore, 1959). The plasma concentration of sodium, which largely accounts for the osmotic pressure, is not greatly altered in low ileal obstruction (Aird, 1941).

Hypotonicity of the plasma may ultimately discourage water from leaving the intestinal lumen in which it will accumulate. Lind et al., (1959) showed that the absorption of water was hindered by reduction of the osmotic pressure of plasma.

CONCLUSIONS.

The altered capacity of the obstructed bowel to absorb and secrete water and electrolytes has been attributed to a number of factors. The main changes occur in the bowel immediately above the obstruction so that local factors would seem to be the most responsible. Increase in the pressure within the lumen of the bowel, produced by the accumulation of fluid and gas, will ultimately hinder the absorption of fluid from the gut, probably on account of a reduction in mucosal blood flow.

Considerable experimental work has already been done on the effect of increase in intra-enteric pressure and of distension upon the absorption of fluids, so that further study of this aspect would seem to be unnecessary.

Distension of the bowel impedes the intra-mural venous circulation. There is some evidence that the resultant congestion impairs fluid and electrolyte absorption. The part played by altered motility of the gut in affecting the transport of fluid and electrolytes is not clear; but the problem is a difficult one to study for the reasons which have been given.

The systemic effects of, and the metabolic response to, obstruction may modify the fluid losses into the obstructed bowel. Some of these factors operate only when the obstruction produces such severe water and electrolyte loss that the osmolality of the plasma is reduced. However, obstruction must constitute a major stress to the body and there is some evidence to suggest that the response to this stress, mediated through the adrenal cortex, will modify intestinal absorption.

The effect of some of the mechanisms responsible for the altered intestinal transport of water and

electrolytes in obstruction can be deduced from the literature. The role, however, of two of them would seem worthy of further study because, in addition, their influence upon the intestinal handling of water and electrolytes is yet not defined - namely, mesenteric venous pressure and the adrenal mineral corticoids.

PART IV

THE EFFECT OF MESENTERIC VENOUS CONGESTION UPON THE INTESTINAL TRANSPORT OF WATER, SODIUM AND POTASSIUM

THE EFFECT OF MESENTERIC VENOUS CONGESTION UPON THE INTESTINAL TRANSPORT OF WATER, SODIUM AND POTASSIUM.

Experiments were performed to define the effect of increase in pressure within the mesenteric veins upon the absorption and secretion of water, sodium and potassium, and, in particular, to observe the alterations in the unidirectional movements of these substances.

In these studies, acute experiments were employed because of the difficulty in producing chronic portal hypertension in dogs (Wiles, Schenk and Lindenberg, 1952).

MATERIALS AND METHODS.

Surgical Procedure.

All observations were made upon the acute preparation for studying intestinal absorption (Part II, Chapter 1). After the absorption tube (Fig. 2) had been placed in the terminal ileum, an inflatable rubber cuff (Fig. 31) was placed round the portal vein. The pancreatico-duodenal and pyloric veins were ligated to place the cuff in the desired position. The uninflated cuff did not narrow the vein. In one dog (no. 12) no cuff was placed round the portal vein.

A fine polyethylene catheter (internal diameter, 1.0 mm) was introduced into the main superior mesenteric trunk through a venous radicle of a loop of small bowel adjacent to that in which absorption was to be measured. The open tip of a second catheter was placed beside the superior mesenteric vein to record intra-abdominal pressure. All tubes and catheters were brought out through the incision, care being taken not to occlude them in closing the wound.

The tube from the inflatable cuff was connected outside the abdomen by a three-way stopcock to a strain-gauge manometer (Statham, no. P23 De) and to an air-compressing cylinder by means of which measured pressures of air were delivered to the cuff. The catheter, whose open tip lay free in the abdominal cavity, and the one in the mesenteric vein, were attached to similar manometers. Systemic blood pressure was measured by the same type of manometer connected to a catheter inserted into the abdominal aorta via the femoral artery. All catheters were filled with heparinised saline. Respiratory movements were recorded by another such manometer connected to a pneumatic stethograph placed round the chest of the dog. The pressures detected by the manometers were recorded

by galvanometers which either reflected a beam of light on to moving photographic film or activated pens writing on a moving strip of paper (Fig. 32). The zero position for the manometer measuring mesenteric vein pressure was adjusted to the level of the vein as determined at operation. All other manometers were placed at the same level. A diagram illustrating the arrangements for these series of experiments is shown in Figure 33. Body temperature was maintained between 37 and 39°C by adequate insulation.

Absorption Experiments.

After completion of the surgical procedure, which lasted on average 40 minutes, the isolated segment was rinsed with Tyrode's solution until the returning fluid was clear. After 30 minutes during which the bowel was undisturbed, test solution was instilled into the loop for 10 minutes in the manner previously described. At 10 minutes as much as possible of the intestinal content was withdrawn, and the segment then rinsed with non-radioactive solution.

At the outset of each experiment at least two tests of absorption were performed with an interval of 30 minutes between tests. The cuff surrounding the portal vein was inflated 15 minutes after the second

test and this was regarded as zero time in the study. All subsequent tests of absorption were performed at 15 minutes, 1, 2, 4, 6, and 8 hours after this zero time.

In twelve dogs the sorption of sodium and water was studied; the sorption of potassium was investigated in another five dogs. This step was necessitated by the lack of equipment at that time to permit differentiation between radioactive isotopes.

(i) Sorption of sodium and water.

In five dogs the mesenteric vein pressure was increased by inflating the cuff and maintained at as constant a level as possible during the 8-hour period of observation (Group I). In other four, the venous pressure was raised and lowered intermittently during the 8-hour period with tests of absorption being performed during and after each increase in venous pressure (Group II). Experiments in a further three dogs provided control information (Group III) - in two the cuff around the portal vein was not inflated and in one (no. 12) no cuff was placed around the vein.

The test solution in these experiments was modified Tyrode's solution containing ^{22}Na (5.4 μc per litre test solution) and D_2O (0.8 ml per litre solution).

(ii) Sorption of potassium.

In three dogs (Group I) the venous pressure was increased to the desired level at which it was maintained for 8 hours. In the remaining two (Group III), the cuff was placed in position but not inflated. The effect of intermittent increase in venous pressure (Croup II) was not investigated.

The test solution contained ^{42}K (4 μc in each litre of Tyrode's solution).

The activities of ^{22}Na and of ^{42}K in solutions were counted in a well-type scintillation counter and in a liquid Geiger-Muller counter respectively. All tubes for counting samples containing ^{22}Na were checked initially for radioactivity. The concentration of deuterium oxide in the test solution was determined by mass spectrometry. Sodium and potassium concentrations were estimated by flame photometry. The details of the various estimations and of the calculations of the rates of movement have already been given.

All dogs were killed at the end of the experiment. At autopsy the serosal area of the isolated segment was

measured, and the following additional observations were made:

(a) the presence of peritonitis,

(b) the state of the mucous membrane,

(c) the position of the tips of the catheters.

RESULTS.

MESENTERIC VEIN PRESSURE.

The pressures within the mesenteric venous trunk with the cuff uninflated were 10 to 15 cm saline (mean, 13 cm saline). Inflation of the cuff around the portal vein was quickly followed by a rise in mesenteric vein pressure, which could be maintained at any desired level (Fig. 32). The central aortic pressure, intra-abdominal pressure, and the depth and amplitude of the respiratory cycle were unaffected.

If the pressure in the mesenteric vein was increased to more than 40 cm saline, the arterial blood pressure fell and the contents of the isolated ileal loop became blood-stained. Complete occlusion of the portal vein produced pressures as high as 70 cm saline but haemorrhagic infarction of the intestine with death of the animal quickly followed.

No tests of absorption were made during complete portal occlusion or at pressures greater than 40 cm saline.

MORPHOLOGY OF SEGMENT.

If the mesenteric vein pressure did not exceed 40 cm saline, the fluid within the lumen of the isolated segment was clear and free from blood. The mucosa appeared normal and the bowel wall was not thickened.

On microscopic examination (Fig. 34), the most obvious feature was dilatation of the blood vessels, especially the veins which had become greatly congested with blood. Round-cell infiltration and oedema of the submucosa and of the cores of the villi were occasionally observed. The mucosa was usually intact and histologically normal.

RATES OF SORPTION OF WATER, SODIUM, AND POTASSIUM.

Original rates (before inflation of cuff).

The rates of movement in each dog, calculated from the first two tests, served as a baseline to which all subsequent rates in the dog were referred; these subsequent rates were expressed as an increase above, or decrease below, the original two rates. This method of expression of results was required because of the variability in rates among the dogs. Since the rates obtained from the first and second tests in each dog did not differ significantly or in a constant direction from

one another, the results of the two initial tests were combined and the mean rates obtained were used as the baseline (Tables 29 and 30).

The ileum absorbed sodium and water, and secreted potassium. The rates of unidirectional movement of sodium, water and potassium in these dogs have already been described in detail in the section dealing with the normal dog (Part II, Chapter 3) and will not be discussed further.

Changes in sorption without alteration in mesenteric vein pressure (Group III).

The rates of movement of water and cations altered during the course of control experiments in which the cuff round the portal vein was not inflated.

In three dogs the rates of water absorption decreased to 40 per cent of their original value within the first 4 hours of the experiment and remained at this level thereafter (Fig. 35). At no time was secretion of water observed. This decrease in absorption was brought about largely by a fall in the rate of water insorption. The rates of water exsorption varied in both directions during the course of a control experiment.

In the same three dogs the rates of sodium absorption fell, particularly in the initial 4 hours, to the same extent as those of water absorption, and levelled

off thereafter (Fig. 36). Sodium was not secreted at any time. The rates of sodium insorption and exsorption during the first hour were sometimes greater and sometimes less than the original baseline rates. Thereafter the rates of insorption decreased and those of exsorption increased. Within 4 hours the rate of insorption was 20 per cent less than the original rates and for the remainder of the 8-hour period remained more or less at this level. The changes in exsorption of sodium were greater and more variable. After 2 hours the rates were increased to between 17 and 40 per cent of their original values and remained elevated within this range subsequently.

In two other control dogs, in which the cuff was not inflated, the rate of potassium secretion increased steadily to twice its original value after 6 and 8 hours (Fig. 37). These changes in net movement were produced by a fall in the rate of insorption and a rise in that of exsorption to 20 - 30 per cent of their original values.

Continuous increase in mesenteric vein pressure (Group I).

During prolonged elevation of mesenteric vein pressure, the rate of water absorption was greatly diminished and, in three out of the five dogs, water was

secreted into the bowel (Fig. 38). The fall in water absorption was greatest after 4 hours of increased venous pressure and remained depressed for the rest of the experiment. There was no relation between the increase in venous pressure and the diminution in absorption. Despite these marked changes in net water movement, the unidirectional fluxes of water were little affected by the increase in mesenteric vein pressure, the majority of the changes being within the range of values obtained during control tests when the venous pressure was not altered (Fig. 38).

The absorption of sodium was also markedly reduced with elevation of the mesenteric vein pressure, and, in four out of five dogs, sodium was secreted into the ileal lumen (Fig. 39). The change in sodium net movement was greatest after 4 hours of continuous increase in venous pressure. There was no strict relationship between the changes in venous pressure and in the absorption of sodium. The reduction in net movement of sodium was brought about largely by an increase in sodium exsorption, for, in every instance in which the mesenteric vein pressure was increased by more than 5 cm saline, the rate at which sodium ions entered the lumen was markedly increased. The rate at which

sodium ions entered the body (insorption) was not significantly affected by alterations in mesenteric vein pressure.

Potassium was secreted into the ileal lumen at almost four times its original rate when the pressure within the mesenteric vein was increased (Fig. 40). The greatest change in the rate of potassium secretion occurred within the first four hours, and was more than double the change observed in control animals. The rate of potassium insorption was little affected by increase in mesenteric vein pressure, and the alterations in secretion were brought about entirely by an increase in the rate of exsorption.

Intermittent increase in mesenteric vein pressure (Group II).

The pressure within the mesenteric vein was raised and lowered intermittently during experiments in four dogs. The changes in the rates of absorption and of unidirectional fluxes of sodium and water were in the same direction as those observed in experiments in which the pressure was elevated continuously for long periods. The change in the rate of sodium movement in a typical study (dog no. 9) is shown in Figure 41. These experiments showed that return of the mesenteric vein

pressure to control, or near control, levels did not result in a return in the rates of sodium movement to control levels. Increase in the venous pressure for periods as short as 15 minutes produced changes in the rate of sodium exsorption from which recovery did not occur during the hour or two following. Intermittent increase in mesenteric vein pressure did not change the rates of water movement to any significant extent.

Ratio of moving sodium to moving water.

The ratio of insorbed sodium to insorbed water remained relatively constant throughout all the tests at all pressures (Group I and Group III dogs), the ratio being 70.4 mEq per litre of water ($\pm$ 1.64 standard error, n = 57). The close relationship between water and sodium insorption is illustrated in Figure 42.

In contrast, the ratio of exsorbed sodium to exsorbed water did not remain constant. In control tests, in which the mesenteric vein pressure was not increased, the ratio increased from an initial value of 45 to a final one of 60 mEq per litre. In tests in which the venous pressure was elevated, the ratio increased to between 60 and 90 mEq per litre, the final value of the ratio being directly related to the increase in pressure (Fig. 43).

DISCUSSION.

These experiments confirm the earlier work of Wells (1940), who found that the absorption of water from isotonic saline solution (as evidenced by a decrease in the volume of intestinal content) was reduced when the pressure within the mesenteric vein was increased. The present study also shows that, in these circumstances, the absorption of sodium ions is diminished and the secretion of potassium greatly enhanced. Wells described that "absorption and secretion forces" balance one another at pressures varying from 8 to 40 cm saline and that, beyond the point of balance, secretion (that is, increase in the volume of intestinal content) occurred. In these studies both water and sodium were secreted when the mesenteric vein pressure was increased by more than 9 cm saline. In both studies, bleeding into the lumen of the bowel was observed at mesenteric venous pressures above 40 cm saline.

Wells found that the effects of venous congestion were reversible. He reported that, within a few minutes of release of mesenteric compression, the intestine resumed absorption of fluid at precisely the same rate as

that obtained before congestion. Such rapid recovery was not found in the present experiments even after short periods of mesenteric vein compression. To an extent this lack of agreement may be related to the differences in experimental technique - in particular, the fact that Wells compressed all the structures within the leaves of the mesentery in contrast to congestion of the veins alone in the present study.

An additional feature of the present study is the measurement of the unidirectional movements of water, sodium and potassium across the intestinal mucosa. The marked changes in the net movement of sodium and potassium were clearly produced by increase in the rates at which these ions entered the intestinal lumen (exsorption). Insorption of both was unaffected. These results indicate a considerable degree of independence of the processes of insorption and exsorption of electrolytes, and suggest that the systems for transport in each direction may differ since movement in one direction (into the lumen) was clearly accelerated by the vis a tergo, but movement in the opposite direction, into the body, continued unimpeded by a steepening of the hydrostatic gradient. Such a concept has recently received support from the work of Schultz and Zalusky

(1964) who, using the isolated ileum of the rabbit, demonstrated that the exsorption of sodium can be attributed to passive diffusion while movement in the opposite direction required active transport of the sodium ions.

Using an in vitro preparation Wilson (1956b) found that the application of a hydrostatic pressure to the serosal surface of the everted intestine brought to a halt the absorption of water, and subsequently water passed from the serosal to the mucosal sides of the intestinal mucosa.

The increase in the rate of exsorption is probably not directly related to the venous pressure. The rise in the rate of exsorption may take an hour to become evident and up to 4 hours to be maximal despite immediate increase in venous pressure. If the acceleration in rate were merely due to the application of a hydrostatic force, then the changes in rates should be observed immediately and, of course, the rate should revert to normal when the increase in pressure is removed. The likelihood is that the mesenteric vein congestion brings about certain changes in the mucosa and in the transport mechanisms, which take an hour or so to develop, and which are not immediately reversible.

Although the net movements of water and sodium responded in a like manner to the increase in venous pressure - reduction of absorption, then conversion to secretion - the changes in unidirectional fluxes did not correspond. There was a marked increase in sodium exsorption compared to water exsorption so that relatively more sodium entered the bowel when the mesenteric venous pressure was raised.

A feature requiring explanation is the marked changes in the net movement of water with mesenteric venous congestion, even although the unidirectional fluxes of water remained within the range observed in control dogs. Net movement, which proceeds at a relatively slow rate, is composed of two opposing, faster-flowing streams of insorption and exsorption. Hence, a slight change in the rate at which water is travelling in one direction will produce a larger proportional change in the rate of absorption or secretion. For example, if a segment of ileum which is insorbing at a rate of 20 ml per 10 minutes increases the rate of insorption to 22 ml per 10 minutes, the change in rate will be only 10 per cent. However, if the rate of absorption was originally 5 ml per 10 minutes, and, if exsorption did not alter, the new rate of absorption

would be 7 ml per 10 minutes, an increase of 40 per cent. Obviously, in this way, the body can vary considerably the net amount of water and electrolyte absorbed from or secreted into the intestine merely by adjusting slightly the rates at which it exchanges those substances across the intestinal mucosa.

The control or resting mesenteric venous pressures, before inflation of the cuff, were higher than those reported by Volwiler, Grindlay and Bollman, (1950) and Hoffbauer, Bollman and Grindlay, (1950) in intact and unanaesthetized dogs. Others (Wiggers, Opdyke and Johnson, 1946) have noted that the splanchnic venous pressure is higher in anaesthetized dogs particularly after operation.

In control dogs in whom the pressure within the mesenteric vein was not changed, the net movements of both electrolytes and water were altered. The rates of absorption of water and sodium were reduced and that of potassium secretion increased. The placement of the cuff round the portal vein did not seem to be responsible for the changes in net movement because similar changes were observed in one dog in whom a cuff was not put in position. It is difficult to escape the conclusion that these changes in intestinal absorption and secretion in

the control dogs were brought about by the operation.

In this study the effect of surgery has not been separately evaluated, but it will be recalled that, in the studies on intestinal obstruction, similar changes affecting particularly potassium transport were observed in dogs which had undergone a 'sham' operation.

Increase in the pressure within the mesenteric veins, with splanchnic congestion, can therefore profoundly alter the intestinal handling of water and electrolytes, leading to their accumulation in the lumen of the bowel. There is ample evidence that such venous congestion occurs in intestinal obstruction. That such congestion contributes to the increased secretion of fluids found in obstruction seems a reasonable assumption.

SUMMARY AND CONCLUSIONS.

The effect of increased mesenteric vein pressure upon the ileal transport of water, sodium and potassium was determined in acute studies in anaesthetized dogs. Mesenteric vein pressure was controlled by an inflatable cuff round the portal vein.

With the cuff in position but not inflated, the absorption of water and sodium was reduced and the secretion of potassium increased. When the pressure within the mesenteric veins was increased, water and sodium absorption ceased, and these substances were then secreted into the ileum. The changes in net sodium movement were produced by an increase in exsorption. Neither the insorption of sodium nor the insorption and exsorption of water was affected by the increase in mesenteric vein pressure. Because more potassium ions entered the ileal lumen, when the venous pressure was elevated, the rate of potassium secretion was increased three-fold.

These results show that mesenteric venous congestion, which is a feature of many forms of intestinal obstruction, can partly be responsible for the increasing secretion of water and cations observed in obstruction.

PART V

THE ACTION OF ALDOSTERONE UPON THE INTESTINAL TRANSPORT OF WATER, SODIUM AND POTASSIUM

THE ACTION OF ALDOSTERONE UPON THE INTESTINAL TRANSPORT OF WATER, SODIUM AND POTASSIUM IN THE DOG AND IN MAN.

In both previous studies (Part III and IV), certain changes in the intestinal handling of water and electrolytes were observed in control animals. The absorption of sodium and water was reduced, and the secretion of potassium increased. All these control experiments were preceded by a surgical operation to prepare the animal. It is possible that the intestine shares in the general metabolic response to surgery. In such a response, the adrenal cortex has an important role. Evidence, supporting this hypothesis, is that the alterations in absorption and secretion after trauma are similar to those which have been observed in states of increased adrenal-cortical activity. However, most observations on the influence of the adrenal cortex upon the bowel have been confined to estimations of the concentrations of electrolytes in the intestinal lumen or in the faeces. Apart from the work of Berger et al. (1960) there have been no recent studies on the effect of mineral-corticoids upon the exchange of fluid and electrolytes across the intestinal mucosa.

Such a study was undertaken for the following reasons:-

(a) Berger et al. found that mineral corticoids had no effect upon the small intestine, despite the evidence in the literature to the contrary.

(b) The natural hormone, aldosterone, is now available. Berger and his colleagues used deoxycorticosterone (DOC) which may not be a secretory product of the adrenal cortex (Kruhøffer et al., 1960).

The experimental work will be described in two parts:-

(A) The action of aldosterone, given intravenously, upon the transport of water, sodium and potassium, into and out of isolated segments of intestine, was investigated in dogs and in two patients. In the experiments in dogs, the blocking action of spironolactone on the intestinal effect of aldosterone was also assessed.

.(B) The exchange of water, sodium and potassium across the mucosa of the intact human colon was determined in four normal subjects, and then compared to that in a patient with primary hyperaldosteronism, before and after the removal of the tumour in the adrenal cortex.

(A) THE ACTION OF ALDOSTERONE UPON ISOLATED SEGMENTS OF INTESTINE.

METHODS.

DOGS.

Five healthy female mongrels, weighing 8 - 15 kg, and freed from intestinal parasites, were trained to lie quietly, without force or admonition, for periods of up to 8 hours. In two dogs, a Thiry-Vella fistula was fashioned from a length of ileum to provide a serosal surface area of 100 cm^2. In the other three, a Thiry-Vella fistula of colon of similar dimensions was prepared. Experiments were begun three weeks after the formation of the fistula. Before an experiment, the dog was fasted for at least 12 hours.

The details of the preparation and care of the Thiry-Vella fistulas are given in Part II, Chapter 1.

EXPERIMENTAL PROCEDURE.

(a) Control experiments.

Each experiment consisted of a series of absorption tests, the first at 9.00 a.m. and the last at about 5.00 p.m. All experiments were carried out at the same time of the day to minimise any variation due to diurnal

rhythm in electrolyte transport.

At the commencement of an experiment, the urinary bladder was emptied via a urethral catheter; thereafter urine was collected hourly. The Thiry-Vella fistula was irrigated with Tyrode's solution until the returning fluid was clear. Thirty minutes later, a series of 10-minute absorption tests were carried out allowing at least 30 minutes between each test. At the end of the second test, an intravenous infusion of 5 per cent (w/v) dextrose was set up and continued at a rate of 40 ml per hour. Absorption tests were then performed at 1, 2, $2\frac{3}{4}$, $3\frac{1}{2}$, 4 and 5 hours after the beginning of the dextrose infusion.

Experiments performed in this way acted as <u>controls</u>, with which other experiments, in which aldosterone and/or spironolactone were given, could be compared. Two such control experiments were performed in each dog except one (no. 34) in which a single control experiment was undertaken. A total of 70 control tests was carried out.

(b) <u>Aldosterone experiments</u>.

Three types of experiments were performed, similar to the control experiments described above, except that

aldosterone in aqueous solution (Aldocorten, CIBA) was administered:-

(i) Aldosterone infusion (high dose):- After the second of the initial two tests, 250 µg aldosterone were injected intravenously and a further 250 µg were added to the dextrose solution and delivered to the dog at a rate of 1 µg per minute for the remainder of the experiment. Two such experiments were undertaken in each dog; 69 absorption tests were performed during the infusion of aldosterone in high dosage.

(ii) Aldosterone infusion (low dose):- Aldosterone, added to the dextrose solution, was infused intravenously at 8 µg per hour after the second of the initial two tests. No preliminary 'boosting' dose of aldosterone was given. One experiment of this type was performed upon each dog; 24 absorption tests were carried out during the infusion of aldosterone in low dosage.

(iii) Injection of aldosterone:- 500 µg aldosterone were injected directly into a vein, over a period of 5 minutes, after the dextrose infusion had been established. Only three experiments of this type were performed, two upon a dog with an ileal fistula, and

one in a dog with a colonic fistula.

(c) Spironolactone experiments.

Three series of experiments were performed, similar to (b) (i) and (b) (ii) above and to the control experiments (a), except that 100 mg spironolactone SC9420 (Aldactone, Searle,) were given by mouth three hours beforehand at 6.00 a.m.

These experiments were designated:-

(i) aldosterone infusion (high dose) + spironolactone. Two experiments were performed in this way.

(ii) aldosterone infusion (low dose) + spironolactone. Four experiments of this type were carried out.

(iii) spironolactone control. Three such experiments were undertaken.

MAN.

The intestinal transport of sodium and potassium was studied in two patients with the colon isolated for several weeks from the rest of the gastro-intestinal tract. In each patient, a carcinoma of the mid-third of oesophagus had been resected and an isolated segment of colon had been placed in the anterior mediastinum, in

preparation for later anastomosis to the cervical oesophagus and the stomach.

Since both ends of the colon opened on to the skin surface, these patients possessed, in effect, a Thiry-Vella fistula. In each patient, two 10-minute absorption tests were performed before and during the infusion of aldosterone. 250 µg aldosterone were given intravenously and thereafter an infusion continued at a rate of 1 µg per minute. The technique of study in the patients was identical to that in the dogs, except that 50 ml test solution were instilled.

ESTIMATIONS

The details of the absorption tests have already been described (Part II, Chapter I). Briefly, each test involved the instillation into the fistula of 25 ml Tyrode's solution containing radioactive sodium (^{24}Na-2 µc/L), radioactive potassium (^{42}K-4 µc/L), and, in most cases, deuterium oxide (1 per cent v/v). After exactly 10 minutes, as much as possible of the fluid within the gut was withdrawn, and the segment rinsed with non-radioactive Tyrode's solution.

The concentrations of sodium and potassium in the test solution, and in the urine, were estimated by flame

photometry. The activities of ^{24}Na and ^{42}K in the test solution and the rinse were determined by differential counting in beta and gamma counters. Deuterium oxide concentration was measured by infra-red spectrophotometry.

RESULTS.

DOG.

(a) ALDOSTERONE EXPERIMENTS.

(i) INFUSION OF ALDOSTERONE (HIGH DOSE).

The action of a continuous infusion of aldosterone upon the intestine is best appreciated by regarding the results of a single experiment (Figs. 44 and 45). In both ileum and colon, the most obvious effect was an increase in the rate at which potassium ions entered the lumen (exsorption); this effect became most marked 4 and 5 hours after the beginning of the aldosterone infusion. Since the rate of potassium movement in the opposite direction (out of the lumen) was unaffected, the net result was an increase in the rate of potassium secretion. In the ileum secretion was increased seven-fold (Fig. 44); in the colon the slight net absorption of potassium, which was observed initially, was converted into secretion ultimately at a rate of 23 μEq per 10 minutes, 5 hours

after the beginning of the aldosterone infusion (Fig. 45). The experiments were usually terminated after 5 hours of continuous infusion because the dogs became restless. The altered rates of potassium transport had returned to normal on the following day.

To allow statistical evaluation of the action of aldosterone, the rates of movement in dogs receiving aldosterone were compared with the rates of movement in the same dogs, at similar times, in control experiments. The effect of an aldosterone infusion was taken as the difference between the rates of movement with and without aldosterone. From these results the mean difference, and its standard error, were calculated along with the probability that it differed from zero. In Tables 31 and 32 are shown the changes in the rates of movement when aldosterone had been infused for 4 and 5 hours, for, at these times, the effects were most pronounced. In the ileum (Table 31) aldosterone produced an increased secretion of potassium, entirely due to increased rate of entry of potassium ions into the lumen; movement of potassium in the opposite direction was unaltered. Apart from an increase in the rate of sodium insorption after 4 hours (without any significant alteration in net

movement), the transport of sodium and of water were unaffected by the infusion of aldosterone. Under control conditions, sodium, potassium and water were secreted into the ileum.

In the colon (Table 32) the action of aldosterone was less pronounced. The exsorption and secretion of potassium were increased significantly after the infusion of aldosterone for 5 hours. The increases in the rates of exsorption and secretion of potassium after 4 hours of infusion of aldosterone were not statistically significant. The rate of potassium insorption, and of the rates of movement of sodium and water were not affected.

Although the type of experiment - control or aldosterone infusion - was randomly selected on each occasion, the statistical treatment outlined above will be valid only if the original rates of movement in dogs receiving aldosterone did not differ significantly from those obtained under control conditions. Neither the mean rates of movement (Table 33) nor their variances (Table 34), calculated from the first two tests, performed before the administration of aldosterone, differed significantly from those obtained at a

corresponding time in control experiments, with the exception of the insorption of sodium in the colon, and water movement in the ileum. No conclusions were, however, drawn from these rates of movement. In all other respects, the rates of movement calculated from the first two tests of the control experiments and of the aldosterone experiments formed a homogenous population so that comparison of the two types of experiment was justified.

Concentration of electrolyte in the intestinal lumen.

The concentration of sodium in the test solution did not change appreciably during ten minutes in the lumen of the ileum and colon whether aldosterone had or had not been given (Table 35). In both ileum and colon, the concentration of potassium in the instilled solution increased after it had been in the bowel for 10 minutes (Table 36). In control experiments, the rise in potassium concentration, although significant, was not great - 0.5 mEq per litre in the ileum and 0.6 mEq per litre in the colon. After the administration of aldosterone the concentration of potassium in the luminal solution rose much higher - 2.19 mEq per litre in the ileum, and 2.29 mEq per litre in the colon. The rise in the concentration of potassium

in the lumen which occurred 4 hours after aldosterone infusion was significantly greater ($P < 0.001$) than the much smaller rise observed at the corresponding times in control experiments.

Relationship between cation and water movements (Table 37).

For each litre of water insorbed from the lumen of the intestine, about 50 mEq cation (sodium + potassium) moved at the same time in the same direction. The administration of aldosterone did not significantly affect this relationship.

In the ileum, approximately 75 mEq cation (Na + K) entered the lumen along with one litre of water; no difference in this ratio was noted when aldosterone was given. Less cation was exsorbed along with each litre of water in the colon than in the ileum.

The solutions, being absorbed or secreted, had a cation concentration of 150 to 200 mEq per litre, whether or not aldosterone had been given. Such a constant relationship was to be expected, since aldosterone did not affect the net movement of water nor the net movement of the predominant cation, sodium.

When the relationship between water movement and potassium movement was examined, it was found that, in the

ileum, where initially 3.1 mEq potassium entered with each litre of water, 6.1 mEq potassium entered along with the same volume of water, 4 hours after the administration of aldosterone. This increase in the ratio of potassium to water exsorption was significant ($t = 11.9$; $P < 0.001$). Aldosterone had a similar effect in the colon in which there was also a significant rise ($t = 3.01$; $P < 0.01$) in the ratio between potassium and water exsorption: initially 1.4 mEq potassium entered with each litre of water; after aldosterone, 3.5 mEq potassium entered with each litre of water. Unfortunately the corresponding observations in control experiments were not sufficient in number to allow similar statistical analysis.

Relationship between sodium and potassium movement.

No correlation could be obtained between sodium and potassium transport to define any ion- for- ion exchange across the intestinal mucosa.

Urine-concentrations of sodium and potassium.

The pattern of urinary electrolyte excretion was altered with the administration of aldosterone: the ratio of sodium to potassium in the urine decreased invariably, while, in control experiments, the ratio

fell slightly, remained constant, or, more frequently, rose during the course of an experiment (Fig. 46).

(ii) ALDOSTERONE INFUSION (LOW DOSE).

When aldosterone was infused intravenously at a rate of 8 µg per hour, the changes in potassium transport, in both ileum and colon, were similar to those observed after the infusion of higher doses of aldosterone. Potassium secretion increased three fold after four hours, because of an increase in potassium exsorption. The rate at which potassium ions entered the body was unaltered. The increase in potassium exsorption with this lower dose of aldosterone was equal in magnitude to that observed with the higher dose (Table 38). Water and sodium transport in both parts of bowel was unaffected by the administration of aldosterone in this dose.

The changes in the concentration of electrolyte in the intestinal lumen and the relationships between electrolyte and water movement were similar to those observed with the higher dose of aldosterone.

(iii) SINGLE INJECTION OF ALDOSTERONE.

Following the injection of 500 µg aldosterone, the rates of movement of sodium, potassium and water into and out of the intestine were not altered markedly.

Any alteration in potassium transport after the single injection of aldosterone was transient and inconstant (Fig. 47).

(b) SPIRONOLACTONE EXPERIMENTS.

To determine whether spironolactone exerted a blocking action upon aldosterone, and to assess the extent of the block, two main effects were considered, using the methods of analysis described by Mills, Thomas and Williamson (1962). First, if the results of experiments, in which aldosterone + spironolactone were given, differed in the appropriate direction from those in which aldosterone was given alone, then spironolactone was considered to exert some blocking action. Secondly, if the results of experiments, in which aldosterone + spironolactone were given, differed from those in which spironolactone was given alone, then the block was incomplete.

The enhancement of potassium exsorption and secretion with aldosterone in low dose was inhibited by spironolactone (Table 39). The blocking action of spironolactone seemed complete because the rates of

potassium exsorption and secretion, following spironolactone + aldosterone (in low dose), did not differ significantly from those observed after spironolactone alone. In addition spironolactone, when given along with aldosterone (low dose), caused a fall in the rate of potassium insorption; however, this blocking action was not complete (Table 39).

Spironolactone given alone had no appreciable effect upon the transport rates of potassium (Table 38), of sodium or of water. In addition the action of aldosterone (in high dose) was not blocked by spironolactone in the dosage given.

MAN.

The intravenous infusion of aldosterone into each patient was followed by a two-fold increase in the rate of entry of potassium ions into the lumen of the isolated colon (Table 40). Since the movement of potassium in the opposite direction was unchanged, potassium accumulated in the colonic lumen. Sodium transport was not affected.

The concentrations of potassium in the test solution increased when the solution had been in the colon for ten minutes, both before and after aldosterone

had been given; but the increase in potassium concentration was much greater after aldosterone. There was no change in the concentration of sodium in the test solution (Table 41).

The histological appearances of the colon from both patients were within normal limits (Fig. 48).

B. THE INFLUENCE OF ALDOSTERONE ON THE TRANSPORT OF WATER, SODIUM AND POTASSIUM IN THE INTACT HUMAN COLON.

A patient with an aldosterone-producing tumour of the adrenal cortex provided an opportunity to study the effect of aldosterone, of endogenous origin, upon the transport of water, sodium and potassium across the intestinal mucosa. The patient was investigated before and after the removal of the tumour, and the results of these studies were compared to those obtained, in a similar manner, in four healthy volunteers.

Because surgery has been shown to affect the movement of electrolytes, particularly of potassium, across the intestinal mucosa, these investigations had to be undertaken with the subject conscious and the intestine intact. Under these circumstances the colon is the most suitable part of the bowel in which to study the bidirectional transport of water and electrolytes because (a) in the prepared subject, there is minimal contamination of the intestinal content with secretions from above, and (b) if a perfusion technique is adopted, almost all the perfusate can be recovered for subsequent analysis. The movement of water and electrolytes was

therefore studied by colonic perfusion, using a modification of the technique described by Levitan et al. (1962)(Figure 49).

METHODS.

Experimental procedure.

The patient and the volunteers, who were healthy adult males, aged 25 - 40, were asked to swallow a polyvinyl tube - internal diameter, 1.5 mm - with a small mercury bag, attached to one end, to expedite the passage of the tube through the intestinal tract. A radio-opaque marker was placed on the tube, 5 cm from its distal end; the short length of tube between this marker and the attachment of the mercury bag was perforated by several small holes. During the 2 - 5 days taken by the perforated end of the tube to reach the caecum, and pass through the ileo-caecal valve, the subjects were given a light diet. The position of the tube was confirmed radiologically, using an image intensifier (Figure 50); the absence of reflux of colonic content into the ileum was checked by injecting a small quantity of water-soluble, radio-opaque solution down the tube. Only one screening session, of short duration, was allowed in each patient whose gonads were

protected. The position of the distal end of the tube could usually be predicted from the length of tube swallowed.

All subjects were fasted for twelve hours before colonic perfusion. One end of a polyvinyl tube of wide bore was inserted for 10 cm into the rectum, by means of a sigmoidoscope. The colonic lumen was then perfused with Tyrode's solution at a rate of 15 ml per minute until the fluid expelled through the rectal tube was clear. Usually 1 - 2 hours were required for such preliminary washing. When the colon had been satisfactorily rinsed, an interval of 2 hours was allowed for the fluid remaining in the bowel to be absorbed or expelled.

Test solution was then perfused through the colon by means of a peristaltic pump at a constant rate of 15 - 20 ml per minute. The perfusate was collected by means of the rectal tube in 10-minute aliquots. The specimens collected during the first 20 - 30 minutes of perfusion were discarded because they could easily have become contaminated by the residue of the rinsing fluid. Extreme care was required, with close attention to the position of the rectal tube, to ensure that the volume of each 10-minute sample was approximately constant and

to avoid pooling of the perfusate in the rectum. Slower rates of perfusion prevented a steady state of inflow and outflow from being established. Usually a litre of test solution was perfused for 60 - 90 minutes.

The test solution was freshly-prepared, modified Tyrode's solution (Appendix 1) containing ^{24}Na (2 μc per litre), ^{42}K (4 μc per litre), D_2O (1% v/v), and polyethylene glycol (PEG), 1 per cent (w/v) of molecular weight 4000. The activities of radio-active sodium and potassium in the test solution, and in each aliquot of perfusate, were determined by simultaneous counting in beta and gamma counters. The concentrations of sodium and potassium were estimated by flame photometry and the concentration of D_2O by infra-red spectrophotometry. The concentrations of PEG in the test solution, and in the perfusate, were estimated by the method of Hyden (1955).

The rates of movement of water, sodium and potassium were calculated, for each 10 minute sample, using the formulae given in Appendix 4, Part II, Equations 8 - 11. These equations differ from those of Levitan et al., (1962), who neglected the changes in the specific activities of the solutions during the perfusion. In the present study, the arithmetic mean of the specific

activities was used. These formulae are obviously closely similar to those of Visscher et al., (1944a and b) for calculating the rates of movement of water and electrolytes in isolated segment of intestine (Appendix 4, Part I, Equations 1 - 6). The same assumptions were considered to apply.

Patient

The transport of water and cations across the colonic mucosa was studied one week before, and three months after, the removal of a tumour of the right adrenal gland.

The pre-operative studies were performed after the potassium deficiency had been corrected by the administration of potassium chloride by mouth and the prescription of a diet, poor in sodium (less than 10 mEq per day) and rich in potassium (150 mEq per day). For the four days preceding colonic perfusion, however, the patient was on a normal ward diet and did not receive any potassium supplements or other medication.

The investigations on the colon were repeated three months after the operation. At this time the patient was well, and did not display any evidence of potassium deficiency. He did not require any medication.

The clinical features of this patient, the details of the other investigations and of the operation and the pathological findings, are given in Appendix 14.

RESULTS.

Healthy volunteers.

The intact human colon absorbs sodium and water, and secretes potassium, when perfused continuously with an isotonic solution. Sodium was absorbed, at a mean rate of 0.32 mEq per minute by the colon: the mean rate of insorption was 0.61 mEq per minute and that of exsorption, 0.29 mEq per minute (Figure 51). Similarly, the mean rate of water insorption (7.5 ml per minute) exceeded that of exsorption (5.4 ml per minute) so that water was absorbed at a mean rate of 2.1 ml per minute (Figure 52). Potassium, on the other hand, was secreted into the colonic lumen, at a mean rate of 0.022 mEq per minute because potassium ions were more rapidly exsorbed (0.040 mEq per minute) than insorbed (0.018 mEq per minute) (Figure 53). The individual data for these experiments are given in Appendix 15.

Patient with primary hyperaldosteronism.

The movement of potassium ions across the colonic mucosa was profoundly altered in the patient with

hyperaldosteronism. Potassium was secreted into the lumen of the colon at more than three times the mean rate in four normal subjects (Figure 54; Table 42). This enhancement of potassium secretion was brought about entirely by a marked increase in potassium exsorption. The rate at which potassium ions left the colonic lumen was identical to the mean rate in normal subjects. The increased rates of potassium secretion in this patient were reflected in the higher daily faecal excretion of potassium (15 mEq per 24 hours, compared to a normal range of 5 to 8 mEq per 24 hours) and a concentration of potassium of 10 mEq per litre in the colonic lumen compared to the normal concentration of 4.5 mEq per litre. Three months after the removal of the tumour, the rates of potassium secretion and of exsorption had returned to normal (Figure 54; Table 42).

Sodium movement before operation was within the range found in the four healthy subjects (Table 42). After the operation, however, the rate of sodium insorption was increased; since the rate of exsorption was not changed appreciably, the absorption of sodium in the colon was also increased, after the removal of the tumour, but only to the upper limit of the range found in the

four normal subjects.

The net movement of water (Table 42), before and after the removal of the tumour, was within normal limits. The unidirectional fluxes of water were not determined in the patient because of a temporary lack of deuterium oxide.

DISCUSSION.

Adrenal-cortical hormones are known to influence extra-renal tissues in a manner qualitatively similar to their striking effect upon the kidney. In sweat (Conn *et al.*, 1948; Conn, 1949) and in saliva (Frawley and Thorn, 1951), the ratio of sodium to potassium is reduced, and occasionally reversed, with increased activity of the adrenal cortex. In a similar way, the electrolyte composition of the intestinal contents can be altered by the salt-active adrenal hormones (see Part I, Chapter 3).

However, alterations in the ionic composition of the intestinal content are brought about by changes in the rates at which electrolytes enter or leave the intestinal lumen. So far, only two studies have been undertaken to describe the effect of mineral corticoids upon the unidirectional movements of electrolytes - that of Berger *et al.*, (1960) and the present study. Berger and his associates, who studied the action of deoxycorticosterone (DOC) in isolated segments of bowel in the dog, observed that, in the large intestine, the absorption of sodium was increased, due to increase in the rate at which sodium ions left the lumen, and the secretion of

potassium was increased because of a relative and absolute increase in the rate at which potassium ions entered the colonic lumen. In the small intestine, DOC did not produce any appreciable effect on the transport of sodium or of potassium.

This present study confirms the observation of Berger et al., that the intestinal transport of electrolytes can be affected by mineral corticoids - in particular the increase in the rate of potassium secretion, caused by an increase in the rate of exsorption. However, in several respects the present findings differed from their observations.

In the first place, in the present study, the small intestine seemed to be responsive to aldosterone, certainly as far as potassium was concerned: the rate of exsorption of potassium ions was increased, bringing about an increase in potassium secretion. Secondly, in both small and large intestine, no effect on sodium transport was demonstrated after the administration of aldosterone.

The reasons for such differences between the two studies remain obscure. Certain factors cannot be held to be responsible:

(a) There would seem to be little justification to ascribe the differences, to the use of DOC in one study and of aldosterone in the other. Although the quantitative differences in the effect of these substances are marked, there is a close qualitative similarity in their actions (Kruhøffer et al., 1960).

(b) The action of mineral corticoids may vary depending on whether the acute or chronic effects of their administration are being studied (Lipsett, Schwartz and Thorn, 1961); but in both these investigations only the acute effects were under investigation. Such acute experiments were necessary in the present work because of the short biological half-life of aldosterone (Ayers et al., 1962), and its ineffectiveness when given by mouth (Ledingham et al., 1961).

(c) The fact that the ileum tended to secrete water and sodium cannot be put forward as an explanation for the failure of the small bowel (in the study of Berger et al.) to respond to the mineral corticoids, for, in both studies, ileal secretion was observed under resting conditions.

In this study, the transport of water and electrolytes in the human colon was also investigated. Several important features have emerged. First, the enhancement of potassium exsorption and secretion, observed in dogs after the intravenous administration of aldosterone, has been confirmed in the isolated human colon. The delay before the changes in potassium movement become manifest, and the lack of alterations in sodium transport, both observed in dogs, have been shown to occur also in man. Second, the rates of absorption of sodium and water, and of secretion of potassium, have been estimated in the intact human colon. The simultaneous measurement of the unidirectional movements of sodium, potassium and water in the intact colon has not been previously reported; Levitan et al. (1962) estimated the net movement of several electrolytes but measured the insorption and exsorption of water only. The relatively high degree of efficiency in sodium absorption possessed by the human colon is noteworthy: less than half the sodium insorbed "leaked" back into the intestinal lumen. Finally, the transport of sodium and potassium into and out of the colonic lumen has been measured before and after the removal of an aldosterone-producing tumour. The human intestine is affected in a

similar way to the kidney by such a disease - the loss of potassium is increased. An increased concentration of potassium in the colonic lumen has been observed in such patients (Wrong, 1964). The present investigations showed that such increased potassium loss has been brought about by increased secretion by the colonic mucosa which allows more potassium ions to enter the lumen than under normal conditions; movement of potassium into the body is not altered. Such a change in the two-way traffic of potassium is identical to the alterations which occur after aldosterone has been given intravenously to normal subjects. The altered handling of potassium by the colon is, however, reversible, returning to normal with the removal of the tumour.

The close similarity between the intestinal and renal actions of aldosterone is striking.

(a) In the intestine of both man and dog at least 1 to 3 hours elapsed after the injection of aldosterone before any alteration in the rate of electrolyte transport became appreciable. A similar delay in the effect of aldosterone upon the renal excretion of electrolyte has been described in the dog (Barger,

Berlin and Tulenko, 1958) and in man (Dingman et al., 1958; Ross et al., 1959).

(b) In the intestine, mainly potassium transport was affected by aldosterone. As far as the renal handling of electrolytes is concerned, the infusion of aldosterone into a renal artery of intact dogs increases the secretion of potassium by the associated kidney but sodium excretion is unaffected (Barger et al., 1958); with the removal of the adrenals, however, the same dog exhibited not only potassium secretion, but also sodium retention, with the same dose of aldosterone. Barger and his associates also noticed that the effects of aldosterone on the urinary excretion of sodium and potassium did not coincide, and suggested that the effect of the mineral corticoids upon potassium transport may be a primary one and not secondary to sodium transport, on an ion-for-ion basis. Certainly there is no evidence that the effect of the mineral corticoids on potassium transport in the gut is anything but primary.

A single intravenous injection of aldosterone did not produce any definite or constant change in electrolyte transport in the bowel. This finding can be attributed

to the short life of aldosterone in the body and the delay after administration before its effect becomes manifest. The more satisfactory preparation was the one in which aldosterone was given by continuous intravenous infusion. The delay in producing a response in the gut cannot be ascribed to the time required to build up an effective concentration of aldosterone in the body, for delay was constantly observed whether or not an initial booster dose of the mineral corticoid had been given. An infusion rate of 8 µg per hour (low dose) is probably greater than the rate of basal secretion of aldosterone in the dog. No accurate figures are available. However, in the sheep, the mean basal output of aldosterone amounts to 0.48 µg per hour; if the sheep is deprived of sodium there is an increase in the rate of secretion of aldosterone to 15 µg per hour when changes in the electrolyte composition of saliva can be observed (Wright, 1962). On the basis of weight, a rate of 8 µg per hour was selected as the rate at which, in the dog, aldosterone might be secreted if the adrenal cortex were stimulated, and at which an effect on extra-renal tissues, such as the gut, might probably be detected. Although the

rate of 1 μg per minute (high dose) is possibly greater than that found under physiological conditions, such a rate has been used by many workers in the past. Certainly, it is no more potent than the slower rate of infusion.

The spironolactones are assumed to act upon the kidney as competitive blockers preventing the access of the adrenal mineral-corticoids to their site of action on the renal tubules (Bartter, 1960). The sodium-retaining effect of aldosterone upon the human kidney can be halved by spironolactone, the blocking action being incomplete (Mills et al., 1962). These authors found that the acute kaliuretic action of aldosterone in man was not so constant as to allow clear assessment of the blocking action of spironolactone upon the renal handling of potassium. More recently, Kagawa, Bouska and Anderson (1964) found that the administration of spironolactone completely inhibited the effect of DOC upon the renal handling of potassium. This blockade was complete. These last authors observed that the renal handling of sodium was only partially blocked by spironolactone. The stimulatory action of aldosterone (low dose) upon potassium movement into the bowel was found to be

completely blocked by spironolactone. The intestinal action of aldosterone, given in larger amounts, could not be inhibited. In this context, we have found that the increased exsorption of potassium, in states of sodium depletion, could not be blocked by spironolactone (Clarke and Shields, 1963). Thus, spironolactones seem incapable of inhibiting the action of aldosterone when excessive quantities of the latter are present but, on the other hand, spironolactones can probably block the intestinal effects of aldosterone in the amount usually present after trauma. It is noteworthy that some of the changes in the renal excretion of electrolytes after operation can be prevented by spironolactone (Johnston, 1964). The blocking action of spironolactone upon the action of aldosterone further emphasises the close qualitative similarity between the intestinal and renal handling of electrolytes.

Within the framework of these experiments the significance of the intestinal action of aldosterone in maintaining homeostasis must be assessed. Caution must be exercised in generalizing uncritically upon the actions of steroids from a single type of experiment - i.e. acute - (Lipsett et al., 1961). In these studies, in man and in the dog, sodium transport was not appreciably

affected by aldosterone. Yet most evidence (see review of the literature) suggests that sodium absorption is probably enhanced by adrenocortical activity. However, under normal conditions, the amount of sodium in the faeces is so slight that a reduction in the faecal excretion of sodium in states of increased adrenal-cortical activity will contribute only slightly to homeostasis. The increased secretion of potassium under the influence of the mineral corticoids may be of clinical importance. The daily faecal excretion of potassium, which represents 20 per cent of the total loss of potassium by all routes, can be increased several-fold so that the extent of the potassium deficit can go undetected if only the urinary losses are measured. For example, in the patient with primary hyperaldosteronism, the daily faecal losses of potassium were occasionally more than half the urinary excretion of potassium which was also increased in this condition. Potassium deficiency may then occur more rapidly than would be anticipated.

Adrenocortical activity has not been specifically studied in intestinal obstruction. However, several aspects of obstruction could presumably elicit an increase

in the secretion of mineral corticoids by the adrenal cortex - the colic and pain of distended bowel, starvation, and the loss of intestinal secretions by vomiting or aspiration with consequent shrinkage of the extra-cellular space. As a result, in the intestine the handling of electrolytes, initially deranged by the local effects of the obstruction, would be further disturbed with increased losses of potassium into the bowel lumen.

SUMMARY

1. The intestinal transport of water, sodium and potassium was studied in isolated segments of small and large intestine of the dog, and in both the isolated and the intact colon of man.

2. When aldosterone, in both high and low dose, was infused intravenously into dogs, the following observations were made:-

(a) the secretion of potassium into the small and large intestine was enhanced by a marked increase in the rate of potassium exsorption.

(b) The movements of sodium and water were not affected.

(c) As a result, the concentration of potassium in the intestinal lumen was increased.

(d) The ratio of sodium to potassium in the urine was lowered or reversed.

(e) If spironolactone was given to the dogs beforehand, subsequent infusion of aldosterone (in low dose) did not produce its usual effect on potassium transport. Spironolactone did not block the intestinal action of the higher dose of aldosterone.

3. A single injection of aldosterone had only a slight and transient effect upon potassium movement.

4. Sodium and potassium were exchanged across the mucosa of the isolated human colon so that sodium was absorbed and potassium was secreted. When aldosterone was infused intravenously, the rates of potassium exsorption, and hence secretion, were increased so that potassium accumulated in the colonic lumen.

5. In the intact colon of four normal volunteers, the bidirectional fluxes of sodium, potassium and water were confirmed. Sodium and water were absorbed and potassium was secreted by the colon.

6. In a patient with a proved aldosterone-producing tumour of the adrenal cortex, the secretion of potassium into the colonic lumen was shown to be markedly increased; the losses of potassium in the faeces were excessive. With the removal of the tumour, the increased rate of potassium exsorption returned to normal.

7. Aldosterone has thus been shown to influence the intestinal handling of electrolytes. In several ways, the action of aldosterone on the intestine closely resembles its effect on other tissues, especially the kidney, viz., the delay between its administration and

the onset of its action, the marked effect on potassium transport in the presence of intact adrenals, and the blockade of its action by spironolactone.

8. Thus the intestinal handling of electrolytes seems to be influenced by the adrenal cortex.

9. In states of increased adrenal cortical activity, potassium losses into the bowel may be high, and go unrecognised clinically.

10. The increased adrenal cortical activity, which probably occurs in intestinal obstruction, will enhance the losses of potassium into the intestinal lumen.

PART VI

GENERAL CONCLUSIONS

Loss of fluid into the lumen of the gastro-intestinal tract constitutes the major hazard of intestinal obstruction. The experimental work, described in this thesis, has shown that the obstructed bowel makes a considerable contribution to the volume of fluid accumulating within its lumen. Although the importance of this aspect of obstruction has been emphasised in the standard surgical textbooks and in the monographs on the subject, the impaired ability of the obstructed bowel to handle water and electrolytes has received little study in the past. The extent and nature of the fluid, lost in this manner, have been quite unknown.

Early, in obstruction, the ability to transfer water and electrolytes out of the intestinal lumen is lost, so that the fluid entering the obstructed bowel, from above and across the intestinal mucosa, will be unable to leave. Later, the rate of accumulation of fluid increases, as the bowel allows water and electrolytes to pass more easily into the intestinal lumen. Depending on the extent to which the bowel is affected, more than a litre of fluid, of electrolyte composition similar to that of plasma, may be lost

into the bowel every hour. Some of this fluid can be reabsorbed in the upper parts of the intestine, if these have not become distended and involved in the obstructive process.

Several mechanisms combine to produce these alterations in the absorption and secretion of fluids in intestinal obstruction. Distension of the gut and increased intra-enteric pressure, due to the accumulation of gas and fluid, will hinder absorption and stimulate secretion by flattening the intestinal mucosa and interfering with the mucosal blood flow. The intramural venous circulation is principally affected. Increase in pressure within the mesenteric veins provokes the bowel to secrete water and electrolytes. Such venous congestion would seem to be a major factor in altering the handling of fluids by the obstructed bowel. To a lesser extent the systemic consequences of intestinal obstruction may contribute to the disturbances in fluid and electrolyte transfer. Increased adrenal-cortical activity can enhance the secretion of potassium into the intestinal lumen, and in late obstruction, when the total osmotic pressure of the plasma is reduced on account of the loss of

sodium ions, the absorption of water from the intestine will be hindered.

These experiments have, at the same time, revealed further knowledge of the physiology of intestinal absorption.

First, increase in the mesenteric venous pressure has been shown to affect the movement of water and electrolytes in one direction only - into the bowel. Since movement in the opposite direction was not altered, a degree of independence of the transport systems for unidirectional movements is suggested: movement into the body may be active, and movement into the intestinal lumen passive and therefore affected by physical factors such as hydrostatic pressure.

Second, the resemblance between the renal and intestinal handling of fluids and electrolytes, pointed out in the review of the literature, has been further strengthened by a series of experimental observations. The gut and the kidney respond in a like manner to previous trauma, by conserving sodium and water, and losing potassium. The mineral-corticoid hormone of the adrenal cortex can also influence electrolyte transfer in the intestine. The similarity in the

renal and intestinal actions of aldosterone is striking, viz., the latent period before its effect becomes manifest and the blockade of its action by spironolactone.

The intestine has its own part to play in maintaining homeostasis. Under normal conditions, the fluid and electrolyte composition of the body is controlled largely by the kidney. It is difficult physiologically to alter the absorption and secretion of water and electrolytes by the intestine. However, in states of fluid depletion, the cause is usually found in the gastro-intestinal tract because disease can easily upset the orderly sequence of secretion and re-absorption. For this reason, the study of the intestinal handling of water and electrolytes presents a challenge to the clinical scientist. In addition, because of its accessibility, the intestine provides the investigator with an opportunity to study the problems of fluid and electrolyte transfer across living membranes in intact man.

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PUBLICATIONS

Parts of the review of the literature are contained in "The surgical aspects of the absorption of water and electrolytes by the intestine" published in Monographs in the Surgical Sciences (1964) 1: 119-172.

The effect of mesenteric venous congestion upon the movement of water and sodium was published in the American Journal of Physiology (1961) 200: 775-780 (with Dr. C. F. Code). The effect of mesenteric venous congestion upon potassium transport has not been reported hitherto.

A preliminary report of some of the observations on water and electrolyte absorption in experimental obstruction has been published in the proceedings of a symposium on the physiology of the gastro-intestinal tract in Edinburgh, June 1962.

The rest of the experimental work is unpublished but much of it has been read in a series of papers given to the Surgical Research Society, Scottish Society for Experimental Medicine and the British Society of Gastroenterology.

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A STUDY OF SEVERAL FACTORS AFFECTING THE INTESTINAL ABSORPTION OF WATER, SODIUM AND POTASSIUM.

VOLUME II

CONTENTS OF VOLUME II

PART A

Tables and Figures are set out in the order in which they occur in the text.

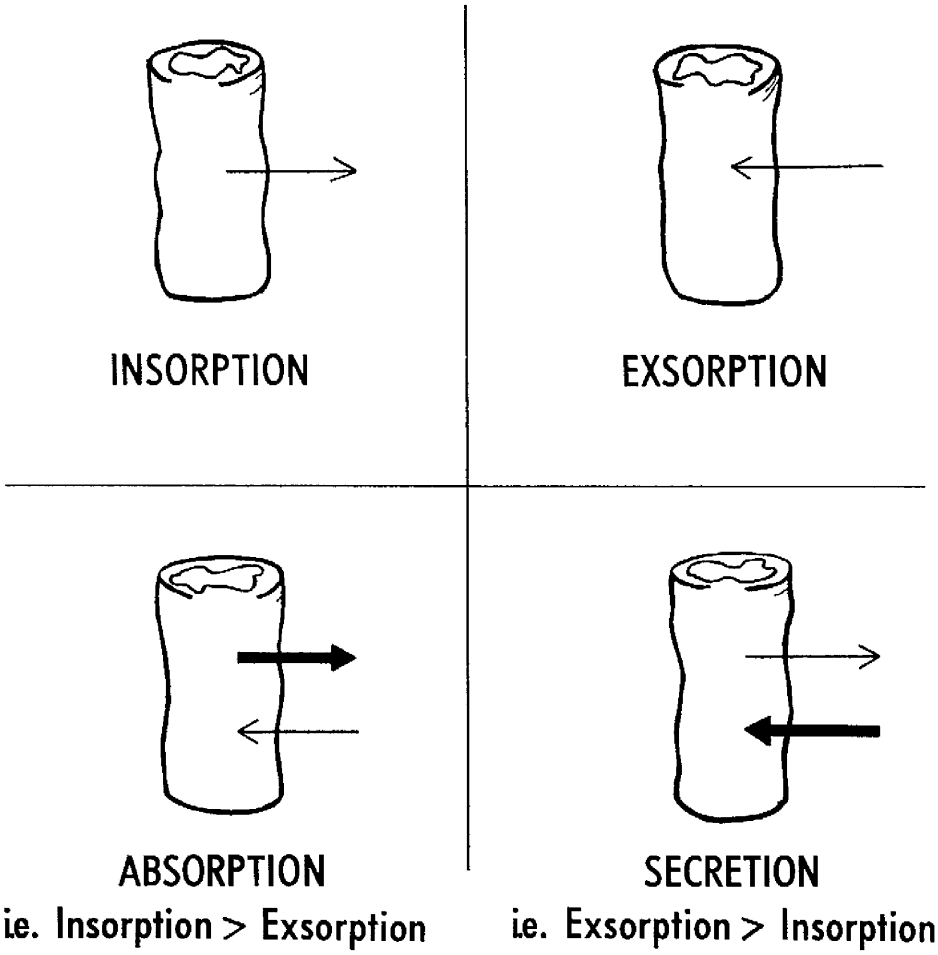


FIGURE 1 The terminology used to describe the sorption of water and electrolytes in the intestine. In the upper diagrams, the direction of unidirectional movement is indicated by the arrow. In the lower diagrams, the heavier arrows represent the direction of the faster rate of movement.

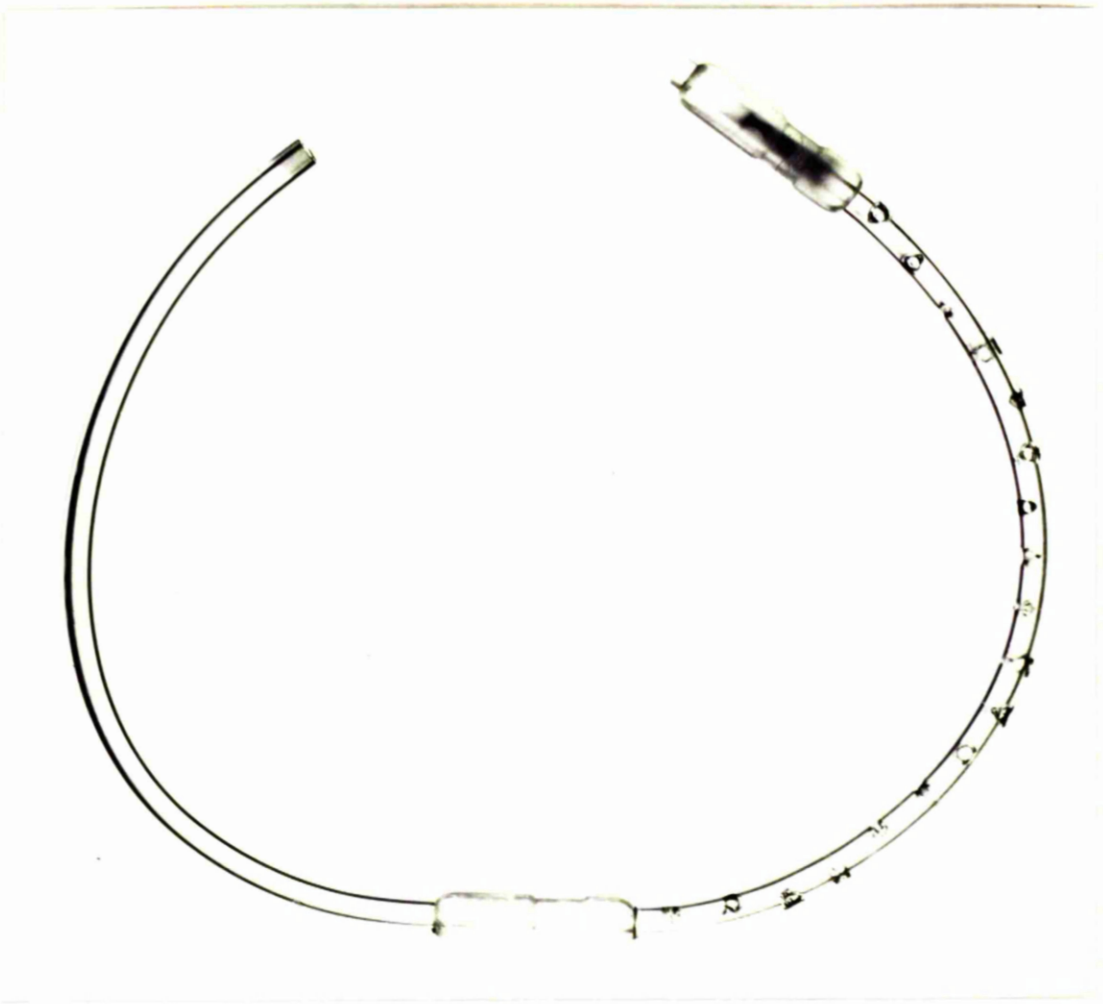


FIGURE 2 The tube is constructed from a length of polyvinyl plastic (internal diameter, 0.5 cm) and is closed at one end. Placed on the tube, 21 cm apart, are two lucite bobbins (external diameter, 1.1 cm) one of which is placed at the closed end. The circumference of each bobbin is etched with a groove to which the bowel can be tied. The tube between the bobbins is perforated with multiple holes (2 mm diameter). A tube of these dimensions isolates a segment of canine ileum whose serosal surface area will be 100 cm^2 approximately.

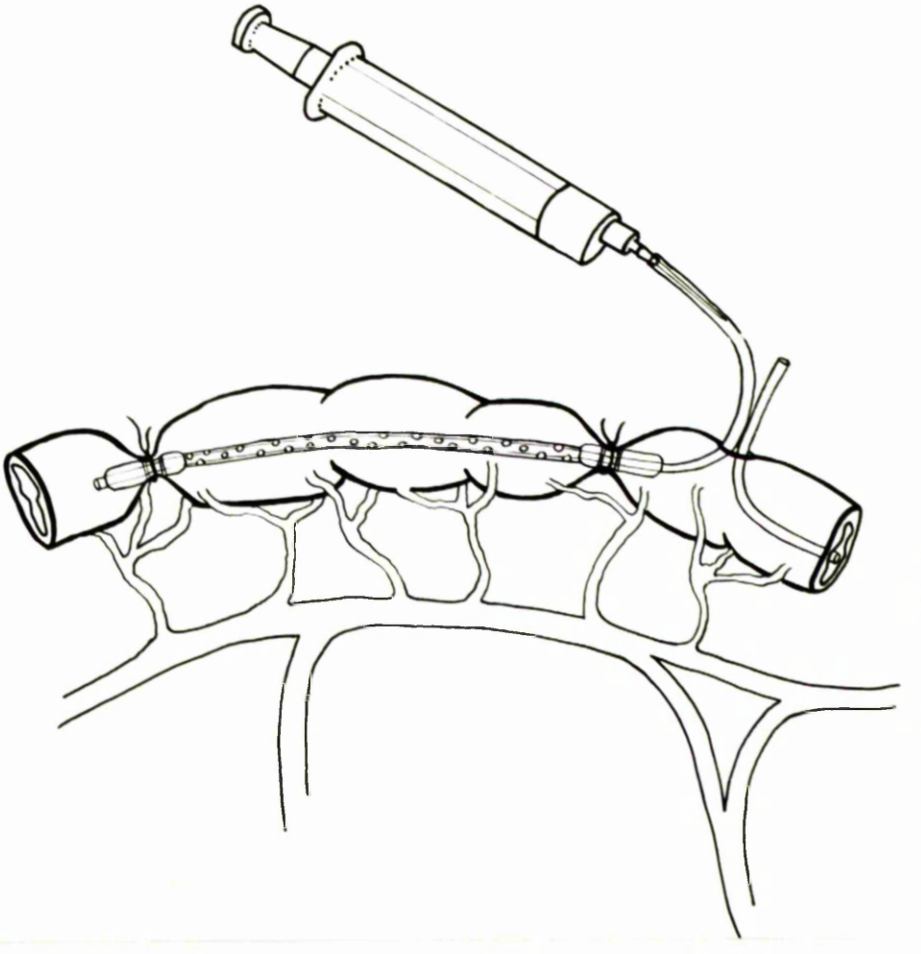


FIGURE 3 A diagram of the acute preparation. A segment of ileum has been "isolated in continuity" by tying the ileum to the absorption tube (Fig. 2). A catheter drains the bowel above. Solutions can be instilled and withdrawn from the isolated segment by means of the syringe.

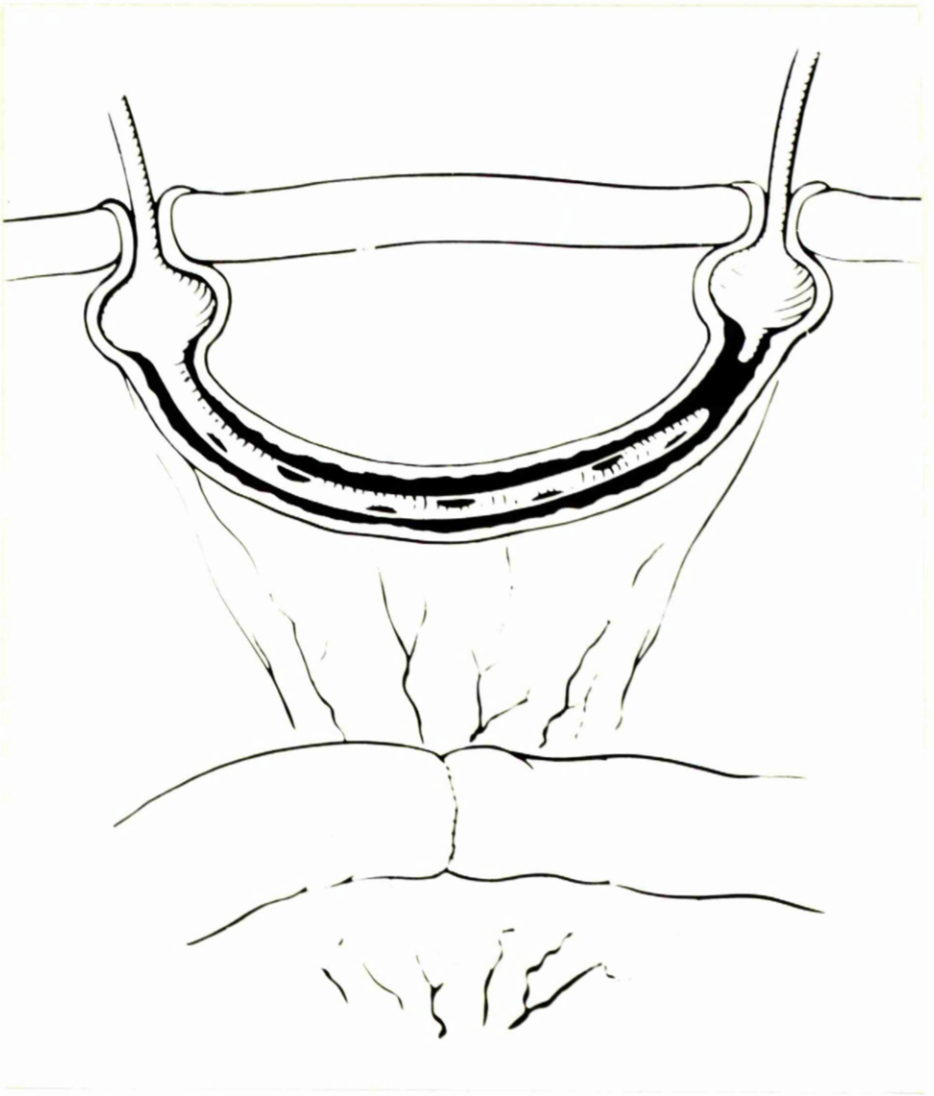


FIGURE 4 A diagram of the chronic preparation. One end of the Thiry-Vella fistula is sealed by the balloon of a Foley catheter. Into the other end is inserted a multiperforate tube carrying a balloon which, when inflated, prevents leakage of the intra-luminal solution.

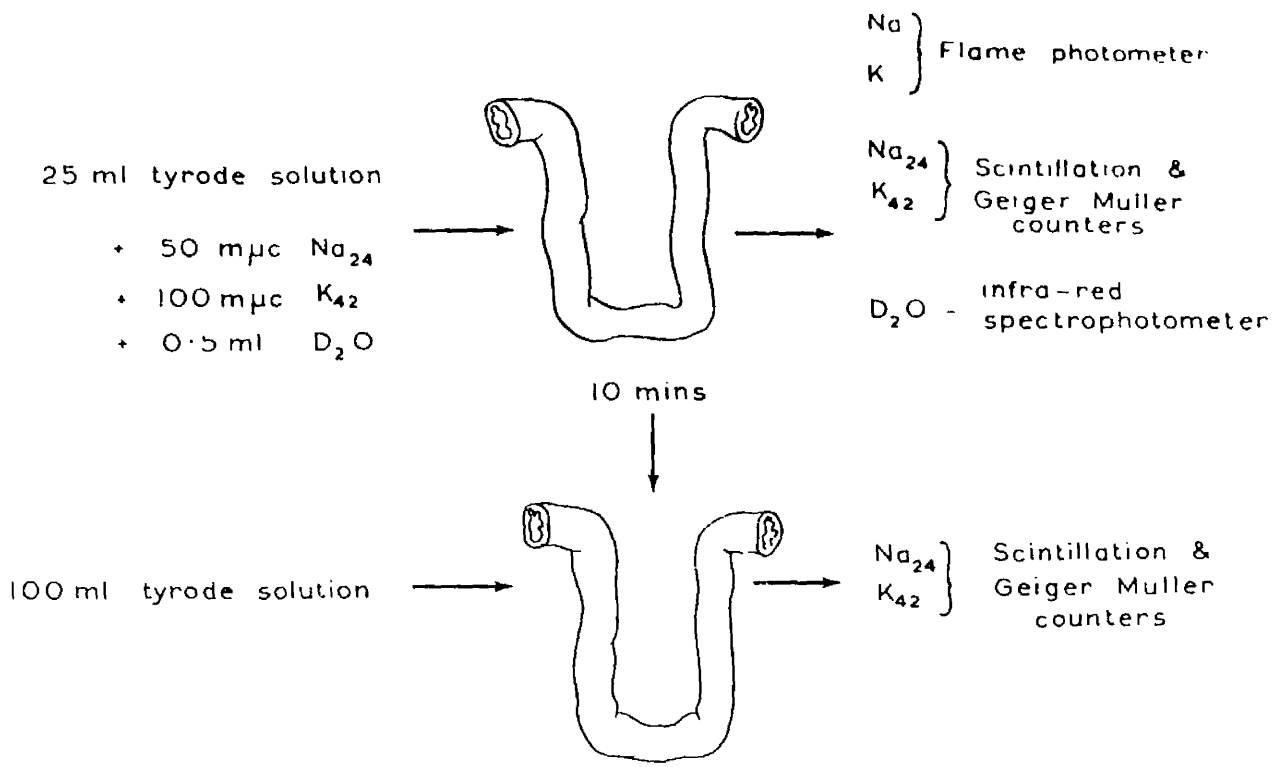


FIGURE 5 A diagram of a single absorption test indicating the composition of, and the estimations performed upon, the test solution and the rinse.

TABLE 1. Error produced by re-entry of insorbed ^{22}Na into luminal solution. (6 experiments).

A Radioactivity acquired after 10 minutes by solution, initially non-radioactive	B Activity in bowel at end of first test (8 absorption tests in each experiment)	Error due to re-entry * $(\frac{A}{B} \times 100)$ %
cps	cps	
23	2367	0.97
10	2580	0.39
16	2383	0.67
11	2783	0.40
18	2186	0.82
13	2643	0.49
Mean 15	2490	0.62

* In this column, the radioactivity acquired by the non-radioactive solution after eight absorption tests had been performed was expressed as a percentage of the radioactivity in the bowel at the end of the first test of the series in each experiment.

TABLE 2. Activity of femoral arterial blood before and after eight 10-minute tests. (Counts per ml per 2000 seconds). Same experiments as in Table 1.

	Before	After
	5081	6332
	4284	5776
	4702	6224
	5222	7018
	5196	6678
	5296	6729
Mean	5003	6490
S.E.M.	189	180

Mean difference	1457
S.E.M. difference	261
t	5.57
P	<0.001

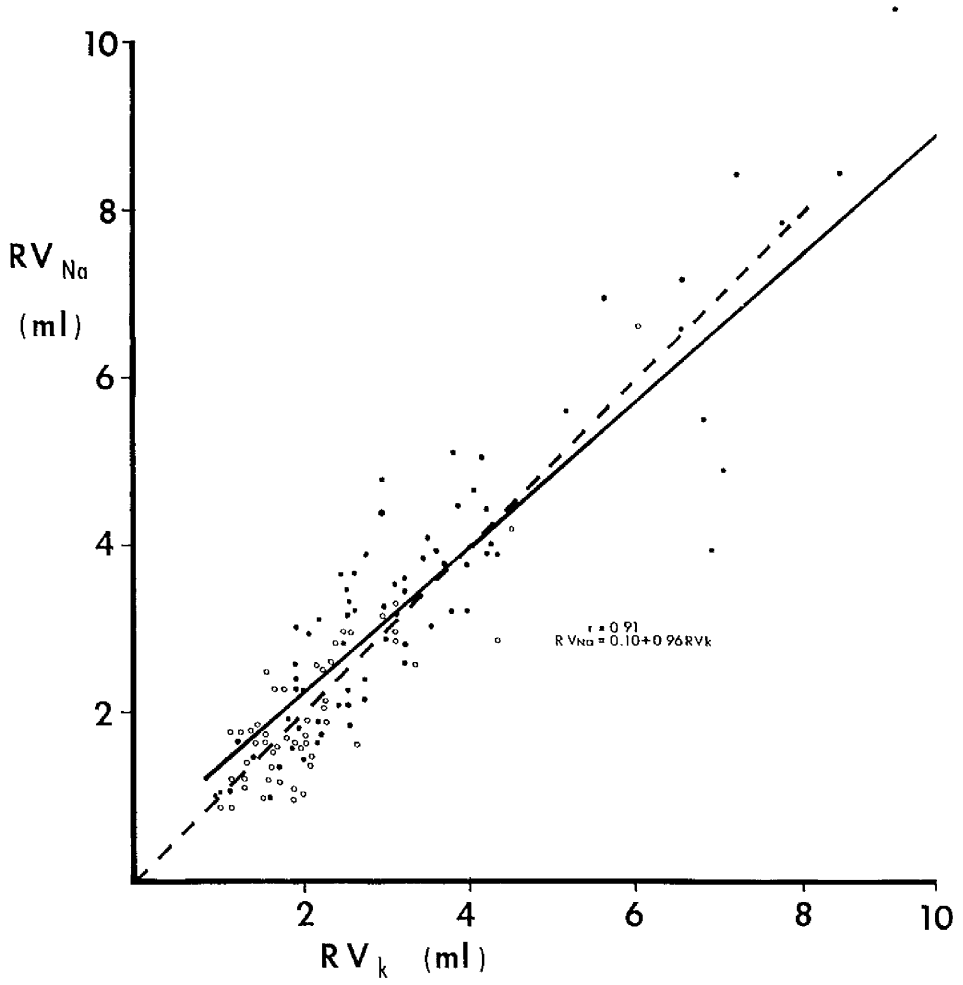


FIGURE 6 The residual volume of the fluid remaining in the isolated segment, calculated from the radioactive sodium data (RV_{Na}), is compared with that calculated from the radioactive potassium data (RV_K).

The open dots represent residual volumes in the ileum; the closed dots, those in the colon. The unbroken line is the regression line of RV_{Na} on RV_K, and the dotted line, the 45° line of identity.

The individual values for RV_{Na} and RV_K are contained in Appendix 13.

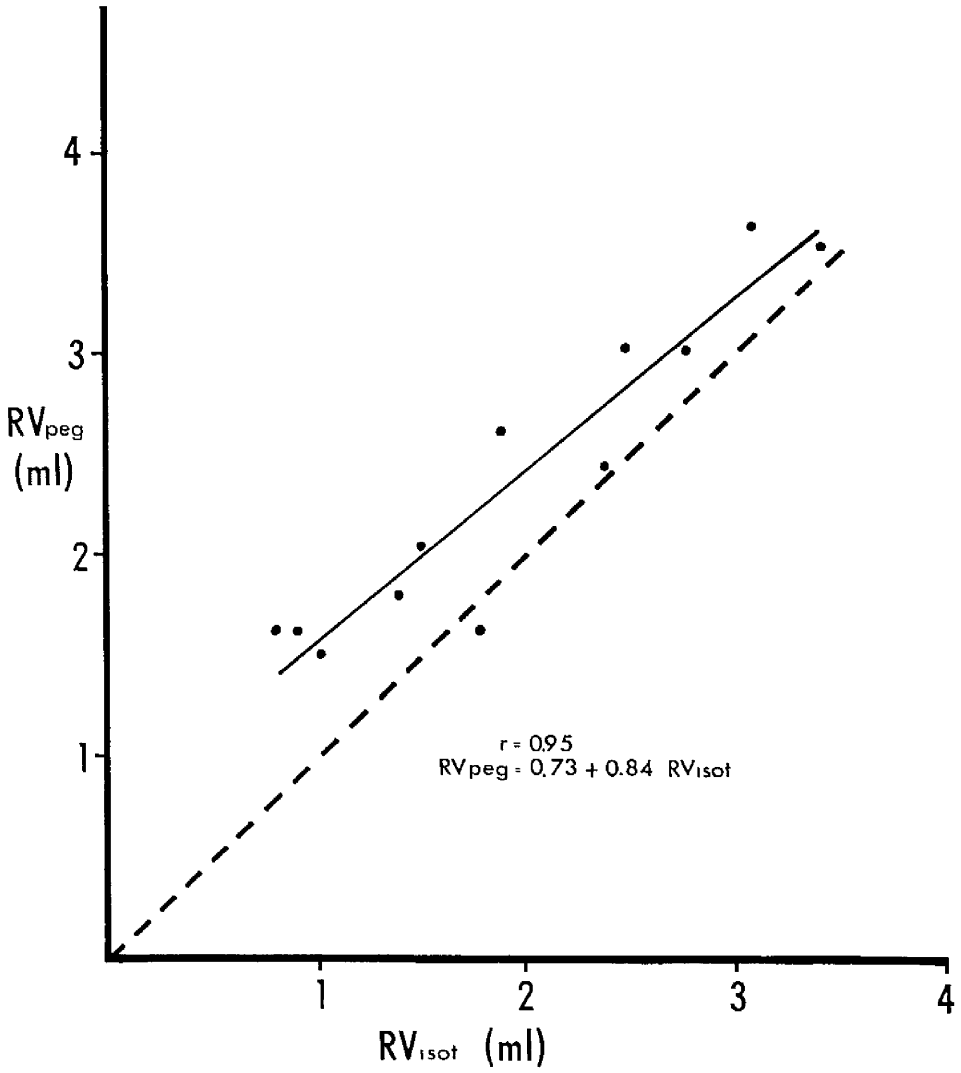


FIGURE 7 The residual volume remaining within the lumen, calculated from the radioactivity of the rinse (RV_{isot}), is compared to that calculated from the recovery of polyethylene glycol (RV_{peg}).
The unbroken line is the regression line of RV_{peg} on RV_{isot}, and the dotted line is the 45^{o} line of identity.
The individual values for RV_{peg} and RV_{isot} are contained in Appendix 9.

TABLE 3. A comparison of known and calculated activities of ^{24}Na and ^{42}K in mixtures. (20 experiments).

	^{24}Na	^{42}K
A Known activity - mean (cps)	3015	3705
S.E.M.	57	103
B Calculated activity - mean (cps)	2935	3763
S.E.M.	52	108
Mean difference $\pm$ S.E.M. difference	80 $\pm$ 77	58 $\pm$ 149
t	1.03	0.39
P	<0.4	<0.7
Recovery $(\frac{B}{A} \times 100)$ %	97.3	101.6

Individual results are contained in Appendix 10.

TABLE 4. Observed and calculated counting rates of ^{24}Na and ^{42}K mixture with coefficients of variation (v) due to counting statistics.

	SCINTILLATION COUNTER		G.M. COUNTER	
	Counts	v%	Counts	v%
Total counts in 100 secs.	24050	1	32404 (a)	1
∴ Observed cps.	241	1	324	1
Background count in 1000 secs.	4000	1.7	1000	3.1
∴ Net observed cps.	237	1	323	1
Derived cps. (c)	130 (b)	3 (d)	300	1 (d)

NOTES (a) Correction for dead-time has been made.

(b) Background count is so low compared to sample count that its error can be neglected.

(c) Derived activities (cps) are the calculated activities of ^{24}Na in the scintillation counter and of ^{42}K in the G.M. counter.

(d) The coefficients of variation of the derived counts were obtained from the formulae of Robinson et al., (1955).

TABLE 5. Errors of method.

Source of error	Degree of error
A Known	
Calculation of residual volume	1%
Re-entry of isotope into luminal solution	0.6%
Counting statistics - sodium	3.0%
" " - potassium	1.0%
Deuterium oxide - (infra-red spectrophotometry)	0.9%
Deuterium oxide - (mass spectrometry)	0.004%
Sodium (flame photometer)	1.3%
Potassium (flame photometer)	2.5%
B Negligible	
Volume of test solution, volume of aspirate, volume of rinse, dilution of standards for counting and for flame photometry	Not significant
C Unknown	
Measurement of surface area of bowel	?

TABLE 6. The rates of transport of sodium, potassium and water in the ileum (acute preparation). (Results given in greater detail in Tables 29 and 30).

	SODIUM (22 tests) μEq per 10 minutes	WATER (22 tests) ml per 10 minutes	POTASSIUM (10 tests) μEq per 10 minutes
INSORPTION			
Mean rate ± S.E.M.	1151 ± 60	16.9 ± 0.6	23.8 ± 1.6
v (%) (a)	24	18	21
EXSORPTION			
Mean rate ± S.E.M.	471 ± 33	12.3 ± 0.7	37.9 ± 1.7
v (%)	33	26	14
NET			
Mean rate ± S.E.M. (b)	+ 680 ± 55	+ 4.6 ± 0.4	- 14.1 ± 0.7
v (%)	39	36	15

(a) v is the coefficient of variation.

(b) A plus sign preceding the mean rate indicates absorption; a minus sign, secretion.

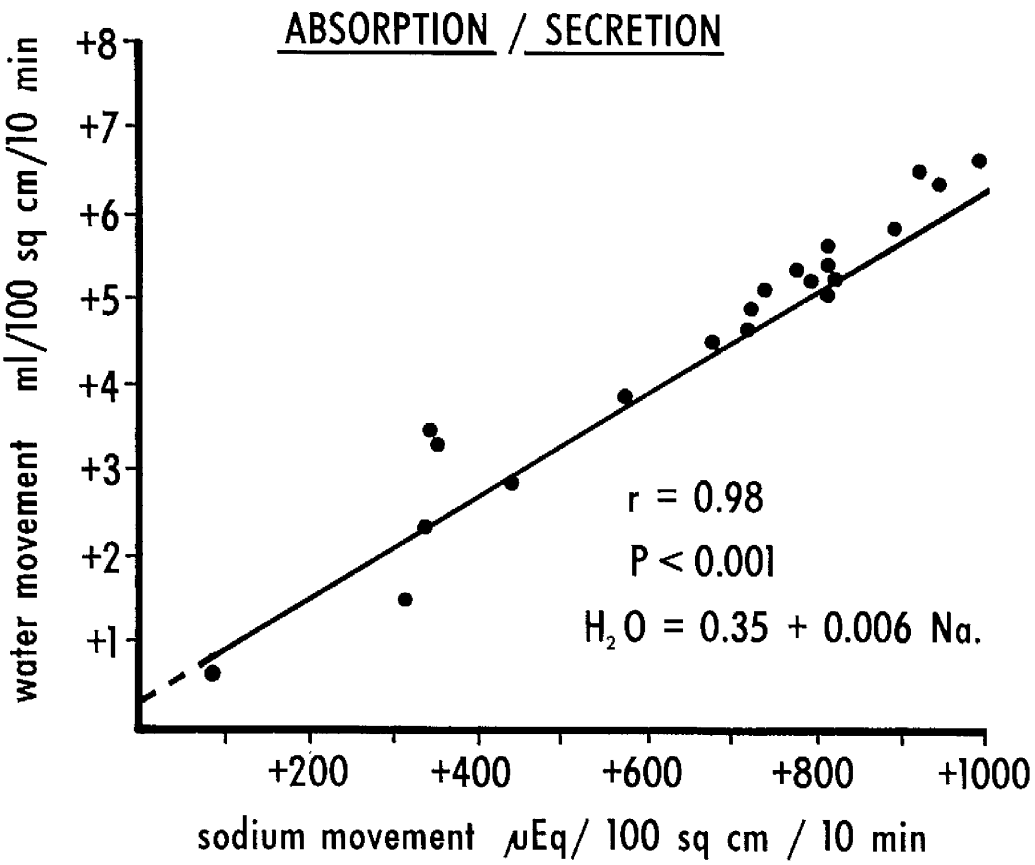


FIGURE 8 Acute preparation (ileum).
The volume of water absorbed has been plotted against the amount of sodium absorbed. The regression line of water absorption on sodium absorption (continuous line) has been extrapolated to the y-axis as a dotted line. The plus sign preceding rates of net movement indicates absorption.

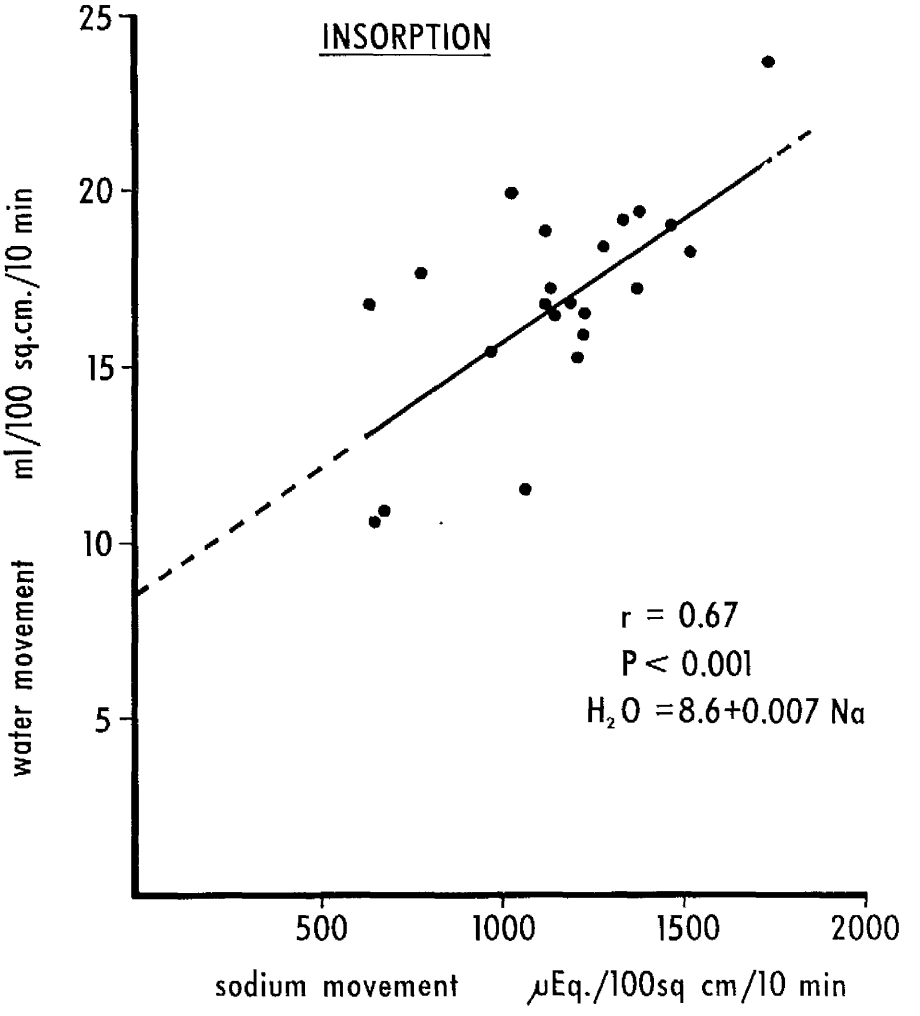


FIGURE 9 Acute preparation (ileum).
The volume of water insorbed has been plotted against the amount of sodium moving in the same direction. The regression line of water insorption on sodium insorption (continuous line) has been extrapolated to the y-axis as a dotted line.

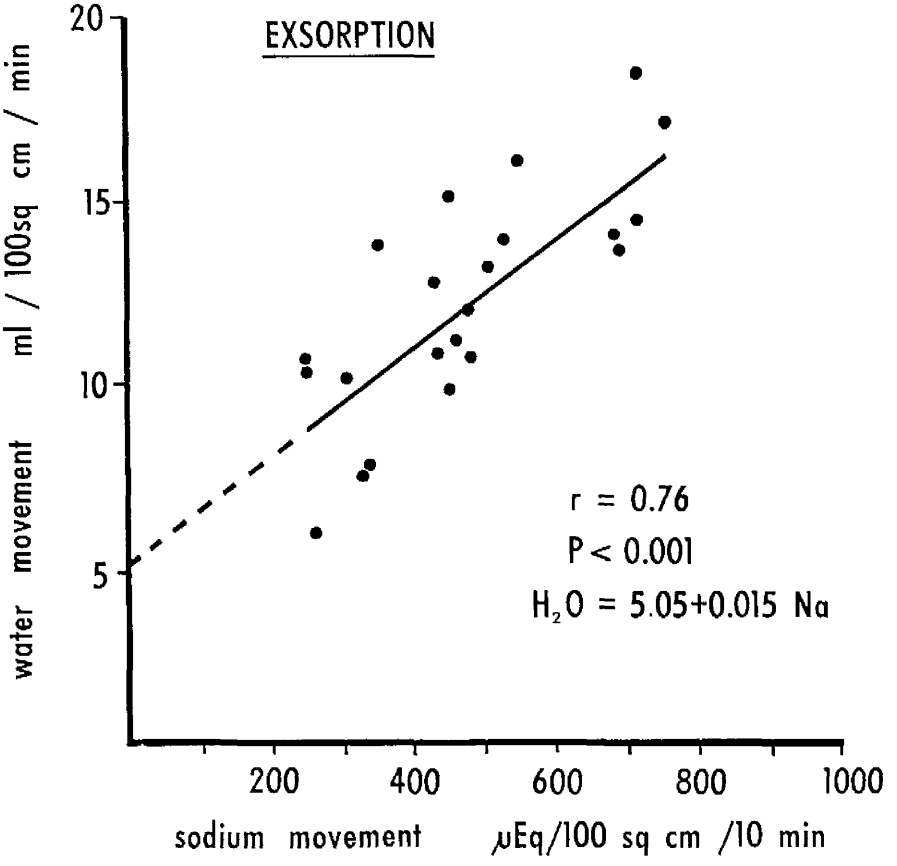


FIGURE 10 Acute preparation (ileum).
The volume of water exsorbed has been plotted against the amount of sodium moving in the same direction. The regression line of water exsorption on sodium exsorption (continuous line) has been extrapolated to the y-axis as a dotted line.

TABLE 7. Concentration of electrolyte in test solution at beginning (t_o) and end (t_{10}) of 10-minute period.
(Mean concentration in mEq/L $\pm$ S.E.M.)

Ion	Preparation*	Concentration at t_o	Concentration at t_{10}	Mean difference	P (Student t test)
		(a) Ileum			
Na	Acute (22)	142 $\pm$ 0.4	140 $\pm$ 0.5	2.0 $\pm$ 0.58	< 0.01
	Chronic (23)	149 $\pm$ 1.7	149 $\pm$ 2.0	0	N.S.
K	Acute (10)	4.0 $\pm$ 0.01	4.8 $\pm$ 0.11	0.8 $\pm$ 0.11	< 0.001
	Chronic (23)	3.5 $\pm$ 0.05	4.0 $\pm$ 0.04	0.5 $\pm$ 0.07	< 0.001
		(b) Colon			
Na	Chronic (29)	151 $\pm$ 1.1	150 $\pm$ 1.3	1.0	N.S.
K	Chronic (29)	3.6 $\pm$ 0.08	4.2 $\pm$ 0.14	0.6 $\pm$ 0.03	< 0.001

NOTE In this Table, and in Figures 11 to 16, the values given for chronic experiments have been taken from 23 tests in the ileum and 29 tests in the colon. These tests were the first two of each experiment and provide strict control information with which the changes after the administration of aldosterone can be compared (see Part V and Tables 35, 36 and 37).

* Figures in parentheses indicate number of tests.

TABLE 8. The rates of transport of sodium, potassium and water in the ileum (chronic Thiry-Vella fistula). (All rates are given as mean rate ± S.E. of mean).

	Dog no. 33	Dog no. 34	Mean
SODIUM (μEq per 10 min)			
Insorpn. rate	609 ± 36	367 ± 39	537 ± 39
n (a)	26	11	37
v (%)(b)	31	35	44
Exsorpn. rate	865 ± 58	795 ± 49	844 ± 56
n	26	11	37
v (%)	35	19	40
Net (c) rate	-256 ± 57	-428 ± 51	-307 ± 45
n	26	11	37
POTASSIUM (μEq per 10 min)			
Insorpn. rate	22.0 ± 1.4	14.2 ± 0.8	19.7 ± 1.3
n	26	11	37
v (%)	30	18	40
Exsorpn. rate	44.1 ± 2.9	34.5 ± 2.8	41.2 ± 3.0
n	26	11	37
v (%)	33	27	45
Net (c) rate	-22.1 ± 22	-20.3 ± 2.2	-21.5 ± 2.1
n	26	11	37
WATER (ml per 10 min)			
Insorpn. rate	13.2 ± 0.8	8.9 ± 0.5	11.6 ± 1.0
n	15	9	24
v (%)	24	15	40
Exsorpn. rate	14.6 ± 1.0	11.5 ± 0.4	13.4 ± 1.1
n	15	9	24
v (%)	27	13	40
Net (c) rate	-1.4 ± 0.4	-2.6 ± 0.2	-1.8 ± 0.3
n	26	18	43

(a) n indicates number of tests.
(b) v is coefficient of variation.
(c) The minus sign preceding mean rate indicates secretion.

TABLE 9. The rates of transport of sodium, potassium and water in the colon (chronic Thiry-Vella fistula). (All rates are expressed as mean rate ± S.E. of mean).

		Dog no. 35	Dog no. 36	Dog no. 37	Mean
SODIUM (μEq per 10 min)					
Insorption	rate	552 ± 48	575 ± 38	645 ± 52	585 ± 27
	n (a)	26	26	18	70
	v % (b)	45	34	35	38
Exsorption	rate	436 ± 36	396 ± 51	650 ± 43	476 ± 28
	n	26	26	18	70
	v %	42	26	28	49
Net (c)	rate	+116 ± 37	+179 ± 35	-5 ± 10	+109 ± 25
	n	26	26	18	70
POTASSIUM (μEq per 10 min)					
Insorption	rate	11.7 ± 1.1	10.3 ± 0.6	19.0 ± 1.6	13.3 ± 0.8
	n	15	26	18	59
	v %	10	31	36	46
Exsorption	rate	17.7 ± 1.9	18.9 ± 1.3	50.6 ± 3.2	28.2 ± 2.3
	n	15	26	18	59
	v %	10	33	27	62
Net	rate	-6.0 ± 2.3	-8.6 ± 1.6	-31.6 ± 4.4	-14.9 ± 2.1
	n	15	26	18	59
WATER (ml per 10 min)					
Insorption	rate	12.8 ± 0.7	12.5 ± 0.4	12.6 ± 0.7	12.7 ± 0.4
	n	19	20	16	55
	v %	25	14	23	20
Exsorption	rate	11.1 ± 0.6	11.4 ± 0.6	13.3 ± 0.8	11.9 ± 0.4
	n	19	20	16	55
	v %	24	24	23	24
Net	rate	+1.0 ± 0.2	+1.4 ± 0.4	-0.4 ± 0.2	+0.9 ± 0.2
	n	26	20	18	70

(a) n indicates number of tests performed.
(b) v is coefficient of variation.
(c) The plus sign preceding mean rate indicates absorption; the minus sign, secretion.

TABLE 10. Comparison of hour-to-hour and day-to-day variability.

Substance	Direction of movement	Source of variation: Days D.F. (a)	Days σ^2 (b)	Hours D.F.	Hours σ^2	F (c)	Significance (d)
		DOG NO. 33 (Ileum)					
SODIUM	Insorption	4	53221	5	7410	7.18	<0.05, >0.01
µEq/10 min	exsorption	4	200115	5	22660	8.83	<0.05, >0.01
POTASSIUM	Insorption	6	66	7	6	11.0	<0.01, >0.001
µEq/10 min	exsorption	6	200	7	36	5.6	<0.05, >0.01
WATER	Insorption	3	25	4	3	9.4	<0.05, >0.01
ml/10 min	exsorption	3	27	4	4	7.2	<0.05, >0.01
		DOG NO. 35 (Colon)					
SODIUM	Insorption	4	96424	5	16159	5.97	<0.05, >0.01
µEq/10 min	exsorption	4	66501	5	6807	9.78	<0.05, >0.01
POTASSIUM	Insorption	2	57	3	12	4.75	<0.2, >0.1
µEq/10 min	exsorption	3	131	4	151	1.17	>0.2
WATER	Insorption	3	7	4	4	1.94	>0.2
ml/10 min	exsorption	3	6	4	2	2.61	<0.2, >0.1
		DOG NO. 36 (Colon)					
SODIUM	Insorption	5	56733	6	8922	6.36	<0.05, >0.01
µEq/10 min	exsorption	5	140993	6	16676	8.45	<0.05, >0.01
POTASSIUM	Insorption	6	22	7	6	3.6	<1.0, >0.05
µEq/10 min	exsorption	6	143	7	8	19.0	<0.001
WATER	Insorption	5	260	6	200	1.3	>0.2
ml/10 min	exsorption	5	826	6	569	1.4	>0.2

NOTES: (a) D.F. stands for degrees of freedom, in this case one less than the number of observations.
(b) σ^2 is the variance estimate.
(c) F variance ratio = $\frac{\text{greater estimate of the variance}}{\text{lesser estimate of the variance}}$
(d) The significance of the F ratios were obtained from Fisher and Yates (1963).

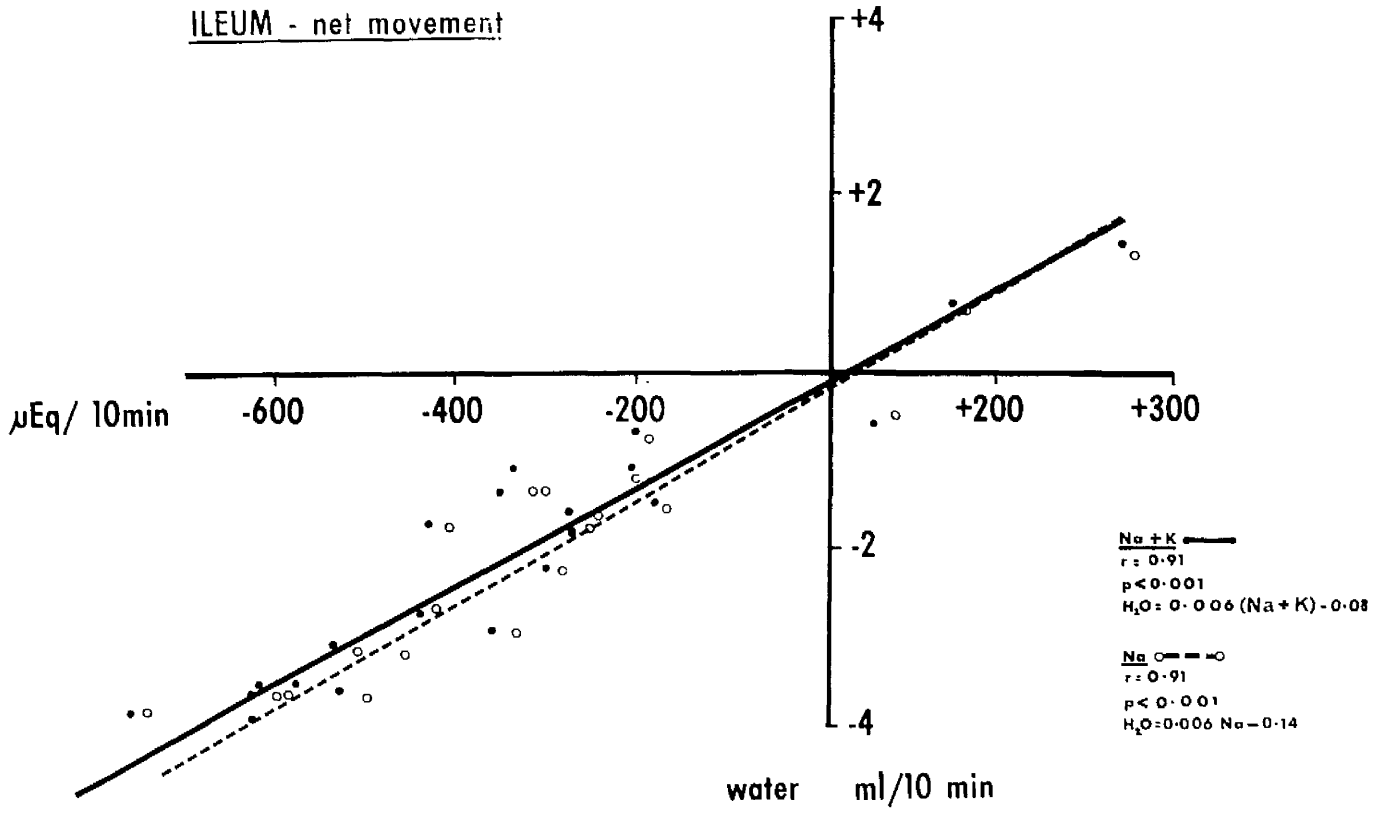


FIGURE 11 Chronic preparation (ileum).

The net volume of water transported was plotted against the net movement of sodium (Na) and of sodium plus potassium (Na + K). The regression line of net water movement on net Na movement is dotted, the individual points being open dots; solid dots are used when net water movement is plotted against net (Na + K) movement, the regression line being continuous.

The plus sign preceding the rates of net movement indicates absorption; a minus sign, secretion.

For Figures 11 to 16, reference should be made to the footnote to Table 7.

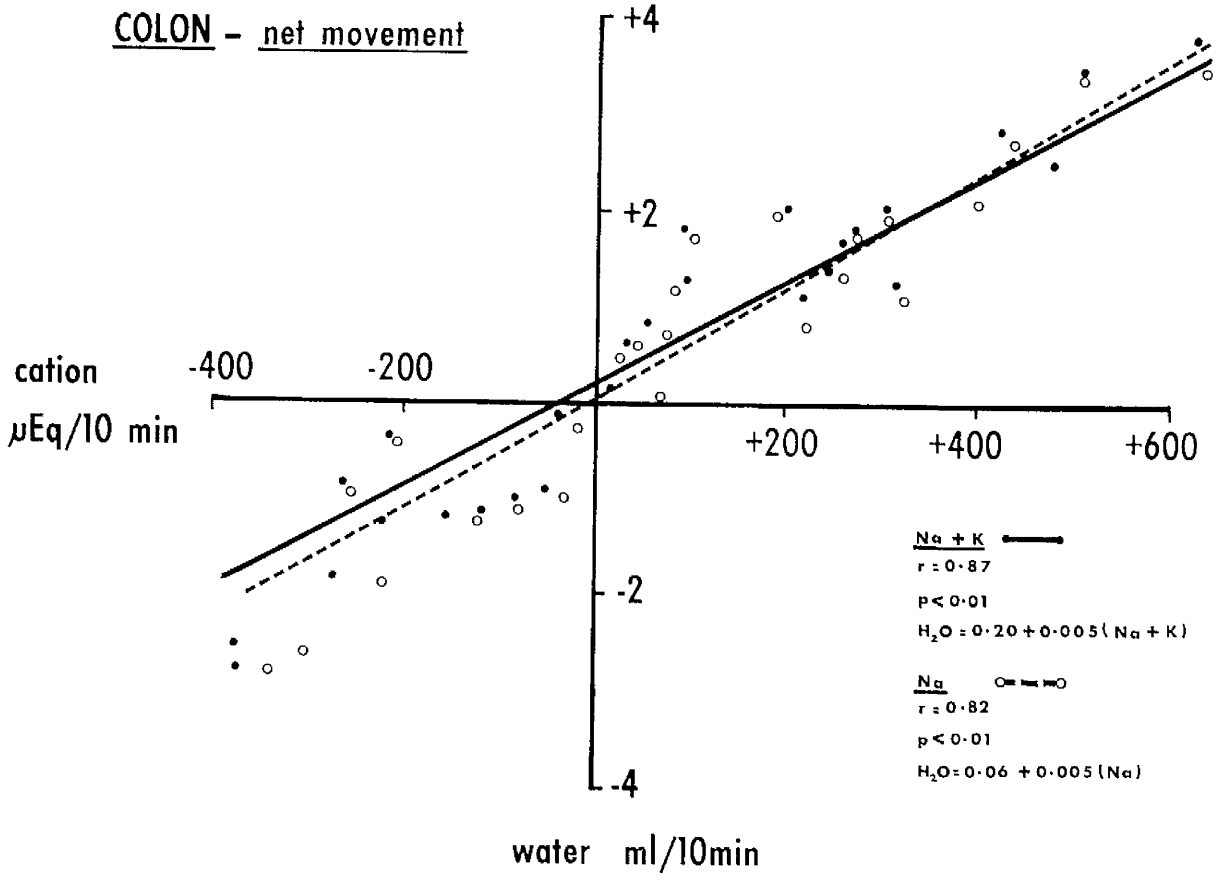


FIGURE 12 Chronic preparation (colon).
Plot of net water movement against net cation movement.
Legend as in Figure 11.

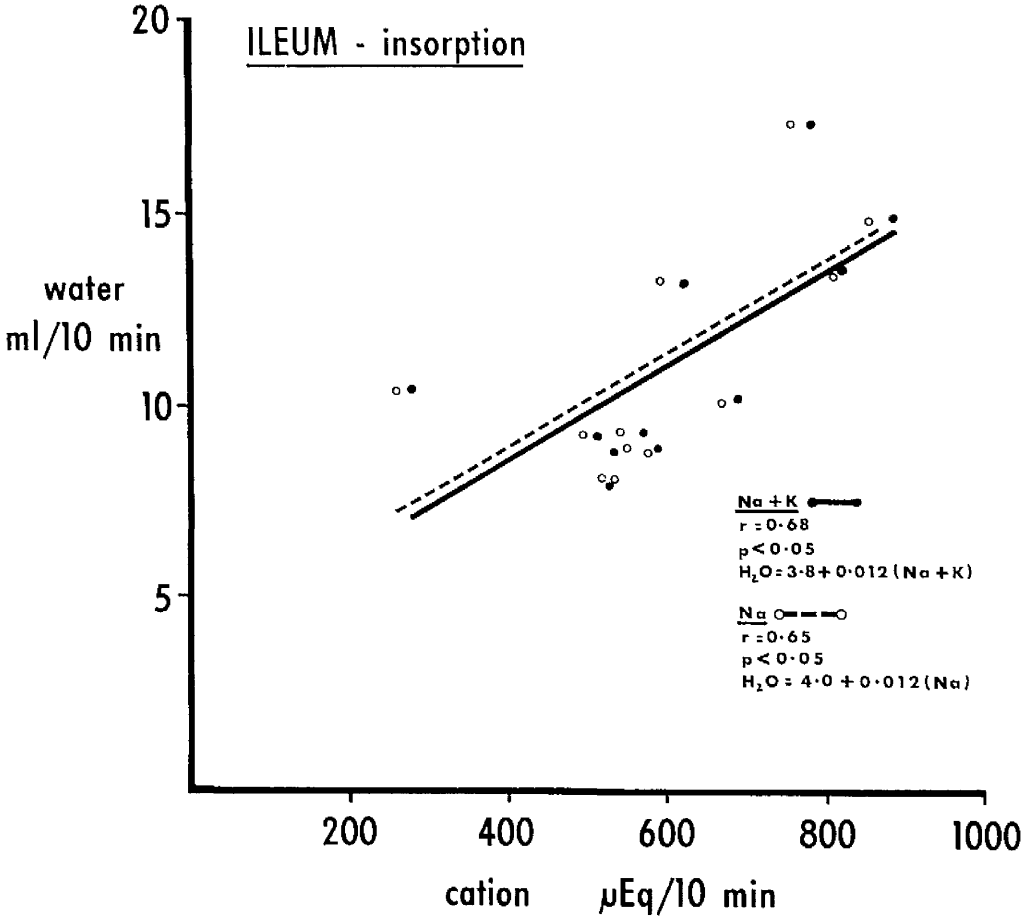


FIGURE 13 Chronic preparation (ileum).

The volume of water insorbed from the lumen has been plotted against the amount of cation moving in the same direction. The continuous line represents the regression line of water insorption on (Na + K) insorption (solid dots); and the dotted line, the regression line of water insorption on Na insorption (open dots).

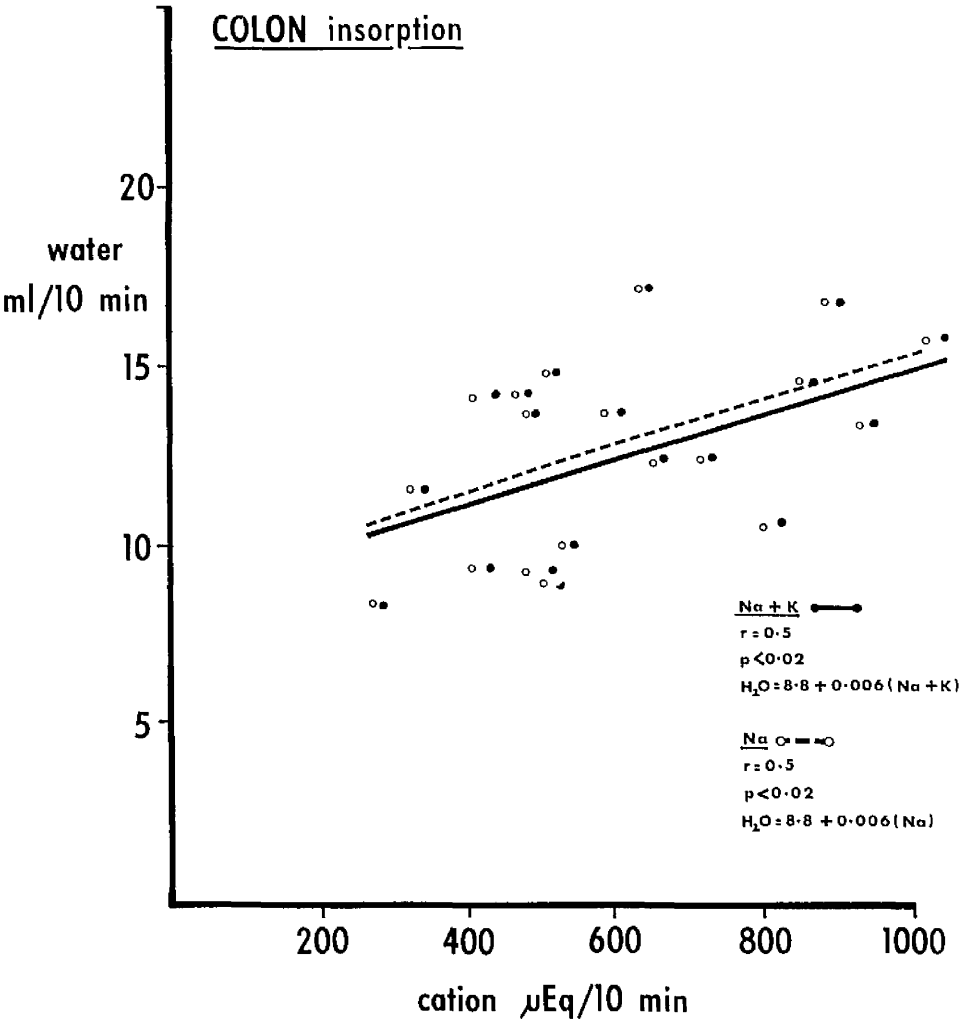


FIGURE 14 Chronic preparation (colon).
Plot of volume of water insorbed against amount of cation insorbed.
Legend as in Figure 13.
(Note: Two solid dots which lie on the continuous regression line have not been shown).

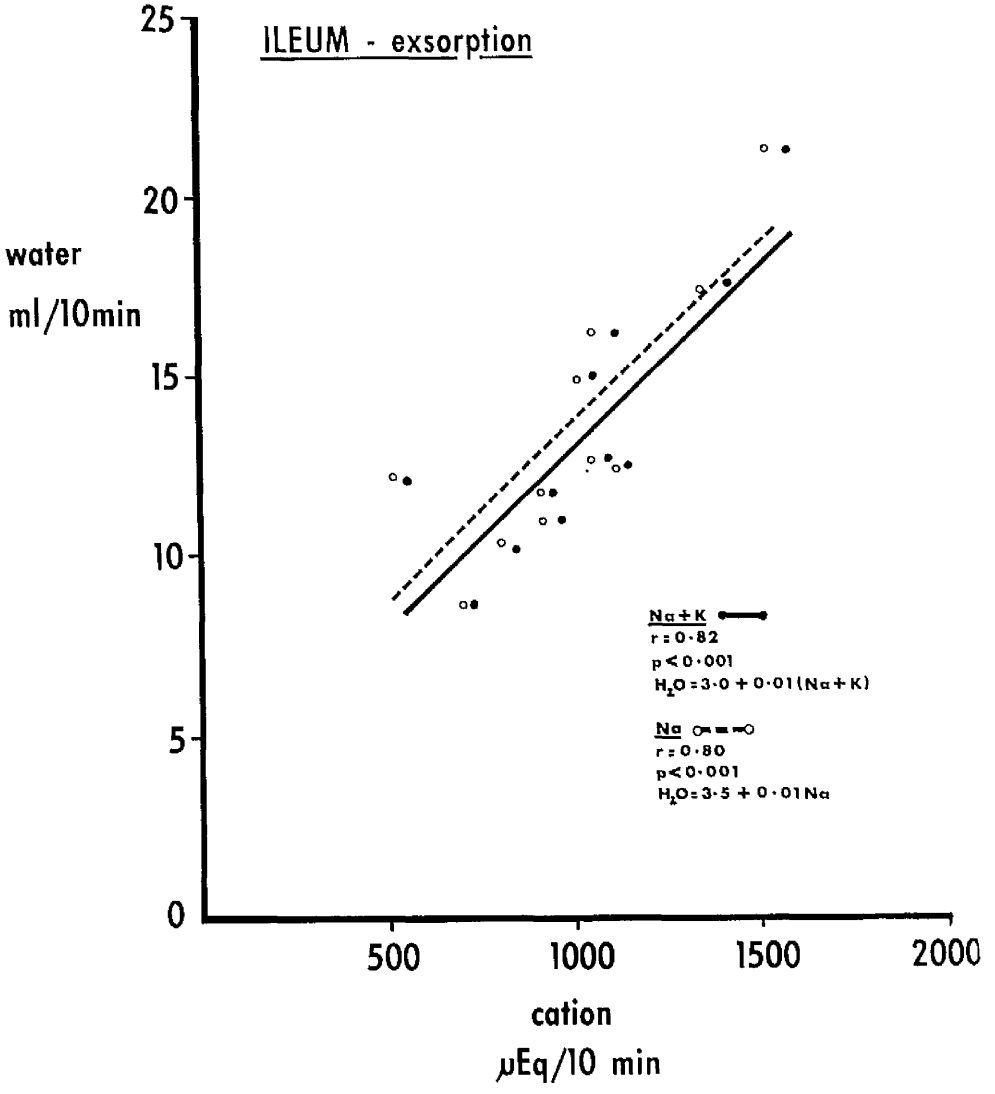


FIGURE 15 Chronic preparation (ileum).
Plot of the volume of water exsorbed against the amount of cation moving in the same direction. The continuous line represents the regression line of water exsorption on (Na + K) exsorption, (solid dots); the dotted line is the regression of water exsorption on (Na) exsorption (open dots).

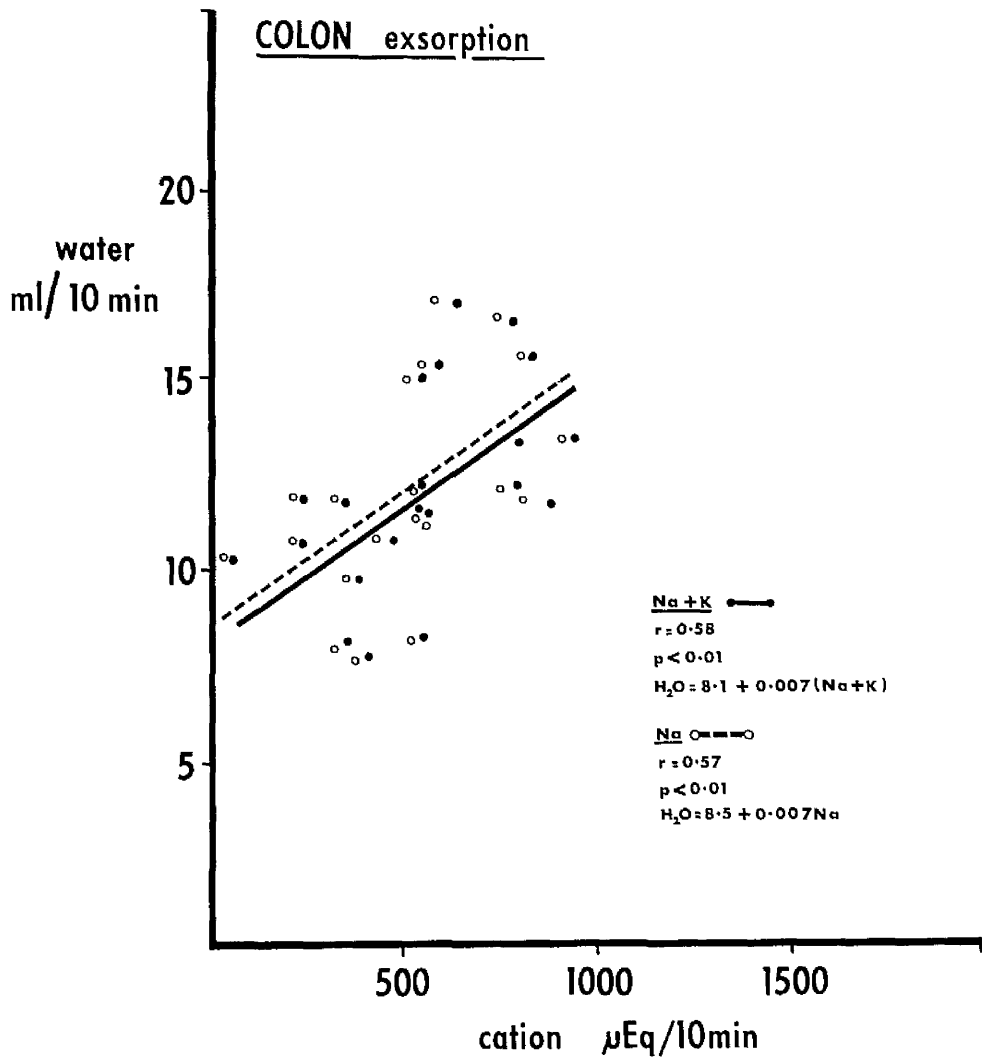


FIGURE 16 Chronic preparation (colon).
Plot of volume of water exsorbed against the amount of cation exsorbed.
Legend as in Figure 15.

TABLE 11. The rates of movement of sodium and potassium into and out of the ileum and colon of the dog *in vivo*.

Substance	Site	Preparation	Insorption	Exsorption	Net	Ref.
Sodium mμM per cm^2 per min	Ileum	Chronic	890	530	+360	1
			750	890	-140	2
			470	789	-319	3
			613	740	-127	4
			1472	984	+488	5
			1483	1000	+483	5
			1713	963	+750	6
			537	844	-307	Present study
		Acute	1150	490	+660	5
			700	510	+190	7
			1151	471	+680	Present study
	Colon	Chronic	870	440	+430	1
			490	330	+160	2
			512	290	+222	3
			552	280	+272	4
			585	476	+109	Present study
		Acute	540	400	+140	7
Potassium mμM per cm^2 per min	Ileum	Chronic	19.8	30.8	-11.0	3
			21.5	32.6	-11.1	4
			57.0	56.0	+ 1.0	5
			53.2	64.3	-11.1	6
			19.7	41.2	-21.5	Present study
		Acute	54.0	84.0	-30.0	5
			23.8	37.9	-14.1	Present study
	Colon	Chronic	19.9	33.7	-13.8	3
			20.2	33.7	-13.5	4
			13.3	28.2	-14.9	Present study

For references see Table 12.

TABLE 12. The rate of movement of water into and out of the ileum and colon of the dog *in vivo*.

Substance	Site	Preparation	Insorption	Exsorption	Net	Ref.
Water μL per cm^2 per min	Ileum	Chronic	20.2	15.6	+4.6	8
			-	-	-2.0	3
			22.1	18.4	+3.7	5
			22.2	19.2	+3.0	5
			23.5	18.0	+5.5	6
			11.6	13.4	-1.8	Present study
		Acute	22.0	18.0	+4.0	5
			8.8	7.4	+1.4	7
			16.9	12.3	+4.6	Present study
	Colon		-	-	+1.2	3
			6.4	4.9	+1.5	7
			30.4	25.1	+5.3	8
			12.7	11.9	+0.8	Present study

References

1. Visscher *et al.*, 1944b.
2. Berger *et al.*, 1959a.
3. Berger *et al.*, 1959b.
4. Berger *et al.*, 1960.
5. Code *et al.*, 1960.
6. Nelson *et al.*, 1962.
7. Grim, 1962.
8. Visscher *et al.*, 1944a.

Notes

The surface area in the above tables is the serosal area obtained from the length and circumference of the bowel. The rates given in the tables have been calculated from the authors' data/

data in the following way:-

(a) Visscher et al., (1944a and b) did not express their results in terms of surface area. They used segments of ileum, 30 to 40 cm long, which would have an average serosal area of 180 cm^2, and segments of colon, 15 to 20 cm long, whose serosal area would be 100 cm^2.

(b) Berger et al., (1959a and b; 1960) used segments of ileum and colon, 20 cm long, whose serosal area would be approximately 100 cm^2.

(c) Code et al., (1960) and Nelson et al., (1962) expressed their results in terms of 100 cm^2 serosal surface area.

(d) The rates given by Grim (1962) were expressed according to mucosal surface area which can be converted to serosal area by multiplying ileal rates by 6.8 and the colonic rates by 1.2 (Davenport, 1961).

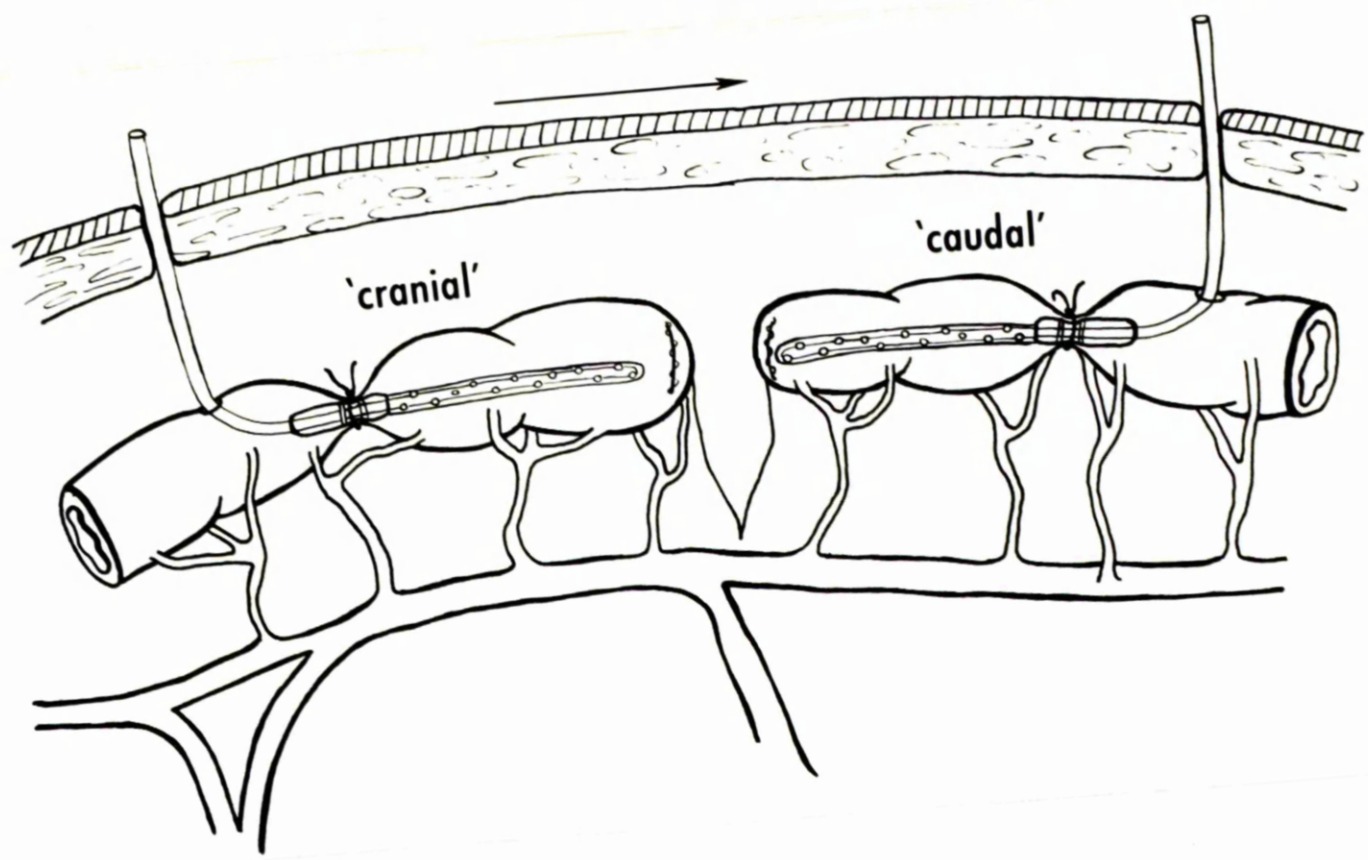


FIGURE 17 Diagram of the experimental preparation for the study of the effect of obstruction upon the sorption of water, sodium and potassium.
The arrow points caudally.

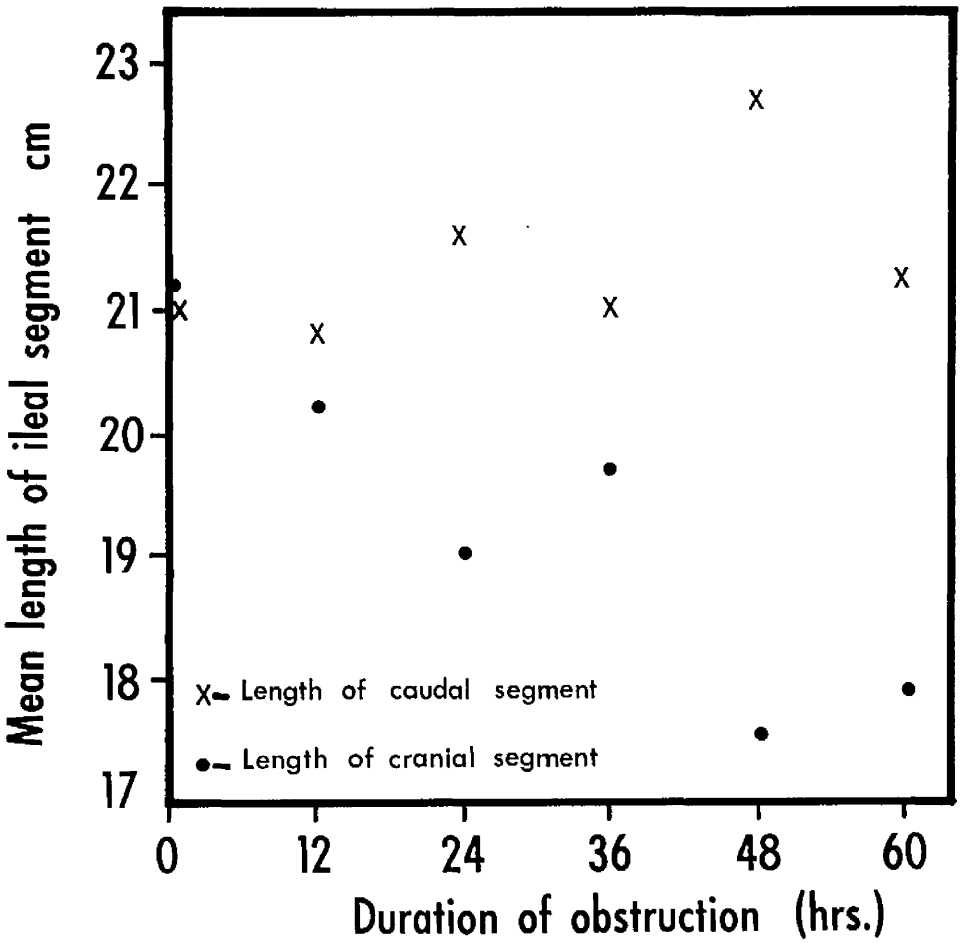


FIGURE 18 Effect of obstruction upon the length of bowel.

In each dog, at the initial operation, a silk suture was placed on the ileum 21 cm cranial and caudal to the obstruction. At subsequent post-mortem examination the distances between the obstruction and the marking sutures were re-measured.

The greater the duration of the obstruction, the shorter became the bowel above the obstruction, while the length of bowel below the obstruction did not alter.

TABLE 13. The effect of obstruction upon the dimensions of ileum.

Dog	Duration of obstruction (hours)	Segment cranial to obstruction			Segment caudal to obstruction		
		length cm	breadth cm	area cm^2	length cm	breadth cm	area cm^2
18	0	21.5	4.5	96.8	21.0	4.5	94.5
19	0	21.0	5.0	105.0	21.0	4.4	92.3
20	12	20.0	5.5	110.0	20.5	4.5	92.3
21	12	20.5	5.0	102.5	21.0	4.5	94.5
22	24	18.5	5.5.	101.8	22.0	4.5	99.0
23	24	19.5	5.5	107.3	21.0	4.0	84.0
24	36	20.0	5.0	100.0	21.5	4.5	96.8
25	36	19.5	5.5	107.3	20.5	4.5	92.3
26	48	17.0	6.0	102.	22.5	4.0	90.0
27	48	18.0	5.5	101.8	23.0	4.0	92.0
28	60	17.5	6.5	113.8	20.5	5.0	102.5
29	60	18.0	7.0	126.0	22.0	4.0	88.0

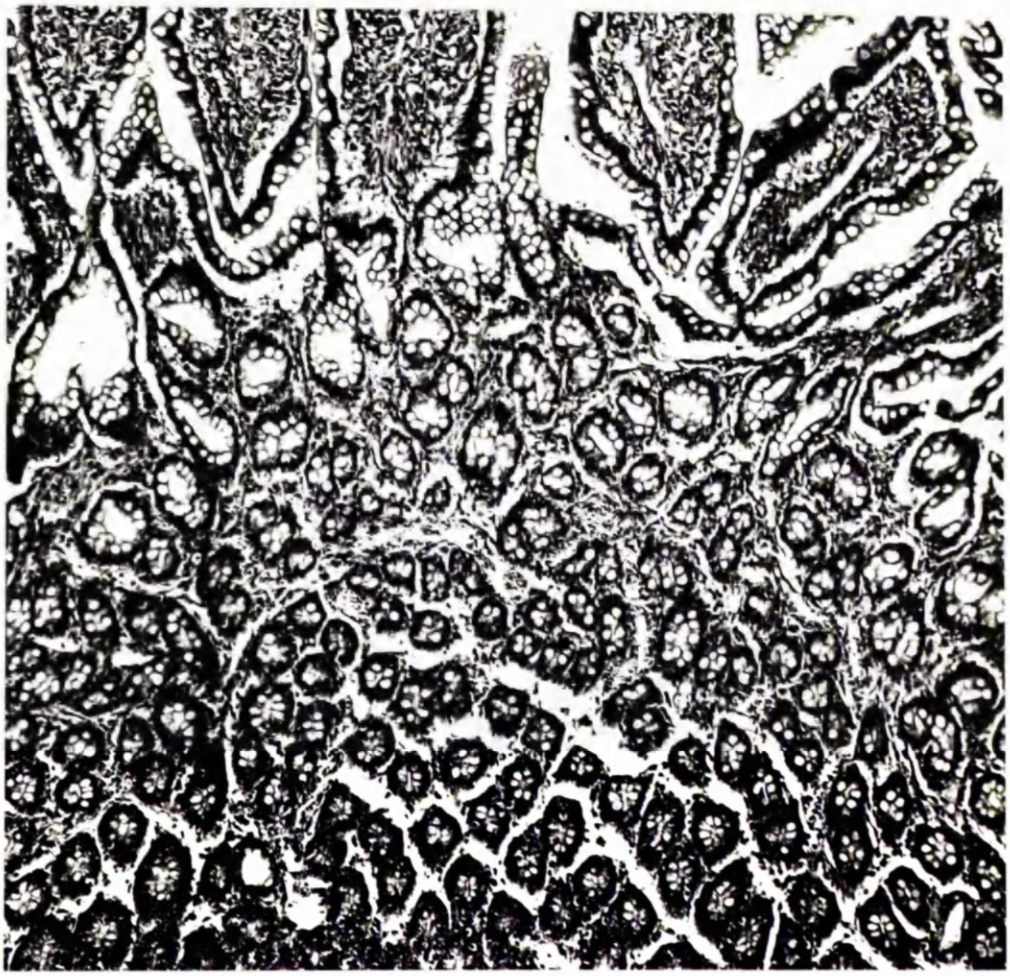


FIGURE 19 Histology of obstructed bowel
Photomicrograph of a section of ileum, cranial to an obstruction of 48 hours duration (dog no. 26), shows capillary dilatation and engorgement of small venules. Round-cell infiltration and oedema of tissue spaces are evident.
Haematoxylin and eosin (H. and E.) x 150.

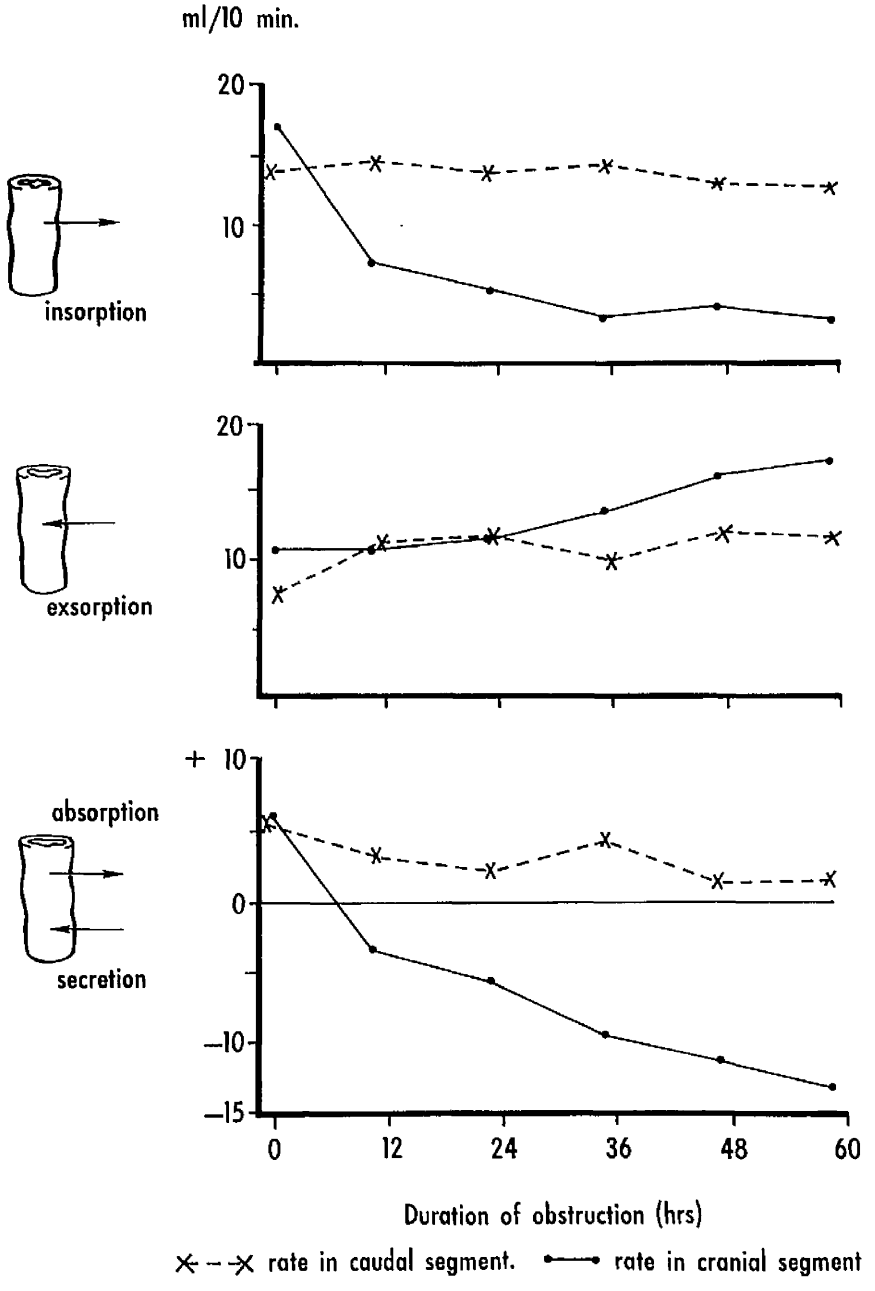


FIGURE 20 The movement of water across the mucosa of ileal segments immediately cranial and caudal to the obstruction.
For significance of difference in mean rates between successive periods of time, see Tables 14 and 18.
For significance of difference in mean rates between cranial and caudal segments, see Table 21.

TABLE 14. The rate of movement of water in ileum immediately cranial to an obstruction.
(ml per 10 min.)

Duration of obstruction (hrs)	Net (a)		Insorption		Exsorption	
	Mean rate ± S.E.M.	P (b)	Mean rate ± S.E.M.	P (b)	Mean rate ± S.E.M.	P (b)
0	+6.2 ± 1.0		17.0 ± 0.6		10.8 ± 1.2	
		< 0.001		< 0.001		< 0.9
12	-3.1 ± 0.2		7.5 ± 0.5		10.6 ± 0.6	
		< 0.001		< 0.05		< 0.4
24	-5.7 ± 0.2		5.7 ± 0.6		11.4 ± 0.6	
		< 0.001		< 0.1		< 0.1
36	-9.6 ± 0.7		3.7 ± 0.8		13.3 ± 0.7	
		< 0.1		< 0.4		< 0.05
48	-11.4 ± 0.6		4.4 ± 0.2		15.8 ± 0.7	
		< 0.1		< 0.2		< 0.1
60	-13.4 ± 0.6		3.1 ± 0.7		16.5 ± 0.9	

(a) Plus sign preceding rate indicates absorption; minus sign, secretion.

(b) P represents the probability that the mean rates of water movement measured at successive periods of time after the formation of the obstruction did not differ from one another.
Test of significance - Student's t test.

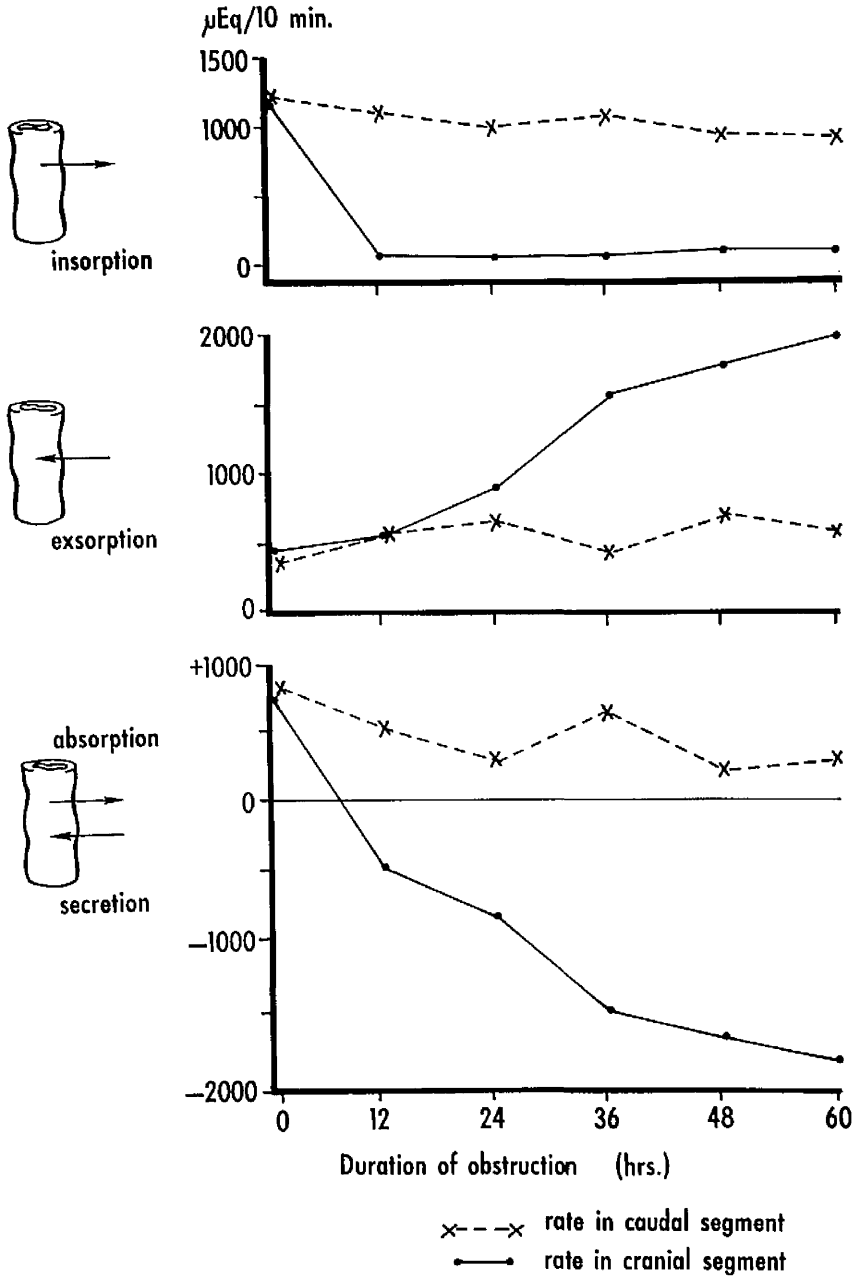


FIGURE 21 The movement of sodium across the mucosa of ileal segments immediately cranial and caudal to the obstruction.
For significance of difference in mean rates between successive periods of time, see Tables 15 and 19.
For significance of difference in mean rates between cranial and caudal segments, see Table 22.

TABLE 15. The rate of movement of sodium in ileum immediately cranial to an obstruction. (μEq per 10 min.)

Duration of obstruction (hrs)	Net		Insorption		Exsorption	
	Mean rate ± S.E.M.	P	Mean rate ± S.E.M.	P	Mean rate ± S.E.M.	P
0	+718 ± 76		1152 ± 63		434 ± 68	
		< 0.001		< 0.001		< 0.1
12	-490 ± 32		45 ± 4.7		535 ± 30	
		< 0.001		< 0.001		< 0.001
24	-842 ± 31		18 ± 1.6		860 ± 30	
		< 0.001		< 0.001		< 0.001
36	-1516 ± 37		44 ± 3.5		1560 ± 40	
		< 0.01		< 0.01		< 0.01
48	-1697 ± 43		61 ± 3.7		1758 ± 46	
		< 0.02		< 0.4		< 0.05
60	-1882 ± 46		53 ± 8.0		1935 ± 51	

Footnotes: see Table 14.

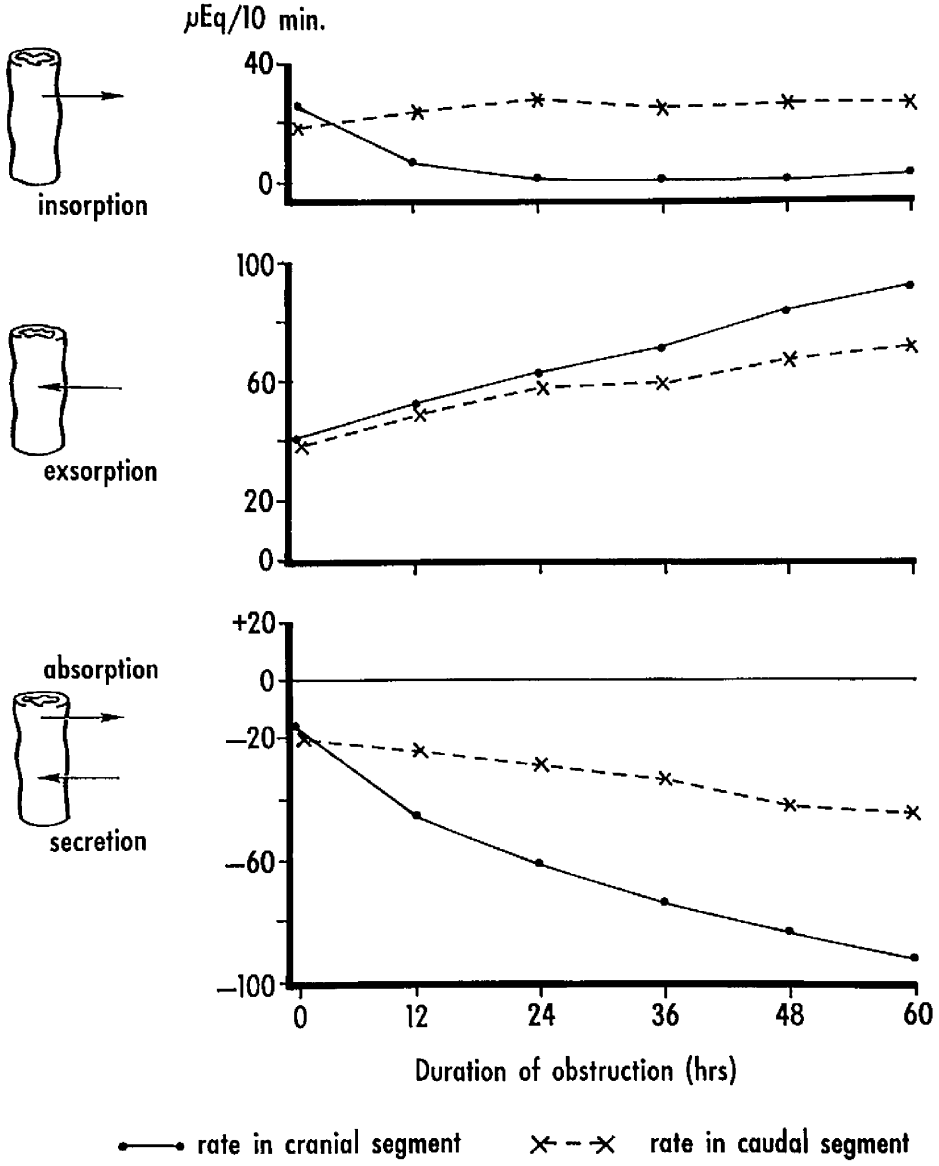


FIGURE 22 The movement of potassium across the mucosa of ileal segments immediately cranial and caudal to the obstruction.
For significance of difference in mean rates between successive periods of time, see Tables 16 and 20.
For significance of difference in mean rates between cranial and caudal segments, see Table 23.

TABLE 16. The rate of movement of potassium in ileum immediately cranial to an obstruction. (μEq per 10 min.)

Duration of obstruction (hrs)	Net		Insorption		Exsorption	
	Mean rate ± S.E.M.	P	Mean rate ± S.E.M.	P	Mean rate ± S.E.M.	P
0	-15.5 ± 2.1		26.0 ± 2.4		41.5 ± 1.1	
		<0.001		< 0.001		< 0.01
12	-45.4 ± 2.6		8.3 ± 0.5		53.7 ± 2.5	
		<0.01		< 0.001		< 0.05
24	-60.8 ± 2.8		2.4 ± 0.3		63.2 ± 2.9	
		<0.02		< 0.9		< 0.2
36	-71.1 ± 3.7		2.3 ± 0.3		73.4 ± 3.5	
		<0.05		< 0.05		< 0.01
48	-83.2 ± 2.5		1.5 ± 0.1		84.7 ± 2.5	
		<0.2		<0.3		< 0.1
60	-90.1 ± 3.3		2.4 ± 0.7		92.5 ± 3.1	

Footnotes: see Table 14.

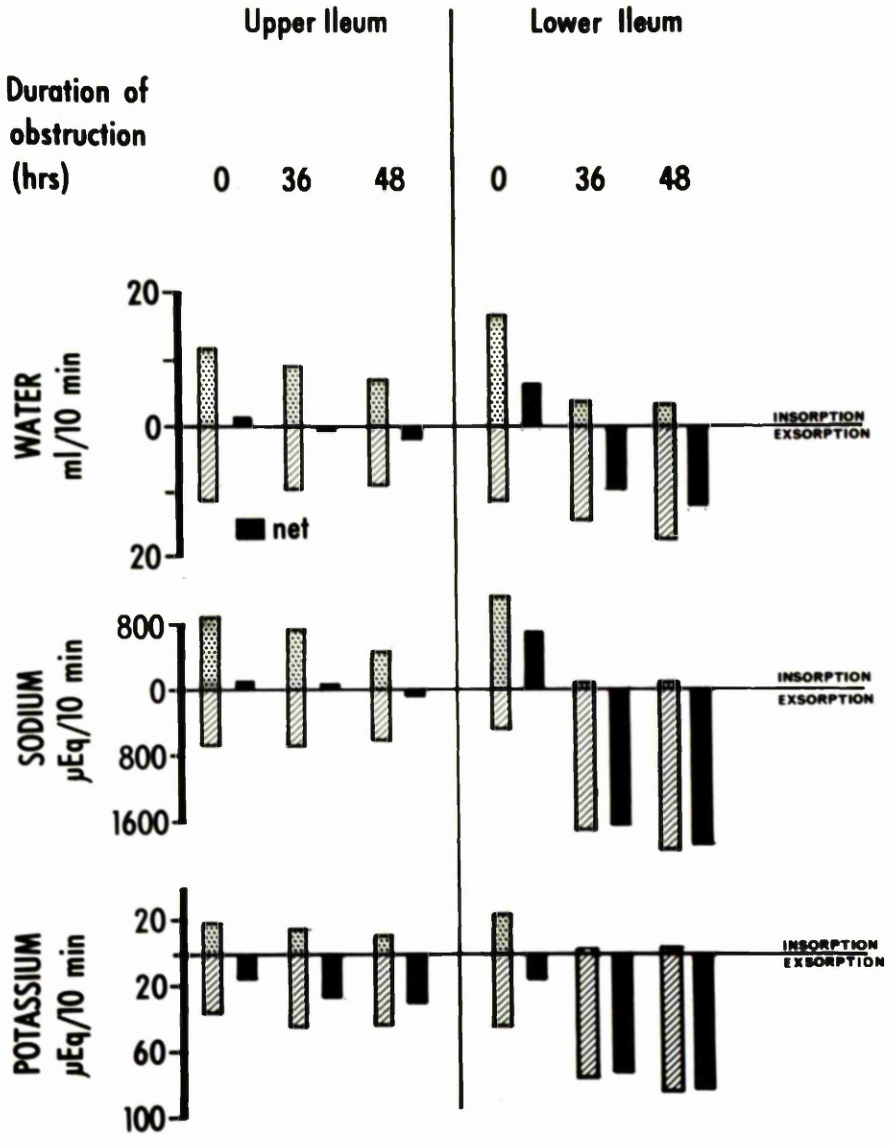


FIGURE 23 The sorption of water, sodium and potassium in the upper ileum is compared to that in the lower ileum immediately cranial to the obstruction.

Insorption (dotted rectangle) is plotted up from the horizontal line and exsorption (hatched rectangle) down from the horizontal line. Net movement is designated by the solid rectangle: absorption is charted above, and secretion below, the line.

TABLE 17. A comparison in the rates of movement of water, sodium and potassium between ileum above but adjacent to obstruction (lower ileum) and ileum above and remote from obstruction (upper ileum).

Substance	Duration of obstruction (hours)					
	0		36		48	
	Upper	Lower	Upper	Lower	Upper	Lower
Water (ml per 10 min)						
Net	+0.9	+6.2	-0.1	-9.6	-1.1	-11.4
Insorption	11.8	17.0	9.6	3.7	7.4	4.4
Exsorption	10.9	10.8	9.7	13.3	8.5	15.8
Sodium (µEq per 10 min)						
Net	+179	+718	+18	-1516	-75	-1697
Insorption	846	1152	753	44	534	61
Exsorption	667	434	735	1560	609	1758
Potassium (µEq per 10 min)						
Net	-15.8	-15.5	-27.2	-71.1	-28.3	-83.2
Insorption	19.6	26.0	16.6	2.3	12.7	1.5
Exsorption	35.4	41.5	43.8	73.4	41.0	84.7

TABLE 18. The rate of movement of water in ileum caudal to an obstruction.
(ml per 10 min.)

Duration of obstruction (hrs)	Net		Insorption		Exsorption	
	Mean rate ± S.E.M.	P	Mean rate ± S.E.M.	P	Mean rate ± S.E.M.	P
0	+5.9 ± 0.6		13.8 ± 0.7		7.9 ± 0.5	
		< 0.05		< 0.6		< 0.05
12	+3.5 ± 0.7		14.5 ± 0.9		11.0 ± 1.2	
		< 0.1		< 0.7		< 0.7
24	+2.1 ± 0.3		13.8 ± 0.9		11.7 ± 0.9	
		< 0.001		< 0.7		< 0.2
36	+4.5 ± 0.6		14.4 ± 0.8		9.9 ± 0.9	
		< 0.001		< 0.1		< 0.2
48	+1.4 ± 0.2		12.9 ± 0.4		11.5 ± 0.5	
		< 0.6		< 0.9		< 0.6
60	+1.7 ± 0.4		12.7 ± 0.9		11.0 ± 0.7	

Footnotes: see Table 14.

TABLE 19. The rate of movement of sodium in ileum caudal to an obstruction.
(μEq per 10 min.)

Duration of obstruction (hrs)	Net		Insorption		Exsorption	
	Mean rate ± S.E.M.	P	Mean rate ± S.E.M.	P	Mean rate ± S.E.M.	P
0	+832 ± 89		1215 ± 93		383 ± 48	
		< 0.1		< 0.3		< 0.2
12	+552 ± 101		1107 ± 28		555 ± 88	
		< 0.6		< 0.01		< 0.4
24	+347 ± 31		996 ± 14		649 ± 29	
		< 0.01		< 0.3		< 0.02
36	+640 ± 85		1047 ± 46		407 ± 71	
		< 0.001		< 0.05		< 0.01
48	+214 ± 14		904 ± 36		690 ± 37	
		< 0.3		< 0.9		< 0.1
60	+302 ± 65		899 ± 49		597 ± 34	

Footnotes: see Table 14.

TABLE 20. The rate of movement of potassium in ileum caudal to an obstruction.
(μEq per 10 min.)

Duration of obstruction (hrs)	Net		Insorption		Exsorption	
	Mean rate ± S.E.M.	P	Mean rate ± S.E.M.	P	Mean rate ± S.E.M.	P
0	-20.5 ± 2.9	<0.2	18.4 ± 2.0	<0.05	38.9 ± 1.9	<0.01
12	-25.3 ± 1.0	<0.02	23.6 ± 0.6	<0.001	48.9 ± 1.5	<0.001
24	-29.1 ± 0.7	<0.01	28.7 ± 1.0	<0.2	57.8 ± 1.1	<0.5
36	-33.4 ± 1.0	<0.001	25.7 ± 1.6	<0.8	59.1 ± 1.1	<0.001
48	-42.5 ± 1.1	<0.5	26.3 ± 0.7	<0.8	68.8 ± 1.5	<0.5
60	-43.7 ± 1.1		26.6 ± 1.2		70.3 ± 1.5	

Footnotes: see Table 14.

TABLE 21. Comparison in rates of water transport in ileum, cranial and caudal to obstruction (a).

	Duration of obstruction (hours)					
	0	12	24	36	48	60
Insorption						
Mean difference between cranial and caudal segments (b).	+3.2	-7.0	-8.1	-10.7	-8.5	-9.6
S.E.M. difference	0.89	0.99	1.2	1.1	0.47	0.36
t	3.6	7.1	6.9	9.8	18.1	26.6
P	<0.01	<0.001	<0.001	<0.001	<0.001	<0.001
Exsorption						
Mean difference between cranial and caudal segments (b)	+2.9	-0.4	-0.3	+3.4	+4.3	+5.5
S.E.M. difference	1.26	1.4	1.8	1.2	0.86	1.2
t	2.3	0.3	0.16	2.9	5.01	4.6
P	<0.05	<0.8	<0.9	<0.02	<0.001	<0.001
Net						
Mean difference between cranial and caudal segments (b)	+0.3	-6.6	-7.8	-14.1	-12.8	-15.1
S.E.M. difference	1.21	0.7	0.65	0.93	0.64	0.74
t	0.25	9.4	12.0	15.1	20.0	20.4
P	<0.9	<0.001	<0.001	<0.001	<0.001	<0.001

(a) At each period of time the mean rate in the cranial segment was compared to the mean rate in the caudal segment, in each case the mean being calculated from six measurements.

(b) A plus sign preceding mean difference indicates that the mean rate in the cranial segment was greater than that in the caudal segment; a minus sign, that the mean rate in cranial segment was less than that in caudal segment.

Mean difference in rates in ml per 10 min.

TABLE 22. Comparison in rates of sodium movement in ileum, cranial and caudal to obstruction. (μEq per 10 min).

	Duration of obstruction (hours)					
	0	12	24	36	48	60
Insorption						
Mean difference between cranial and caudal segments.	-63	-1062	-974	-1003	-843	-846
S.E.M. difference	113	29	13	46	36	50
t	0.56	37	71	22	23	17
P	<0.6	<0.001	<0.001	<0.001	<0.001	<0.00
Exsorption						
Mean difference between cranial and caudal segments.	+51	-20	+211	+1153	+1068	+133
S.E.M. difference	83	93	42	81	59	6
t	0.61	0.22	5.0	14	18	2
P	<0.6	<0.9	<0.001	<0.001	<0.001	<0.00
Net						
Mean difference between cranial and caudal segments.	-114	-1042	-1189	-2156	-1911	-218
S.E.M. difference	116	106	44	92	49	8
t	0.98	9.8	27	23	38	2
P	<0.4	<0.001	<0.001	<0.001	<0.001	<0.00

See footnotes of Table 21.

TABLE 23. Comparison in rates of potassium movement in ileum, cranial and caudal to obstruction. (μEq per 10 min).

	Duration of obstruction (hours)					
	0	12	24	36	48	60
Insorption						
Mean difference between cranial and caudal segments.	+7.6	-15.3	-25.3	-23.4	-24.8	-24.2
S.E.M. difference	2.6	0.77	1.02	1.6	0.73	1.4
t	2.98	21.0	24.8	14.7	34	17.5
P	<0.02	<0.001	<0.001	<0.001	<0.001	<0.00
Exsorption						
Mean difference between cranial and caudal segments.	+2.6	+4.8	+5.4	+14.3	+15.9	+22.2
S.E.M. difference	2.0	2.9	3.1	3.8	2.9	3.4
t	0.13	1.6	1.74	3.1	5.5	6.5
P	<0.9	<0.2	<0.2	<0.02	<0.001	<0.00
Net						
Mean difference between cranial and caudal segments.	+5.0	-20.1	-31.7	-37.7	-40.7	-46.4
S.E.M. difference	3.6	2.8	2.8	3.6	2.7	3.5
t	1.4	7.1	11.2	11.0	14.8	13.2
P	<0.2	<0.001	<0.001	<0.001	<0.001	<0.00

See footnotes of Table 21.

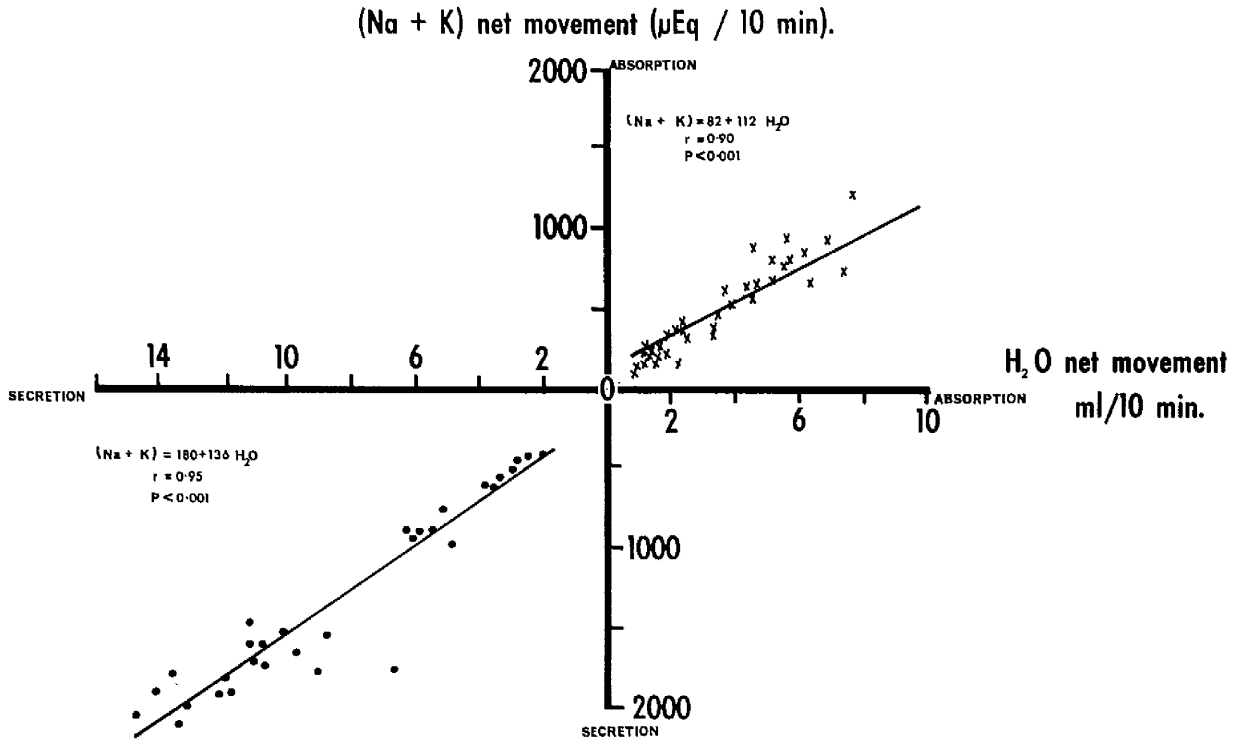


FIGURE 24 The net cation (Na + K) movement is plotted against the net water movement for the segments of ileum, cranial (●) and caudal (X) to the obstruction.

TABLE 24. Mean ratios of cation (Na + K) to water movement in ileum cranial and caudal to obstruction. (mEq per litre ± S.E. of mean). (Each mean ratio is calculated from six values).

Duration of obstruction (hrs)	Insorption		Exsorption	
	Cranial segment	Caudal segment	Cranial segment	Caudal segment
0	56.6 ± 4.0	77.9 ± 5.1	37.1 ± 6.6	43.3 ± 5.1
12	7.0 ± 0.7	79.3 ± 5.0	55.7 ± 3.2	54.4 ± 4.5
24	3.7 ± 0.4	75.4 ± 4.0	84.3 ± 6.6	63.9 ± 3.9
36	16.0 ± 4.3	75.3 ± 4.4	123.9 ± 7.0	46.9 ± 4.9
48	14.3 ± 0.6	72.6 ± 2.8	117.4 ± 5.1	66.6 ± 4.0
60	11.8 ± 2.9	73.5 ± 2.6	124.4 ± 6.6	61.6 ± 4.1

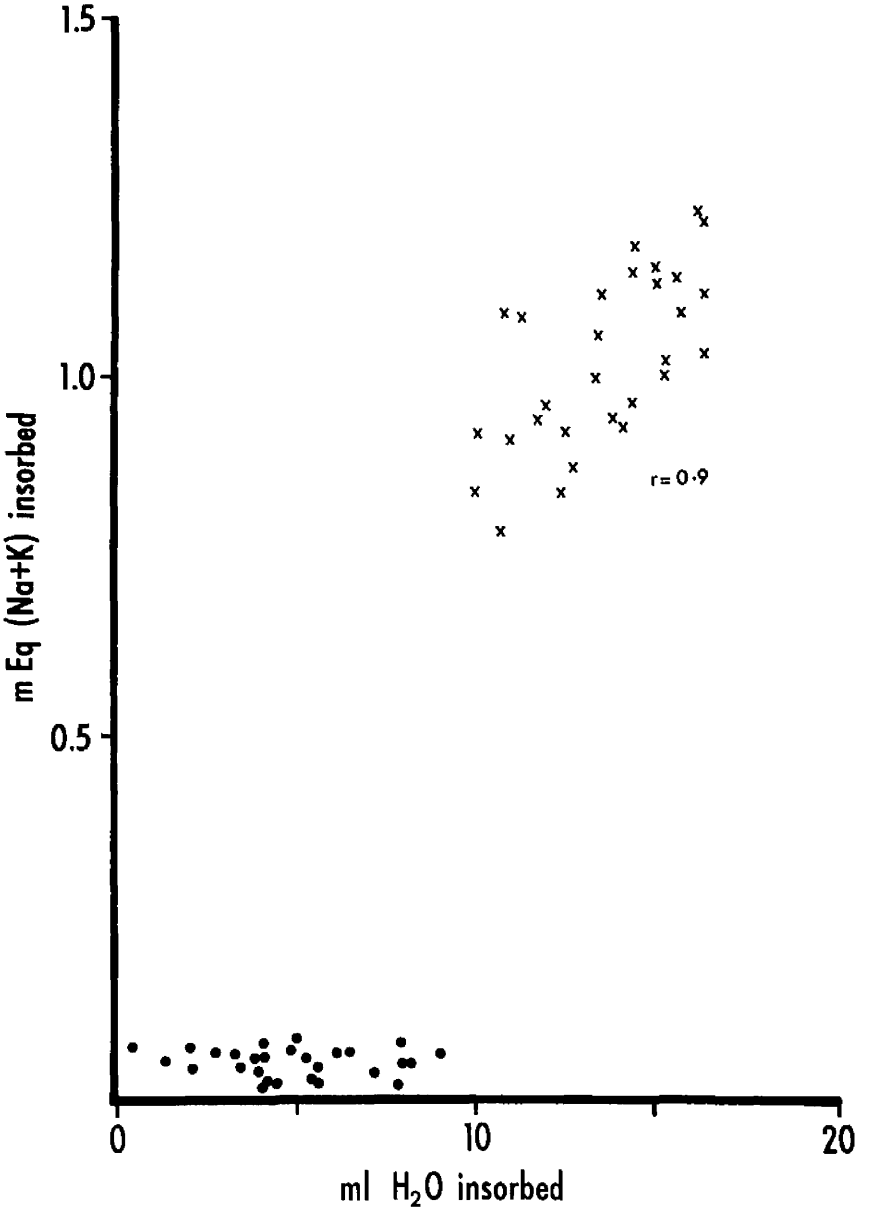


FIGURE 25 The amount of cation (Na + K) insorbed was plotted against the volume of water moving simultaneously in the same direction in the cranial (•) and caudal (×) segments of obstructed ileum.

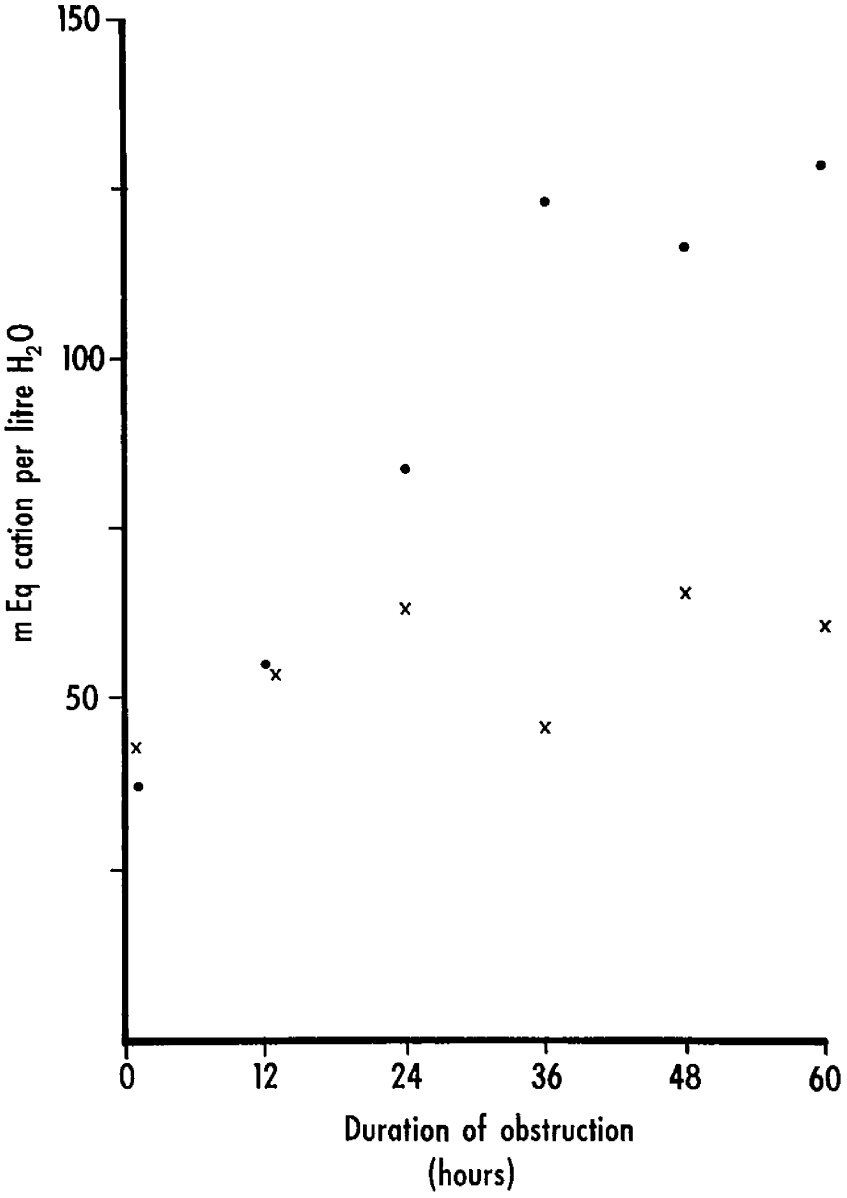


FIGURE 26 The mean cation composition of the fluid entering the cranial (•) and caudal (×) segments of obstructed ileum was related to the duration of the obstruction.

TABLE 25. The concentration of sodium in the test solution at beginning (t_o) and end (t_{10}) of ten-minute test.
(mEq per litre ± S.E. of mean).

	Mean concentration of test solution at t_o	Mean concentration of test solution at t_{10}	
		Cranial segment	Caudal segment
Unobstructed ileum (6 tests)	140.5 ± 0.2	150.0 ± 7.3*	140.3 ± 4.8
Mean change in concentration ± S.E.M. difference		+9.5 ± 5.0	-0.2 ± 3.3
t		1.89	0.06
P		<0.1	>0.9
Obstructed ileum (30 tests)	141.2 ± 0.1	143.4 ± 1.0	139.4 ± 1.7
Mean change in concentration ± S.E.M. difference		+2.2 ± 1.0	-1.8 ± 0.5
t		2.2	3.3
P		<0.05	<0.01

* The large increase in mean concentration was produced by abnormally high concentrations of sodium in the test solution in 2 tests out of 6 in one dog (no. 18). The reason for these high values is not clear but if they are ignored, the mean concentration of sodium in the cranial segment of unobstructed ileum would be 135.2 mEq per litre.

TABLE 26. The concentration of potassium in the test solution at beginning (t_o) and end (t_{10}) of ten-minute test.
(mEq per litre $\pm$ S.E.M.).

	Mean concentration of test solution at t_o	Mean concentration of test solution at t_{10}	
		Cranial segment	Caudal segment
Unobstructed ileum (6 tests)	3.9 $\pm$ 0.02	6.2 $\pm$ 0.42	6.3 $\pm$ 0.21
Mean change in concentration $\pm$ S.E.M. difference		+2.3 $\pm$ 0.42	+2.4 $\pm$ 0.21
t		5.5	11.4
P		<0.001	<0.001
Obstructed ileum (30 tests)	4.1 $\pm$ 0.02	5.2 $\pm$ 0.05	6.2 $\pm$ 0.09
Mean change in concentration $\pm$ S.E.M. difference		+1.1 $\pm$ 0.06	+2.1 $\pm$ 0.09
t		18.6	23.5
P		<0.001	<0.001

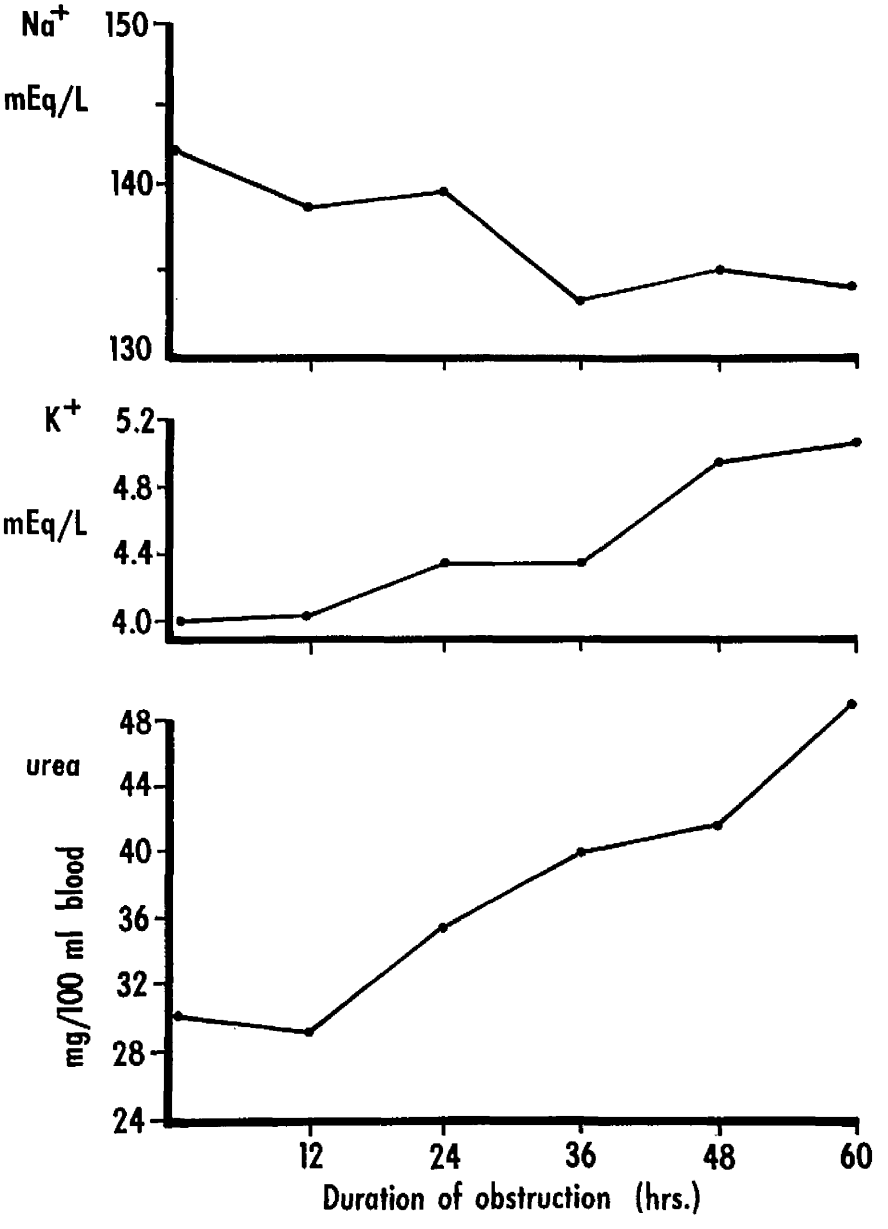


FIGURE 27 The concentrations of sodium and potassium in the serum, and of urea in the blood, in the dogs with intestinal obstruction. Each point represents the mean of duplicate concentrations estimated in two dogs.

TABLE 27. Effect of previous 'sham' operation on the intestinal transport of sodium, potassium and water.

	Interval between previous surgery and absorption tests (hours)			
	0 (a)	24 (b)	36 (b)	48 (b)
SODIUM (μEq per 10 min)				
Net (c)	+832 ± 89	+380	+308	+196
Insorption	1215 ± 93	1140	941	827
Exsorption	383 ± 48	760	633	631
POTASSIUM (μEq per 10 min)				
Net (c)	-20.5 ± 2.9	-29.9	-34.4	-41.0
Insorption	18.4 ± 2.0	22.9	21.0	21.3
Exsorption	38.9 ± 1.9	52.8	55.4	62.3
WATER (ml per 10 min)				
Net (c)	+5.9 ± 0.6	+2.7	+2.0	+1.1
Insorption	13.8 ± 0.7	14.5	12.1	11.6
Exsorption	7.9 ± 0.5	11.8	10.1	10.5

(a) Mean rate ± S.E.M. of six tests.

(b) The rates at 24, 36 and 48 hours are the means of three tests.

(c) Plus sign preceding mean rate represents absorption; minus sign, secretion.

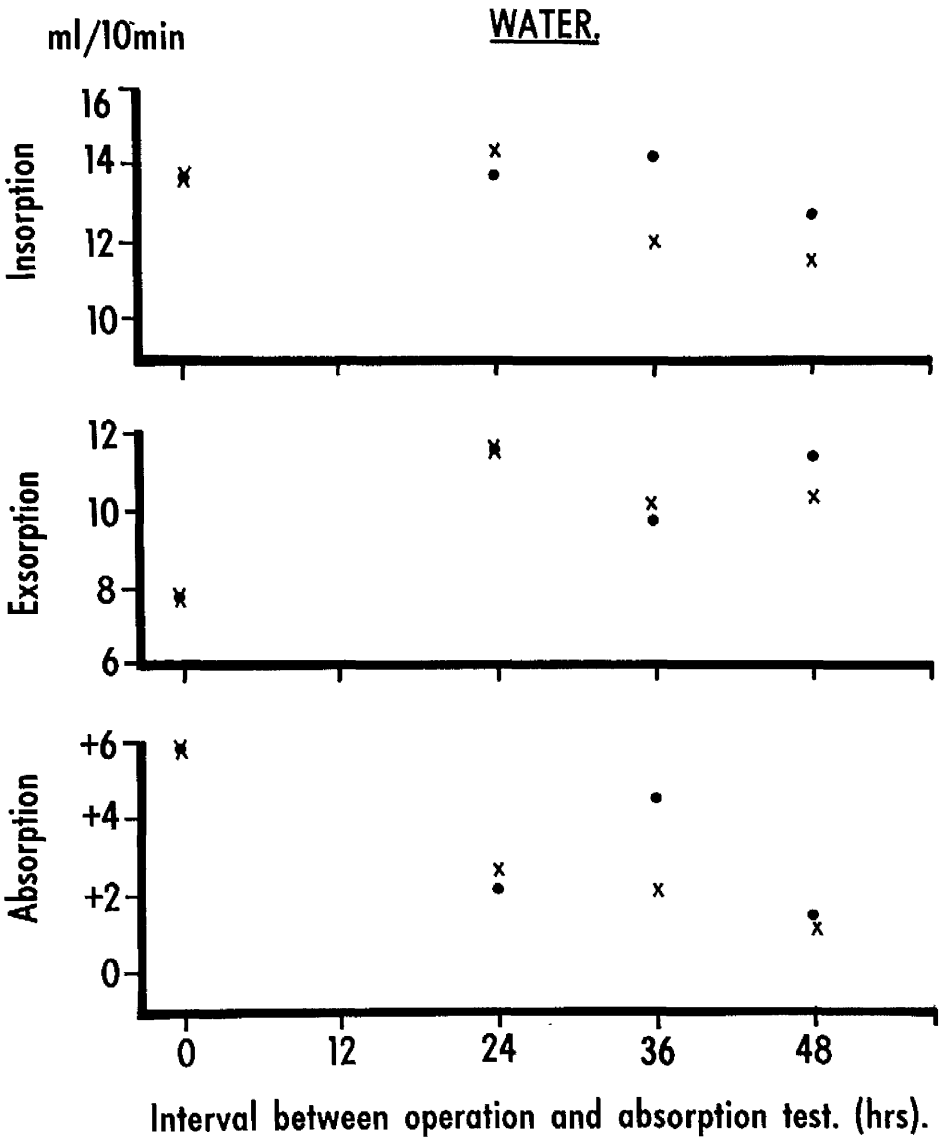


FIGURE 28 The mean rates of movement of water in the ileum of dogs previously subjected to a 'sham' operation (×) were compared to the mean rates in segments of ileum caudal to an obstruction (•).

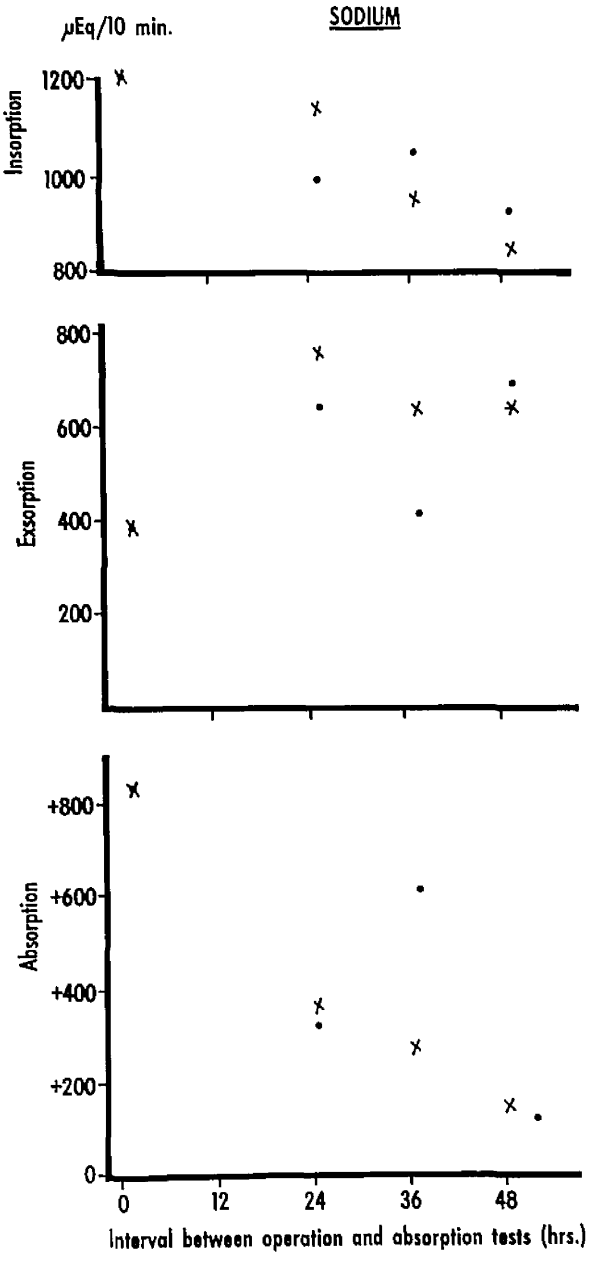


FIGURE 29 The mean rates of movement of sodium in the ileum of dogs previously subjected to a 'sham' operation (×) were compared to the rates obtained in the segments of ileum caudal to an obstruction (•).

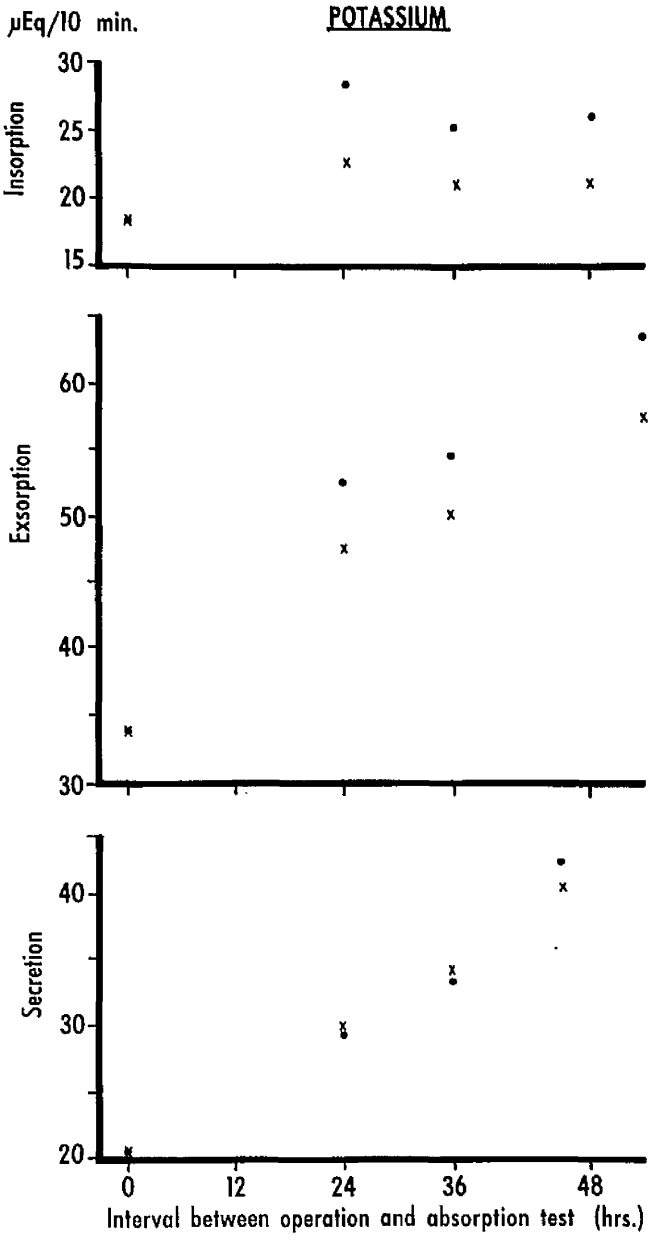


FIGURE 30 The mean rates of movement of potassium in the ileum of dogs previously subjected to a 'sham' operation (×) were compared to the rates in segments of ileum caudal to an obstruction (•).

TABLE 28. Comparison between ileum, after 'sham' operation, and ileum, distal to obstruction.

Feature	Ileum after 'sham' operation	Ileum distal to obstruction
1. Ratio of cation (Na + K) to water movement (mEq/L ± S.E.M.		
absorption	139.3 ± 4.2	142.2 ± 5.1
insorption	78.3 ± 3.6	77.9 ± 5.1
exsorption	68.6 ± 3.5	43.3 ± 5.1
2. Change in concentration of electrolyte in test solution during 10 min test (mEq/L ± S.E.M. difference)		
decrease in sodium	1.0 ± 0.56 (not significant)	0.2 ± 3.3 (not significant)
increase in potassium	1.93 ± 0.06 $P < 0.01$	2.07 ± 0.1 $P < 0.01$

FIGURE 31 Inflatable rubber cuff, manufactured by Davol Rubber Company, Providence, Rhode Island, (Jacobson and McAllister, 1957), was used to compress the portal vein. It consists of a balloon, supported externally by rubberised cloth, and formed in the shape of an incomplete ring so that it could be slipped round the portal vein. The ring was made complete by sewing together the attached leaflets. Leading from the balloon was a hollow stem of rubberised cloth to which was attached an air-compressing cylinder, and a strain-gauge manometer.

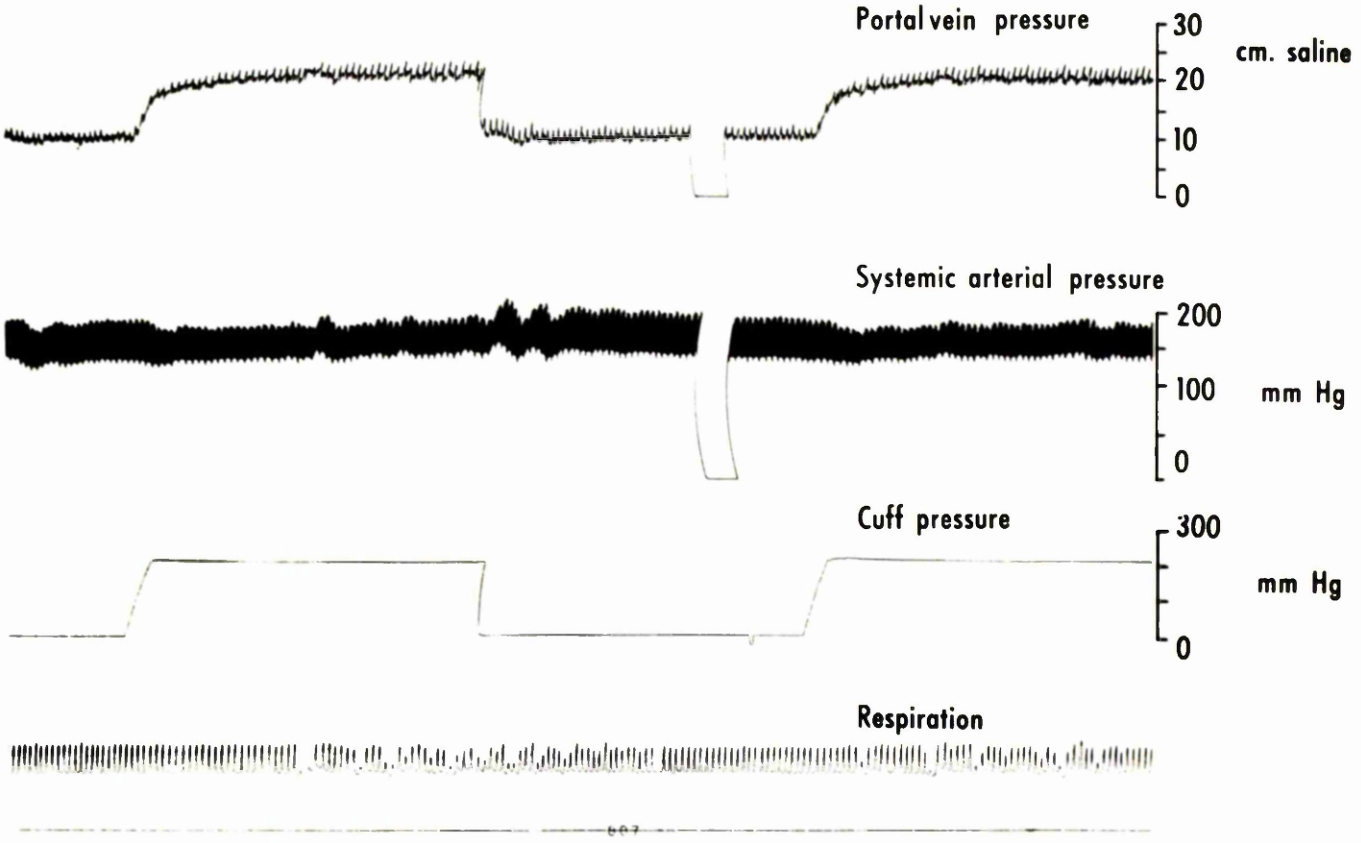


FIGURE 32 Photograph of a recording, illustrating the rise in mesenteric vein pressure in response to inflation of the cuff round the portal vein.

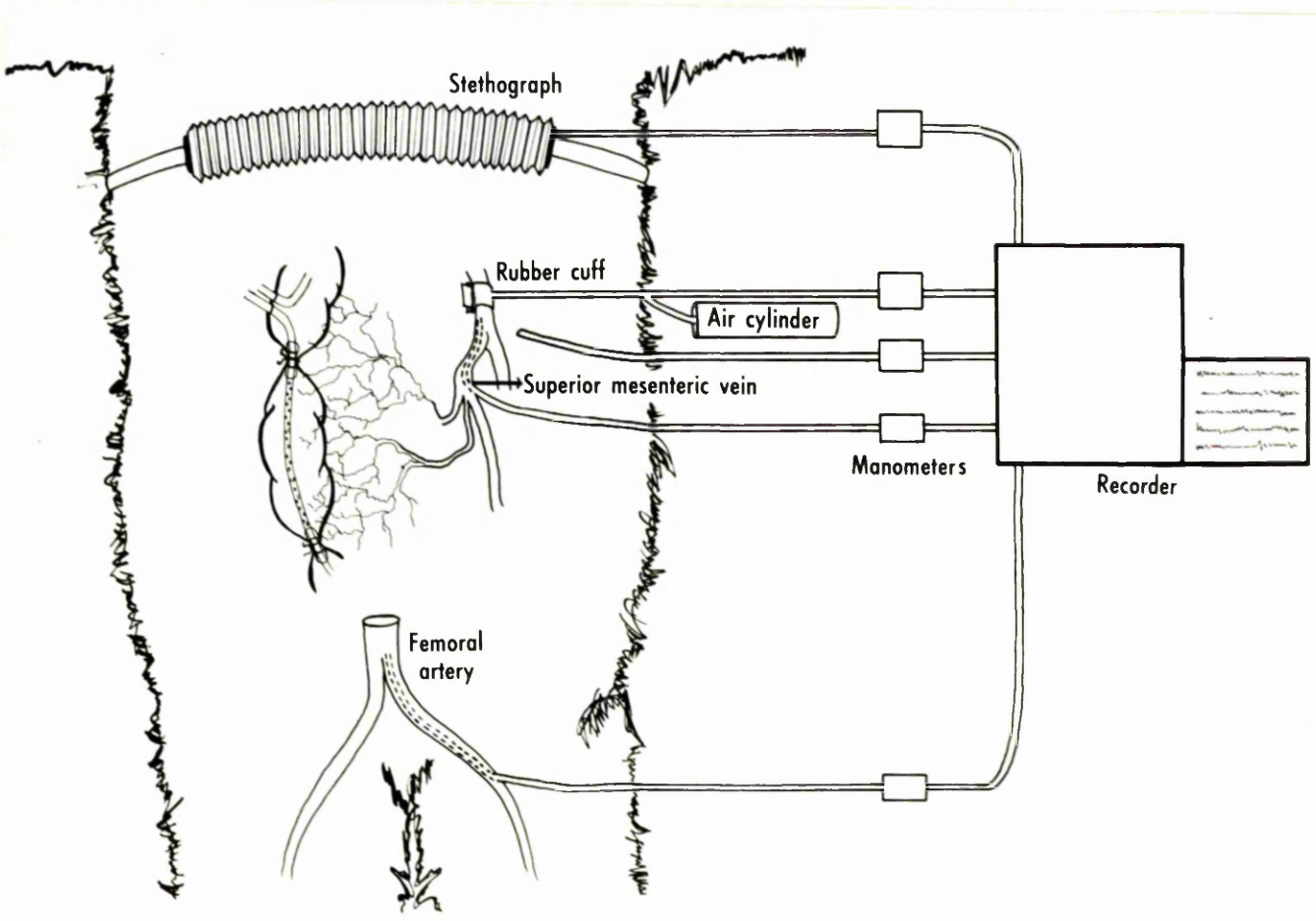


FIGURE 33 Diagram of the experimental preparation to study the effect of mesenteric venous congestion upon the intestinal transport of water, sodium and potassium.

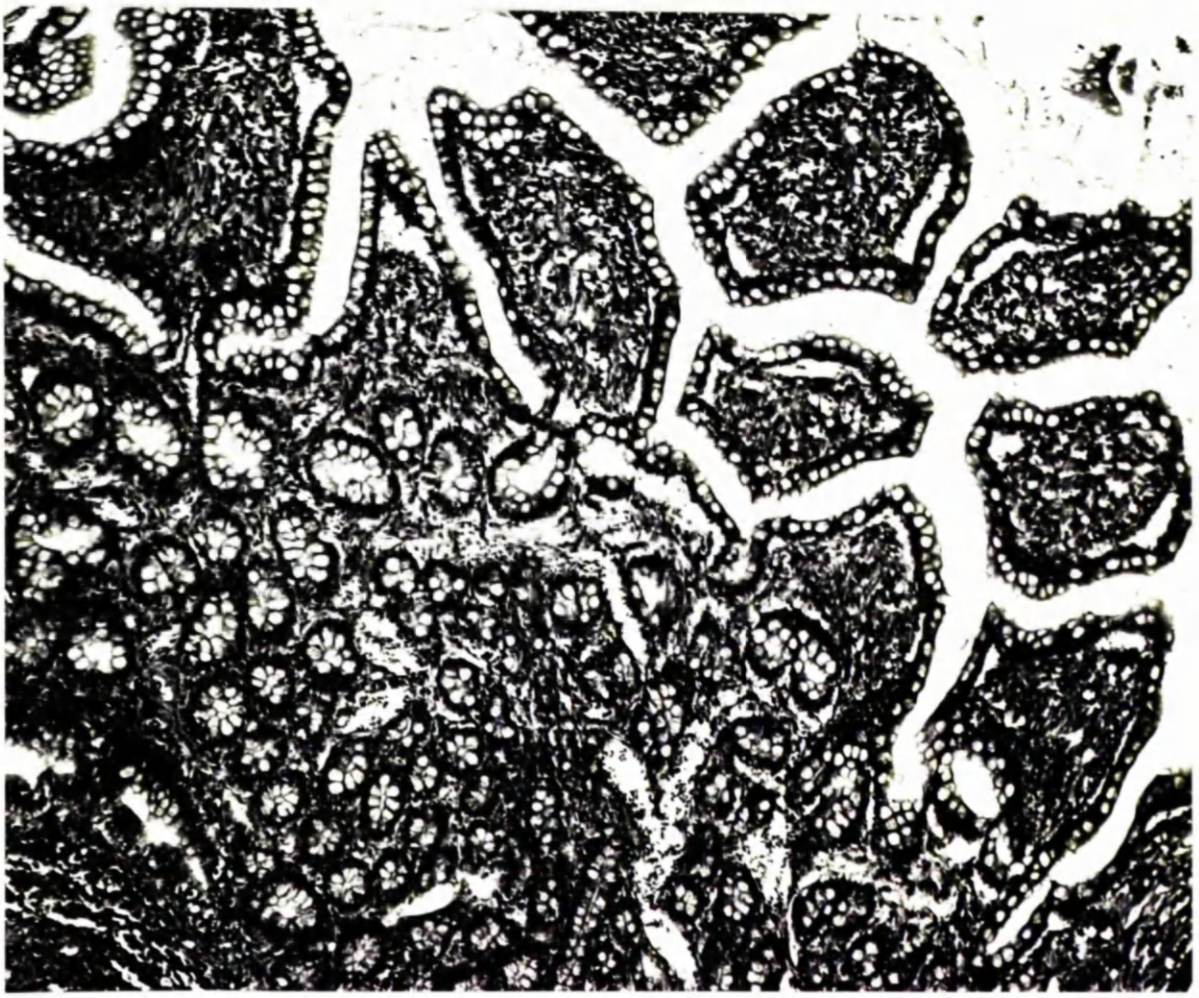


FIGURE 34 Photomicrograph of ileum after 8 hours of continuous increase in mesenteric vein pressure, showing engorgement of the small venules. The mucous membrane is intact. (H. and E.) x 150.

TABLE 29. Baseline rates of movement of water and sodium (a).

Dog no. (b)	Initial mesenteric vein pressure (cm saline)	Sodium (μEq/10 min)				Water (ml/10 min)			
		Insorption		Exsorption		Insorption		Exsorption	
		1	2	1	2	1	2	1	2
Group I									
1	12.5	783	628	442	546	17.6	16.8	15.1	16.1
2	12.5	1740	1477	751	689	23.7	19.0	17.1	13.7
3	15.0	1316	1138	501	426	19.1	17.4	13.9	12.8
4	15.0	1148	-	472	-	16.5	-	12.0	-
5	10.0	683	680	330	333	10.9	10.8	7.5	7.5
Group II									
6	15.0	1019	1123	705	688	19.9	16.7	18.4	13.8
7	10.0	1213	1144	316	341	16.5	18.9	10.7	13.8
8	15.0	1189	1078	252	267	16.8	11.5	10.3	5.9
9	12.0	973	-	250	-	15.4	-	10.5	-
Group III									
10	15.0	1383	1525	437	459	17.2	18.4	10.9	11.1
11	15.0	1221	1223	450	479	15.2	15.9	9.8	10.7
12	10.0	1287	1341	713	522	18.4	19.4	14.5	14.0
Mean of all tests 1 and 2	13.1	1163	1136	468	475	17.3	16.5	12.6	11.9
Grand mean of tests 1 and 2 combined		1151		471		16.9		12.3	

(a) Only the results of the initial two tests are given.
(b) In Group I and Group II dogs tests were subsequently performed during continuous and intermittent increases of mesenteric vein pressure: in Group III dogs control tests only were performed.

TABLE 30. Baseline rates of movement of potassium (a).

Dog no. (b)	Initial mesenteric vein pressure (cm saline)	Potassium μEq/10 min			
		Insorption		Exsorption	
		1	2	1	2
Group I					
13	15	20.4	15.4	32.3	27.1
14	12.5	17.6	20.1	33.2	37.2
15	10	27.3	27.8	40.1	42.9
Group III					
16	13	25.0	27.6	40.1	44.0
17	15	30.1	26.6	41.2	40.9
Mean of all tests 1 and 2		24.1	23.5	37.4	38.4
Grand mean of first and second tests combined		23.8		37.9	

(a) See Table 29, footnote (a).

(b) See Table 29, footnote (b).

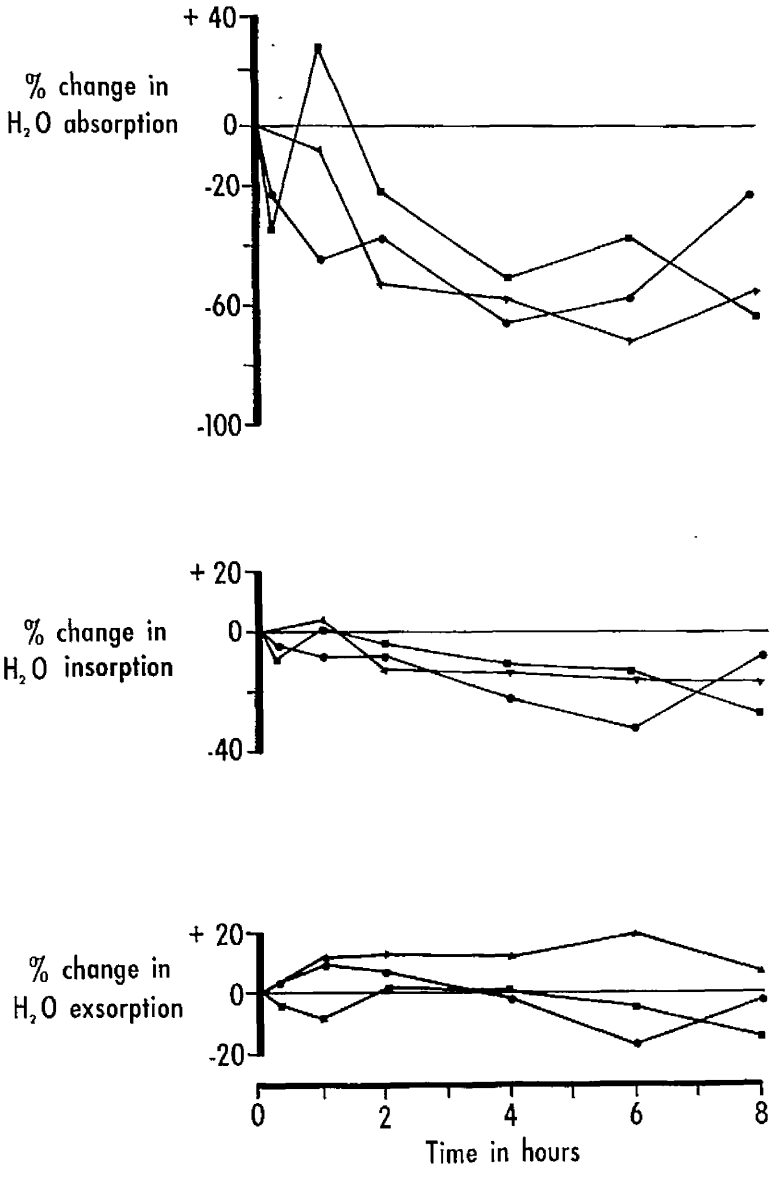


FIGURE 35 Change in the rate of water transport in the ileum of three control dogs (Group III) in which the cuff round the portal vein was not inflated.

Each set of symbols represents a different dog (▲ - dog no. 10; ● - dog no. 11; ■ - dog no. 12).

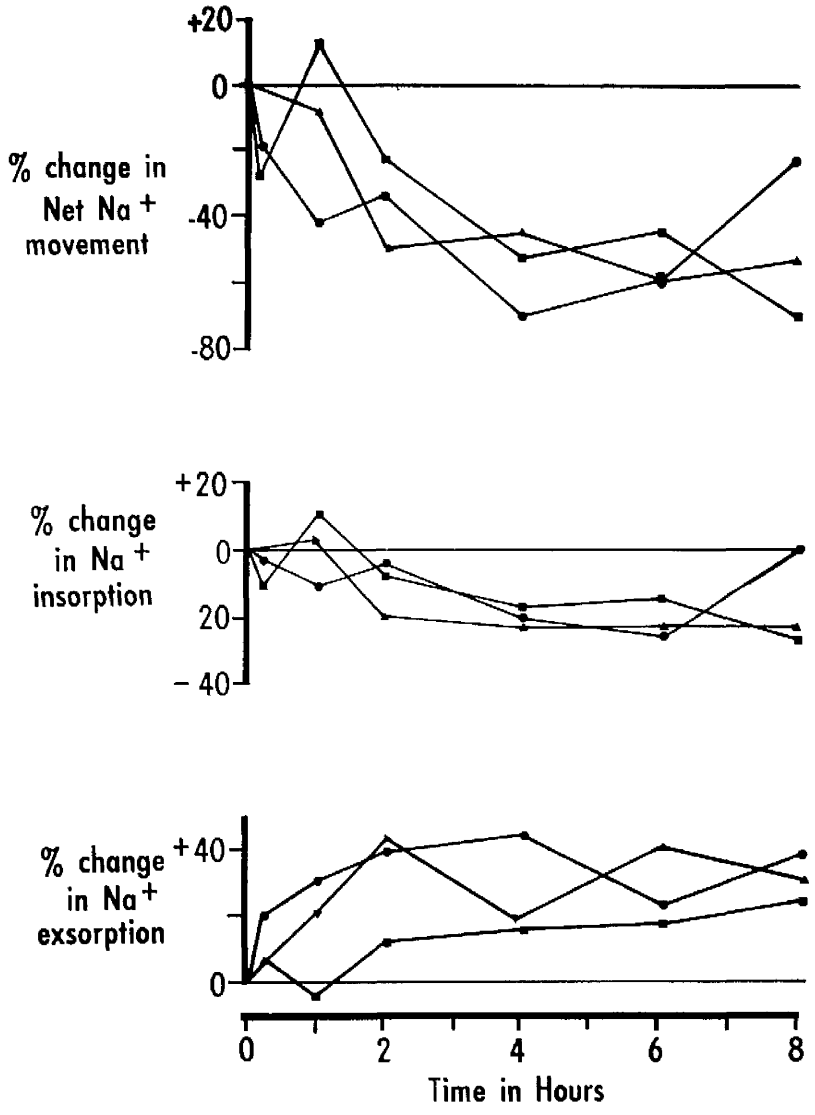


FIGURE 36 Change in the rate of sodium transport in the ileum of three control dogs (Group III) in which the cuff round the portal vein was not inflated. Each set of symbols represents a different dog (see legend for Figure 35).

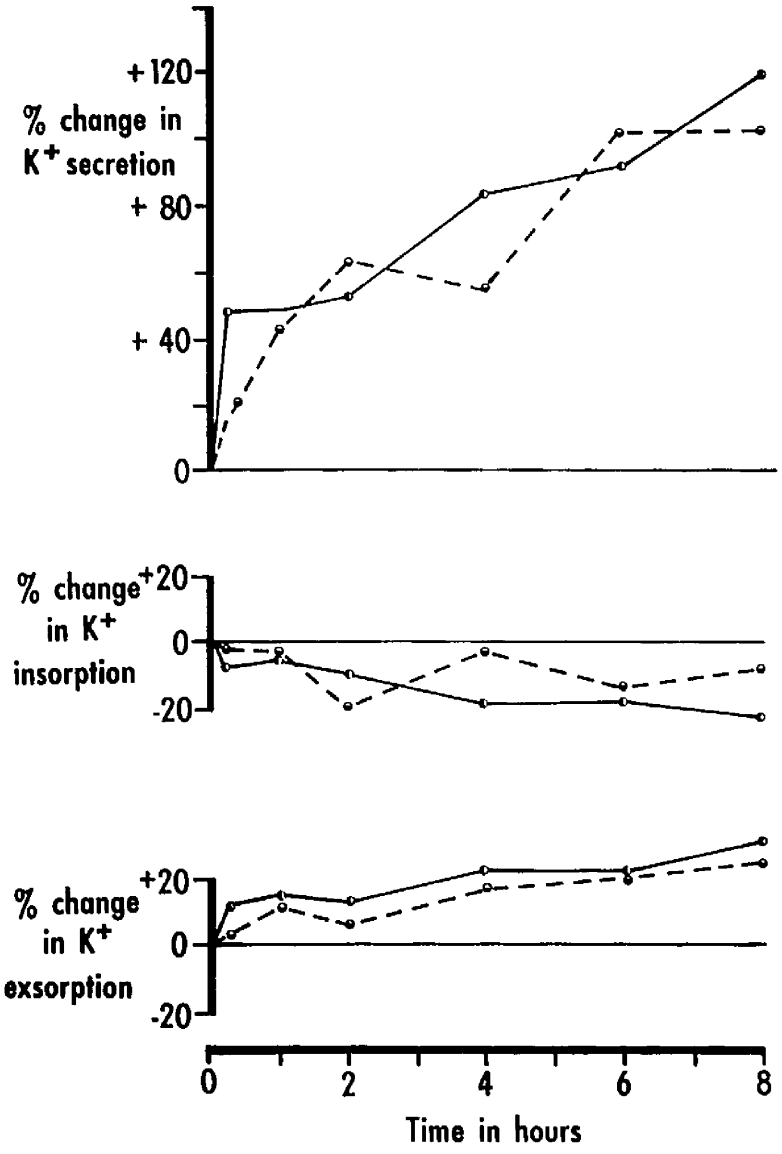


FIGURE 37 Change in the rate of potassium transport in the ileum of two control dogs (Group III) in which the cuff round the portal vein was not inflated.

Each set of symbols represents a different dog (◐ - dog no. 16; ◒ - dog no. 17).

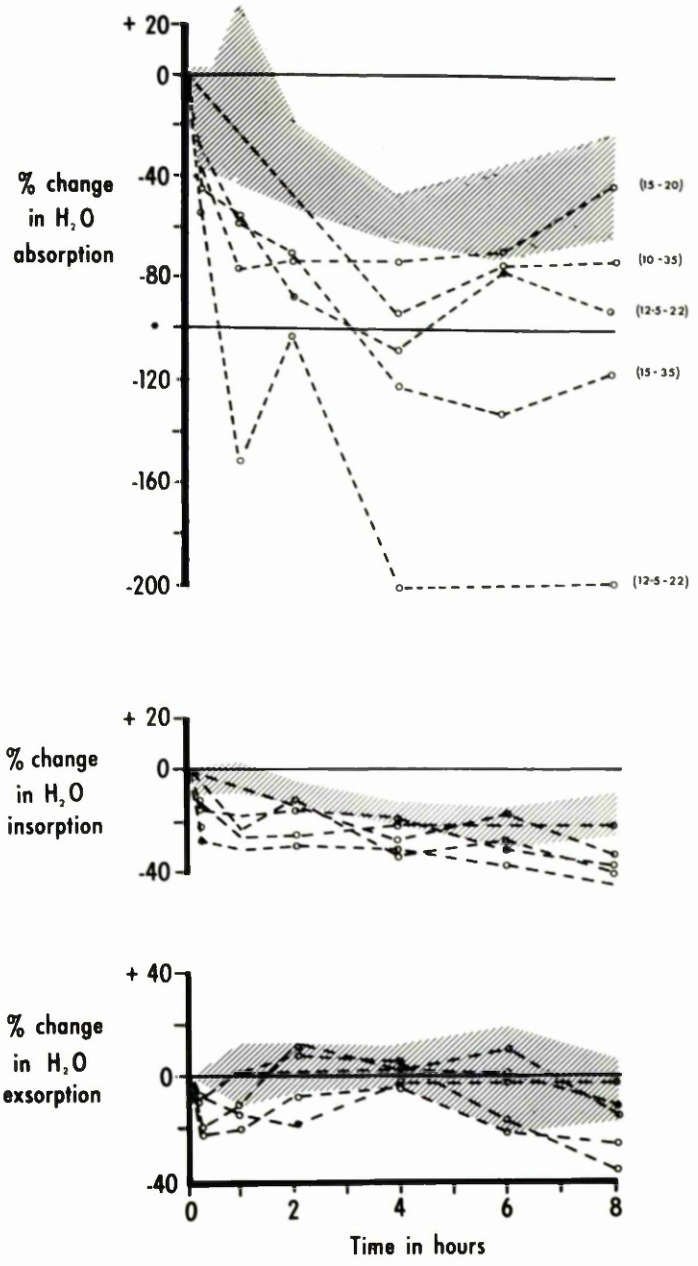


FIGURE 38 Change in the rate of water transport in the ileum of five dogs during continuous increase in mesenteric venous pressure (Group I). Values in parentheses indicate the original and final venous pressures in centimetres of saline. Shaded areas delineate the range of values during control tests (Fig. 35).
* When the decrease in the rate of absorption was greater than 100 per cent, secretion had taken place.

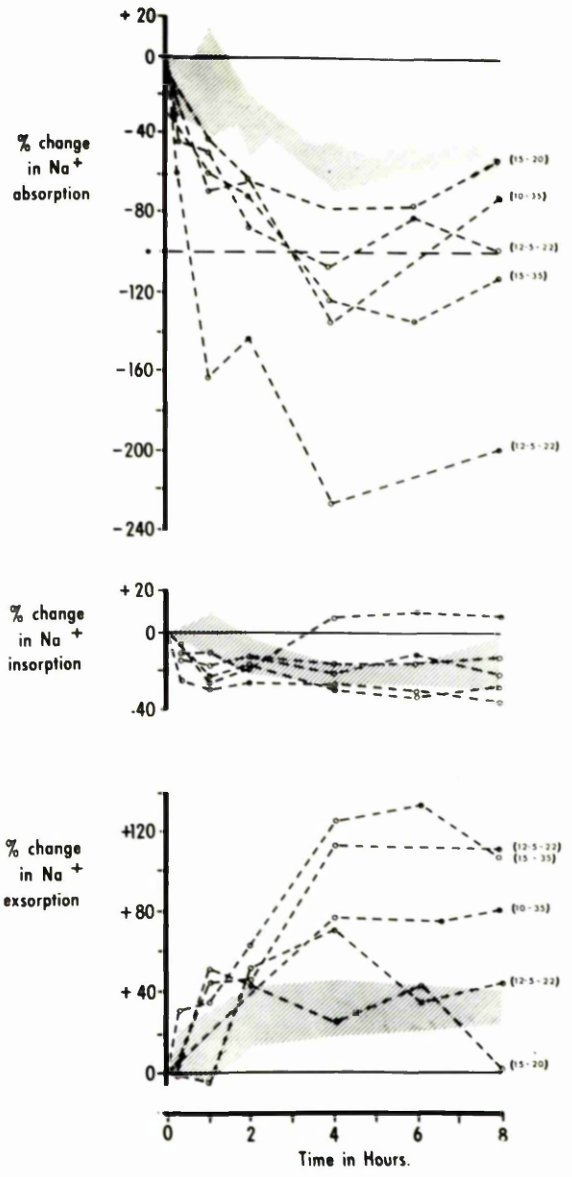


FIGURE 39 Change in the rate of sodium transport in the ileum of five dogs during continuous increase in mesenteric venous pressure (Group I).

Shaded areas delineate the ranges of values during control tests (Fig. 36).

* When the decrease in the rate of absorption was greater than 100 per cent, secretion had taken place.

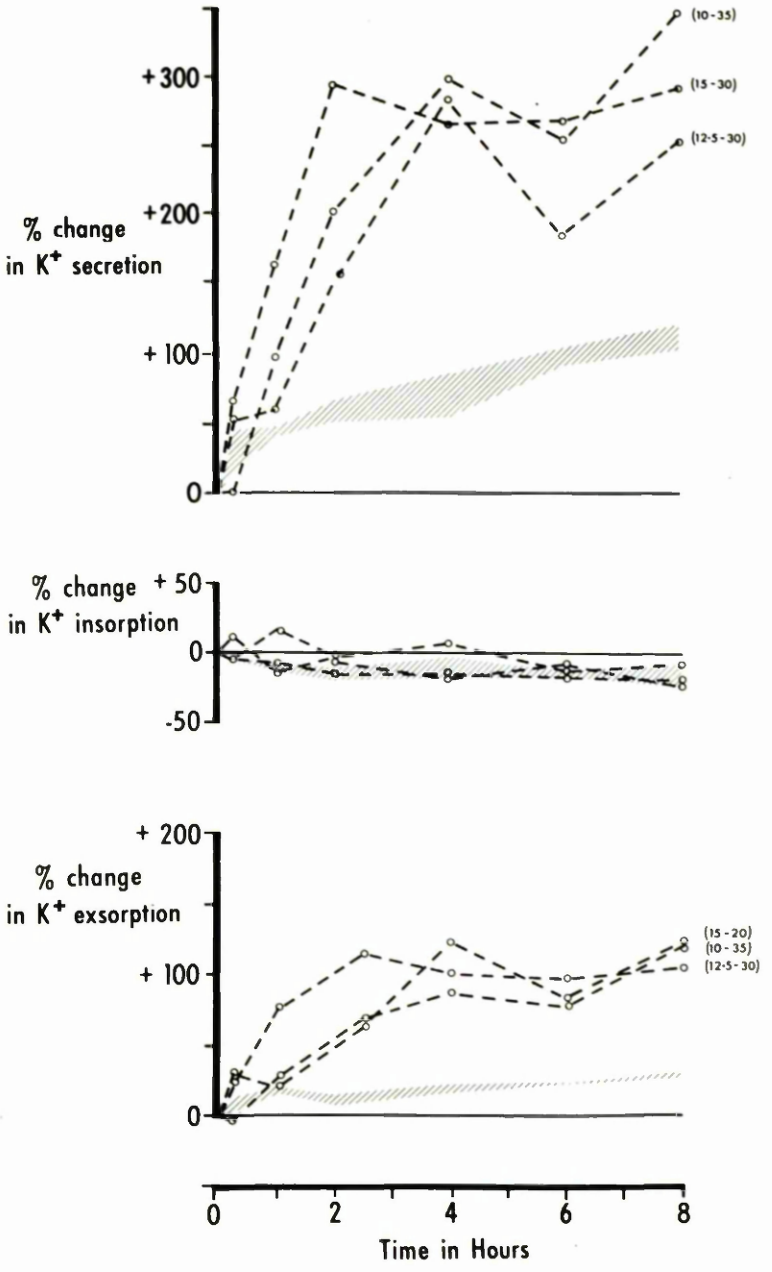


FIGURE 40 Change in the rate of potassium transport in the ileum of three dogs during continuous increase in mesenteric vein pressure (Group I). Shaded areas delineate the range of values during control tests (Fig. 37).
The values in parentheses indicate the original and final venous pressures in centimetres of saline.

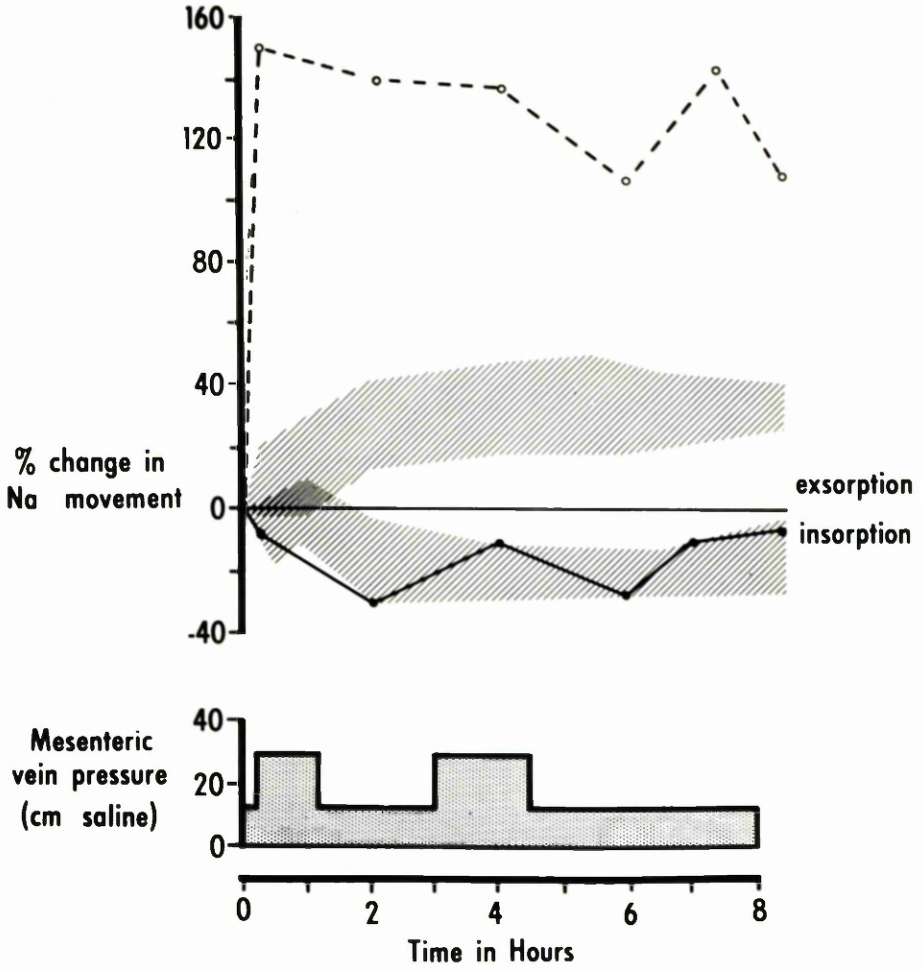


FIGURE 41 Insorption and exsorption of sodium in the ileum of dog no. 9 (Group II) during intermittent elevation of mesenteric venous pressure.

The shaded areas represent the range of control values (Fig. 36).

Open dots represent per cent change in exsorption; solid dots, per cent change in insorption.

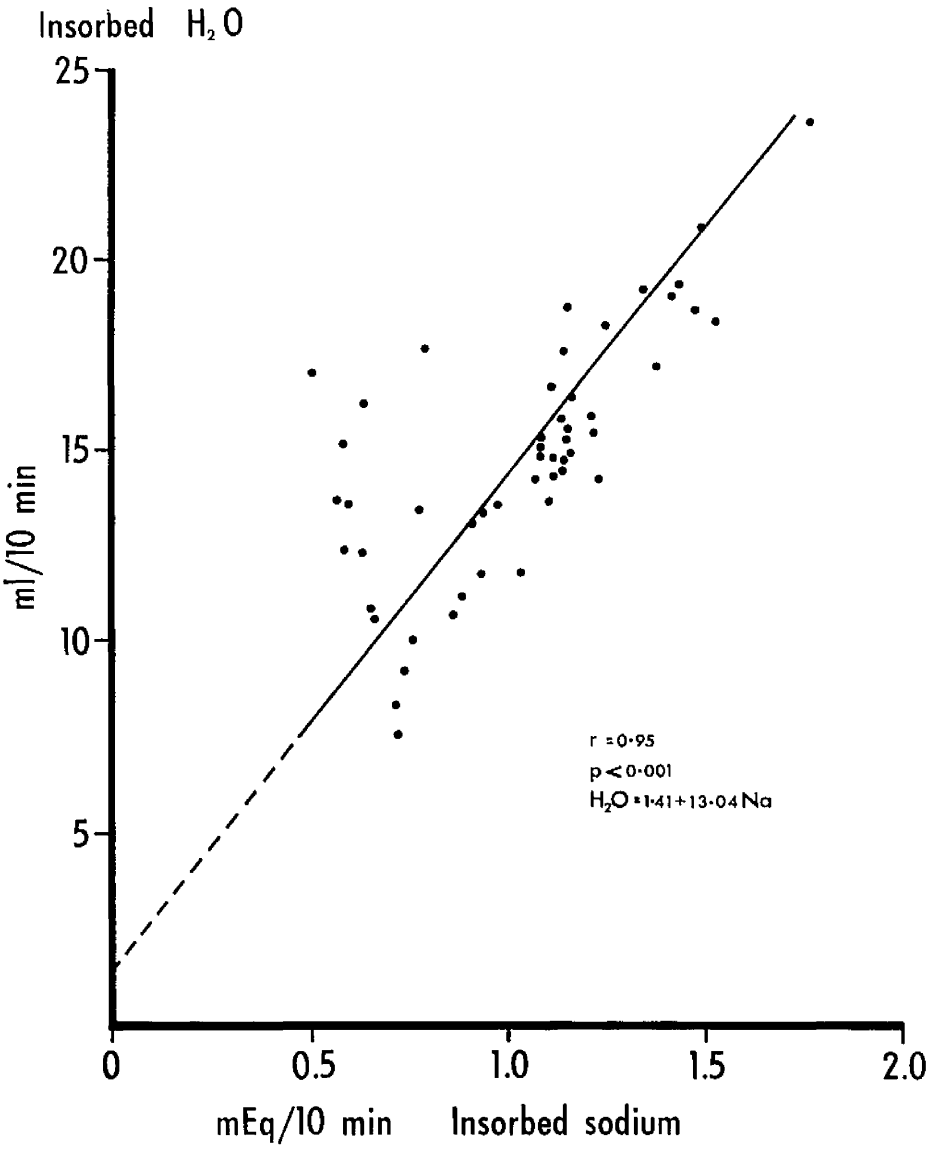


FIGURE 42 The relationship between sodium and water insorption in control dogs and those with continuous increase in mesenteric vein pressure.

The continuous line is the regression line of water insorption on sodium insorption, extrapolated to the y-axis.

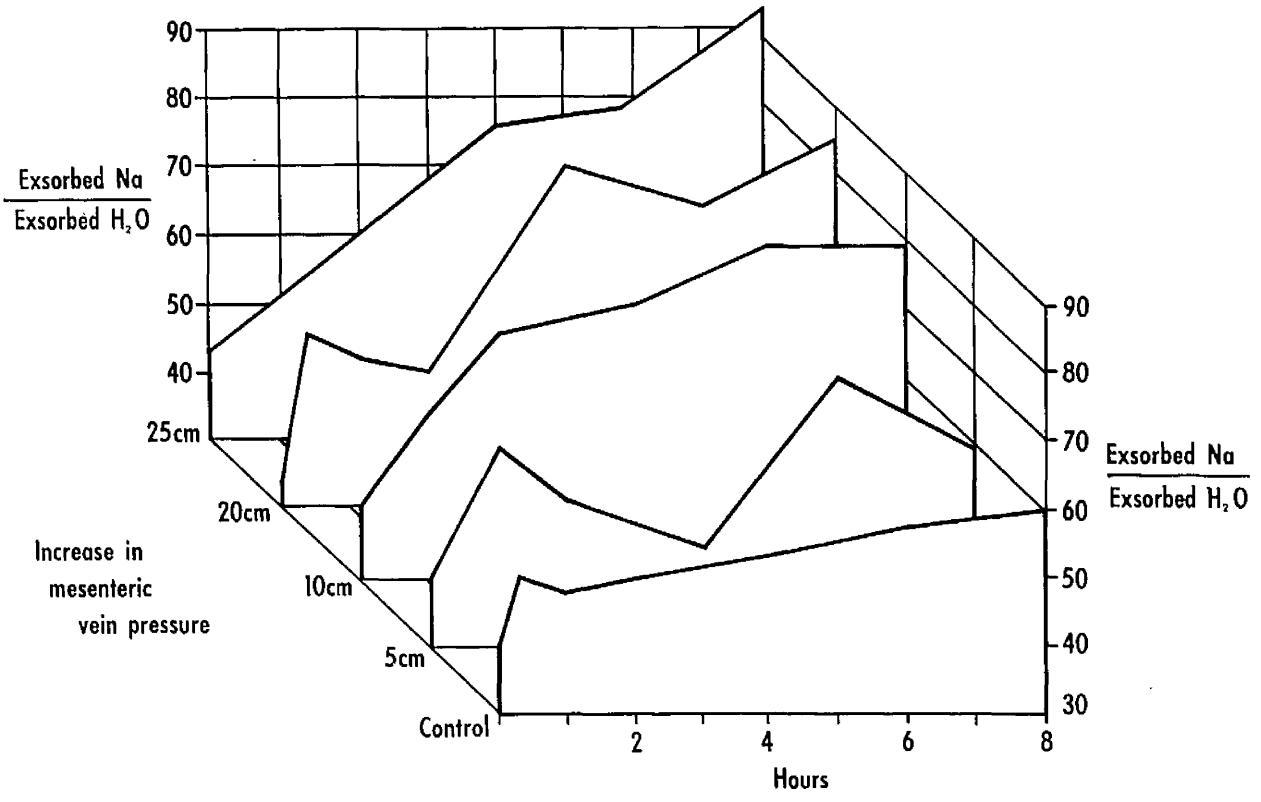


FIGURE 43 A three-dimensional graph illustrating the marked rise in the ratio of exsorbed sodium to exsorbed water (in mEq per litre) in those dogs whose mesenteric venous pressure was elevated, compared to the slight rise in control dogs.

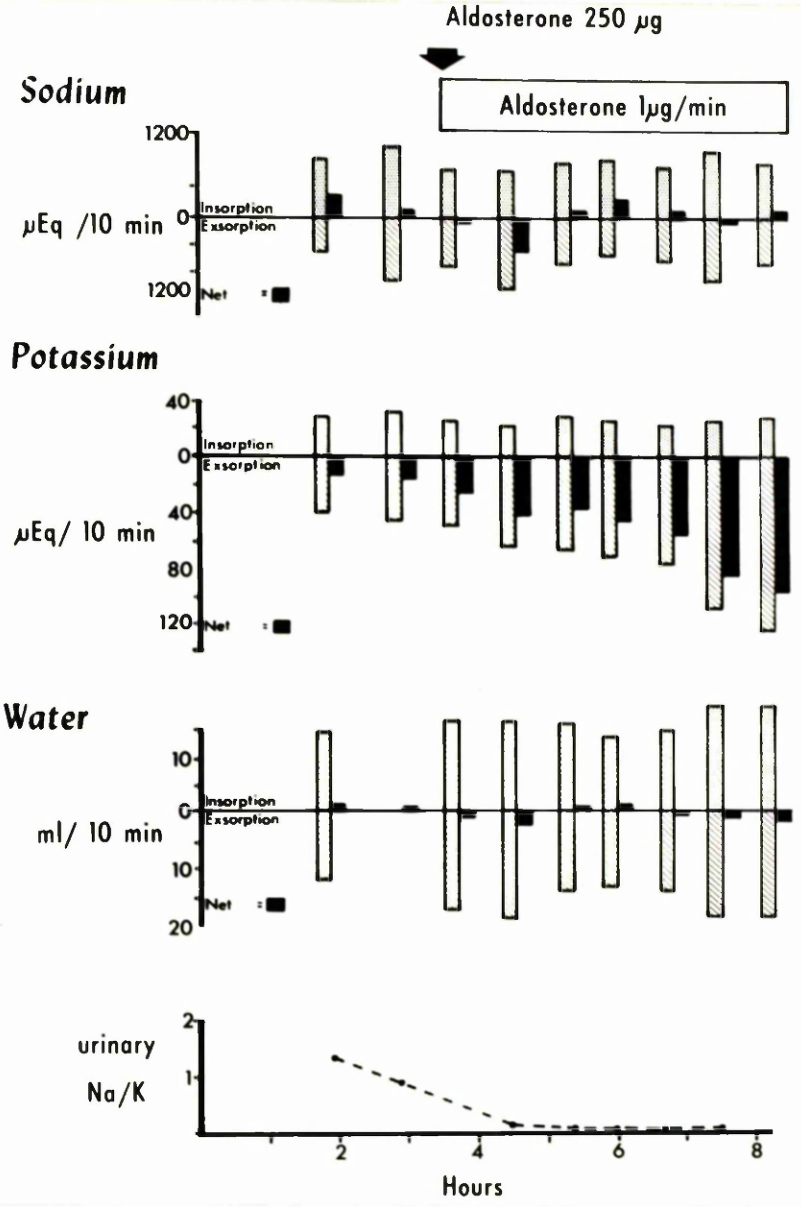


FIGURE 44 The effect of continuous infusion of aldosterone upon the transport of sodium, potassium and water in a Thiry-Vella fistula of ileum.
The rates of insorption (stippled block) are charted above, and those of exsorption (hatched block) below, the horizontal line. Net movement (solid block) is charted so that height above the line represents the rate of absorption, and the depth below the line, rate of secretion.
Data from experiment on dog no. 33 on 14th March, 1962.

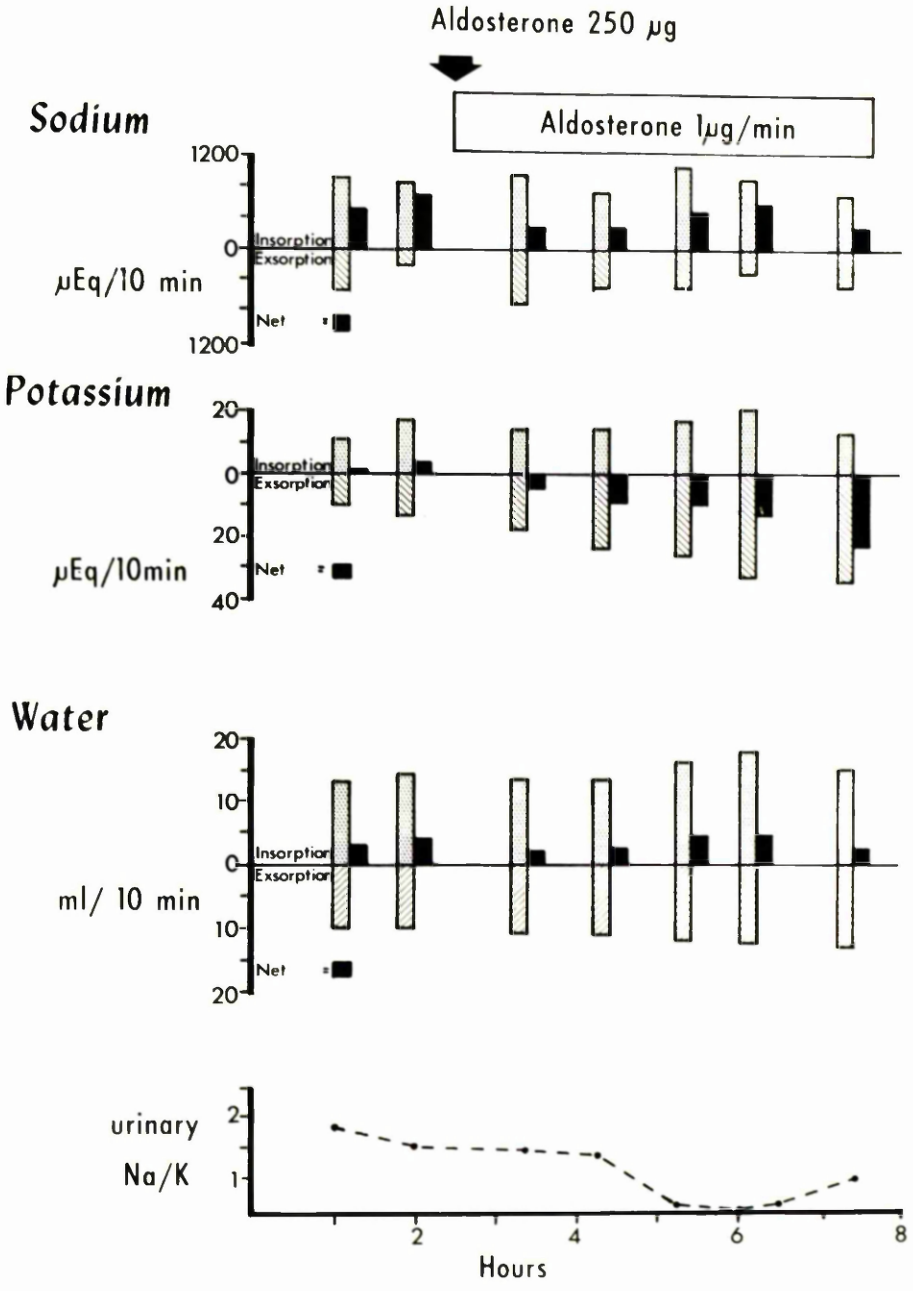


FIGURE 45 The effect of a continuous infusion of aldosterone upon the transport of sodium, potassium and water in a Thiry-Vella fistula of colon. The conventions used for charting direction and rate of movement are identical to those of Figure 44.

Data from experiment on dog no. 36 on 15th March, 1962.

TABLE 31. Mean rates of transport in the ileum of control dogs, 4 and 5 hours after beginning of dextrose infusion and difference in rates when aldosterone was given. (The figures in parentheses indicate the number of tests performed).

Substance	Direction of movement	Mean rate in controls at 4 hours (a)	Mean difference with aldosterone ± S.E.M. difference (b)	P (c)	Mean rate in controls at 5 hours (a)	Mean difference with aldosterone ± S.E.M. difference (b)	P (c)
Sodium (μEq/10 min)	Insorption	294 (3)	+295 ± 48 (6)	< 0.01	358 (3)	+88 ± 54 (6)	<0.2
	Exsorption	824 (3)	-20 ± 76 (6)	< 0.9	837 (3)	-152 ± 78 (6)	<0.2
	Net	-530 (3)	+196 ±126 (6)	< 0.2	-479 (3)	+122 ±110 (6)	<0.4
Potassium (μEq/10 min)	Insorption	14 (3)	+2 ± 3 (6)	< 0.4	18 (3)	-3 ± 3 (6)	< 0.4
	Exsorption	42 (3)	+31 ± 10 (6)	< 0.06	40 (3)	+41 ± 11 (6)	< 0.02
	Net	-28 (3)	-31 ± 9 (6)	< 0.05	-22 (3)	-44 ± 24 (6)	< 0.01
Water (ml/10 min)	Insorption	10.3 (2)	+0.8 ±1.9 (5)	< 0.7	12.5 (2)	-0.5 ±1.9 (4)	< 0.7
	Exsorption	13.4 (2)	+0.9 ±1.9 (5)	< 0.7	14.9 (2)	-0.6 ±2.2 (4)	< 0.8
	Net	-2.7 (4)	+1.3 ±0.6 (6)	< 0.1	-2.3 (4)	+0.5 ±0.6 (6)	< 0.5

Notes:
(a) In this column the minus sign before mean rate indicates secretion.
(b) In this column the plus sign indicates increase above, and minus sign decrease below, mean rate in control experiments.
(c) P represents the probability that the mean difference in rates of movement is zero.

TABLE 32. Mean rates of transport in the colon of control dogs, 4 and 5 hours after beginning of dextrose infusion, and difference in rates when aldosterone was given. (The figures in parentheses indicate the number of tests performed).

Substance	Direction of movement	Mean rate in controls at 4 hours	Mean difference with aldosterone ± S.E.M. difference	P	Mean rate in controls at 5 hours	Mean difference with aldosterone ± S.E.M. difference	P
Sodium (μEq/10 min)	Insorption	520 (5)	+20 ± 125 (5)	<0.9	577 (4)	+30 ± 128 (5)	<0.9
	Exsorption	368 (5)	-47 ± 106 (5)	<0.7	382 (4)	-18 ± 67 (5)	<0.8
	Net	+152 (5)	+69 ± 94 (5)	<0.6	+195 (4)	+48 ± 146 (5)	<0.8
Potassium (μEq/10 min)	Insorption	14 (4)	-2 ± 3 (5)	<0.6	14 (3)	-4 ± 3 (5)	<0.3
	Exsorption	27 (4)	+29 ± 16 (5)	<0.2	27 (3)	+43 ± 16 (5)	<0.05
	Net	-13 (4)	-31 ± 18 (5)	<0.2	-13 (3)	-47 ± 16 (5)	<0.05
Water (ml/10 min)	Insorption	13.1 (4)	-1.1 ± 1.8 (4)	<0.6	13.0 (3)	+0.1 ± 1.3 (4)	>0.9
	Exsorption	11.9 (4)	-0.2 ± 1.5 (4)	>0.9	12.3 (3)	-0.6 ± 0.8 (4)	<0.5
	Net	+1.1 (5)	+0.2 ± 1.1 (5)	<0.9	+0.8 (4)	+0.7 ± 0.9 (5)	<0.5

See footnotes of Table 31.

TABLE 33. Initial rates of transport, with and without aldosterone.
(Figures in parentheses indicate number of tests).

Segment	Substance	Direction of movement	Mean initial rates (± S.E. of mean)		Mean difference ± S.E.M. difference	t	P
			Control experiment	Aldosterone experiment			
Ileum	Sodium (μEq/10 min)	Insorption	563 ± 76 (6)	608 ± 60 (11)	45 ± 99	0.45	<0.7
		Exsorption	1047 ± 131 (6)	802 ± 65 (11)	245 ± 130	1.89	<0.1
	Potassium (μEq/10 min)	Insorption	20.2 ± 2.9 (6)	19.9 ± 2.2 (11)	0.3 ± 3.7	0.08	>0.9
		Exsorption	45.2 ± 6.4 (6)	36.7 ± 2.8 (11)	8.5 ± 6.0	1.4	<0.2
	Water (ml/10 min)	Insorption	15.4 ± 1.9 (4)	9.9 ± 0.9 (7)	5.5 ± 1.8	2.9	<0.05
		Exsorption	11.3 ± 0.5 (4)	19.2 ± 2.1 (7)	7.9 ± 1.4	5.6	<0.001
Colon	Sodium	Insorption	520 ± 50 (11)	731 ± 72 (13)	211 ± 96	2.09	<0.05
		Exsorption	611 ± 43 (11)	546 ± 83 (13)	65 ± 105	0.62	<0.1
	Potassium	Insorption	12.4 ± 1.6 (10)	16.2 ± 2.7 (13)	3.8 ± 3.4	1.09	<0.4
		Exsorption	38.6 ± 8.3 (10)	22.9 ± 3.7 (13)	15.7 ± 8.2	2.04	<0.1
	Water	Insorption	12.1 ± 1.4 (7)	12.8 ± 0.7 (11)	0.7 ± 1.4	0.5	<0.1
		Exsorption	12.9 ± 1.4 (7)	11.6 ± 0.7 (11)	1.3 ± 1.4	0.9	<0.4

TABLE 34. Analysis of variance in rates of movement calculated from the first two tests in control experiments and (b) experiments in which aldosterone was given after the second test.

I. ILEUM

Substance	Direction of movement	Source of variation	Variance estimate	D. of F	F	P
Sodium	Insorption	Between experiments (B.E.)	7876	1	4.85	>0.2
		Within experiments (W.E.)	38199	15		
	Exsorption	B.E.	231820	1	3.56	<0.1
		W.E.	65091	15		
Potassium	Insorption	B.E.	0	1	∞	N.S.
		W.E.	5.27	15		
	Exsorption	B.E.	277	1	1.99	<0.2
		W.E.	139	15		
Water	Insorption	B.E.	47.3	1	8.81	<0.05
		W.E.	5.37	7		
	Exsorption	B.E.	97.1	1	32.1	<0.001
		W.E.	3.6	7		

TABLE 34 (contd.)

II. COLON

Substance	Direction of movement	Source of variation	Variance estimate	D. of F.	F	P
Sodium	Insorption	B.E.	236310	1	4.77	<0.05
		W.E.	49453	20		
	Exsorption	B.E.	22750	1	2.46	>0.2
		W.E.	56044	21		
Potassium	Insorption	B.E.	73	1	1.21	>0.2
		W.E.	60.6	20		
	Exsorption	B.E.	1418	1	4.19	<0.1
		W.E.	338	20		
Water	Insorption	B.E.	2.5	1	3.04	>0.2
		W.E.	7.6	15		
	Exsorption	B.E.	10	1	1.38	>0.2
		W.E.	72	15		

TABLE 35. Concentration of sodium (mEq/L ± S.E.M.) in intestinal lumen at beginning (t_o) and end (t_{10}) of 10-minute absorption tests.

Segment	Solution	Aldosterone infusion experiments	Control experiments
Ileum	Concentration in test solution at t_o	149 ± 3.8 (12)	149 ± 1.1 (6)
	Concentration in test solution at t_{10}	146 ± 2.9 (12)	151 ± 1.3 (6)
	Mean change in concentration ± S.E.M.	-3.0 ± 4.8	+2.0 ± 1.7
	t	0.59	1.39
	P	< 0.6	< 0.3
Colon	Concentration in test solution at t_o	147 ± 1.9 (10)	153 ± 1.65 (7)
	Concentration in test solution at t_{10}	145 ± 2.8 (10)	152 ± 2.1 (7)
	Mean change in concentration ± S.E.M.	-2.0 ± 3.5	-1.0 ± 2.7
	t	0.59	0.37
	P	< 0.6	< 0.8

(Figures in parentheses indicate number of tests).

The concentrations were measured in tests performed 4 and 5 hours after the beginning of the dextrose infusion, with and without the administration of aldosterone. The changes in the sodium concentration of the test solution in tests before the beginning of the dextrose infusion are given in Table 7.

TABLE 36. Concentration of potassium (mEq/L ± S.E.M.) in intestinal lumen at beginning (t_o) and end (t_{10}) of 10-minute absorption tests.

Segment	Solution	Aldosterone infusion experiments	Control experiments
Ileum	Concentration in test solution at t_o	3.50 ± 0.07 (12)	3.47 ± 0.11 (6)
	Concentration in test solution at t_{10}	5.69 ± 0.21 (12)	3.98 ± 0.07 (6)
	Mean change in concentration ± S.E.M.	+2.19 ± 0.22	+0.51 ± 0.13
	t	10.1	3.8
	P	< 0.001	< 0.01
Colon	Concentration in test solution at t_o	3.57 ± 0.17 (10)	3.67 ± 0.13 (7)
	Concentration in test solution at t_{10}	5.86 ± 0.65 (10)	4.27 ± 0.20 (7)
	Mean change in concentration ± S.E.M.	+2.29 ± 0.68	+0.60 ± 0.18
	t	3.4	3.3
	P	< 0.01	< 0.01

(Figures in parentheses indicate the number of tests performed).

The concentrations were obtained in tests performed 4 and 5 hours after the beginning of the dextrose infusion, with and without the administration of aldosterone. The change in the potassium concentration of the test solution in tests performed before the beginning of the dextrose infusion are given in Table 7.

TABLE 37. Relationship of cation (Na + K) transport to water transport. (mEq/L ± S.E.M.).

Segment	Direction of movement	Control experiments		Aldosterone infusion experiments	
		Before dextrose infusion	4 and 5 hours after dextrose infusion	Before aldosterone/ dextrose infusion	4 and 5 hours after aldosterone/dextrose infusion
Ileum	Insorption	52.5 (2)	37.0 (2)	62.5 ± 1.5 (7)	52.5 ± 5.9 (9)
	Exsorption	79.1 (2)	69.3 (2)	80.4 ± 6.0 (7)	70.5 ± 7.6 (9)
	Net	161.7 ± 12 (6)	174.8 ± 18.7 (6)	208.4 ± 28.0 (10)	165.3 ± 36.8 (9)
Colon	Insorption	47.6 ± 4.2 (6)	45.2 ± 11.4 (4)	52.6 ± 4.0 (11)	41.4 ± 4.7 (8)
	Exsorption	55.5 ± 5.7 (6)	36.8 ± 7.0 (4)	41.2 ± 5.6 (11)	26.3 ± 3.9 (8)
	Net	170.7 ± 62.1 (8)	147.1 ± 5.2 (7)	150.3 ± 17.6 (13)	156.9 ± 24 (9)

Note: Figures in parentheses represent number of absorption tests.

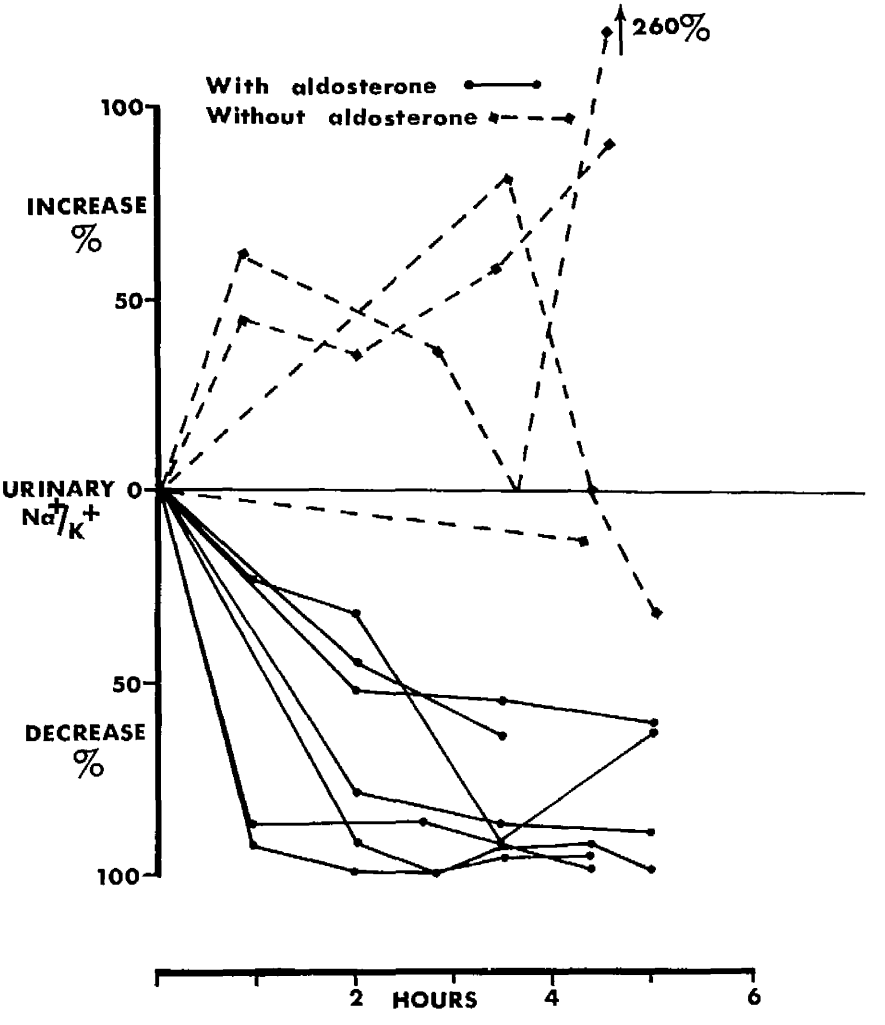


FIGURE 46 The effect of a continuous intravenous infusion of aldosterone upon the urinary sodium : potassium ratio.

TABLE 38. Mean rates of potassium transport under control conditions, and mean difference when aldosterone (in high and low dosage) and/or spironolactone were given. ($\pm$ S.E. of difference; P, probability that the difference is zero).

	Insorption	Exsorption	Net *
Control experiments (μEq/10 min)	15	33	-18
Difference when high dose of aldosterone was given **	-1.5 $\pm$ 1.3	+37.7 $\pm$ 6.4	-38.9 $\pm$ 6.7
P	<0.3	< 0.01	<0.001
Difference when low dose of aldosterone was given **	-0.3 $\pm$ 2.3	+37.6 $\pm$ 8.3	-37.9 $\pm$ 9.8
P	<0.8	< 0.01	< 0.01
Difference when spironolactone was given **	-1.3 $\pm$ 1.7	-5.0 $\pm$ 6.0	-6.3 $\pm$ 7.6
P	< 0.5	< 0.5	< 0.5

* The minus sign preceding the mean rate of potassium movement indicates secretion.

** The plus and minus signs preceding the mean differences indicate increase above, or decrease below, the mean rates in control experiments.

NOTE: The rates of transport in ileum and colon have been combined since the actions of aldosterone and/or spironolactone in both parts of the intestine are identical. In this analysis the rates of transport, 4 and 5 hours after the beginning of the dextrose infusion, have been compared.

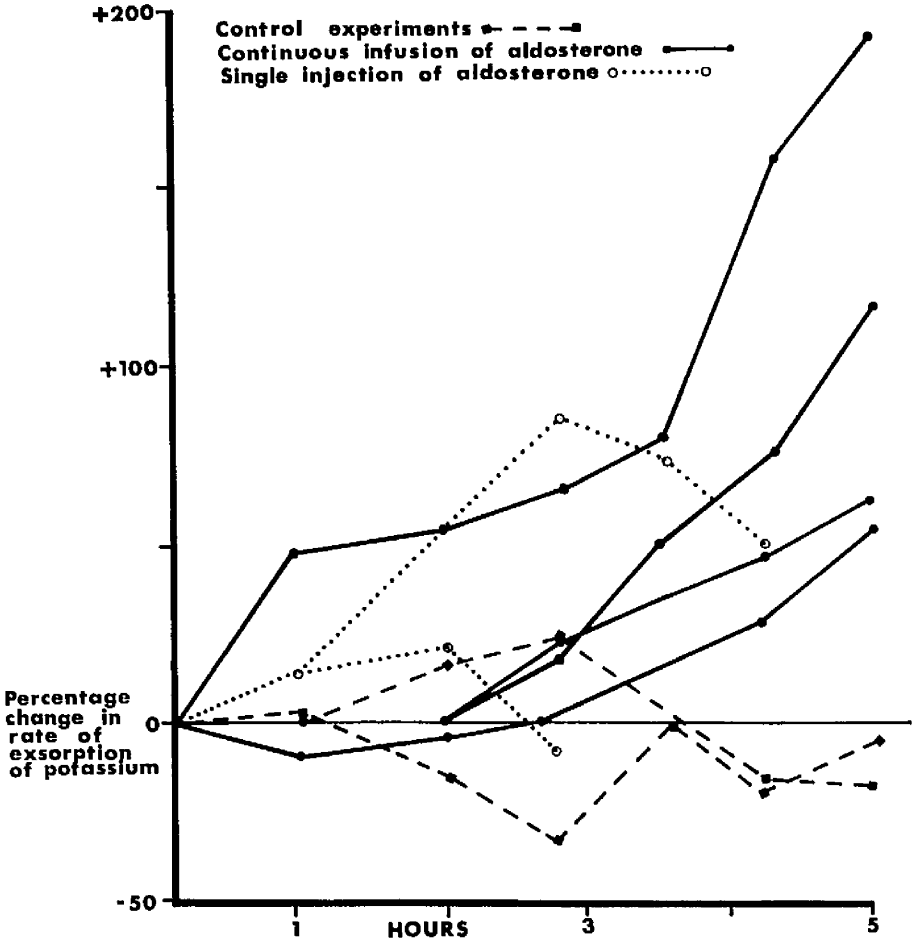


FIGURE 47 The effect upon the rate of potassium exsorption, into a Thiry-Vella fistula of ileum, of a single injection of aldosterone compared to that of a continuous infusion of aldosterone.

TABLE 39. Mean rates of potassium transport in ileum and colon after aldosterone infusion (low dose) or spironolactone, and difference when dog received both drugs.
($\pm$ S.E. of difference; P, probability that the difference is zero)

	Insorption	Exsorption	Net*
Aldosterone (low dose) alone (μEq/10 min)	15	70	-55
Difference when spironolactone was also given**	-5.5 $\pm$ 1.6	-24.6 $\pm$ 3.7	+19.1 $\pm$ 4.0
P	<0.01	<0.001	0.01
Spironolactone alone (μEq/10 min)	13	31	-18
Difference when aldosterone was also given**	-4.5 $\pm$ 0.5	+2.0 $\pm$ 6.0	-6.5 $\pm$ 5.7
P	<0.001	<0.8	<0.3

*The minus sign preceding the mean rate of net potassium movement indicates secretion.

**The plus and minus signs preceding the mean differences indicate increase above and decrease below mean rates when either aldosterone or spironolactone was given alone.

See footnote to Table 38.

TABLE 40. Effect of aldosterone upon the transport of sodium and potassium in the isolated human colon.
(mEq per 30 cm length per 10 minutes)

Patient	Time	Sodium movement			Potassium movement		
		Insorption	Exsorption	Net*	Insorption	Exsorption	Net*
1	Before aldosterone	1.06	0.11	+0.95	0.018	0.348	-0.330
	" "	1.58	0.60	+0.98	0.034	0.387	-0.353
	Twenty minutes after beginning of infusion	1.55	0.71	+0.84	0.005	0.483	-0.478
	Sixty minutes after beginning of infusion	1.29	1.36	-0.07	0	0.661	-0.661
2	Before aldosterone	1.35	0.50	+0.85	0.026	0.480	-0.454
	" "	1.29	0.39	+0.90	0.028	0.288	-0.260
	Thirty minutes after beginning of infusion	1.48	0.73	+0.75	0.023	0.522	-0.499
	Eighty minutes after beginning of infusion	1.37	0.91	+0.46	0.029	0.729	-0.700

* The plus and minus signs preceding the rates of net movement indicate absorption and secretion respectively.

TABLE 41. The concentrations of sodium and potassium (mEq/L) in the lumen of isolated human colon before and after aldosterone.

Patient	Time	SODIUM concentration at		POTASSIUM concentration at	
		t_o	t_{10}	t_o	t_{10}
1.	Before aldosterone	149	150	4.1	5.2
		149	150	4.1	5.0
	After aldosterone	149	148	4.1	5.9
		149	152	4.1	6.1
2.	Before aldosterone	147	148	3.8	4.3
		147	145	3.8	4.4
	After aldosterone	147	149	3.8	5.6
		147	144	3.8	5.9

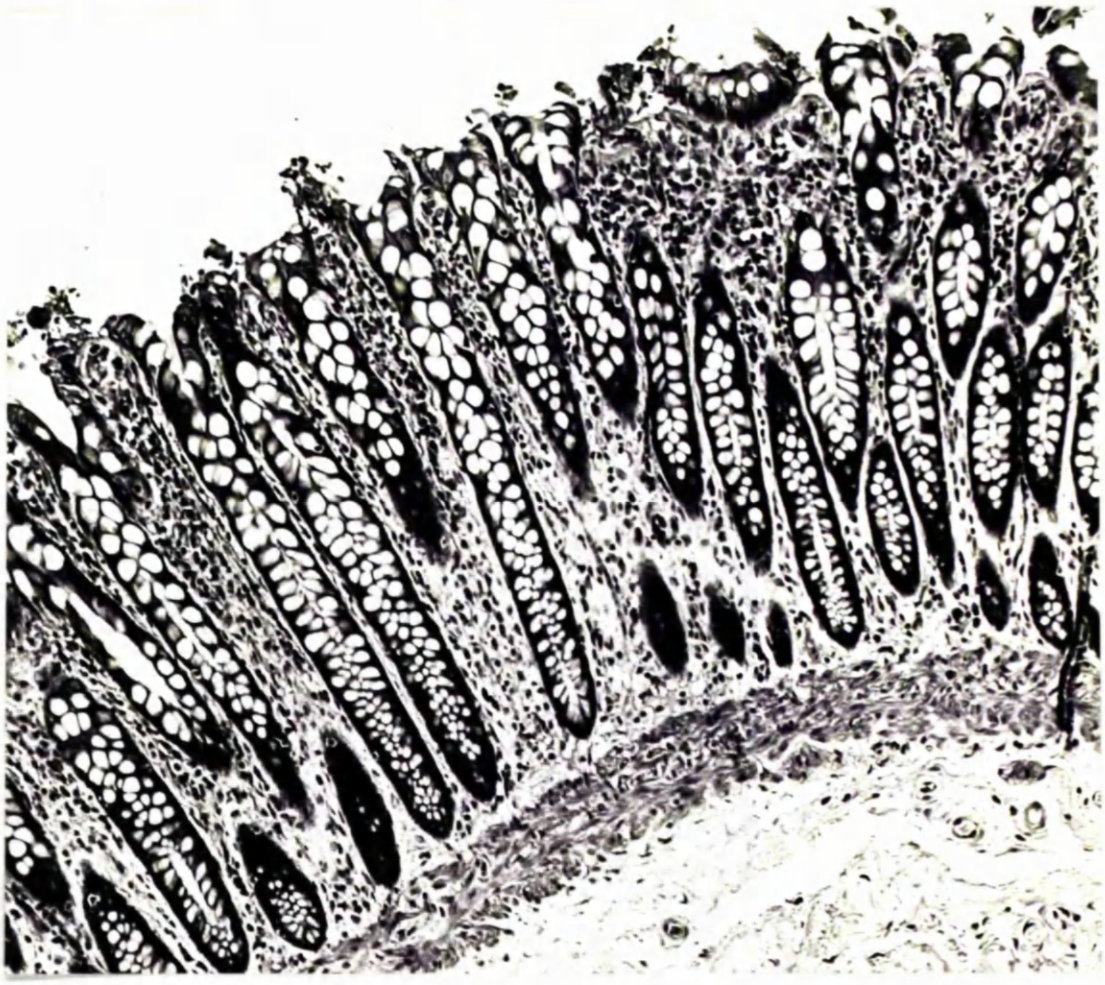


FIGURE 48 Histology of human colon.

Photomicrograph of section of colon 'isolated' in the mediastinum for 3 weeks. (H. and E.) x 100.

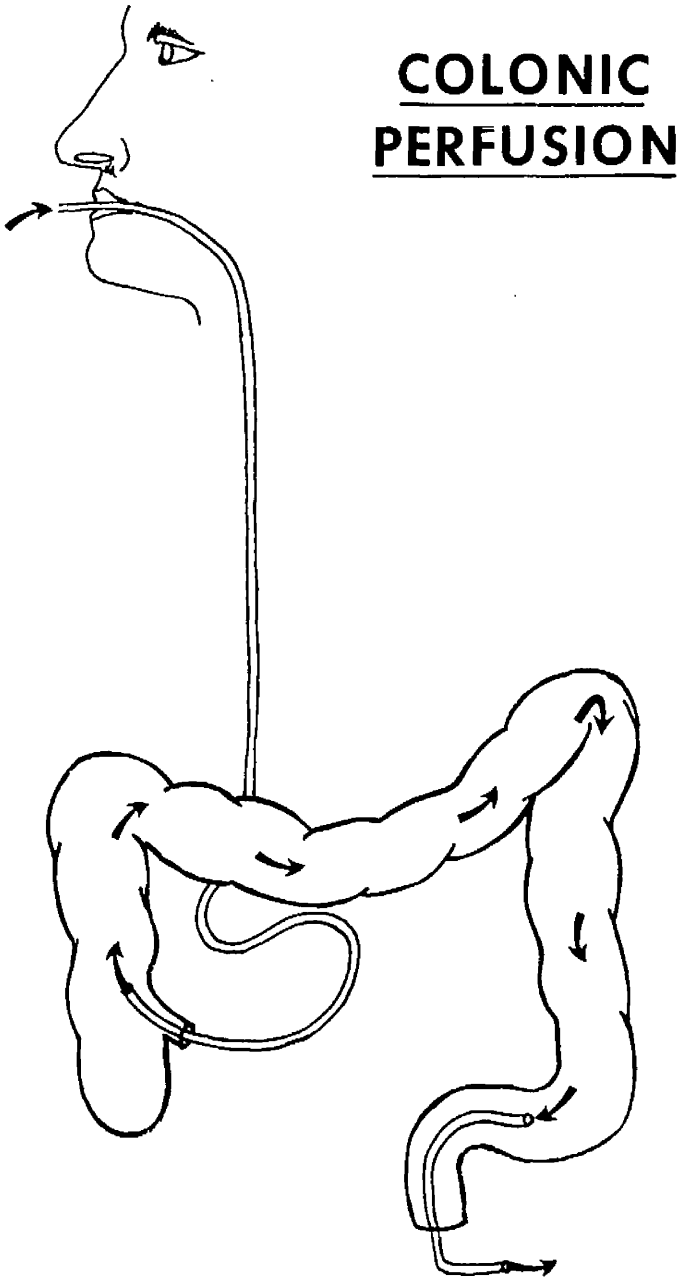


FIGURE 49 Diagram of colonic perfusion technique.

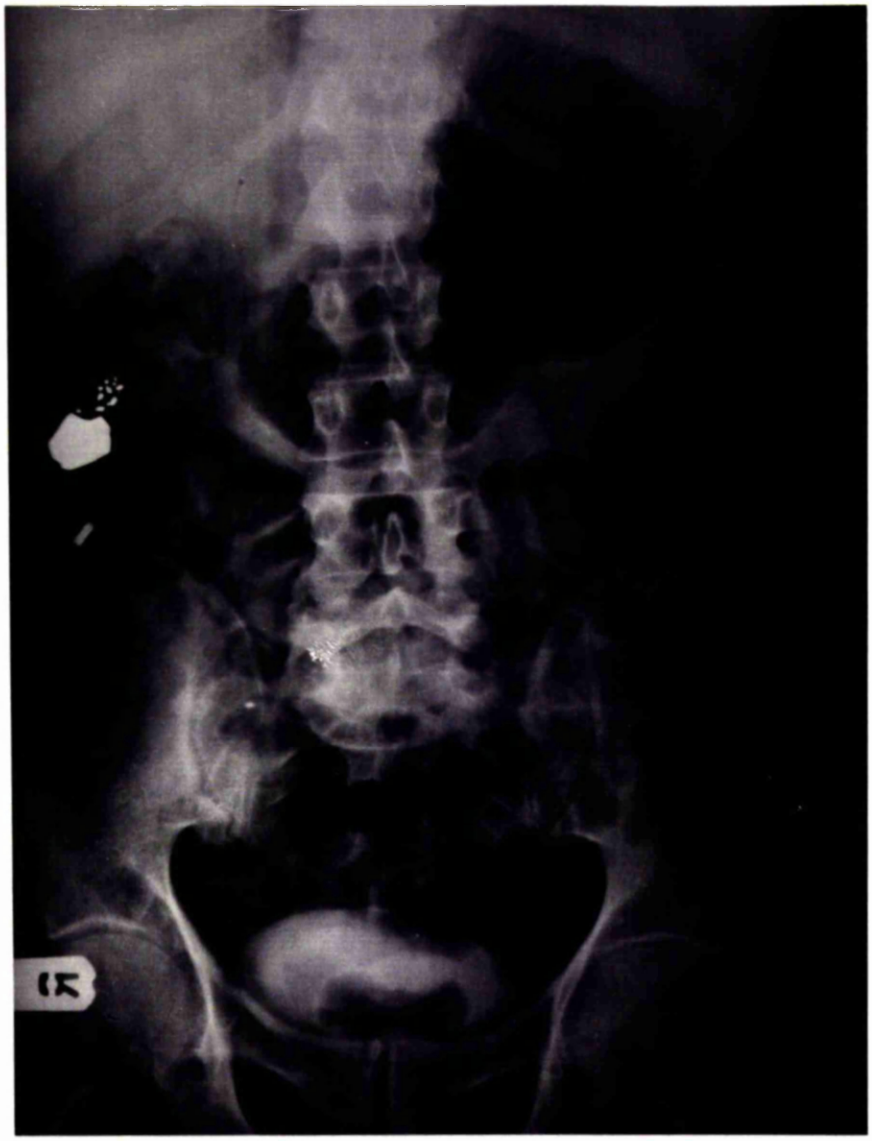


FIGURE 50 A radiograph showing the tube in position for colonic perfusion. The radio-opaque marker can be seen inferior to the bag containing mercury.

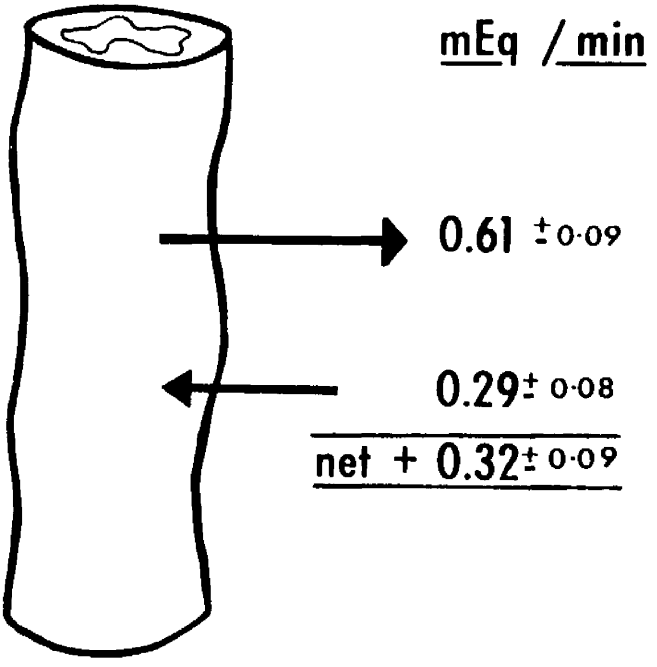


FIGURE 51 Diagram of the rates of unidirectional and net sodium transport in the intact colon of four normal subjects.
The mean rates are followed by the standard deviations.

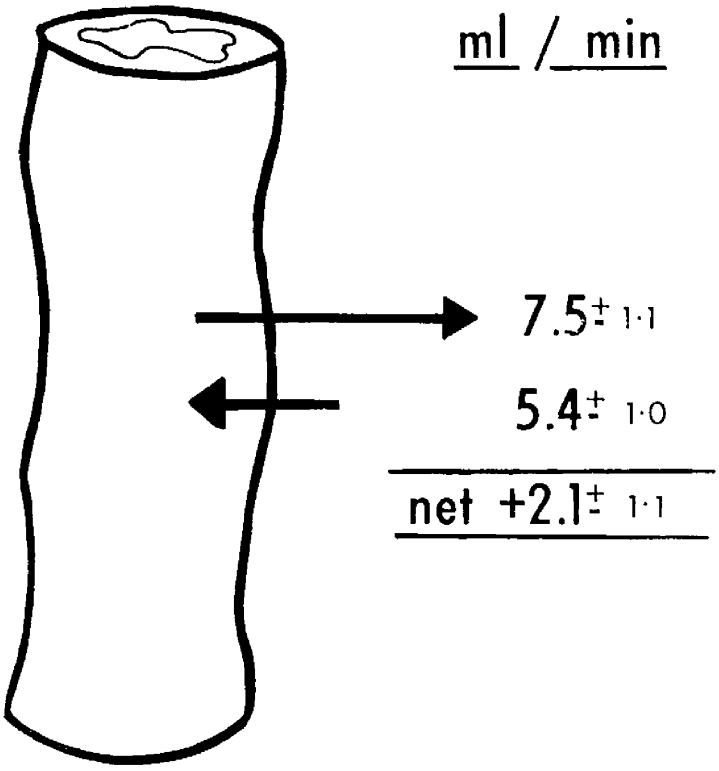


FIGURE 52 Diagram of the rates of unidirectional and net water transport in the intact colon of four normal subjects.
The mean rates are followed by the standard deviations.

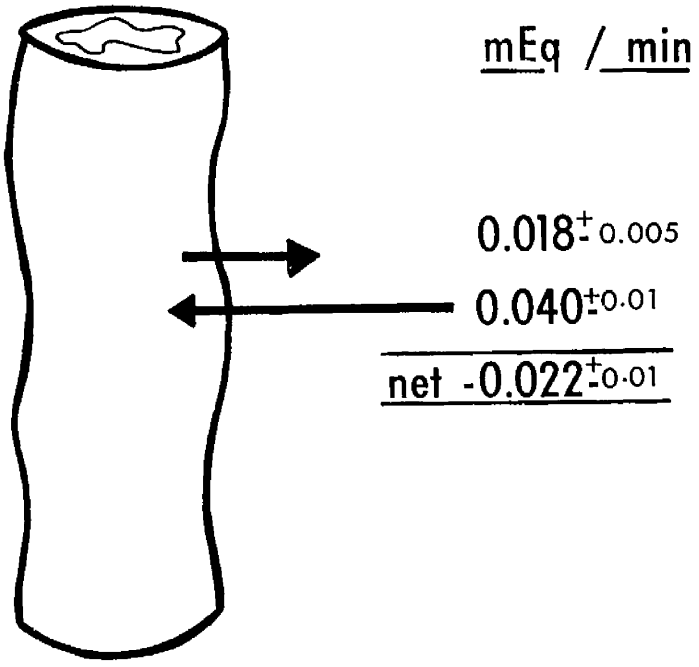


FIGURE 53 Diagram of the rates of unidirectional and net potassium transport in the intact colon of four normal subjects.
The mean rates are followed by the standard deviations.

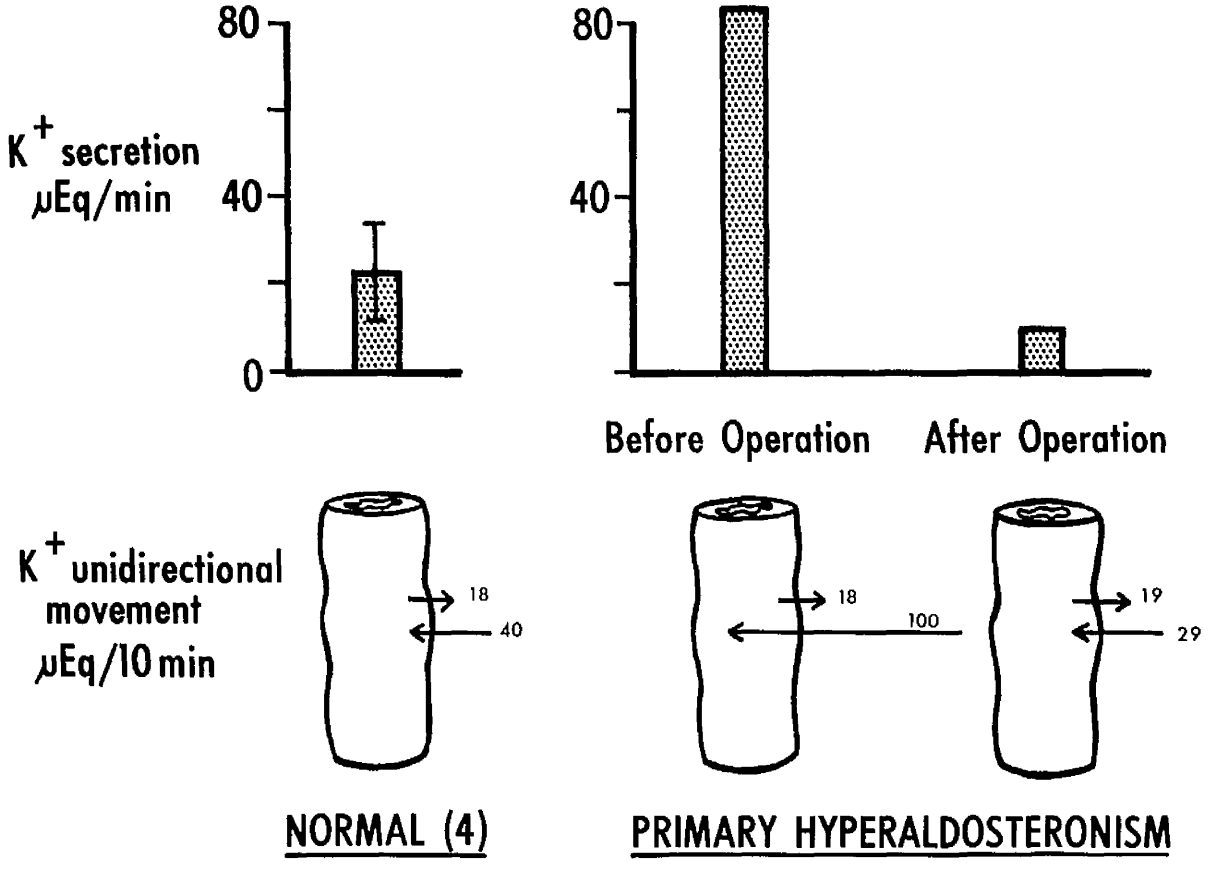


FIGURE 54 Diagram illustrating the abnormal exchange of potassium across the colonic mucosa in the patient with hyperaldosteronism. After operation the rates of potassium movement returned to normal.
The vertical lines above and below the mean rate of potassium secretion in the four normal subjects indicate one standard deviation.

TABLE 42. The rates of movement of sodium, potassium and water across the mucosa of intact colon of a patient with primary hyperaldosteronism, before and after operation, compared to those in four normal subjects.

Subject	Sodium (mEq/min)			Potassium (mEq/min)			Water (ml/min)
	Ins.	Exs.	Net	Ins.	Exs.	Net	Net
Patient							
Before operation	0.27	0.10	+0.17	0.025	0.136	-0.111	+1.1
	0.53	0.39	+0.14	0.011	0.061	-0.050	+0.1
Mean	0.40	0.25	+0.15	0.018	0.100	-0.082	+0.6
After operation	0.90	0.60	+0.30	0.013	0.033	-0.020	+0.3
	0.80	0.24	+0.56	0.018	0.024	-0.006	+2.8
	1.08	0.29	+0.79	0.026	0.031	-0.005	+4.7
Mean	0.93	0.38	+0.55	0.019	0.029	-0.010	+2.3
Normal subjects							
Mean	0.61	0.29	+0.32	0.018	0.040	-0.022	+2.1
S.D.	0.09	0.08	0.09	0.005	0.01	0.01	1.1

PART B

APPENDICES

APPENDIX 1. COMPOSITION OF THE TEST SOLUTION

Sodium chloride	8.0 g
Potassium chloride (10% w/v)	2.5 ml
Calcium chloride (10% w/v)	1.5 ml
Magnesium chloride (1% w/v)	1.0 ml
Dextrose	0.9 g
Sodium dihydrogen phosphate	0.05 g
Sodium bicarbonate	1.0 g
Sodium - 24 *	2 μc
Potassium - 42 *	4 μc
Deuterium oxide ** (99.7% v/v)	10 ml
Triple distilled water	to one litre

The analytical grade of reagents was used.

* The isotopic data are detailed in Appendix 2.

** Deuterium oxide (Norsk Hydro) was obtained from the Imperial Chemical Industries. In several experiments, 20 ml, instead of 10 ml, deuterium oxide were added to the test solution.

Concentration of electrolytes (mEq/L)

K^+	3.3	Cl^-	143.0
Na^+	149.0	HCO_3^-	12.0
Ca^+	2.7	HPO_4^-	0.7
Mg^+	0.2		

APPENDIX 2. RADIO-ISOTOPIC DATA.

(a) Sodium - 24

Obtained weekly from the Radiochemical Centre, Amersham, this isotope is presented in a sterilised isotonic solution of sodium chloride, with the following specifications:

Half-life	15.0 hours	
Emission	Beta (Mev)	Gamma (Mev)
	1.39 (100%)	1.37 (100%)
		2.75 (100%)
Daughter	^{24}Mg (stable)	
Radioactive concentration*	~ 1 mc ^{24}Na per ml	
Specific activity*	~ 300 mc ^{24}Na per g Na	
Radioisotopic purity*	^{42}K < 0.005%	
	^{82}Br < 0.005%	
Radiochemical purity	$^{24}NaCl$ 100%	
pH	6 - 8	

(b) Potassium - 42

Obtained weekly from the Radiochemical Centre, this isotope is presented in a sterilised isotonic solution of potassium chloride with the following specifications:

Half-life	12.45 hours	
Emission	Beta (Mev)	Gamma (Mev)
	2.0 (18%)	1.5 (18%)
	3.6 (82%)	
Daughter	^{42}Ca (stable)	

Specific activity*	~20 mc ^{42}K per g K
Radioactive concentration*	~0.1 mc ^{42}K per ml
Radioisotopic purity*	^{24}Na < 0.05%; ^{82}Br < 0.005%
Radiochemical purity	^{42}KCl 100%
pH	6 - 8

*The values are given at the time of dispensing.

(c) Sodium - 22

Half-life	2.6 years
Emission	Beta: 0.54 Mev, 89%; 1.83 Mev, 0.06% EC: 11% Gamma: 0.51 Mev from beta; 1.28 Mev 100%
Radioactive concentration	0.5 - 2 mc per ml
Radioisotopic purity	No other radionuclides.
Chemical purity	Other substances less than 10 parts per million
Specific activity	Not less than 1 mc per mg Na

APPENDIX 3. CORRECTION FOR 'DEAD-TIME' OF BETA COUNTER (VEALL AND VETTER, 1958)

The beta counter was set to have a 'dead-time' of 300 microseconds, during which it was insensitive to radioactive disintegration.

A correction for this dead-time was made using the formula

$$R = R'/(1 - R'.t)$$

where R = true counts per second

R' = observed counts per second

t = dead time = 300 microseconds

APPENDIX 4. THE FORMULAE FOR THE CALCULATION OF THE RATES OF MOVEMENT OF WATER, SODIUM AND POTASSIUM.

I. IN ISOLATED SEGMENTS OF INTESTINE.

A. The calculation of the rate of net movement of water (H_2O_{net})

$$H_2O_{net} = V_o - V_t \quad \text{----------} \quad (1)$$

where V_o is the volume of solution instilled and V_t the volume of solution unabsorbed after time t.

B. The calculation of the rate of net movement of electrolyte (e.g., Na^+_{net})

$$Na^+_{net} = [Na^+]_o . V_o - [Na^+]_t . V_t \quad \text{-------} \quad (2)$$

where $[Na^+]_o$ and $[Na^+]_t$ are the chemical concentrations (in mEq/L) of sodium ions (labelled and unlabelled) in the test solution instilled and withdrawn from the gut after time t.

C. The calculation of the rate of insorption of electrolytes (e.g., Na^+_{ins})

The formula, given by Visscher et al. (1944b), was written by the authors as

$$Na^+_{ins} = \frac{[Na^+]_o \cdot V_o - [Na^+]_o \cdot V_t \cdot A_{na.t} \; A_{na.o}}{\frac{1}{2}\left(1 + \frac{A_{na.t}\,[Na^+]_o}{A_{na.o}\,[Na^+]_t}\right)} \quad \text{--(3)}$$

where $\underline{A}_{na.o}$ and $\underline{A}_{na.t}$ are the counts per second per ml due to radiosodium in the solutions, instilled and withdrawn respectively.

This formula may be simplified and made more meaningful by multiplying the numerator by $A_{na.o}/A_{na.o}$.

Thus

$$Na^+_{ins} = \frac{[Na^+]_o.V_o.A_{na.o} - [Na^+]_o.V_t.\frac{A_{na.t}.A_{na.o}}{A_{na.o}.A_{na.o}}}{\frac{1}{2}\left(\frac{[Na^+]_o.A_{na.o}}{[Na^+]_o.A_{na.o}} + \frac{[Na^+]_o.A_{na.t}}{[Na^+]_t.A_{na.o}}\right)} \quad \text{-------(4)}$$

$$= \frac{A_{na.o}.V_o - A_{na.t}.V_t}{\frac{1}{2}\,(A_{na.o}/[Na^+]_o + A_{na.t}/[Na^+]_t)} \quad \text{---------(5)}$$

$$= \frac{\text{Quantity of isotope moved out of lumen}}{\text{Arithmetic mean of the specific activity of the luminal solution}} \quad \text{--(6}$$

The rate of insorption of potassium can be calculated from a corresponding formula.

D. <u>The calculation of the rate of insorption of water (Visscher et al., 1944a)</u>.

$$H_2O_{ins} = (D_o.V_o - D_t.V_t)/\tfrac{1}{2}.(D_o - D_t) \quad \text{---------(7)}$$

where $\underline{D}_o$ and $\underline{D}_t$ are the concentrations of D_2O (in atoms per cent excess) in the test solution instilled and withdrawn after time $\underline{t}$.

II. IN COLONIC PERFUSION EXPERIMENTS.

E. The calculation of the rate of net movement of water (H_2O_{net} - ml/min).

$$H_2O_{net} = V_{in} - (V_{in}.PEG_{in}/PEG_{out}) \quad \text{----------(8)}$$

where V_{in} is the volume of solution infused (ml/min), PEG_{in} and PEG_{out} are the concentrations of PEG in the infused solution and perfusate.

F. The calculation of the rate of net movement of electrolyte (e.g. Na^+_{net} - mEq/min).

$$Na^+_{net} = ([Na^+]_{in}.V_{in}) - ([Na^+]_{out}.V_{in}.PEG_{in}/PEG_{out}) \quad \text{-----(9)}$$

where $[Na^+]_{in}$ and $[Na^+]_{out}$ are the concentrations of sodium (in mEq/L) in the infused solution and perfusate.

G. The calculation of the rate of insorption of electrolyte (e.g. Na^+_{ins} - mEq/min).

$$Na^+_{ins} = \frac{(A_{na.in}.V_{in}) - (A_{na.out}.V_{in}.PEG_{in}/PEG_{out})}{\frac{1}{2}\,(A_{na.in}/[Na^+]_{in} + A_{na.out}/[Na^+]_{out})} \quad \text{-----(10)}$$

where $A_{na.in}$ and $A_{na.out}$ are the activities of sodium in the infused solution and perfusate.

APPENDIX 4 (contd.)

H. The calculation of the rate of insorption of water (H_2O_{in} - ml/min).

$$H_2O_{in} = \frac{(D_{in} \cdot V_{in}) - (D_{out} \cdot V_{in} \cdot PEG_{in}/PEG_{out})}{\frac{1}{2}(D_{in} + D_{out})} \quad \text{------(11)}$$

where D_{in} and D_{out} are the concentrations of D_2O in infused solution and perfusate.

APPENDIX 5. The protocol of a single 10-minute test and the calculation of the rates of movement of sodium, potassium and water.

DATA.

1. Volumes

Volume of solution instilled, (V_o) = 25.0 ml
Volume of solution aspirated at 10 minutes = 17.5 ml
Volume of rinse instilled = 100.0 ml
Volume of rinse withdrawn = 96.0 ml

2. Radioactivity measurements

Mean background count in scintillation counter = 5 counts per second (cps)

Solution	Counter (a)	Time (b)	Counts	Secs.	cps	Corrected cps (c)	cps/ml (d)
Test	S	11.34	24011	100	240	235	47
	G-M	bg(e)	44	100	1	-	-
	G-M	11.35	39036	100	390	432	43
Na standard	S	11.40	13404	100	134	129	26
	G-M	bg	39	100	1	-	-
	G-M	11.47	25144	400	63	62	6
K standard	S	11.57	10821	100	108	103	21
	G-M	bg	55	100	1	-	-
	G-M	11.58	24794	100	248	267	27
Aspirate	S	13.12	18891	100	189	184	37
	G-M	bg	21	100	1	-	-
	G-M	13.13	25487	100	255	275	28
Rinse	S	13.23	12120	1000	12	7	1
	G-M	bg	43	100	1	-	-
	G-M	13.24	12830	1000	13	12	1
Test	S	17.40	18036	100	180	175	35
	G-M	bg	26	100	1	-	-
	G-M	17.43	24903	100	249	262	26
K Standard	S	17.50	31148	400	78	73	15
	G-M	bg	46	100	1	-	-
	G-M	17.51	19513	100	195	206	21
Na standard	S	18.00	10252	100	103	98	20
	G-M	bg	52	100	1	-	-
	G-M	18.02	19568	400	49	48	5

Notes

(a) The scintillation counter is designated by S; the Geiger-Muller, by G-M.

(b) The time noted is the mid-time of the count.

(c) The appropriate correction for dead time was applied to all beta counts, before the background of the G-M counter was subtracted. The mean background count was subtracted from all scintillation counts.

(d) In the scintillation counter, 5 ml sample was used for counting; the capacity of the G-M tube was 10 ml.

(e) The background of the G-M tube was obtained before the sample was instilled.

3. Chemical measurements

Concentration of sodium in instilled solution, $[Na^+]_o$	= 151 mEq/L
Concentration of sodium in aspirate $[Na^+]_t$	= 151 mEq/L
Concentration of potassium in instilled solution, $[K^+]_o$	= 4.0 mEq/L
Concentration of potassium in aspirate $[K^+]_t$	= 4.25 mEq/L

4. Deuterium oxide

Concentration of D_2O in instilled solution, D_o	= 1.92 per cent
Concentration of D_2O in aspirate, D_t	= 0.72 per cent

APPENDIX 5 (contd.)

CALCULATIONS

1. ^{24}Na and ^{42}K activities

Let the zero time for the experiment be 1200 hours to which all counts are corrected. Then,

	1	2	Mean
Count rate of ^{24}Na std. in scintillation counter	25	26	26
Count rate of ^{24}Na std. in the G-M counter	6	6	6
Count rate of ^{42}K std. in the scintillation counter	21	20	20
Count rate of ^{42}K std. in the G.M counter	27	28	27

The formulae used to differentiate sodium and potassium radioactivity in a mixture are given in the text of Part II, Chapter 2, Equations 4 to 7.

Therefore,

$$p = 20/27 = 0.741 \quad \text{and} \quad q = 6/26 = 0.231$$

and

^{24}Na activity in aspirate = (37 - (0.741 x 28))/0.829 cps per ml

= 20 cps/ml

= 21 cps/ml (adjusted to zero time)

^{24}Na activity in rinse = (1 - (0.741 x 1))/0.829 cps per ml

= 1 cps/ml

= 1 cps/ml (adjusted to zero time)

APPENDIX 5 (contd.)

^{42}K activity in aspirate = (28 - (0.231 x 37))/0.829 cps per ml
= 23 cps/ml
= 24 cps/ml (adjusted to zero time)

^{42}K activity in rinse = (1 - (0.231 x 2))/0.829 cps per ml
= 1 cps/ml
= 1 cps/ml (adjusted to zero time)

2. Residual volume and net water movement

	From ^{24}Na data	From ^{42}K data
Total activity of test solution, cps	25 x 26 = 650	25 x 27 = 675
Activity of aspirate, cps	17.5 x 21 = 368	17.5 x 24 = 420
Activity of rinse, cps	96 x 1 = 96	96 x 1 = 96
Percentage of isotope dose absorbed	28%	23%
Residual volume, ml	96/21 = 4.6	96/24= 4.0
Volume unabsorbed, ml (V_t)	17.5+4.6 = 22.1	17.5+4.0 = 21.5
Net movement of water, ml/10 min ($V_o - V_t$)	+ 2.9	+ 3.5

∴ Mean residual volume, 4.3 ml

and mean volume of unabsorbed fluid, 21.8 ml

and mean net water movement, (H_2O_{net}) +3.2 ml

APPENDIX 5 (contd.)

3. Sodium movement

$$Na^+_{ins} = \frac{(0.025 \times 26) - (0.0218 \times 21)}{\frac{1}{2}(26/151 + 21/151)} \quad \text{mEq per 10 min}$$

$$= 1.27 \text{ mEq per 10 min}$$

$$Na^+_{net} = (0.025 \times 151) - (0.0218 \times 151) \quad \text{mEq per 10 min}$$

$$= +0.49 \text{ mEq per 10 min}$$

$$\therefore Na^+_{exs} = 0.78 \text{ mEq per 10 min}$$

4. Potassium movement

$$K^+_{ins} = \frac{(0.025 \times 27) - (0.0218 \times 24)}{\frac{1}{2}(27/4 + 24/4.25)} \quad \text{mEq per 10 min}$$

$$= 0.025 \text{ mEq per 10 min}$$

$$K^+_{net} = (0.025 \times 4.0) - (0.0218 \times 4.25) \quad \text{mEq per 10 min}$$

$$= +0.007 \text{ mEq per 10 min}$$

$$\therefore K^+_{exs} = 0.018 \text{ mEq per 10 min}$$

5. Water movement

$$H_2O_{ins} = \frac{(1.92 \times 25) - (0.72 \times 21.8)}{\frac{1}{2}(1.92 + 0.72)} \quad \text{ml per 10 min}$$

$$= 24.5 \text{ ml per 10 min}$$

since

$$H_2O_{net} = +3.2 \text{ ml per 10 min}$$

$$\therefore H_2O_{exs} = 21.3 \text{ ml per 10 min}$$

APPENDIX 6. The errors in estimating sodium and potassium.

The total error in estimating sodium and potassium by flame photometry is composed of:

A The variation among replicate determinations (within-run precision).

	Sodium mEq/litre	Potassium mEq/litre
Known concentration	141.5	4.0
Estimated concentration (10 replicates)	141.0	4.1
	141.0	3.9
	142.4	4.1
	141.2	4.0
	142.8	3.9
	142.8	3.9
	139.0	3.9
	142.2	4.1
	142.0	4.1
	141.0	3.9
Mean estimated concentration	141.5	3.99
Standard deviation	1.2	0.06
Coefficient of variation	0.8%	1.49%

B The variation between days in estimating the same sample.

The standard deviation (s) of these measurements was obtained from

$$s = \sqrt{\left(\sum (d^2)/N \right)}$$

where d is the difference between duplicate determinations measured on 30 occasions on the same sample, and N is the total number of determinations (60).

The coefficient of variation was found to be 1 per cent for sodium and 2 per cent for potassium.

The total error is given by $\sqrt{(A^2 + B^2)}$ and was calculated as 1.3 per cent for sodium estimations and 2.5 per cent for potassium estimations.

APPENDIX 7. The error in estimating deuterium oxide by infra-red spectrophotometry.

Method

The concentration of deuterium oxide was determined in duplicate on 10 unknown samples.

Result

Deuterium oxide (atoms per cent excess)	
1.96	1.97
0.74	0.75
1.00	1.01
0.96	0.95
0.76	0.75
1.26	1.28
0.84	0.86
1.54	1.52
0.99	0.99
0.98	0.97

Mean concentration 1.104

Standard deviation s of the difference between 10 duplicate determinations is given by

$$s = \sqrt{\left(\sum (d^2)/N \right)}$$

where d is the difference between duplicates and N is the total number of determinations N.

$$s = 0.0095$$

$$\text{coefficient of variation} = \frac{0.0095}{1.104} \times 100 = 0.86 \text{ per cent}$$

APPENDIX 8. The histology of a Thiry-Vella fistula.

The isolated segment of bowel was washed with more than a litre of isotonic saline solution every second day. On each occasion the segment was distended with fluid at least once. This practice ensured that the dimensions of the isolated bowel and its histological characteristics were preserved.

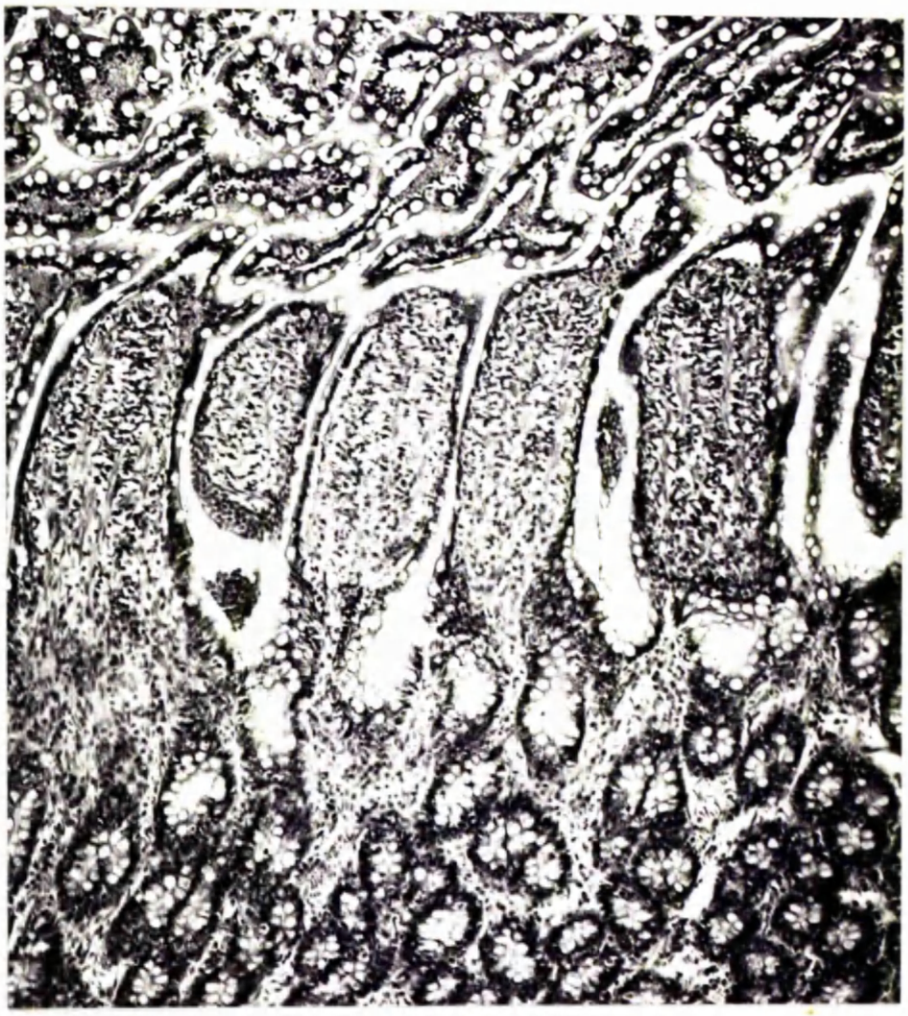


FIGURE 55 Normal canine ileum
(H. and E.) x 100

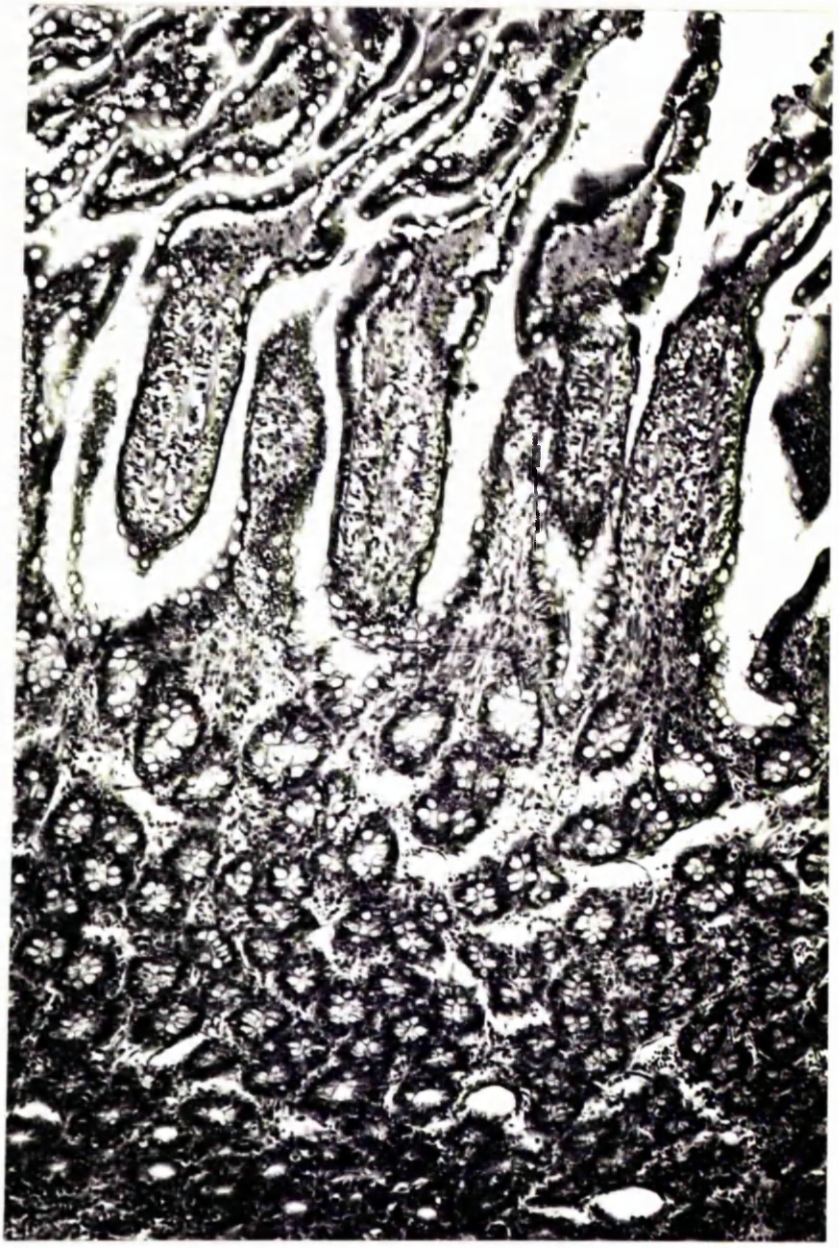


FIGURE 56 Thiry-Vella fistula of ileum washed every second day. Fistula was formed six months previously.
(H. and E.) x 100

If a segment were not rinsed so frequently, the mucosa became thin and flattened with stunting of the villi. The calibre of the fistula was narrowed and its luminal capacity reduced.

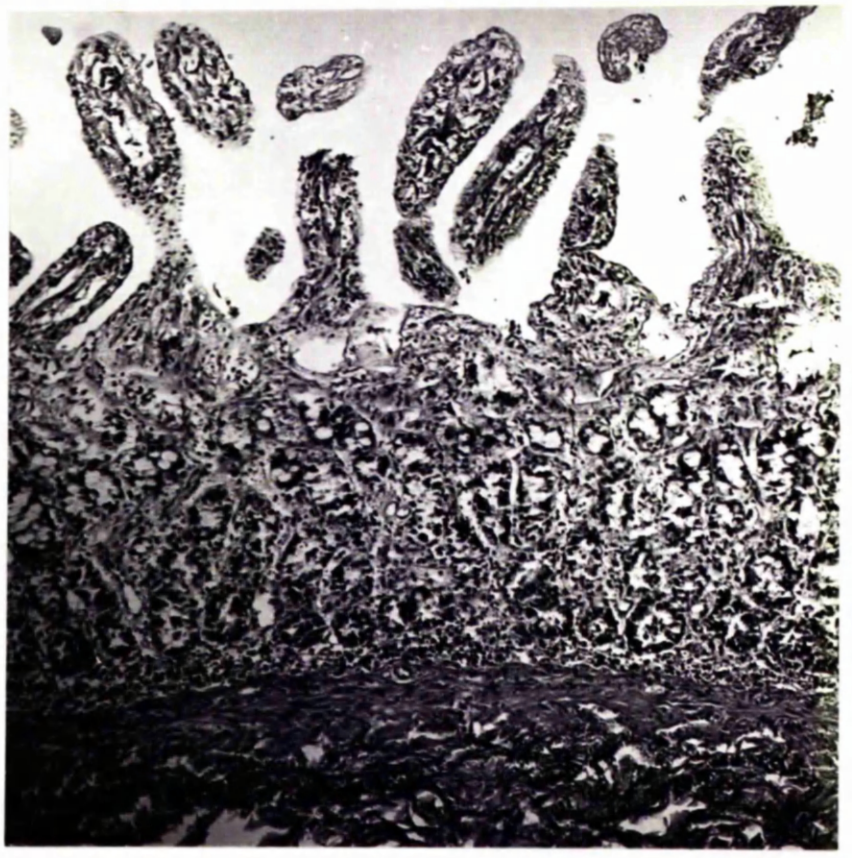


FIGURE 57 Thiry-Vella fistula of ileum, neglected for one month.
(H. and E.) x 100

APPENDIX 9. Residual volumes calculated simultaneously from recovery of polyethylene glycol (RV_{peg}) and from radioactivity of the rinse (RV_{isot}).

	RV_{peg} (ml)	RV_{isot} (ml)
	1.5	1.0
	2.0	1.5
	1.9	1.4
	3.6	3.1
	1.6	0.9
	3.0	2.8
	1.6	0.8
	3.5	3.4
	2.8	1.9
	2.4	2.4
	1.6	1.8
	3.0	2.5
Mean $\pm$ S.E.M.	2.4 ± 0.2	2.0 ± 0.3
Mean difference	0.4	
S.E.M. difference	0.3	
t	1.30	
P	$< 0.4, > 0.3$	

APPENDIX 10. Known and calculated activities of ^{24}Na and ^{42}K in mixtures.

SODIUM			POTASSIUM		
Known activity (cps)	Calculated activity (cps)	Recovery %	Known activity (cps)	Calculated activity (cps)	Recovery %
2891	2855	99	4444	4557	103
3131	2990	96	4312	4497	104
2519	2414	96	3225	3384	105
2934	2759	94	4158	4398	106
2960	2954	100	3891	3926	101
2825	2782	98	4048	4023	99
3623	3165	87	4516	4668	103
2778	2645	95	3838	3897	102
3181	3184	100	3537	3649	103
3086	3136	102	3784	3654	97
3158	3174	101	3760	3703	98
3156	3083	98	3748	3761	100
3097	3031	98	3288	3311	101
2922	2751	94	2922	2972	102
3348	3338	100	3758	3668	98
3118	3074	99	3585	3656	102
2854	2818	99	3881	3854	99
3277	3138	95	3151	3218	102
2612	2655	102	2998	3081	103
2827	2850	101	3257	3388	104
ean* 3015	2935	97	3705	3763	102

*The arithmetic mean was calculated for the known and calculated activities, and the geometric mean for the percentage recoveries.

Appendix 11

Intestinal transport of water, sodium and potassium in experimental obstruction - individual results.

APPENDIX 11. Effect of obstruction on rates of sodium transport (μEq per 10 min).

INSORPTION

Duration of obstruction (hours)	Dog no.	Cranial segment tests 1	2	3	Caudal segment tests 1	2	3	Upper ileal segment tests 1	2	3
0	18	1350	1276	1193	1178	1082	1314	-	-	-
	19	1000	950	1145	1620	1121	973	940	813	786
	Mean ± S.E.M.	1152 ± 63			1215 ± 93			846		
12	20	43	36	55	1083	1208	1070			
	21	63	35	36	1111	1160	1011			
	Mean ± S.E.M.	45 ± 4.7			1107 ± 28					
24	22	21	15	20	1122	1070	913			
	23	12	22	20	1080	890	901			
	Mean ± S.E.M.	18 ± 1.6			996 ± 14					
36	24	45	56	31	1130	1208	986			
	25	39	48	47	895	995	1066	756	809	695
	Mean ± S.E.M.	44 ± 3.5			1047 ± 46			753		
48	26	68	59	73	913	804	885			
	27	48	55	64	976	1031	816	583	406	613
	Mean ± S.E.M.	61 ± 3.7			904 ± 36			534		
60	28	54	59	43	1101	809	931			
	29	21	65	78	764	850	940			
	Mean ± S.E.M.	53 ± 8.0			899 ± 49					

APPENDIX 11 (contd.)

EXSORPTION

Duration of obstruction (hours)	Dog no.	Cranial segment tests 1	2	3	Caudal segment tests 1	2	3	Upper ileal segment tests 1	2	3
0	18	400	708	275	593	265	400			
	19	513	260	45	386	376	275	690	750	560
	Mean ± S.E.M.	434 ± 68			383 ± 48			667		
12	20	620	600	575	643	321	250			
	21	436	488	491	740	641	738			
	Mean ± S.E.M.	535 ± 30			555 ± 88					
24	22	871	916	860	665	680	680			
	23	847	726	940	731	530	605			
	Mean ± S.E.M.	860 ± 30			649 ± 29					
36	24	1505	1700	1431	706	309	271			
	25	1511	1589	1634	504	403	250	701	753	751
	Mean ± S.E.M.	1562 ± 40			407 ± 71			735		
48	26	1922	1802	1785	650	609	643			
	27	1584	1753	1705	750	850	640	619	571	639
	Mean ± S.E.M.	1758 ± 46			690 ± 37			609		
60	28	2085	2015	1884	498	578	675			
	29	1729	1901	1996	518	709	605			
	Mean ± S.E.M.	1935 ± 51			597 ± 34					

APPENDIX 11 (contd.)

NET*

Duration of obstruction (hours)	Dog no.	Cranial segment tests 1	2	3	Caudal segment tests 1	2	3
0	18	+950	+568	+918	+628	+817	+914
	19	+487	+690	+695	+1234	+745	+698
	Mean ± S.E.M.	+718 ± 76			+839 ± 89		
12	20	-567	-564	-520	+440	+887	+820
	21	-373	-453	-455	+371	+519	+273
	Mean ± S.E.M.	-490 ± 32			+552 ± 101		
24	22	-850	-901	-840	+457	+390	+233
	23	-835	-704	-920	+349	+360	+296
	Mean ± S.E.M.	-842 ± 31			+347 ± 31		
36	24	-1450	-1644	-1400	+424	+899	+715
	25	-1492	-1541	-1587	+391	+592	+816
	Mean ± S.E.M.	-1516 ± 37			+640 ± 85		
48	26	-1854	-1743	-1712	+263	+195	+242
	27	-1536	-1698	-1641	+226	+181	+176
	Mean ± S.E.M.	-1697 ± 43			+214 ± 14		
60	28	-2031	-1956	-1841	+603	+231	+256
	29	-1708	-1836	-1918	+246	+141	+335
	Mean ± S.E.M.	-1882 ± 46			+302 ± 65		

*The rates of net sodium movement in the upper ileal segment are given on the following page.

APPENDIX 11 (contd.)

Duration of obstruction (hours)	Dog no.	Upper ileal segment tests 1	2	3
0	19	+250	+63	+226
	Mean		+179	
36	25	+ 55	+56	- 56
	Mean		+18	
48	27	- 36	-165	- 26
	Mean		- 75	

APPENDIX 11 (contd.)

Effect of obstruction on rates of potassium transport (μEq per 10 min).

INSORPTION

Duration of obstruction (hours)	Dog no.	Cranial segment Tests 1	2	3	Caudal segment Tests 1	2	3
0	18	30.1	28.8	29.3	21.1	19.6	8.5
	19	22.0	23.2	22.8	19.5	22.4	19.5
	Mean ± S.E.M.	26.0 ± 24			18.4 ± 20		
12	20	9.4	8.6	7.3	23.6	22.0	22.3
	21	10.1	6.8	7.6	24.6	25.0	24.2
	Mean ± S.E.M.	8.3 ± 0.5			23.6 ± 0.6		
24	22	2.3	2.5	1.9	28.1	29.3	27.6
	23	1.8	3.6	2.5	24.9	31.8	30.5
	Mean ± S.E.M.	2.4 ± 0.3			28.7 ± 1.0		
36	24	2.8	1.0	2.3	27.2	21.3	25.4
	25	3.1	1.9	2.5	29.2	30.1	21.2
	Mean ± S.E.M.	2.3 ± 0.3			25.7 ± 1.6		
48	26	1.2	1.8	1.9	27.3	28.1	26.1
	27	1.6	1.6	1.0	23.4	27.6	25.4
	Mean ± S.E.M.	1.5 ± 0.1			26.3 ± 0.7		
60	28	3.1	0.5	2.6	31.8	27.6	26.8
	29	2.8	4.9	0.6	24.1	23.8	25.6
	Mean ± S.E.M.	2.4 ± 0.7			26.6 ± 1.2		

APPENDIX 11 (contd.)

Duration of obstruction (hours)	Dog no.	Upper ileal segment Tests 1	2	3
0	19	19.4	20.6	18.9
	Mean		19.6	
36	25	15.6	17.8	16.3
	Mean		16.6	
48	27	14.3	12.1	11.8
	Mean		12.7	

APPENDIX 11 (contd.)

EXSORPTION

Duration of obstruction (hours)	Dog no.	Cranial segment Tests 1	2	3	Caudal segment Tests 1	2	3
0	18	39.0	38.6	44.5	37.3	34.5	40.1
	19	40.0	42.1	44.8	34.8	40.1	46.8
	Mean ± S.E.M.	41.5 ± 1.1			38.9 ± 1.9		
12	20	54.0	59.1	62.4	44.6	46.0	47.4
	21	48.2	46.3	52.4	54.7	50.8	50.3
	Mean ± S.E.M.	53.7 ± 2.5			48.9 ± 1.5		
24	22	56.3	63.5	65.8	56.0	57.9	58.1
	23	53.6	69.2	71.5	55.1	62.9	57.0
	Mean ± S.E.M.	63.3 ± 2.9			57.8 ± 1.1		
36	24	68.4	80.3	82.3	60.7	58.1	57.3
	25	58.2	66.3	71.1	59.0	63.7	56.2
	Mean ± S.E.M.	73.4 ± 3.5			59.1 ± 1.1		
48	26	87.2	81.2	92.0	67.5	69.9	71.7
	27	76.6	80.9	90.2	66.6	66.5	60.8
	Mean ± S.E.M.	84.7 ± 2.5			68.8 ± 1.5		
60	28	92.3	96.1	83.8	73.6	69.7	73.5
	29	83.2	98.3	101.6	63.9	69.7	71.2
	Mean ± S.E.M.	92.5 ± 3.1			70.3 ± 1.5		

APPENDIX 11 (contd.)

Duration of obstruction (hours)	Dog no.	Upper ileal segment Tests 1	2	3
0	19	32.8	34.8	38.6
	Mean		35.4	
36	25	43.5	46.8	41.2
	Mean		43.8	
48	27	43.2	41.3	38.6
	Mean		41.0	

APPENDIX 11 (contd.)

NET

Duration of obstruction (hours)	Dog no.	Cranial segment Tests 1	2	3	Caudal segment Tests 1	2	3
0	18	-8.9	-9.8	-15.2	-16.2	-14.9	-31.6
	19	-18.0	-18.9	-22.0	-15.3	-17.7	-27.3
	Mean ± S.E.M.	-15.5 ± 2.1			-20.5 ± 2.9		
12	20	-44.6	-50.5	-55.1	-23.0	-24.0	-25.1
	21	-38.1	-39.5	-44.8	-30.1	-25.8	-26.1
	Mean ± S.E.M.	-45.4 ± 2.6			-25.3 ± 1.0		
24	22	-54.0	-61.0	-63.9	-27.9	-28.6	-30.5
	23	-51.8	-65.6	-69.0	-30.2	-31.1	-26.5
	Mean ± S.E.M.	-60.8 ± 2.8			-29.1 ± 0.7		
36	24	-71.2	-81.3	-84.6	-33.5	-36.8	-31.9
	25	-61.3	-68.2	-73.6	-29.8	-33.6	-35.0
	Mean ± S.E.M.	-71.1 ± 3.7			-33.4 ± 1.0		
48	26	-86.0	-79.4	-90.1	-40.2	-41.8	-45.6
	27	-75.0	-79.3	-89.2	-43.2	-38.9	-45.4
	Mean ± S.E.M.	-83.2 ± 2.5			-42.5 ± 1.1		
60	28	-89.2	-95.6	-81.2	-41.8	-42.1	-46.7
	29	-80.4	-93.4	-101.0	-39.8	-45.9	-45.6
	Mean ± S.E.M.	-90.1 ± 3.3			-43.7 ± 1.1		

APPENDIX 11 (contd.)

Duration of obstruction (hours)	Dog no.	Upper ileal segment Tests 1	2	3
0	19	-13.4	-14.2	-19.7
	Mean		-15.8	
36	25	-27.9	-29.0	-24.9
	Mean		-27.2	
48	27	-28.9	-29.2	-26.8
	Mean		-28.3	

APPENDIX 11 (contd.)

Effect of obstruction upon rates of water transport (ml per 10 min).

INSORPTION

Duration of obstruction (hours)	Dog no.	Cranial segment Tests 1	2	3	Caudal segment Tests 1	2	3
0	18	17.0	18.3	16.5	12.1	11.5	13.7
	19	18.9	15.2	16.3	15.5	15.2	15.0
	Mean ± S.E.M.	17.0 ± 0.6			13.8 ± 0.7		
12	20	8.5	8.2	6.4	13.6	16.3	10.9
	21	7.9	5.5	8.4	15.2	14.5	16.5
	Mean ± S.E.M.	7.5 ± 0.5			14.5 ± 0.9		
24	22	5.4	7.8	4.2	14.5	15.8	11.8
	23	4.1	7.3	5.6	16.5	10.1	14.2
	Mean ± S.E.M.	5.7 ± 0.6			13.8 ± 0.9		
36	24	3.5	6.2	3.9	15.2	16.5	15.3
	25	2.1	1.4	5.3	12.6	15.4	11.4
	Mean ± S.E.M.	3.7 ± 0.8			14.4 ± 0.8		
48	26	4.2	4.1	5.1	14.1	12.5	11.1
	27	3.9	4.2	4.8	13.4	13.5	12.5
	Mean ± S.E.M.	4.4 ± 0.2			12.9 ± 0.4		
60	28	3.4	2.8	5.6	15.8	10.1	12.1
	29	4.3	2.1	0.5	10.9	12.8	14.5
	Mean ± S.E.M.	3.1 ± 0.7			12.7 ± 0.9		

APPENDIX 11 (contd.)

Duration of obstruction (hours)	Dog no.	Upper ileal segment Tests 1	2	3
0	19	12.3	12.4	10.8
	Mean		11.8	
36	25	9.8	10.1	8.9
	Mean		9.6	
48	27	7.6	6.4	8.2
	Mean		7.4	

APPENDIX 11 (contd.)

EXSORPTION

Duration of obstruction (hours)	Dog no.	Cranial segment Tests 1	2	3	Caudal segment Tests 1	2	3
0	18	10.2	9.8	6.8	8.4	5.8	9.1
	19	15.5	10.6	12.0	7.8	7.9	8.6
	Mean ± S.E.M.	10.8 ± 1.2			7.9 ± 0.5		
12	20	12.4	11.8	9.8	10.8	10.6	5.8
	21	10.4	8.3	11.3	12.9	11.1	14.8
	Mean ± S.E.M.	10.6 ± 0.6			11.0 ± 1.2		
24	22	11.0	13.9	10.1	12.1	12.4	10.2
	23	10.4	12.5	10.5	14.2	8.2	12.9
	Mean ± S.E.M.	11.4 ± 0.6			11.7 ± 0.9		
36	24	14.1	12.8	14.9	13.1	10.4	10.2
	25	10.8	12.6	14.9	9.2	10.9	5.9
	Mean ± S.E.M.	13.3 ± 0.7			9.9 ± 0.9		
48	26	16.3	16.1	18.7	12.9	11.4	9.5
	27	14.8	13.3	15.8	11.9	11.4	11.6
	Mean ± S.E.M.	15.8 ± 0.7			11.5 ± 0.5		
60	28	19.9	17.6	17.5	12.1	8.9	10.8
	29	14.1	16.4	13.6	9.1	11.9	13.2
	Mean ± S.E.M.	16.5 ± 0.9			11.0 ± 0.7		

APPENDIX 11 (contd.)

Duration of obstruction (hours)	Dog no.	Upper ileal segment Tests 1	2	3
0	19	11.1	12.0	9.6
	Mean		10.9	
36	25	9.6	9.9	9.6
	Mean		9.7	
48	27	8.4	8.5	8.5
	Mean		8.5	

APPENDIX 11 (contd.)

NET

Duration of obstruction (hours)	Dog no.	Cranial segment Tests 1	2	3	Caudal segment Tests 1	2	3
0	18	+6.8	+8.5	+9.7	+3.7	+5.7	+4.6
	19	+3.4	+4.6	+4.3	+7.7	+7.3	+6.4
	Mean ± S.E.M.	+6.2 ± 1.0			+5.9 ± 0.6		
12	20	-3.9	-3.6	-3.4	+2.4	+5.7	+5.1
	21	-2.5	-2.8	-2.9	+2.3	+3.4	+1.7
	Mean ± S.E.M.	-3.1 ± 0.2			+3.5 ± 0.7		
24	22	-5.6	-6.1	-5.9	+2.4	+3.4	+1.6
	23	-6.3	-5.2	-4.9	+2.3	+1.9	+1.3
	Mean ± S.E.M.	-5.7 ± 0.2			+2.1 ± 0.3		
36	24	-10.6	-6.6	-11.0	+2.1	+6.1	+5.1
	25	-8.7	-11.2	-9.6	+3.4	+4.5	+5.5
	Mean ± S.E.M.	-9.6 ± 0.7			+4.5 ± 0.6		
48	26	-12.1	-12.0	-13.6	+1.2	+1.1	+1.6
	27	-10.9	-9.1	-11.0	+1.5	+2.1	+0.9
	Mean ± S.E.M.	-11.4 ± 0.6			+1.4 ± 0.2		
60	28	-13.5	-14.8	-11.9	+3.7	+1.2	+1.3
	29	-10.8	-14.3	-13.1	+1.8	+0.9	+1.3
	Mean ± S.E.M.	-13.4 ± 0.6			+1.7 ± 0.4		

APPENDIX 11 (contd.)

Duration of obstruction (hours)	Dog no.	Upper ileal segment Tests 1	2	3
0	19	+1.2	+0.4	+1.2
	Mean		+0.9	
36	25	+0.2	+0.2	-0.7
	Mean		-0.1	
48	27	-0.8	-2.1	-0.3
	Mean		-1.1	

APPENDIX 11 (contd.) Concentration of sodium (mEq/L) in test solution at beginning (t_o) and end (t_{10}) of 10-minute tests performed in segments cranial and caudal to obstruction.

Duration of obstruction (hrs)	Dog no.	Concentration at t_o	Concentration at t_{10} in cranial segment 1	cranial segment 2	cranial segment 3	caudal segment 1	caudal segment 2	caudal segment 3
0	18	140	140	177	168	135	139	127
	19	141	141	137	137	132	157	152
	Mean ± S.E.M.	140.5 ± 0.2	150 ± 7.3			140.3 ± 4.8		
12	20	141	142	143	143	136	137	136
	21	141	142	143	143	139	139	140
24	22	141	143	140	141	136	145	141
	23	141	139	140	149	140	137	136
36	24	142	140	164	138	137	140	143
	25	142	149	140	148	146	144	140
48	26	142	146	143	136	138	140	141
	27	141	141	153	143	140	146	139
60	28	141	145	138	146	138	139	138
	29	141	146	136	143	141	140	134
	Mean ± S.E.M.	141.2 ± 0.1	143.4 ± 1.0			139.4 ± 1.7		

Concentration of sodium (mEq/L) in test solution at beginning (t_o) and end (t_{10}) of 10-minute tests performed in segment in upper ileum.

Duration of obstruction (hours)	Dog no.	Concentration at t_{10} in upper ileum 1	upper ileum 2	upper ileum 3
0	19	141	138	140
	Mean		140	
36	25	144	140	140
48	27	139	150	143
	Mean		143	

APPENDIX 11 (contd.) Concentration of potassium (mEq/L) in test solution at beginning (t_o) and end (t_{10}) of 10-minute tests performed in segments cranial and caudal to obstruction.

Duration of obstruction (hrs)	Dog no.	Concentration at t_o	Concentration at t_{10} in cranial segment 1	cranial segment 2	cranial segment 3	caudal segment 1	caudal segment 2	caudal segment 3
0	18	4.0	6.0	6.7	7.5	5.5	6.0	6.5
	19	3.9	5.3	5.7	5.8	6.9	6.5	6.7
	Mean ± S.E.M.	3.9 ± 0.02	6.2 ± 0.42			6.3 ± 0.21		
12	20	4.2	5.2	5.4	5.6	5.7	6.7	6.5
	21	4.1	5.1	5.1	5.3	5.9	5.9	5.5
24	22	4.1	5.1	5.3	5.4	5.8	6.1	5.7
	23	4.0	4.8	5.5	5.7	5.7	5.7	5.3
36	24	4.3	5.1	6.0	5.3	6.2	7.6	7.0
	25	3.9	4.7	4.6	4.9	5.9	6.4	6.8
48	26	4.2	5.1	5.0	5.1	6.1	6.1	6.4
	27	4.1	4.9	5.3	5.3	6.2	6.2	6.1
60	28	4.0	4.9	4.9	5.1	6.7	6.0	6.1
	29	4.2	5.2	5.0	5.4	6.2	6.3	6.4
	Mean ± S.E.M.	4.1 ± 0.02	5.2 ± 0.05			6.2 ± 0.09		

Concentration of potassium (mEq/L) in test solution at beginning (t_o) and end (t_{10}) of 10-minute tests performed in segment in upper ileum.

Duration of obstruction (hours)	Dog no.	Concentration at t_{10} in upper ileum 1	upper ileum 2	upper ileum 3
0	19	5.4	4.8	6.1
	Mean		5.4	
36	25	5.8	5.3	6.1
48	27	6.8	6.3	6.3
	Mean		6.1	

APPENDIX 11 (contd.) Ratio of cation (Na + K) to water movement in segments cranial and caudal to obstruction.

(See Table 24 for means and standard errors).

Duration of obstruction (hrs)	Dog no.	Ratio of cation to water movement (mEq/L) in cranial segment			caudal segment		
		1	2	3	1	2	3
		(i) insorption					
0	18	61.8	54.4	54.7	80.0	77.6	89.7
	19	41.3	71.0	56.2	92.3	59.3	68.3
12	20	6.1	5.4	9.7	81.4	75.5	100.2
	21	8.0	7.6	5.2	74.7	81.7	62.7
24	22	4.3	2.2	5.2	79.3	69.6	79.7
	23	3.4	3.5	4.0	66.9	91.3	65.6
36	24	13.6	9.2	8.5	76.1	74.5	66.1
	25	20.0	35.6	9.3	73.3	66.6	95.4
48	26	16.5	14.8	14.7	66.7	66.6	82.1
	27	12.7	13.5	13.5	74.6	78.4	67.3
60	28	16.8	21.3	8.1	71.7	82.8	79.2
	29	5.5	3.3	15.7	72.3	68.3	66.6
		(ii) exsorption					
0	18	35.4	68.3	33.9	66.2	39.8	39.6
	19	30.5	20.6	33.8	45.0	42.5	26.5
12	20	54.4	55.9	65.0	63.7	34.6	51.3
	21	46.5	64.3	48.1	61.6	62.3	53.3
24	22	84.3	70.4	91.7	59.6	72.5	72.4
	23	86.4	63.6	109.5	55.4	72.3	51.3
36	24	111.5	139.0	101.6	58.5	35.2	32.2
	25	145.3	131.4	114.4	61.2	42.8	51.9
48	26	123.3	116.9	100.4	55.6	59.6	75.2
	27	112.2	137.9	113.6	68.6	80.4	60.4
60	28	109.4	119.9	112.4	47.2	72.7	69.3
	29	128.5	121.9	154.2	63.9	65.4	51.2

APPENDIX 11 (contd.)

Duration of obstruction (hrs)	Dog no.	Ratio of cation to water movement (mEq/L) in cranial segment 1	cranial segment 2	cranial segment 3	caudal segment 1	caudal segment 2	caudal segment 3
		(iii) net					
0	18	138.4	65.0	93.2	165.4	140.7	191.9
	19	138.0	145.8	161.6	158.3	99.7	104.8
12	20	159.3	170.7	169.2	173.5	151.4	155.9
	21	164.4	175.9	172.3	148.2	145.1	145.2
24	22	161.4	159.2	154.0	178.9	106.3	126.7
	23	140.8	148.0	201.8	138.6	173.1	207.3
36	24	143.5	261.4	134.9	176.7	141.3	133.9
	25	176.2	143.6	173.0	106.2	124.1	142.0
48	26	160.3	151.8	132.5	185.6	139.3	122.8
	27	147.8	195.3	157.3	121.9	67.6	145.2
60	28	157.0	138.6	161.5	151.7	157.4	161.0
	29	165.6	134.9	154.1	114.5	105.7	222.6

Ratio of cation (Na + K) to water movement in upper ileum.

Duration of obstruction (hours)	Dog no.	Upper ileum 1	Upper ileum 2	Upper ileum 3
		(i) insorption		
0	19	78.0	67.1	74.5
36	25	78.7	81.9	79.9
48	27	78.6	65.3	76.2
		(ii) exsorption		
0	19	65.0	65.4	62.4
36	25	77.5	71.3	82.5
48	27	78.8	72.0	79.7
		(iii) net		
0	19	197.1	122.0	171.9
36	25	135.5	135.0	144.1
48	27	81.1	92.5	176.0

APPENDIX 11 (contd.) Concentrations of sodium and potassium in the serum (mEq/L), and of urea in blood (mg/100 ml) in obstruction.

Dog no.	Before obstruction			During obstruction			
	Na	K	urea	Duration	Na	K	urea
18	142	4.2	28	0	-	-	-
19	139	4.4	31		-	-	-
20	140	3.6	28	12	138	4.1	25
21	144	3.8	35		140	4.0	33
22	142	3.6	30	24	142	4.1	35
23	143	4.1	32		138	4.6	36
24	144	4.2	28	36	135	4.6	40
25	145	3.9	35		132	4.1	41
26	138	3.9	31	48	131	5.0	43
27	146	4.1	33		140	5.1	40
28	139	4.1	30	60	133	5.2	48
29	144	4.0	25		136	5.0	50

APPENDIX 11 (contd.) Effect of previous 'sham' operation on sorption of sodium, potassium and water.

Interval between sham operation and tests (hours)	Dog no.	Insorption	Exsorption	Net
		(i) sodium movement (μEq/10 min)		
24	30	1189	839	+350
		1230	780	+450
		1000	660	+340
		Mean 1140	Mean 760	Mean +380
36	31	951	653	+298
		997	621	+376
		876	626	+250
		Mean 941	Mean 633	Mean +308
48	32	811	621	+190
		879	659	+220
		790	614	+176
		Mean 827	Mean 631	Mean +196
		(ii) potassium movement (μEq/10 min)		
24	30	24.1	54.6	-30.5
		23.8	54.8	-31.0
		21.0	49.2	-28.2
		Mean 22.9	Mean 52.8	Mean -29.9
36	31	22.1	56.7	-34.6
		21.0	57.8	-36.8
		19.9	51.8	-31.9
		Mean 21.0	Mean 55.4	Mean -34.4
48	32	19.5	61.1	-41.6
		23.5	62.0	-38.5
		20.9	63.9	-43.0
		Mean 21.3	Mean 62.3	Mean -41.0

APPENDIX 11 (contd.)

Interval between sham operation and tests (hours)	Dog no.	Insorption	Exsorption	Net
		(iii) water (ml/10 min)		
24	30	14.1	11.6	+2.5
		13.3	9.9	+3.4
		16.1	13.8	+2.3
		Mean 14.5	Mean 11.8	Mean +2.7
36	31	13.0	11.1	+1.9
		11.5	9.0	+2.5
		11.8	10.3	+1.5
		Mean 12.1	Mean 10.1	Mean +2.0
48	32	11.0	10.1	+0.9
		10.8	9.6	+1.2
		12.9	11.9	+1.0
		Mean 11.6	Mean 10.5	Mean +1.1

Effect of previous 'sham' operation on ratio of cation (Na + K) to water movement (mEq/L).

24	30	86.0	77.1	127.6
		94.3	84.3	123.2
		63.4	51.4	135.6
		Mean 81.2	Mean 70.9	Mean 128.8
36	31	74.8	64.0	138.4
		88.5	75.4	135.6
		75.9	65.8	145.3
		Mean 79.7	Mean 68.4	Mean 139.8
48	32	75.5	67.5	164.4
		83.6	75.1	150.8
		62.8	57.0	133.0
		Mean 73.9	Mean 66.5	Mean 149.4

APPENDIX 12 The effect of mesenteric venous congestion upon the intestinal transport of water, sodium and potassium.

Individual Results

NOTE In the following tables the initial two base-line tests are termed as 0 hr; all subsequent tests are timed in hours after zero-time which was selected as 15 minutes after the end of the second test.

APPENDIX 12. The effect of continuous increase in mesenteric vein pressure upon the movement of sodium and water. (Group I).

Dog no.	Time (hr)	Mesenteric venous pressure (cm saline)	SODIUM (μEq per 10 min)			WATER (ml per 10 min)		
			Ins.	Exs.	Net	Ins.	Exs.	Net
1	0	12.5	783	442	+341	17.6	15.2	+2.4
	0	12.5	628	546	+ 82	16.8	16.1	+0.7
	0.25	22.0	589	503	+ 86	15.1	14.5	+0.6
	1	22.0	581	715	-134	12.7	13.3	-0.6
	2	22.0	616	705	- 89	12.5	12.6	-0.1
	4	22.0	572	1054	-482	13.6	15.2	-1.6
	8	22.0	600	1000	-400	13.6	15.1	-1.5
2	0	12.5	1740	751	+989	23.7	17.1	+6.6
	0	12.5	1477	689	+788	19.0	13.7	+5.3
	0.25	20	1193	697	+496	15.2	11.8	+3.4
	1	22	1112	679	+433	14.9	12.2	+2.7
	2	22	1183	1079	+104	15.0	14.2	+0.8
	4	22	1148	1224	- 76	14.5	15.0	-0.5
	6	22	1100	941	+159	13.6	12.1	+1.5
	8	23	1027	978	+ 49	11.9	11.4	+0.5
3	0	15	1316	501	+815	19.1	13.9	+5.2
	0	15	1138	426	+712	17.4	12.8	+4.6
	0.25	35	1145	604	+541	14.3	10.8	+3.5
	1	35	933	619	+314	13.8	11.9	+1.9
	2	35	1010	750	+260	16.4	14.8	+1.6
	4	35	865	1038	-173	12.4	13.5	-1.1
	6	35	806	1074	-268	13.0	14.7	-1.7
	8	35	860	971	-111	10.9	11.5	-0.6
4	0	15	1148	472	+676	16.5	12.0	+4.5
	1	20	882	710	+172	13.1	12.0	+1.1
	2	20	906	670	+236	14.3	13.1	+1.2
	4	20	791	576	+215	13.5	12.4	+1.1
	6	20	889	675	+214	11.1	9.7	+1.4
	8	20	765	442	+323	10.0	7.5	+2.5
5	0	10	683	330	+350	10.9	7.5	+3.4
	0	10	680	333	+347	10.8	7.5	+3.3
	1	35	499	302	+197	-	-	-
	2	35	520	293	+137	-	-	-
	4	35	590	728	-138	8.1	7.9	+0.2
	6	35	581	739	-158	9.4	7.5	+1.9
	8	35	711	599	+112	7.5	6.6	+0.9

APPENDIX 12 (contd.) The effect of intermittent increase in mesenteric vein pressure upon the movement of sodium and water. (Group II).

Dog no.	Time (hr)	Mesenteric venous pressure (cm saline)	SODIUM (µEq per 10 min)			WATER (ml per 10 min)		
			Ins.	Exs.	Net	Ins.	Exs.	Net
6	0	15	1019	705	+314	19.9	18.4	+1.5
	0	15	1123	688	+435	16.7	13.8	+2.9
	0.25	40	1131	759	+372	15.3	13.1	+2.2
	1	15	958	654	+304	19.2	17.7	+1.5
	2	40	1083	642	+441	13.5	10.9	+2.6
	4	15	772	731	+ 41	14.2	14.4	-0.2
	8	40	948	870	+ 77	12.4	13.2	-0.8
7	0	10	1213	316	+897	16.5	10.7	+5.8
	0	10	1144	341	+803	18.9	13.8	+5.1
	0.25	35	1300	414	+886	15.0	9.5	+5.5
	1	12	1392	421	+971	17.9	11.7	+6.2
	2	41	1625	364	+1261	15.5	7.5	+8.0
	4	15	1392	497	+895	18.2	13.1	+5.1
	8	45	1324	478	+846	13.7	9.2	+4.5
8	0	15	1189	252	+937	16.8	10.3	+6.5
	1	25	1078	267	+811	11.5	5.9	+5.6
	2	40	827	488	+339	10.3	8.1	+2.2
	4	15	941	475	+466	10.6	7.2	+3.4
	8	40	1175	593	+582	12.0	8.4	+3.6
9	0	12	973	250	+723	15.4	10.5	+4.9
	0.25	30	874	632	+242	13.9	12.1	+1.8
	2	12	671	599	+ 72	10.7	10.4	+0.3
	4	30	850	600	+250	11.4	9.0	+2.4
	6	12	688	515	+173	11.1	10.1	+1.0
	7	12	880	608	+272	11.4	9.2	+2.2
	8	12	895	530	+365	12.3	9.3	+3.0

APPENDIX 12 (contd.) Control experiments. No change in mesenteric venous pressure. (Group III).

Dog no.	Time (hr)	Mesenteric venous pressure (cm saline)	SODIUM (µEq per 10 min)			WATER (ml per 10 min)		
			Ins.	Exs.	Net	Ins.	Exs.	Net
10	0	15	1383	437	+946	17.2	10.9	+6.3
	0	15	1525	459	+1066	18.4	11.1	+7.3
	1	15	1485	553	+932	18.6	12.3	+6.3
	2	15	1145	646	+499	15.8	12.5	+3.3
	4	15	1091	529	+562	15.4	12.5	+2.9
	6	15	1095	682	+413	15.3	13.5	+1.8
	8	15	1098	598	+500	14.9	11.8	+3.1
11	0	15	1221	450	+771	15.2	9.8	+5.4
	0	15	1223	479	+744	15.9	10.7	+5.2
	0.25	15	1175	554	+621	14.9	10.8	+4.1
	1	15	1066	621	+445	14.3	11.4	+2.9
	2	15	1161	652	+509	14.4	11.0	+3.4
	4	15	913	689	+224	12.0	10.2	+1.8
	6	15	869	562	+307	10.8	8.6	+2.2
	8	15	1251	651	+600	14.2	10.2	+4.0
12	0	10	1287	713	+574	18.4	14.5	+3.9
	0	10	1341	522	+819	19.4	14.0	+5.4
	0.25	10	1173	671	+502	17.1	14.0	+3.1
	1	10	1482	583	+899	19.1	13.2	+5.9
	2	10	1243	692	+551	18.3	14.6	+3.7
	4	10	1082	738	+344	16.7	14.4	+2.3
	6	10	1142	743	+399	16.6	13.7	+2.9
	8	10	977	772	+205	13.4	11.7	+1.7

APPENDIX 12 (contd.) Concentrations of sodium (in mEq/L) in test solution at beginning (t_o) and end (t_{10}) of 10-minute tests performed before and after continuous and intermittent increases in mesenteric vein pressure (Groups I and II), and in control experiments (Group III).

Dog no.	Concentration at t_o	Concentration at t_{10}: Baseline tests before zero-time		Tests performed after zero time at: 0.25	1	2	4	6	8
Group I									
1	142	143	143	142	144	145	140	-	144
2	141	138	139	140	139	141	142	143	144
3	144	141	142	142	143	142	144	145	145
4	143	141	-	-	142	140	140	142	144
5	140	144	145	-	146	145	146	147	146
Group II									
6	143	139	142	142	141	142	145	-	144
7	143	139	138	140	139	143	140	-	146
8	139	137	-	-	139	142	144	-	144
9	137	134	-	139	-	141	143	143	144
Group III									
10	141	138	139	-	139	139	135	135	138
11	143	142	142	141	141	141	144	143	141
12	144	142	141	141	141	143	143	144	145
Mean	142	140							
S.E.M.	0.4	0.5							

APPENDIX 12 (contd.) Ratio of sodium movement to water movement before and after continuous and intermittent increase in mesenteric vein pressure (Groups I and II), and in control experiments (Group III).

Dog no.	Ratio of sodium to water (mEq/L) in: Baseline tests before zero time		Tests performed after zero time at: 0.25	1	2	4	6	8
		(i) Insorption						
Group I								
1	44	37	39	46	49	42	-	44
2	73	77	78	75	79	79	81	86
3	68	65	80	67	62	70	62	79
4	69	-	-	67	63	59	80	76
5	63	64	-	-	-	89	78	95
Group II								
6	51	67	74	50	80	54	-	76
7	73	61	87	77	105	76	-	96
8	71	-	-	93	80	89	-	98
9	63	-	63	-	63	77	62	73
Group III								
10	80	83	-	80	73	71	71	74
11	80	76	79	75	81	76	80	88
12	70	70	69	77	68	65	69	73
Mean	68.2							
S.E.M.	2.9							
		(ii) Exsorption						
Group I								
1	29	34	35	54	56	60	-	66
2	44	50	59	56	76	82	78	90
3	36	33	56	52	51	77	73	85
4	39	-	-	59	51	46	69	59
5	44	45	-	-	-	75	77	91
Group II								
6	38	49	58	37	59	51	-	66
7	30	25	43	36	49	38	-	52
8	25	-	-	45	60	65	-	70
9	23	-	52	-	58	66	51	57

APPENDIX 12 (contd.)

Dog no.	Ratio of sodium to water (mEq/L) in Baseline tests before zero time		Tests performed after zero time at 0.25	1	2	4	6	8
	(ii) Exsorption (contd.)							
Group III								
10	40	41	-	45	52	42	50	50
11	46	45	51	55	59	68	66	65
12	50	37	48	44	48	51	54	66
Mean	38.5							
S.E.M.	1.8							
	(iii) Net							
Group I								
1	139	119	151	205	148	305	-	256
2	148	149	146	159	141	177	115	94
3	154	153	155	158	171	153	163	198
4	149	-	-	161	187	195	156	128
5	104	105	-	-	-	520	125	119
Group II								
6	203	152	169	198	173	240	-	93
7	154	160	161	155	158	174	-	187
8	144	-	-	144	153	139	-	160
9	149	-	132	-	230	119	170	121
Group III								
10	150	145	-	146	153	196	219	162
11	144	144	152	152	152	124	136	150
12	150	152	162	153	151	152	138	124
Mean	145.9							
S.E.M.	4.2							

APPENDIX 12 (contd.) The effect of continuous increase in mesenteric vein pressure upon the movement of potassium (Group I).

Dog no.	Time (hrs)	Mesenteric venous pressure (cm saline)	Potassium (μEq per 10 min)		
			Insorp.	Exsorp.	Net
13	0	15	20.4	32.3	-11.9
	0	15	15.4	27.1	-11.7
	0.25	30	17.2	36.8	-19.6
	1	30	21.3	52.1	-30.8
	2	30	17.6	64.3	-46.7
	4	30	18.2	61.2	-43.0
	6	30	15.8	58.9	-43.1
	8	30	16.4	62.7	-46.3
14	0	12.5	17.6	33.2	-15.6
	0	12.5	20.1	37.2	-17.1
	0.25	30	21.0	45.6	-24.6
	1	30	16.6	42.3	-25.7
	2	30	18.4	58.9	-40.5
	4	30	15.3	78.3	-63.0
	6	30	17.2	64.2	-47.0
	8	30	15.0	72.8	-57.8
15	0	10	27.3	40.1	-12.8
	0	10	27.8	42.9	-15.1
	0.25	35	26.4	40.2	-13.8
	1	35	25.0	52.3	-27.3
	2	35	24.6	68.9	-44.3
	4	35	23.2	78.6	-55.4
	6	35	23.5	72.9	-49.4
	8	35	22.1	85.6	-63.5

APPENDIX 12 (contd.) Control experiments. No change in mesenteric venous pressure (Group III).

Dog no.	Time (hr)	Mesenteric venous pressure (cm saline)	Potassium (μEq per 10 min)		
			Insorp.	Exsorp.	Net
16	0	13	25.0	40.1	-15.1
	0	13	27.6	44.0	-16.4
	0.25	13	24.2	47.6	-23.4
	1	13	25.1	48.3	-23.2
	2	13	23.6	47.6	-24.0
	4	13	21.8	50.8	-29.0
	6	13	22.1	52.4	-30.3
	8	13	20.4	55.2	-34.8
17	0	15	30.1	41.2	-11.1
	0	15	26.6	40.9	-14.3
	0.25	15	27.6	42.3	-14.7
	1	15	27.4	45.6	-18.2
	2	15	22.6	43.8	-21.2
	4	15	27.8	47.6	-19.8
	6	15	24.1	50.0	-25.9
	8	15	26.2	52.1	-25.9

APPENDIX 13. The action of aldosterone and spironolactone upon the intestinal transport of water, sodium and potassium in dogs.

The individual results are presented in the following order:

I - control experiments
II - aldosterone infusion (high dose)
III - aldosterone infusion (low dose)
IV - aldosterone injection
V - spironolactone + aldosterone (high dose)
VI - spironolactone + aldosterone (low dose)
VII - spironolactone control
VIII - miscellaneous experiments.

The following abbreviations are used in the tables:-

(a) Na ins, Na exs, Na net - refer to rates of insorption, of exsorption, and of net movement of sodium (μEq per 10 minutes). Similarly, K ins, etc., refer to rates of movement of potassium (μEq per 10 minutes), and H_2O ins, etc., to rates of movement of water (ml per 10 minutes).

(b) Na t_o, K t_o, Na t_{10}, and K t_{10}, refer to concentrations of sodium and potassium in the test solution at beginning and end of 10-minute test.

(c) RV_{Na} and RV_K represent the residual volumes (in ml) of test solution left in lumen after withdrawal of aspirate, calculated from sodium and potassium activity of the rinse.

(d) Na (urine) and K (urine) indicate the concentration of sodium and potassium in the urine (in mEq per litre).

APPENDIX 13. I. Control experiments.

Dog no. 33 (ileum) - 22nd March 1962.

		Tests before dextrose infusion		Tests after dextrose infusion at following times (hrs).				
				1.00	2.00	2.45	4	5
Na	ins.	782	750	767	793	915	264	591
	exs.	1379	1508	1236	1241	1261	1013	1056
	net	-597	-758	-469	-448	-346	-749	-465
K	ins.	29	29	30	30	35	15	27
	exs.	61	68	64	70	72	53	54
	net	-32	-39	-34	-40	-37	-38	-27
H_2O	ins.	13.5	17.2	15.6	17.5	17.9	10.4	13.1
	exs.	17.1	21.1	17.3	19.7	19.5	15.0	16.2
	net	-3.6	-3.9	-1.7	-2.2	-1.6	-4.6	-3.1
Na	t_o	150	150	150	150	150	150	150
	t_{10}	152	156	158	158	154	152	150
K	t_o	3.2	3.2	3.2	3.2	3.2	3.2	3.2
	t_{10}	3.9	4.1	4.3	4.4	4.4	4.0	3.8
RV_{Na}		6.7	4.2	1.5	1.6	1.4	1.8	1.7
RV_K		5.6	4.4	1.9	2.0	1.7	1.3	1.9
Na (urine)		9	27	13	-	11	-	9
K (urine)		15	8	12	-	17	-	20

APPENDIX 13 (contd.)

Dog no. 33 (ileum) - 19th April 1962.

		Tests before dextrose infusion		Tests after dextrose infusion at following times (hrs). 1.00	2.00	2.45	3.30	4.00	5.00
Na	ins.	568	543	352	468	428	465	490	377
	exs.	901	826	778	665	526	677	665	700
	net	-333	-283	-426	-197	-98	-212	-176	-323
K	ins.	18	13	13	14	15	17	16	18
	exs.	46	33	40	33	26	38	32	37
	net	-28	-20	-27	-19	-11	-22	-16	-19
H_2O	net	-2.9	-2.2	-2.6	-1.3	-1.0	-1.4	-1.5	-1.3
Na	t_o	152	152	152	152	152	152	152	152
	t_{10}	151	153	156	155	153	155	153	156
K	t_o	3.4	3.4	3.4	3.4	3.4	3.4	3.4	3.4
	t_{10}	4.0	3.8	4.0	3.9	3.7	4.0	3.8	3.9
RV_{Na}		1.0	0.9	1.3	1.2	0.9	1.3	1.1	1.1
RV_K		1.4	0.9	1.4	1.4	1.1	1.5	1.3	1.4
Na (urine)		28	17			19	-	-	18
K (urine)		21	5.6			6.6	-	-	8.6

APPENDIX 13 (contd.)

Dog no. 34 (ileum) - 23rd April 1962

		Tests before dextrose infusion		Tests after dextrose infusion at following times (hrs).					
				1.00	2.00	2.45	3.30	4.15	5.00
Na	ins.	288	446	537	349	274	236	211	231
	exs.	710	956	758	844	652	758	809	796
	net	-422	-510	-221	-495	-378	-522	-598	-565
K	ins.	14	18	18	16	14	14	14	14
	exs.	29	36	37	54	36	36	41	35
	net	-15	-18	-17	-38	-22	-22	-27	-21
H_2O	net	-2.7	-3.1	-1.4	-3.2	-2.4	-3.0	-3.9	-3.5
Na	t_o	146	146	146	146	146	146	146	146
Na	t_{10}	147	147	147	147	147	149	147	147
K	t_o	3.8	3.8	3.8	3.8	3.8	3.8	3.8	3.8
K	t_{10}	4.0	4.0	4.3	4.7	4.3	4.2	4.2	4.2
RV_{Na}		1.4	1.2	2.5	1.2	1.2	3.0	1.5	1.5
RV_K		1.1	1.1	4.2	1.6	1.3	2.8	1.7	1.6

Dog no. 34 (ileum) - 17th May 1962*

		Tests before dextrose infusion		Tests after dextrose infusion at following times (hrs)				
				1.00	2.00	2.45	3.30	4.00
H_2O	ins.	7.9	9.2	7.8	8.1	8.6	10.1	12.0
	exs.	10.8	12.6	10.9	10.4	12.4	11.8	13.6
	net	-2.9	-3.4	-3.1	-2.3	-3.8	-1.8	-1.6

* The unidirectional fluxes of cations were not measured; because of lack of isotopes.

APPENDIX 13 (contd.)

Dog no. 35 (colon) - 23rd March 1962*

		Test before dextrose infusion	Tests after dextrose infusion at following times (hrs)				
			1.00	2.00	2.45	4.00	5.00
Na	ins.	955	940	876	594	765	802
	exs.	705	800	641	598	673	646
	net	+250	+140	+235	-5	+92	+156
K	ins.	9	-	-	-	-	-
	exs.	7	-	-	-	-	-
	net	+2	-	-	-	-	-
H_2O	ins.	10.6	10.0	8.8	9.6	13.3	11.1
	exs.	9.0	9.1	7.6	9.9	12.4	9.8
	net	+1.6	+0.9	+1.2	-0.3	+0.9	+1.3
Na	t_o	156	156	156	156	156	156
Na	t_{10}	156	156	154	156	158	158
K	t_o	4.3	-	-	-	-	-
K	t_{10}	4.4	-	-	-	-	-
RV_{Na}		2.7	2.6	5.8	2.6	3.4	3.0
Na (urine)		-	44	-	50	-	40
K (urine)		-	10	-	10	-	10

*Apart from first test, fluxes of potassium were not calculated because of contamination of potassium standard for flame photometry.

APPENDIX 13 (contd.)

Dog no. 35 (colon) - 20th April 1962

		Tests before dextrose infusion		Tests after dextrose infusion at following times (hrs)				
				1.00	2.00	2.45	4.00	5.00
Na	ins.	338	333	170	390	339	471	456
	exs.	588	542	177	297	288	440	230
	net	-250	-209	-7	+93	+51	+31	+226
K	ins.	11	6	10	8	8	8	8
	exs.	23	16	27	24	27	24	22
	net	-12	-10	-17	-16	-19	-16	-14
H_2O	net	-0.9	-0.4	-0.1	+0.6	+0.6	+0.5	+1.1
Na	t_o	157	157	157	157	157	157	157
Na	t_{10}	161	163	157	157	159	159	159
K	t_o	3.8	3.8	3.8	3.8	3.8	3.8	3.8
	t_{10}	4.2	4.2	4.1	4.2	4.3	4.2	4.2
RV	N_a	3.0	1.9	2.1	2.1	2.2	2.4	2.7
RV	K	3.4	2.2	2.4	2.3	2.6	2.6	2.8

APPENDIX 13 (contd.)

Dog no. 36 (colon) - 21st March 1962

		Tests before dextrose infusion		Tests after dextrose infusion at following times (hrs)				
				1.00	2.00	2.45	3.30	4.00
Na	ins.	549	611	619	359	539	426	480
	exs.	508	511	514	269	267	111	210
	net	+41	+100	+105	+90	+272	+315	+270
K	ins.	7	11	8	11	12	16	14
	exs.	16	17	16	20	15	17	16
	net	-9	-6	-8	-9	-3	-1	-2
H_2O	ins.	8.8	12.8	12.1	12.4	13.5	14.4	13.6
	exs.	8.2	11.5	11.4	11.8	12.0	12.3	11.8
	net	+0.6	+1.3	+0.7	+0.6	+1.5	+2.1	+1.8
Na	t_o	150	150	150	150	150	150	150
Na	t_{10}	152	154	150	150	148	150	150
K	t_o	3.2	3.2	3.2	3.2	3.2	3.2	3.2
K	t_{10}	3.6	3.6	3.6	3.6	3.5	3.5	3.5
RV	N_a	2.9	1.6	2.5	1.7	3.5	2.3	2.2
RV	K	2.0	1.8	2.1	2.2	2.5	1.6	2.2
Na (urine)		96	79	65	87	35	-	105
K (urine)		52	49	22	34	19	-	16

APPENDIX 13 (contd.)

Dog no. 36 (colon) - 18th April 1962

		Test before dextrose infusion	Tests after dextrose infusion at following times (hrs)				
			1.00	2.00	2.45	3.30	5.00
Na	ins.	797	661	806	548	653	801
	exs.	493	419	398	381	348	409
	net	+304	+242	+408	+167	+305	+392
K	ins.	14	10	10	8	9	14
	exs.	24	18	15	23	16	18
	net	-10	-8	-5	-15	-7	-4
H_2O	net	+2.0	+1.2	+2.0	+0.7	+1.3	+2.2
Na	t_o	152	152	152	152	152	152
Na	t_{10}	152	150	148	150	148	150
K	t_o	3.2	3.2	3.2	3.2	3.2	3.2
K	t_{10}	3.9	3.7	3.7	3.9	3.7	3.7
RV	Na	2.9	1.3	1.8	2.2	2.3	1.9
RV	K	3.1	1.5	2.2	2.4	4.7	2.5
Na	(urine)	226	214	86	33	63	-
K	(urine)	57	37	16	5	8	-

APPENDIX 13 (contd.)

Dog no. 37 (colon) - 16th May 1962

		Tests before dextrose infusion		Tests after dextrose infusion at following times (hrs)			
				1.00	2.45	3.30	4.00
Na	ins.	414	497	781	410	431	804
	exs.	745	797	611	295	421	374
	net	-331	-300	+170	+115	+10	+430
K	ins.	16	10	13	9	8	25
	exs.	55	85	49	46	49	32
	net	-39	-75	-36	-37	-41	-6
H_2O	ins.	9.6	9.3	10.4	9.2	7.8	10.4
	exs.	12.4	11.9	10.2	9.1	8.4	7.6
	net	-2.8	-2.6	+0.2	+0.1	-0.6	+2.8
Na	t_o	158	158	158	158	158	158
Na	t_{10}	154	154	152	154	154	154
K	t_o	4.1	4.1	4.1	4.1	4.1	4.1
K	t_{10}	5.1	5.1	5.3	5.6	5.6	4.9
RV	Na	3.9	1.9	1.4	3.1	1.8	3.1
RV	K	6.5	1.6	1.7	2.2	3.6	3.6

APPENDIX 13 (contd.)

Dog no. 37 (colon) - 30th May 1962

		Tests before dextrose infusion		Tests after dextrose infusion at following times (hrs)					
				1.00	2.00	2.45	3.30	4.00	5.00
Na	ins.	632	510	548	571	596	559	419	476
	exs.	582	737	892	692	726	632	544	506
	net	+50	-227	-344	-121	-130	-73	-125	-30
K	ins.	20	17	17	22	16	17	18	19
	exs.	55	56	68	67	62	53	49	43
	net	-35	-39	-51	-45	-46	-36	-31	-24
H_2O	ins.	17.1	14.9	13.9	11.6	13.0	15.0	14.3	14.3
	exs.	17.1	16.8	16.6	12.8	14.6	16.2	15.5	15.2
	net	0	-1.9	-2.7	-1.2	-1.6	-1.2	-1.2	-0.9
Na	t_o	148	148	148	148	148	148	148	148
Na	t_{10}	146	146	146	146	144	144	146	146
K	t_o	3.8	3.8	3.8	3.8	3.8	3.8	3.8	3.8
K	t_{10}	4.4	4.4	5.4	5.4	5.3	5.0	4.8	4.6
RV	Na	3.7	3.2	8.4	7.7	6.2	3.7	3.8	5.6
RV	K	3.3	3.6	8.2	7.7	6.3	3.8	3.5	5.1

APPENDIX 13 (contd.) II. Aldosterone infusion (high dose).

Dog no. 33 (ileum) - 14th March 1962

		Tests before infusion		Tests after infusion at following times (hrs) 0.30	1.15	2.00	2.45	3.30	4.15	5.00
Na	ins.	856	1094	683	633	791	805	651	876	714
	exs.	515	939	782	1057	753	588	621	906	688
	net	+341	+155	-99	-424	+38	+217	+30	-30	+26
K	ins.	29	31	26	22	29	25	21	24	28
	exs.	40	46	49	64	66	71	77	110	125
	net	-11	-15	-23	-42	-37	-46	-55	-86	-97
H_2O	ins.	14.8	-	17.0	16.8	15.3	13.9	14.7	18.4	18.4
	exs.	12.2	-	17.7	18.8	14.7	13.1	14.8	19.3	19.5
	net	+1.4	+0.7	-0.7	-2.0	+0.6	+0.8	-0.1	-0.9	-1.1
Na	t_o	152	152	152	152	152	152	152	152	152
Na	t_{10}	143	150	152	156	154	148	150	148	144
K	t_o	3.3	3.3	3.3	3.3	3.3	3.3	3.3	3.3	3.3
K	t_{10}	4.0	4.0	4.1	4.6	4.9	5.3	5.5	6.5	6.9
RV	Na	2.8	1.5	0.9	2.0	2.6	2.0	1.4	2.7	2.7
RV	K	3.0	2.2	1.5	2.2	3.2	2.1	2.1	2.1	2.7
Na	(urine)	34	14	2	4	2	2	2	2	2
K	(urine)	26	16	15	35	63	23	18	18	108

APPENDIX 13 (contd.)

Dog no. 33 (ileum) - 5th April 1962

		Tests before infusion		Tests after infusion at following times (hours) 1.00	2.00	2.45	3.30	4.00	5.00
Na	ins.	672	549	498	330	432	393	652	327
	exs.	922	1053	903	654	946	692	838	484
	net	-250	-504	-405	-324	-514	-299	-186	-158
K	ins.	18	17	21	15	19	20	18	23
	exs.	36	47	46	42	54	63	75	91
	net	-18	-30	-25	-27	-35	-43	-57	-68
H_2O	ins.	10.0	8.9	9.9	11.5	9.5	10.4	10.1	11.6
	exs.	11.8	12.7	13.4	14.9	14.1	13.6	13.0	14.6
	net	-1.8	-3.8	-3.5	-3.4	-4.6	-3.2	-2.9	-3.0
Na	t_o	160	160	160	160	160	160	160	160
Na	t_{10}	153	157	157	155	155	155	153	151
K	t_o	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
K	t_{10}	3.9	4.0	3.9	4.0	4.1	4.6	5.5	5.6
RV	Na	1.5	1.0	1.0	1.4	1.1	1.4	1.4	1.5
RV	K	1.1	0.9	1.1	1.2	1.0	1.0	1.2	2.0
Na (urine)		47	-	-	28	9.7	-	-	-
K (urine)		12.5	-	-	13.2	6.8	-	-	-

APPENDIX 13 (contd.)

Dog no. 33 (ileum) - 10th May 1962

		Tests before infusion		Tests after infusion at following times (hrs) 1.00	2.00	2.45	4.00	5.00
Na	ins.	499	543	527	302	529	708	650
	exs.	813	946	861	593	880	878	904
	net	-314	-403	-334	-291	-351	-170	-254
K	ins.	19	20	17	21	13	16	13
	exs.	33	42	34	36	37	48	59
	net	-14	-22	-17	-15	-24	-32	-46
H_2O	ins.	9.1	9.3	8.0	8.2	7.9	8.9	9.2
	exs.	10.2	11.0	9.1	8.8	8.9	8.7	9.9
	net	-1.1	-1.7	-1.1	-0.4	-1.0	+0.2	-0.7
Na	t_o	143	143	143	143	143	143	143
Na	t_{10}	149	149	149	150	151	151	149
K	t_o	3.4	3.4	3.4	3.4	3.4	3.4	3.4
K	t_{10}	3.8	4.0	3.9	3.9	4.2	4.7	5.1
RV	Na	1.8	1.7	1.9	1.7	1.5	2.8	1.5
RV	K	2.0	1.8	1.8	1.9	1.7	2.8	1.8

APPENDIX 13 (contd.)

Dog no. 33 (ileum) - 24th May 1962

		Tests before infusion		Tests after infusion at following times (hours) 1.00	2.00	2.45	3.30	4.00	5.00
Na	ins.	562	436	588	662	540	593	576	565
	exs.	493	690	795	593	456	433	567	680
	net	+69	-254	-207	+69	+84	+160	+9	-115
K	ins.	29	22	22	26	32	26	22	24
	exs.	44	41	42	41	52	56	61	64
	net	-15	-19	-20	-15	-20	-30	-39	-40
H_2O	net	-0.6	-1.6	-1.3	-0.6	-0.5	0	-1.0	-0.3
Na	t_o	159	159	159	159	159	159	159	159
Na	t_{10}	151	159	159	151	151	151	151	151
K	t_o	3.9	3.9	3.9	3.9	3.9	3.9	3.9	3.9
K	t_{10}	4.5	4.5	4.6	4.5	4.8	5.4	5.6	5.8
RV	Na	1.4	2.1	1.9	1.4	1.9	1.9	1.7	1.2
RV	K	1.4	2.1	1.8	1.4	2.0	2.3	1.4	1.6

APPENDIX 13 (contd.)

Dog no. 34 (ileum) - 31st May 1962

		Test before infusion	Tests after infusion at following times (hrs) 1.00	2.45	4.00	5.00
Na	ins.	536	431	439	511	361
	exs.	1133	731	693	1046	918
	net	-597	-300	-254	-535	-557
K	ins.	13	21	16	14	9
	exs.	33	47	71	96	103
	net	-20	-26	-55	-82	-94
H_2O	ins.	8.9	12.8	10.0	11.2	11.6
	exs.	12.5	14.8	12.4	14.4	15.7
	net	-3.6	-2.0	-2.4	-3.2	-4.1
Na	t_o	150	150	150	150	150
Na	t_{10}	152	150	146	152	148
K	t_o	3.7	3.7	3.7	3.7	3.7
K	t_{10}	4.0	4.5	5.5	6.3	6.5
RV	Na	1.3	1.5	1.4	1.2	2.2
RV	K	1.3	1.4	1.3	1.2	2.0

APPENDIX 13 (contd.)

Dog no. 34 (ileum) - 9th May 1962

		Tests before infusion		Tests after infusion at following times (hrs) 1.00	2.00	2.45	3.30	4.00	5.00
Na	ins.	424	518	481	345	266	312	378	310
	exs.	613	708	594	586	505	498	617	521
	net	-189	-190	-113	-241	-239	-186	-239	-211
K	ins.	12	9	15	11	11	7	7	5
	exs.	24	18	27	30	34	42	53	56
	net	-12	-9	-12	-19	-23	-35	-46	-51
H_2O	ins.	-	8.0	7.2	7.3	5.3	6.0	7.0	-
	exs.	-	8.7	7.3	8.4	6.8	7.5	8.5	-
	net	-1.1	-0.7	-0.1	-1.1	-1.5	-1.5	-1.5	-1.7
Na	t_o	124	124	124	124	124	124	124	124
Na	t_{10}	126	128	128	128	126	124	128	126
K	t_o	3.3	3.3	3.3	3.3	3.3	3.3	3.3	3.3
K	t_{10}	3.7	3.6	3.8	3.9	4.1	4.4	4.9	5.0
RV	Na	1.4	2.3	1.5	1.8	2.0	1.1	1.7	2.3
RV	K	1.3	2.1	1.6	1.8	1.9	1.5	1.5	1.9

APPENDIX 13 (contd.)

Dog no. 35 (colon) - 7th February 1962

		Test before infusion	Tests after infusion at following times (hrs) 1.00	2.45	3.30	4.00
Na	ins.	271	555	108	312	196
	exs.	354	317	574	282	151
	net	-83	+238	-466	+30	+45
K	ins.	10	17	11	10	7
	exs.	9	13	41	46	46
	net	+1	+4	-30	-36	-39
H_2O	ins.	8.4	11.0	7.5	10.4	8.3
	exs.	9.4	9.6	10.5	11.0	9.4
	net	-1.0	+1.6	-3.0	-0.6	-1.1
Na	t_o	132	132	132	132	132
Na	t_{10}	130	130	130	130	124
K	t_o	3.2	3.2	3.2	3.2	3.2
K	t_{10}	3.0	3.2	3.7	4.5	4.5
RV	Na	5.1	5.0	4.7	2.7	4.7
RV	K	4.1	3.7	3.6	2.2	4.0
Na	(urine)	165	42	12	10	6
K	(urine)	85	17	4	8	12

APPENDIX 13 (contd.)

Dog no. 35 (colon) - 29th March 1962

		Tests before infusion		Tests after infusion at following times (hrs) 1.00	2.00	2.45	3.30	4.00	5.00
Na	ins.	605	537	434	417	367	-	474	235
	exs.	519	345	349	331	150	-	193	87
	net	+86	+192	+85	+86	+217	+240	+281	+148
K	ins.	16	13	12	11	14	12	11	12
	exs.	13	7	10	11	15	20	28	29
	net	-3	-6	-2	0	-1	-8	-17	-17
H_2O	ins.	12.9	10.0	9.2	11.0	9.7	9.3	10.0	9.3
	exs.	11.6	8.0	7.3	10.0	8.0	7.7	8.1	7.9
	net	+1.3	+2.0	+1.9	+1.0	+1.7	+1.6	+1.9	+1.4
Na	t_o	148	148	148	148	148	148	148	148
Na	t_{10}	153	153	157	153	150	148	148	151
K	t_o	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
K	t_{10}	3.6	3.6	3.7	3.7	3.8	4.1	4.6	4.7
RV	Na	1.3	1.0	1.0	1.5	1.1	1.4	1.7	2.1
RV	K	1.2	1.0	1.4	1.5	1.2	1.5	1.6	1.7
Na (urine)		113		14			1.6		1.6
K (urine)		16		9			1.6		2.1

APPENDIX 13 (contd.)

Dog no. 36 (colon) - 7th March 1962

		Tests before infusion		Tests after infusion at following times (hrs) 1.00	2.00	2.45	3.30	4.00
Na	ins.	593	330	279	661	329	446	307
	exs.	330	13	211	298	67	267	124
	net	+263	+317	+68	+363	+262	+179	+183
K	ins.	11	10	8	13	10	8	8
	exs.	12	17	16	18	24	26	30
	net	-1	-7	-8	-5	-14	-18	-22
H_2O	ins.	13.6	11.5	11.5	15.6	14.2	13.6	12.4
	exs.	11.9	10.3	11.5	13.6	12.8	12.4	11.5
	net	+1.7	+1.2	0	+2.0	+1.4	+1.2	+0.9
Na	t_o	156	156	156	156	156	156	156
Na	t_{10}	156	150	154	154	154	156	154
K	t_o	3.3	3.3	3.3	3.3	3.3	3.3	3.3
K	t_{10}	3.6	3.8	3.6	3.8	4.1	4.2	4.3
RV	Na	4.9	2.5	3.4	2.6	3.3	2.2	3.2
RV	K	6.6	2.1	3.1	2.3	3.0	2.1	3.1
Na (urine)		108	-	4	0	0	4	7.5
K (urine)		18	-	7	2	2	11	28

APPENDIX 13 (contd.)

Dog no. 36 (colon) - 15th March 1962

		Tests before infusion		Tests after infusion at following times (hrs) 1.00	2.00	3.30	4.00	5.00
Na	ins.	947	851	996	792	1050	929	732
	exs.	462	219	756	448	516	333	460
	net	+485	+632	+240	+344	+534	+596	+272
K	ins.	11	17	14	14	16	20	12
	exs.	10	13	18	23	26	33	35
	net	-1	-4	-4	-9	-10	-13	-23
H_2O	ins.	13.2	14.5	13.9	13.9	16.0	17.5	15.5
	exs.	10.7	10.7	11.6	11.2	12.0	12.8	13.3
	net	+2.5	+3.8	+2.3	+2.7	+4.0	+4.7	+2.2
Na	t_o	144	144	144	144	144	144	144
Na	t_{10}	142	140	148	146	146	148	146
K	t_o	3.2	3.2	3.2	3.2	3.2	3.2	3.2
K	t_{10}	3.5	3.5	3.7	4.0	4.3	4.6	4.5
RV	Na	6.9	7.0	4.3	10.2	5.7	3.9	8.4
RV	K	5.2	6.3	4.1	8.4	6.4	2.5	7.2
Na	(urine)	30	26	2	4	1	1	4
K	(urine)	26	25	12	5	38	21	8

APPENDIX 13 (contd.)

Dog no. 36 (colon) - 28th March 1962

		Tests before infusion		Tests after infusion at following times (hrs) 1.00	2.00	2.45	3.30	5.00
Na	ins.	735	663	496	741	726	491	575
	exs.	937	769	885	653	495	147	436
	net	-202	-106	-389	+88	+231	+344	+139
K	ins.	3	4	5	1	0	4	2
	exs.	20	23	29	8	13	24	50
	net	-17	-19	-24	-7	-13	-20	-48
H_2O	ins.	12.4	12.4	10.5	13.5	13.7	13.4	11.2
	exs.	13.7	13.5	13.0	12.7	12.6	12.1	10.7
	net	-1.3	-1.1	+2.5	+0.8	+1.1	+1.3	+0.5
Na	t_o	155	155	155	155	155	155	155
Na	t_{10}	155	153	156	157	153	149	153
K	t_o	3.1	3.1	3.1	3.1	3.1	3.1	3.1
K	t_{10}	3.6	3.7	3.7	3.5	3.8	4.1	5.1
RV	Na	4.0	1.6	2.3	1.7	4.2	1.8	2.0
RV	K	3.5	1.6	1.8	1.6	3.7	1.6	2.0
Na (urine)		60		10		4		4
K (urine)		40		14		5.2		6.4

APPENDIX 13 (contd.)

Dog no. 37 (colon) - 25th May 1962

		Tests before infusion		Tests after infusion at following times (hrs) 2.00	2.45	3.30	4.00	5.00
Na	ins.	949	1110	375	545	625	707	753
	exs.	964	854	628	774	761	718	675
	net	-15	+256	-253	-229	-136	-9	+78
K	ins.	29	30	13	10	11	9	15
	exs.	39	45	101	158	190	130	134
	net	-10	-15	-88	-148	-179	-121	-119
H_2O	net	-0.1	+1.4	-1.7	-1.9	-2.0	-0.4	-0.5
Na	t_o	149	149	149	149	149	149	149
Na	t_{10}	149	147	149	147	143	147	143
K	t_o	4.5	4.5	4.5	4.5	4.5	4.5	4.5
K	t_{10}	4.9	5.4	7.5	9.7	10.8	9.2	8.8
RV	Na	3.9	4.0	2.6	3.0	3.2	2.8	2.8
RV	K	4.2	4.0	3.2	2.8	3.8	3.0	3.2

APPENDIX 13 (contd.)

Dog no. 37 (colon) - 6th June 1962

		Tests before infusion		Tests after infusion at following times (hrs) 1.00	2.00	3.30	5.00
Na	ins.	1019	892	996	1090	1079	865
	exs.	515	814	722	1018	979	311
	net	+504	+78	+274	+72	+100	+554
K	ins.	29	27	30	22	12	14
	exs.	29	46	42	66	120	113
	net	0	-19	-12	-44	-108	-99
H_2O	ins.	15.6	16.7	17.2	18.7	-	16.8
	exs.	12.1	15.9	15.3	18.9	-	14.2
	net	+3.5	+0.8	+1.9	-0.2	0	+2.6
Na	t_o	144	144	144	144	144	144
Na	t_{10}	144	142	144	140	140	136
K	t_o	3.7	3.7	3.7	3.7	3.7	3.7
K	t_{10}	4.3	4.5	4.5	5.4	8.0	8.5
RV	Na	8.9	3.2	5.6	3.5	3.0	2.2
RV	K	9.6	4.4	5.8	3.8	3.3	2.7

APPENDIX 13 (contd.). III. Aldosterone infusion (low dose).

Dog no. 33 (ileum) - 7th June 1962

		Tests before infusion		Tests after infusion at following times (hrs) 1.00	2.00	2.45	3.30	4.00	5.00
Na	ins.	1189	1265	1209	1000	1179	1339	1228	902
	exs.	577	833	874	590	753	857	819	607
	net	+612	+432	+335	+410	+426	+482	+409	+295
K	ins.	35	31	30	28	32	34	31	29
	exs.	34	38	41	39	50	61	61	71
	net	-1	-7	-11	-11	-18	-27	-30	-42
H_2O	net	+3.9	+3.3	+2.9	+2.5	+2.6	+3.3	+2.8	+1.7
Na	t_o	146	146	146	146	146	146	146	146
Na	t_{10}	144	146	150	144	144	146	146	144
K	t_o	3.7	3.7	3.7	3.7	3.7	3.7	3.7	3.7
K	t_{10}	4.4	4.6	4.7	4.6	5.0	5.5	5.5	5.8

APPENDIX 13 (contd.)

Dog no. 34 (ileum) - 5th June 1962

		Tests before infusion		Tests after infusion at following times (hrs) 1.00	2.00	3.30	4.00	5.00
Na	ins.	252	367	446	141	398	465	363
	exs.	335	435	516	280	526	557	413
	net	-83	-68	-70	-139	-128	-92	-50
K	ins.	14	11	14	9	12	17	17
	exs.	25	18	25	30	37	45	52
	net	-11	-7	-11	-21	-25	-28	-35
H_2O	net	-0.2	+0.2	+0.5	-0.9	-0.5	-0.6	0
Na	t_o	154	154	154	154	154	154	154
Na	t_{10}	156	156	160	154	156	154	156
K	t_o	3.6	3.6	3.6	3.6	3.6	3.6	3.6
K	t_{10}	4.0	3.9	4.1	4.3	4.5	4.6	5.0

Dog no. 35 (colon) - 11th June 1962

K	ins.	11	9	9	7	8	8	6
	exs.	38	31	50	54	71	72	89
	net	-27	-22	-41	-47	-63	-64	-83
H_2O	net	-4.1	-3.0	-2.3	-1.4	-1.4	-1.0	-1.2
K	t_o	3.7	3.7	3.7	3.7	3.7	3.7	3.7
K	t_{10}	4.1	4.1	4.9	5.5	5.9	6.0	6.7

(Sodium fluxes were not estimated in this experiment).

APPENDIX 13 (contd.)

Dog no. 36 (colon) - 8th June 1962

		Tests before infusion		Tests after infusion at following times (hrs) 1.00	3.30	4.00	5.00
Na	ins.	12	31	44	27	23	25
	exs.	589	297	132	101	163	70
	net-	-577	-266	-88	-74	-140	-35
K	ins.	6	8	16	8	7	8
	exs.	17	18	24	33	40	40
	net	-9	-10	-8	-25	-33	-32
Na	t_o	148	148	148	148	148	148
Na	t_{10}	148	148	148	148	150	150
K	t_o	4.1	4.1	4.1	4.1	4.1	4.1
K	t_{10}	4.2	4.3	4.5	5.0	5.3	5.4

APPENDIX 13 (contd.)

Dog no. 37 (colon) - 6th June 1962

		Tests before infusion		Tests after infusion at following times (hrs) 1.00	2.00	4.00	5.00
Na	ins.	1019	892	996	1090	1079	865
	exs.	515	814	722	1018	979	311
	net	+504	+78	+274	+72	+100	+554
K	ins.	29	27	30	22	12	14
	exs.	29	46	42	66	120	112
	net	0	-19	-12	-44	-108	-98
Na	t_o	144	144	144	144	144	144
Na	t_{10}	144	142	144	140	140	136
K	t_o	3.7	3.7	3.7	3.7	3.7	3.7
K	t_{10}	4.3	4.5	4.5	5.4	8.0	8.5

APPENDIX 13 (contd.) IV. Injection of aldosterone.

Dog no. 33 (ileum) - 14th February 1962

		Test before injection	Tests after injection at following times (hrs) 1.00	3.30	4.00	5.00
Na	ins.	565	513	404	516	525
	exs.	417	574	460	560	371
	net	+147	+61	-56	-44	+154
K	ins.	18	17	21	23	23
	exs.	26	29	48	45	39
	net	-8	-12	-27	-22	-16
H_2O	ins.	10.2	15.3	15.4	17.2	16.8
	exs.	8.4	14.5	15.6	17.2	16.4
	net	+1.8	+0.9	-0.2	0	+0.4

APPENDIX 13 (contd.)

Dog no. 33 (ileum) - 31st January 1962

		Tests before injection		Tests after injection at following times (hrs) 1.00	2.00	2.45	5.00
Na	ins.	737	763	721	781	614	378
	exs.	677	591	361	503	425	208
	net	+60	+172	+361	+278	+189	+170
K	ins.	24	26	29	27	27	23
	exs.	35	30	32	35	40	30
	net	-11	-4	-3	-8	-13	-7
H_2O	ins.	14.3	16.9	16.6	17.4	15.9	12.8
	exs.	11.6	15.0	13.3	14.3	13.7	10.9
	net	+2.7	+1.9	+3.3	+3.1	+2.2	+1.9

APPENDIX 13 (contd.)

Dog no. 35 (colon) - 1st February 1962

		Tests before injection		Tests after injection at following times (hrs) 1.00	2.00	3.30
Na	ins.	742	392	335	452	343
	exs.	389	292	142	212	147
	net	+353	+101	+193	+240	+196
K	ins.	23	16	15	12	15
	exs.	22	23	17	11	8
	net	+1	-7	-2	+1	-3
H_2O	ins.	16.6	12.4	11.9	11.9	11.4
	exs.	13.9	11.4	10.8	10.9	10.7
	net	+2.7	+1.0	+1.1	+1.0	+0.7

APPENDIX 13 (contd.) V. Spironolactone + aldosterone infusion (high dose).

Dog no. 33 (ileum) - 20th June 1962

		Tests before infusion		Tests after infusion at following times (hrs) 1.00	2.00	3.30	4.00	5.00
Na	ins.	426	474	370	238	292	336	263
	exs.	579	519	539	273	347	491	396
	net	-153	-45	-169	-35	-55	-155	-133
K	ins.	14	15	11	12	13	11	13
	exs.	27	32	33	38	47	62	59
	net	-13	-17	-22	-26	-34	-51	-46
H_2O	net	-0.9	-0.5	-1.2	-0.8	-0.4	-1.1	-0.4
Na	t_o	141	141	141	141	141	141	141
	t_{10}	142	140	141	138	141	141	144
K	t_o	3.4	3.4	3.4	3.4	3.4	3.4	3.4
K	t_{10}	3.8	4.0	4.0	4.3	4.7	5.2	5.1

APPENDIX 13 (contd.)

Dog no. 36 (colon) - 21st June 1962

		Tests before infusion		Tests after infusion at following times (hrs) 1.00	2.00	2.45	3.30	4.00
Na	ins.	324	500	413	374	458	492	469
	exs.	224	335	182	204	130	169	190
	net	+100	+165	+231	+170	+328	+323	+279
K	ins.	5	10	10	10	9	8	8
	exs.	15	18	18	19	34	44	57
	net	-10	-8	-8	-9	-25	-36	-49
H_2O	net	-0.4	+0.1	+0.7	+0.3	+0.7	+0.5	+0.2
Na	t_o	156	156	156	156	156	156	156
Na	t_{10}	150	150	151	151	147	146	146
K	t_o	3.8	3.8	3.8	3.8	3.8	3.8	3.8
K	t_{10}	4.1	4.1	4.2	4.2	4.9	5.3	5.8

APPENDIX 13 (contd.) VI. Spironolactone + aldosterone infusion (low dose).

Dog no. 33 (ileum) - 14th June 1962

		Tests before infusion		Tests after infusion at following times (hrs) 2.00	2.45	3.30	4.00	5.00
Na	ins.	1329	918	808	731	686	669	661
	exs.	884	810	736	775	686	669	661
	net	+445	+108	+72	-44	0	0	0
K	ins.	27	15	17	16	17	18	17
	exs.	31	31	30	35	35	41	40
	net	-4	-16	-13	-19	-18	-23	-23
H_2O	net	+3.3	+0.4	+0.5	-0.3	0	0	0
Na	t_o	148	148	148	148	148	148	148
Na	t_{10}	150	146	148	148	148	148	148
K	t_o	5.5	5.5	5.5	5.5	5.5	5.5	5.5
K	t_{10}	4.2	4.2	4.1	4.2	4.4	4.4	4.4

APPENDIX 13 (contd.)

Dog no. 34 (ileum) - 12th July 1962

		Tests before infusion		Tests after infusion at following times (hrs) 1.00	2.00	3.30	4.00	5.00
Na	ins.	290	326	277	203	245	364	458
	exs.	509	708	581	535	588	578	687
	net	-219	-382	-304	-332	-343	-214	-229
K	ins.	14	14	13	12	13	13	12
	exs.	34	36	38	46	39	37	36
	net	-20	-22	-25	-34	-26	-24	-24
H_2O	net	-1.2	-1.6	-1.8	-2.0	-1.7	-0.8	-0.9
Na	t_o	139	139	139	139	139	139	139
Na	t_{10}	144	145	141	141	143	143	143
K	t_o	3.6	3.6	3.6	3.6	3.6	3.6	3.6
K	t_{10}	4.2	4.2	4.2	4.6	4.7	4.8	4.8

APPENDIX 13 (contd.)

Dog no. 35 (colon) - 13th July 1962

		Tests before infusion		Tests after infusion at following times (hrs) 1.00	2.00	2.45	4.00	5.00
Na	ins.	851	115	341	224	260	301	247
	exs.	1378	1014	843	905	972	811	905
	net	-527	-899	-502	-681	-712	-510	-658
K	ins.	17	10	12	7	4	4	4
	exs.	40	43	31	30	39	38	44
	net	-23	-33	-19	-23	-35	-34	-40
H_2O	net	-3.2	-5.7	-2.3	-3.1	-3.3	-2.0	-2.6
Na	t_o	147	147	147	147	147	147	147
Na	t_{10}	149	149	153	155	155	155	157
K	t_o	3.7	3.7	3.7	3.7	3.7	3.7	3.7
K	t_{10}	4.1	4.1	4.1	4.1	4.5	4.7	4.8

APPENDIX 13 (contd.)

Dog no. 36 (colon) - 13th June 1962

		Tests before infusion		Tests after infusion at following times (hrs) 2.00	2.45	3.30	4.00	5.00
Na	ins.	304	190	282	219	201	474	205
	exs.	968	420	495	417	453	407	91
	net	-664	-230	-213	-198	-252	+67	+114
K	ins.	5	6	5	6	3	5	5
	exs.	35	25	23	27	23	17	20
	net	-30	-19	-18	-21	-20	-12	-15
H_2O	net	-5.1	-2.0	-1.5	-1.4	-1.4	+0.4	+0.1
Na	t_o	142	142	142	142	142	142	142
Na	t_{10}	140	140	142	142	144	142	138
K	t_o	3.3	3.3	3.3	3.3	3.3	3.3	3.3
K	t_{10}	3.8	3.7	3.8	3.9	3.9	3.9	3.9

APPENDIX 13 (contd.) VII. Spironolactone Controls.

Dog no. 33 (ileum) - 6th July 1962

		Tests before dextrose infusion		Tests after dextrose infusion at following times (hours)				
				1.00	2.00	3.30	4.00	5.00
Na	ins.	455	328	280	436	145	234	401
	exs.	567	664	630	727	416	461	571
	net	-112	-336	-350	-291	-271	-227	-170
K	ins.	16	18	18	17	19	21	22
	exs.	27	34	33	30	35	36	35
	net	-11	-16	-15	-13	-16	-15	-13
H_2O	net	-1.3	-2.1	-2.2	-1.8	-2.4	-2.1	-1.7
Na	t_o	147	147	147	147	147	147	147
Na	t_{10}	144	148	148	148	144	144	144
K	t_o	4.4	4.4	4.4	4.4	4.4	4.4	4.4
K	t_{10}	4.6	4.7	4.6	4.7	4.6	4.6	4.6

Dog no. 35 (colon) - 4th July 1962

Na	ins.	212	307	69	46	258	191	307
	exs.	437	512	600	380	539	263	357
	net	-225	-204	-531	-334	-281	-72	-50
K	ins.	10	7	7	7	6	9	7
	exs.	19	20	35	35	26	26	21
	net	-9	-13	-28	-28	-21	-17	-14
H_2O	net	-0.5	-0.7	-3.1	-3.1	-1.4	-0.5	0
Na	t_o	144	144	144	144	144	144	144
Na	t_{10}	150	148	147	140	147	144	146
K	t_o	3.5	3.5	3.5	3.5	3.5	3.5	3.5
K	t_{10}	3.8	3.9	4.1	4.1	4.1	4.1	4.1

APPENDIX 13 (contd.)

Dog no. 36 (colon) - 15th June 1962

		Tests before dextrose infusion		Tests after dextrose infusion at following times (hours)		
				2.00	4.00	5.00
Na	ins.	184	240	199	207	154
	exs.	617	482	397	208	169
	net	-433	-242	-198	-1	-15
K	ins.	1	6	8	11	10
	exs.	36	33	36	34	33
	net	-35	-27	-28	-23	-23
H_2O	net	-3.7	-2.0	-1.7	-0.7	-0.8
Na	t_o	148	148	148	148	148
Na	t_{10}	144	146	146	144	144
K	t_o	4.1	4.1	4.1	4.1	4.1
K	t_{10}	4.0	4.8	4.9	4.9	4.9

APPENDIX 13 (contd.) VIII. Miscellaneous experiments.

These are several tests performed on the dogs with a Thiry-Vella fistula. No drugs had been given, nor dextrose infusion set up.

Dog no. 35 (colon) - 14th December 1961

Na	ins.	809	452	997
	exs.	195	203	256
	net	+614	+249	+741
H_2O	ins.	17.8	14.8	19.9
	exs.	14.3	13.1	14.9
	net	+3.5	+1.7	+5.0

Dog no. 35 (colon) - 15th February 1962

Na	ins.	319	263	495	493	678
	exs.	611	303	497	241	373
	net	-292	-40	-2	+252	+305
K	ins.				17	14
	exs.				13	9
	net				+4	+5
H_2O	ins.	15.8	12.8	9.3	11.5	10.1
	exs.	16.9	13.3	8.8	9.8	8.2
	net	-1.1	-0.5	+0.5	+1.7	+1.9

Dog no. 36 (colon) - 15th February 1962

Na	ins.	490	456	622	207	296
	exs.	267	184	159	224	57
	net	+223	+272	+463	-17	+239
K	ins.	11	9	13	8	11
	exs.	20	16	17	18	20
	net	-9	-7	-5	-9	-9
H_2O	ins.	12.6	11.9	11.9	10.3	11.5
	exs.	10.4	9.7	7.9	8.2	7.6
	net	+2.2	+2.2	+4.0	+2.1	+3.9

APPENDIX 13 (contd.)

Dog no. 36 (colon) - 4th April 1962

Na	ins.	216	713
	exs.	771	1078
	net	-555	-365
K	ins.	7	10
	exs.	36	39
	net	-29	-29
H_2O	ins.	10.3	17.1
	exs.	14.0	20.0
	net	-3.7	-2.9

APPENDIX 14. Summary of clinical details of patient with primary hyperaldosteronism.

HISTORY

1959 - noted to have systemic arterial hypertension (200/100 mm Hg) at examination for life insurance.

1963 - undue dyspnoea on exertion and nocturia, voiding urine hourly at night. No features of 'prostatism'.

1964 - cramps in legs and arms.
Muscular weakness.

No history of diuretic therapy.

EXAMINATION

Healthy-looking man of 58 years.

No external evidence of endocrinopathy.

B.P. 200/100 mm Hg. No cardiomegaly.

E.C.G. - depression of ST segments (see Figure).

INVESTIGATIONS

(a) On admission

serum K^+ - 1.8 mEq/L
serum Na^+ - 149 mEq/L

(b) After high K^+ diet (150 mEq/day) and normal Na^+ diet

serum K^+ 1.8 $\longrightarrow$ 3.0 $\longrightarrow$ 2.4 mEq/L

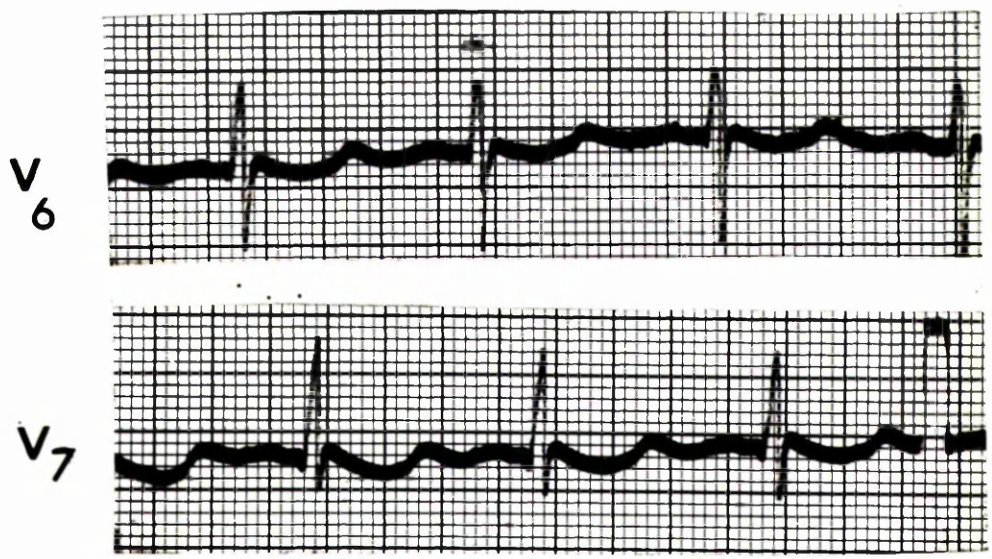


FIGURE 58 Electrocardiogram showing characteristic changes of potassium deficiency.

APPENDIX 14 (contd.)

(c) After high K^+ diet and low Na^+ diet (10 mEq/day)

serum K^+	2.4	⟶ 4.2	mEq/L
urine K^+	30	⟶ 10	mEq/24 hours
urine Na^+	100	⟶ 14	mEq/24 hours

(d) Low K^+ diet (20 mEq/day)

urine K^+ - 30 mEq/24 hours

(e) K^+ balance during K^+ repletion (see (b) and (c) above)

Total K^+ deficit calculated as 950 mEq.

(f) Faecal electrolytes

	Patient	Normal range
Na^+ (mEq/24 hours)	6	1 - 5
K^+ (mEq/24 hours)	15	5 - 8

(g) Diurnal rhythms of K^+ urinary excretion

Reversed. Maximum excretion at night in patient, compared to normal maximum excretion at noon (Elmslie, Mulholland and Shields, 1964) - see Figure.

(h) Plasma volume (by radio-iodinated human serum albumin)

3900 ml (normal for patient of similar height and weight = 2900 ml - Nadler, Hidalgo and Bloch, 1962).

(i) Acid base status (by micro-Astrup technique)

pH	7.54
PCO_2	48 mm Hg
Standard bicarbonate	38 mEq/L

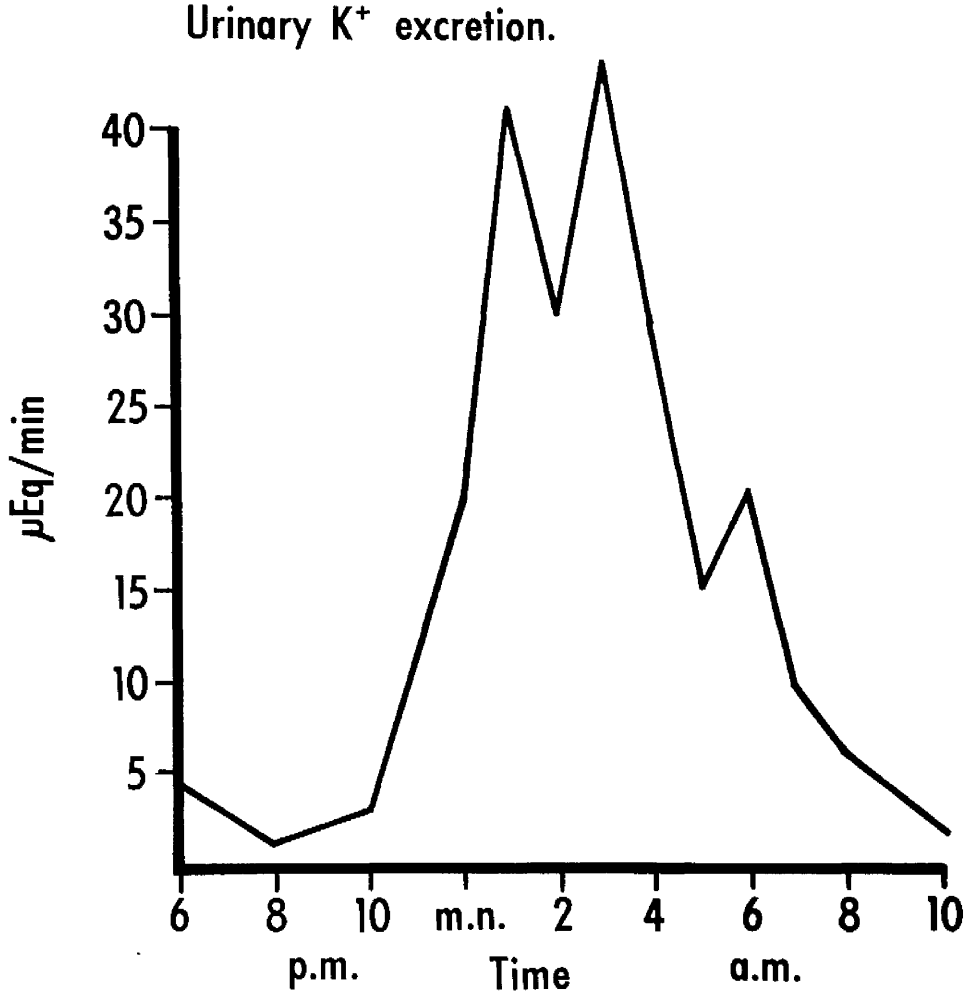
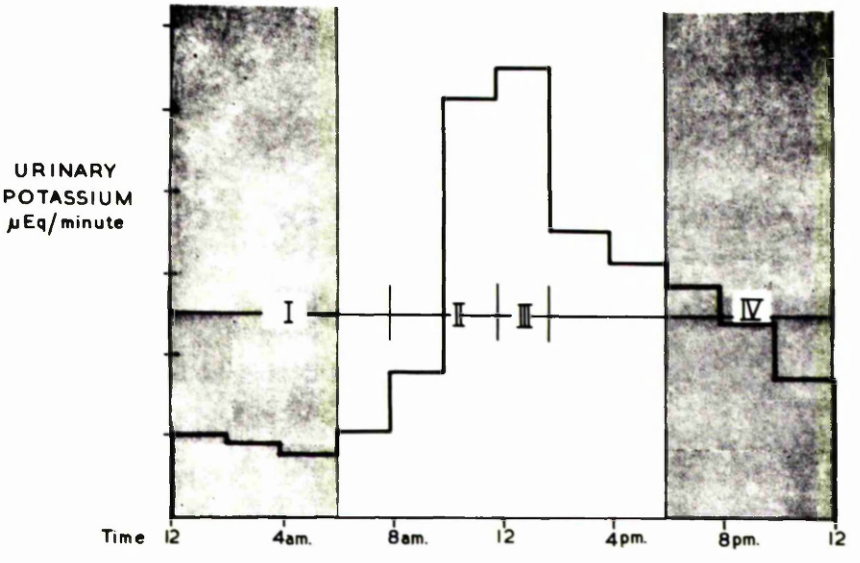


FIGURE 59 Diagram illustrating reversal of diurnal pattern of urinary K^+ excretion in the patient with hyperaldosteronism.
The normal pattern of urinary K^+ excretion is illustrated in Figure 60.

APPENDIX 14 (contd.)



PHASE I midnight – 8am MINIMUM POTASSIUM EXCRETION

PHASE II 8am – midday RISE IN POTASSIUM EXCRETION

PHASE III midday – 2pm. MAXIMUM POTASSIUM EXCRETION

PHASE IV 2pm – midnight GRADUAL FALL IN POTASSIUM EXCRETION

FIGURE 60 The normal diurnal pattern of urinary K^+ excretion.
(From Elmslie, Mulholland and Shields, 1964).

APPENDIX 14 (contd.)

Renal investigations

Albuminuria		
Concentration-dilution tests	:	SG 1010 - 1001
Diurnal output (mean of 3 days)	:	night - 1309 ml day - 592 ml
Urine reaction	:	usual - pH 7 after acid load - pH 5.8

(Ammonium chloride, 0.1 g/Kg body weight).

Steroid investigations (by courtesy of Dr. J. K. Grant)

Aldosterone excretion		6.8 µg/24 hours
aldosterone secretion	(i)	524 µg/24 hours
(normal 300 µg/24 hours)	(ii)	2.4 mg/24 hours
urinary 17-ketosteroids		14 mg/24 hours
urinary 17-hydroxysteroids		16 mg/24 hours

Radiology

Intravenous pyelography, peri-renal insufflation with oxygen and aortography did not reveal any abnormality.

OPERATION (by Professor A. P. M. Forrest)

A tumour, 2.5 cm diameter (see Figure), was found in the right adrenal gland. Both the tumour and the gland were removed.

PATHOLOGY (report by Professor T. Symington)

Appearances of the growth are those of a benign tumour of the adrenal cortex associated with primary aldosteronism (see Figure).

POST-OPERATIVE COURSE

Developed small pulmonary infarct on fourteenth post-operative day.

FIGURE 61 Cut surface of the tumour of the right adrenal gland.

FIGURE 62 Photomicrograph of benign tumour of adrenal cortex in the patient with primary hyperaldosteronism. The tumour is composed of cells similar morphologically to those of the zona fasciculata of the normal adrenal cortex (Professor Symington).

(H. and E.) x 50

APPENDIX 14 (contd.)

Three months after operation -

well and free of symptoms
serum K^+ - 3.8 mEq/L
blood pressure - 190/100 mm Hg
blood urea - 60 mg per 100 ml blood.

No medication required.

APPENDIX 15. Rates of movement of sodium, potassium and water in four human volunteers.

Subject: R.C.

Substance	Direction	1	2	3	4	Mean
Sodium (mEq/min)	insorpn.	0.53	0.61	0.68	0.51	0.58
	exsorpn.	0.18	0.22	0.26	0.28	0.24
	net	+0.35	+0.39	+0.42	+0.23	+0.34
Potassium (mEq/min)	insorpn.	0.012	0.014	0.013	0.013	0.013
	exsorpn.	0.036	0.041	0.044	0.041	0.041
	net	-0.024	-0.027	-0.031	-0.027	-0.028
Water (ml/min)	insorpn.	7.6	7.4	8.6	7.1	7.7
	exsorpn.	5.6	5.7	6.2	5.9	5.9
	net	+2.0	+1.7	+2.4	+1.2	+1.8

Subject: G.F.

Substance	Direction	1	2	3	Mean
Sodium (mEq/min)	insorpn.	0.49	0.68	0.55	0.57
	exsorpn.	0.19	0.25	0.26	0.23
	net	+0.30	+0.43	+0.29	+0.34
Potassium (mEq/min)	insorpn.	0.018	0.017	0.021	0.019
	exsorpn.	0.044	0.041	0.035	0.040
	net	-0.026	-0.024	-0.014	-0.021
Water (ml/min)	insorpn.	8.7	9.0	8.8	8.8
	exsorpn.	6.4	7.0	6.2	6.5
	net	+2.3	+2.0	+2.4	+2.3

APPENDIX 15 (contd.)

Subject: B.T.

Substance	Direction	1	2	3	4	5	6	Mean
Sodium (mEq/min)	Insorption	0.62	0.68	0.71	0.54	0.58	0.60	0.62
	Exsorption	0.31	0.29	0.39	0.31	0.48	0.25	0.34
	Net	+0.31	+0.39	+0.32	+0.23	+0.10	+0.35	+0.28
Potassium (mEq/min)	Insorption	0.020	0.019	0.022	0.024	0.025	0.026	0.023
	Exsorption	0.051	0.050	0.037	0.060	0.031	0.051	0.047
	Net	-0.031	-0.031	-0.015	-0.036	-0.006	-0.025	-0.024
Water (ml/min)	Insorption	6.2	6.0	8.3	6.4	6.7	6.4	6.7
	Exsorption	4.8	3.8	5.0	3.6	6.2	5.0	4.7
	Net	+1.4	+2.2	+3.3	+2.8	+0.5	+1.4	+2.0

Subject: M.K.

Substance	Direction	1	2	3	4	5	Mean
Sodium (mEq/min)	Insorption	0.86	0.50	0.54	0.61	0.61	0.62
	Exsorption	0.40	0.32	0.21	0.29	0.25	0.29
	Net	+0.46	+0.18	+0.33	+0.32	+0.36	+0.33
Potassium (mEq/min)	Insorption	0.015	0.018	0.023	0.011	0.009	0.015
	Exsorption	0.019	0.039	0.025	0.040	0.029	0.030
	Net	-0.004	-0.021	-0.002	-0.029	-0.020	-0.015
Water (ml/min)	Insorption	7.6	5.4	8.9	7.7	7.4	7.4
	Exsorption	5.0	2.9	4.9	6.1	6.1	5.0
	Net	+2.6	+2.5	+4.0	+1.6	+1.3	+2.4

APPENDIX 15 (contd.)

Grand mean rates ± S.D.

Substance	Direction	Mean	S.D.
Sodium	Insorption	0.61	0.09
	Exsorption	0.29	0.08
	Net	+0.32	0.09
Potassium	Insorption	0.018	0.005
	Exsorption	0.040	0.01
	Net	-0.022	0.01
Water	Insorption	7.5	1.1
	Exsorption	5.4	1.0
	Net	+2.1	1.1