THE NEURO-ENDOCRINE RESPONSE TO INJURY

THESIS SUBMITTED FOR THE DEGREE OF

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By

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ACKNOWLEDGMENTS

Metabolic and clinical endocrinological research has become sufficiently difficult to require team work for the production of worthwhile results. Collaboration is inevitable and also desirable because ideas and solutions to problems are more easily and frequently found in a group than in the mind of a single worker. My fellow investigators have been many but Dr E.B. Boling, Dr J.S. Robson, Mr L.P. le Quesne and Mr Bruce C. Paton must be especially mentioned. My interest in metabolic research was first aroused by Mr A.W. Wilkinson and received great stimulus from Professor Francis D. Moore who provided the extensive facilities of his laboratory for much of the work described in Part I of this thesis. Dr C.P. Stewart and Dr I.D.E. Storey have since continued this biochemical help and Dr Stewart has guided and made possible the hormonal measurements of adreno-cortical activity described in Part II. Throughout the formative years of my research training, Sir James Learmonth and more recently Professor John Bruce have not only allowed me access to their patients but have also constructively criticised my efforts.

The support for this work has come from various sources. During 1953-54 I was granted the Wilkie Surgical Research Scholarship of the University of Edinburgh which made my visit to the United States possible. In Dr Moore's laboratory /

laboratory grants from the Atomic Energy Authority and the Surgeon General's Office aided the prosecution of work on antidiuretic hormone and on total body water. In this country the Scottish Hospitals Endowments Research Trust have granted direct support to myself (through the kindness of Mr A.B. Wallace) and have also, through grants to Dr C.P. Stewart and Dr J.S. Robson, aided the work on hormone assay.

CONTENTS

PART II

INTRODUCTION

Biochemical processes constitute the physical basis of life and to investigate the body's adjustments to its external environment an endeavour must be made to comprehend something of biochemistry's terminology and techniques. Unfortunately, the methods and nomenclature of metabolic study have grown so complex and have advanced so fast and in so many directions that it is impossible for the surgeon to take more than a limited part in the advancement of knowledge in the field of intermediate chemical processes. However, this shortcoming of the clinician is offset by his ability to observe physiological processes in the individual as a whole and to correlate chemical and other changes with the clinical condition of his patient. His method is indeed the epitome of Pope's overworked phrase that "the proper study of mankind is man".

This thesis is concerned with one particular aspect of a group of processes which are now usually referred to as the metabolic response to injury. The detailed ramifications of this complex of biochemical adjustment are still largely unknown but diligent research over the past fifty years has sketched a broad scheme about which there is considerable agreement. As always when some pattern of activity is observed two questions may be asked: first, how /

how is the process controlled and secondly, what is its purpose? The second, and teleological, question is perhaps better disregarded, but the first is a legitimate physiological enquiry. Control over any physiological process is exercised largely by adjustments in activity of the central nervous system and, through this system, by pathways partly known and partly unknown, that lead to the endocrine glands. It is therefore natural for the clinician to look to the physiology of these nervous and endocrine systems for an answer to the problem of the control of the metabolic response to injury. A vast amount of work has already been done but the questions that remain to be answered are still numerous and, it is hoped, justify the title of this thesis.

For purposes of analysis the metabolic alterations that constitute the major part of the "metabolic response to injury" affect chiefly water, sodium, potassium and nitrogen. Water metabolism and its control after injury are considered in the first part of this thesis, the instigation and control of changes in sodium, potassium and nitrogen metabolism in the second part. So vast has the subject become that only a few aspects, which have for the most part been the subject of personal investigation, are discussed.

PART I

POST-OPERATIVE ANTIDIURESIS: THE NEURO-ENDOCRINE CONTROL OF BODY WATER AFTER INJURY

The greater part of the control of body water after injury is exerted through the activity of the kidney and therefore it is desirable first to review the available evidence on the normal regulation of body water by alterations in renal function.

THE NORMAL CONTROL OF BODY WATER AND OF THE VOLUME AND CONCENTRATION OF THE URINE

In normal circumstances water enters an individual by unselective absorption from the gastro-intestinal tract and is then distributed throughout the body liquids as a whole because of the free permeability of the natural membranes to the water molecule. Intake may vary considerably from hour to hour or day to day and in order that the body water and also the concentration of dissolved substances may remain constant it is necessary that output should be regulated to achieve equality with intake. Of the two routes of loss of water, the renal and the extrarenal (lungs and sweat), only the former can be varied by the control mechanisms of the body, although insensible losses may, of course, undergo considerable unregulated fluctuations as a result /

result of changes in the external environment. It follows, therefore, that the chief means by which the volume and tonicity of body water are maintained constant is by changes in urine volume.

THE PHYSIOLOGICAL ADJUSTMENT OF THE VOLUME OF THE URINE

It is generally agreed that the urine is elaborated from a protein-free plasma filtrate produced at the glomerulus and therefore that processes of concentration, dilution, selective reabsorption and possibly secretion must take place at varying levels in the renal tubules to produce the urine. To avoid adherence to any particular theory of tubular activity or of anatomical localisation of function it is permissible to regard the tubule in a general sense as "operating" upon the plasma. Within such a general description, the factors which determine the volume of the urine and hence the control of body water are as follows: (1) antidiuretic hormone; (2) solute load; (3) renal blood flow; and (4) other factors.

(1) Antidiuretic Hormone.- It has been known since 1898 (Howell, 1898) that the posterior lobe of the pituitary is the site of manufacture and the storehouse for a potent hormonal substance; initially this was thought to be diuretic in its effect on the kidney but subsequent research, stimulated by the pathological association between the /

the clinical condition of diabetes insipidus and lesions of the posterior pituitary (Frank, 1912), demonstrated that the physiological action of the substance was antidiuretic (Farmi, 1913; Van den Velden, 1913; Dale, 1957). The substance is now usually known as the posterior pituitary antidiuretic hormone. Further, the demonstration of nervous connections between the hypothalamus and the posterior pituitary suggested that the secretion of the antidiuretic hormone might be under the control of the nervous system and confirmation of this hypothesis was obtained experimentally by the production of lesions in the hypothalamus which resulted in failure of conservation of body water, and by the demonstration of diabetes insipidus in patients and in animals with hypothalamic injury (Fisher et al., 1938; Le Gros Clark et al., 1939). Therefore it seemed probable that at least in part the concentrating operation of the kidney was controlled by the level of circulating antidiuretic hormone; this hypothesis had previously received some experimental support from the observation that the heart-lung-kidney preparation produced a hypotonic urine, but that hypertonicity could be restored by the inclusion in the circuit of an isolated but otherwise normal head (Verney, 1926). Verney (1947), by the intracarotid injection of solutions of varying tonicity, established beyond doubt that certain cells in the hypothalamus are capable of responding to changes in the osmotic pressure of the /

the plasma that perfuses them and that this response results in a change in the rate of liberation of antidiuretic hormone from the pituitary gland. Thus, if water is added to the plasma so that it becomes relatively hypotonic, the secretion of antidiuretic hormone is diminished and the kidney is able to release more water into the urine. Conversely an increase in the tonicity of the plasma increases the rate of release of antidiuretic hormone and therefore reduces the volume of the urine and increases its concentration. By this mechanism the tonicity of the extracellular fluid is maintained within very narrow limits. The free permeability of water across all cellular barriers implies that this mechanism controls the tonicity of the body as a whole, although it cannot exert any direct influence upon total volume unless the amount of electrolytes and other dissolved substances is maintained constant by some other means. In the course of his long series of experiments, Verney also observed that pain, fright and other emotions inhibited diuresis by increasing the output of antidiuretic hormone. Apparently such non-osmotic stimuli can override the normal control of the release of antidiuretic hormone.

It is thus clear that there is a potent method for the fine control of urine volume in the neuro-humoral apparatus of the hypothalamus and pituitary gland and that this apparatus may respond to such stimuli as are part of any normal /

normal surgical operation or injury. The mechanism of action of antidiuretic hormone is quite unknown but the site of the concentrating and diluting operation in the kidney is probably either in the distal tubule or in the collecting ducts (Smith, 1956; Wirz, 1957). Many problems regarding this operation remain to be solved but their elucidation cannot be expected until more is known of the exact site and mode of action of the antidiuretic hormone.

(2) Solute Load.- Amongst the many functions of the kidney are elimination of waste products, the regulation of the body's content of electrolyte, the control of acid-base balance and the excretion of substances actually or potentially toxic to the body. Dissolved solids of varying nature are thus always demanding excretion: their total quantity in the urine constitutes at any given time the solute load and requires a definite volume of urine for its elimination. Solute load is mathematically measured by the product of urinary concentration and volume. The greater the concentrating ability of the kidney, the smaller the obligatory volume of urine necessary to excrete the solute load. Similarly, the greater the solute load, the larger the volume of urine necessary for its elimination irrespective of the concentrating ability of the kidney. Finally, numerous experiments (McCance, 1945; Rapoport et al., 1949; Brodsky et al., 1953) have shown that under conditions of maximum water conservation (the so-called hydropenic /

hydropenic state) as the load of any given substance is increased, the volume of the urine rises and its concentration falls.* The rise in rate of flow of urine is a function of the solute load, whereas the decline in concentration is an exponential function of either of these parameters.†

(3) Measurement of Urinary Concentration and of Solute Load. The Concepts of Osmolar and of Free Water Clearance.- The concentration of the urine is conveniently expressed in terms of its "osmolarity" which is the colligative property of a solution that determines its vapour pressure and freezing point. Osmolar strength is a direct function of the number of free particles or of ions present in a solution and is thus dependent not only on molecular weight but also, if the substance is ionisable, on the degree of dissociation. Under most circumstances, osmolarity and specific gravity are closely related (see Jones and DeWardener, 1956; Joekes et al., 1957) but the latter is directly proportional to the weight of substance dissolved and is not affected by molecular size, shape and number or by the degree of dissociation of an ionic solution. Osmolarity may be conveniently /

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* Robinson (1954) has pointed out that this phenomenon was well known to physiologists at the beginning of the twentieth century but it was not analysed until McCance's investigation in 1945.

† More accurately in terms of current renal physiology, the greater the rate of flow of urine as a result of an increase in the solute load, the closer does the ratio of solute concentration in the urine to solute concentration in the plasma (the U/P ratio) approach unity (Smith, 1956).

TABLE I

Maximal Urinary Concentration

Author	Method	Maximal Concentration of Urine mOs/l.
Koranyi *et al.* (cited by Hamburger, 1902)	Exsiccation	1100 - 1200
McCance (1945)	Exsiccation	1110 - 1380
Gamble (1944)	Exsiccation	1400
Miles *et al.* (1954)	Exsiccation and Antidiuretic Hormone	935 - 1027
Frank *et al.* (1957)	Exsiccation	1076 ± 167
Boyarsky and Smith (1957)	Exsiccation and Antidiuretic Hormone	614 - 975

conveniently measured by the determination of the freezing point* (a procedure first introduced by Dreser in 1892) and in all the investigations described below this method was used. (A description of the techniques involved and of the apparatus used is given in the section on Methods, p. 112). The maximum concentration of the urine is reached when the kidney finds it impossible to withdraw any more water from the tubular urine against the urine/plasma concentration gradient (Gamble, 1954). The attainable osmolarity of the urine varies from individual to individual and from determination to determination and is also, as has been mentioned, dependent upon the "solute load", that is, upon the amount of dissolved substances (measured in osmolar terms) which demand excretion. Gamble (1947) under conditions of starvation and water deprivation in his life-raft experiments found maximal urinary concentrations of about 1400 milli-osmols per litre and de Wardener and Jones (1956) found values of between 900 and 1100 in man after water deprivation (see Table I). There are theoretical objections to a further increase in the osmolarity of the urine in man above 1450 which have been summarised by Gamble (1954), but in all probability the lower levels of between 900 and 1100 milli-osmols per litre are those usually found /

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* Certain inaccuracies are introduced if the osmolarity of a complex fluid such as urine or plasma is equated with the freezing point depression as referred to standard solutions of strong electrolytes (see Rapoport et al., 1949) but for practical purposes in clinical studies these corrections (which are related to the differences between electrolytes and non-electrolytes) can be neglected.

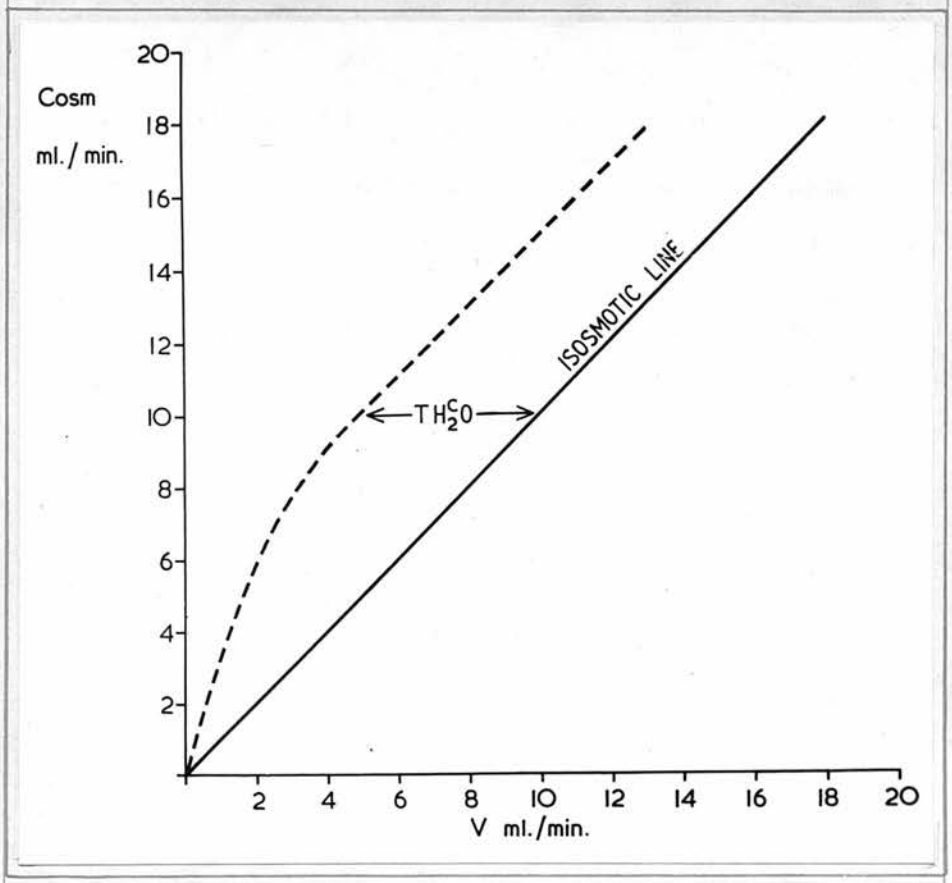

Fig. 1

Graphical representation of the relationship between total osmolar clearance during the hydropenic state, and urine flow. TH_2^C0 indicates the maximum value of free water clearance attained above values of V of 5 ml./min.

found during dehydration for short periods (Boyarsky and Smith, 1957).

Osmolar and Free Water Clearance.- The clearance concept (Smith, 1951) can be applied to the excretion of total solutes and of water. Clearance is defined as the theoretical quantity of plasma from which the substance under consideration is completely removed in each minute and is given by the mathematical relationship

$$\frac{\text{Urinary concentration of substance}}{\text{Plasma concentration of substance}} \times \text{minute volume of urine}$$

The solute clearance is given by

$$Cosm = \frac{Uosm}{Posm} . V.$$

Where Uosm = urine osmolarity
Posm = plasma osmolarity
V = minute volume of urine

The difference between this figure and the total volume of the urine is a measure of "free water" or "osmotically unobligated water" clearance.

$$T_{H_2O} = V - \frac{Uosm}{Posm} . V.$$

Thus if $\frac{Uosm}{Posm}$ is greater than 1, T_{H_2O} is a negative quantity, if less free water clearance is positive; when Uosm = Posm free water clearance is zero. For zero values of free water clearance a graph which relates solute clearance and urine flow will be a straight line at 45° to the ordinate and abscissa (Fig. 1). Zak et al. (1954) have designated this line the isosmotic parameter: points to the left of this line indicate a negative free water clearance, points /

points to the right a positive. In hydropenic individuals or those under the influence of exogenous antidiuretic hormone, the line which relates minute volume and osmolar clearance becomes linear above values for V of approximately 5 ml. minute. The horizontal distance between this line and the isosmotic parameter then represents the maximum free water clearance (Fig. 1).

(4) Renal Blood Flow.- Smith (1956) aptly summed up modern views of the influence of renal blood flow on the formation of urine when he stated that "the most remarkable feature of the renal circulation is its autonomy". Total renal haemodynamic resistance remains almost constant in spite of wide changes in perfusion pressure. Under physiological circumstances it is doubtful if the rich renal sympathetic vasomotor innervation has any part to play in the control of the renal circulation and it is particularly inapt to ascribe to these nerves any similar function to that of the vasomotor fibres which supply the vessels of the skin. Nevertheless, emotional stimuli (Smith et al., 1939; Smith, 1940), fright, pain, cold, haemorrhage and other noxious circumstances all promote renal vasoconstriction - perhaps partly by humoral mechanisms - and reduce renal blood flow. Glomerular filtration rate is also sometimes affected although balanced changes in the afferent and efferent arterioles of the glomerulus may keep filtration relatively constant and thus /

thus maintain the volume of the urine. With the exception of changes in sodium and chloride excretion (see Chalmers et al., 1951; Wesson, 1957) the exact effects in man of pronounced reduction in the glomerular filtration rate on the volume and composition of the urine have received remarkably little direct study. In the dog, recent work on graded constriction of the renal arteries has yielded conflicting results. Leaf et al., (1954) concluded that an acute reduction in glomerular filtration rate does not cause the kidney to excrete a concentrated urine, although the volume of the urine falls and a close relationship between filtration rate and the total solute excretion persists. More recently del Greco and de Wardener (1956) and Berliner and Davidson (1957), both of whom employed more severe restriction of renal blood flow, achieved a rise in concentration of the urine so that it became hypertonic with respect to the plasma. However, the maximal osmolar concentration obtained was in the region of 450-500 mOs/l.* In all three groups of experiments adequate care was taken to see that secretion of antidiuretic hormone did not cause the observed changes.

Thus /

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* It is of interest that this figure corresponds closely to the "fixed solute concentration" urine seen in the diuretic phase after recovery from acute tubular necrosis (Robson, Dudley and Lambie, unpublished). Such urine has been previously thought of as corresponding to glomerular filtrate but this is in fact not the case and other mechanisms than complete failure of distal tubular function must be found to account for its appearance.

Thus it is possible that in some circumstances renal blood flow may be a factor of importance in determining the volume and concentration of the urine in man, although the scanty evidence available suggests that under conditions of reduced renal blood flow the concentration of the urine will differ markedly from that which occurs in oliguria which is the result of the secretion of antidiuretic hormone. In the human subject after surgical operation discrimination between the effects of the two processes may, provided they are also separated in time, prove possible by the observation of differences in solute concentration and solute output in the urine.

(5) Other Factors.- It seems probable that under certain circumstances a renal concentrating operation can operate in the absence of antidiuretic hormone or as a supplementary process to it. Thus del Greco and de Wardener noted a change in the concentration of the urine from hypotonic to hypertonic in patients with diabetes insipidus who were receiving an infusion of mannitol. Further, Dicker (1957) has shown that during dehydration in the rat the urine volume is ten times lower than that found during maximal antidiuresis induced by exogenous posterior pituitary hormone. Jones and de Wardener (1956) have demonstrated that concentration is raised higher by dehydration in man than by the administration of antidiuretic hormone although paradoxically this concentration can be maintained in the face /

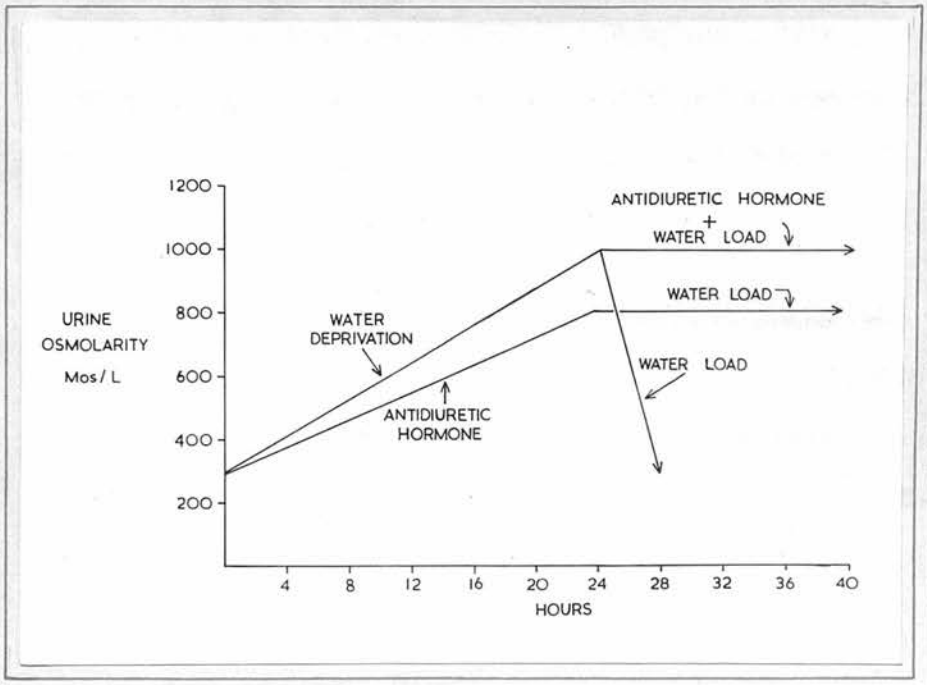

Fig. 2

Schematic representation of the experiments of Jones and de Wardener (1956) described in the text. Exogenous antidiuretic hormone maintains the extreme urinary hyperosmolarity of water deprivation although the same level of tonicity cannot be achieved by the administration of this hormone alone.

face of a water load if antidiuretic hormone is administered concurrently (see Fig. 2). Morphine and possibly other similar drugs can also reduce the rate of flow of urine without the intervention of antidiuretic hormone, an observation that must be taken into account when the effects of a surgical procedure, in which opiates are employed as pre-operative and post-operative medication, are studied. The nature of the renal operation involved in the production of these high concentrations and low rates of flow is unknown although in the rat haemodynamic factors may play a part.

RENAL EXCRETION OF WATER AFTER INJURY AND OPERATION

History

Claude Bernard in 1859 was almost certainly the first to report, if not to observe, that the volume of urine in experimental animals and in man was diminished after injury: at this juncture his preoccupation with vasomotor activity led him to conclude without further experiments that the oliguria was probably caused by a vasoconstrictive reduction in renal blood flow. Malcolm in 1893 commented again on the oliguria that follows injury but his and Bernard's observations and conclusions apparently remained largely unnoticed. It was not until 1905 that Pringle, Maunsell and Pringle, in a carefully conducted investigation on patients who received ether anaesthesia followed by a variety of surgical procedures on the abdomen, neck and limbs, showed that /

that the volume of urine (and incidentally its urea-nitrogen content) was reduced for at least 24 hours after anaesthesia or operation. These workers considered that the oliguria was a result of a deleterious effect upon the kidney of the anaesthetic agent. Post-operative oliguria was thereafter repeatedly if sporadically commented upon, more frequently so as interest in parenteral therapy quickened after the introduction of continuous intravenous infusion by Matas in 1924 and as it came to be realised that a definite sequence of biochemical events was set in train by operation or by injury. Cuthbertson in 1934, Naunton-Morgan and Avery Jones in 1938 and Stewart and O'Rourke in 1942 had all recorded the relative oliguria that followed injury, and with the advent of more exact techniques for the assessment of renal function and blood flow, numerous investigators attempted to find changes in these factors that might explain the observed post-traumatic oliguria. That the renal circulation enjoyed a considerable degree of autonomy and appeared to be largely uninfluenced by a wide variety of circumstances as long as blood volume was maintained had already been demonstrated by Smith et al. (1939; see p. 25), and it was therefore not surprising to find that only slight and transient changes in renal function could be demonstrated in the immediate post-operative and post-anaesthetic period (Coller et al., 1943; Ariel and Miller, 1950; Moyer, 1950). It seemed improbable that these small alterations could explain the observed /

observed oliguria and the apparent inability of the kidney to excrete in a normal manner a load of either water or of "physiological" (0.9%) sodium chloride (Stewart and O'Rourke, 1942; Coller et al., 1944; Limbert et al., 1945; Berry et al., 1948; Cooper et al., 1949; Elman et al., 1949; Ariel, 1951). Other physiological mechanisms were therefore invoked and in 1950 Hardy suggested that post-operative oliguria might be part of the general metabolic response to injury, the pattern of which had been emerging as a result of the great number of investigations that had followed Cuthbertson's initial demonstration that nitrogen and electrolyte metabolism were greatly altered after injury (Cuthbertson, 1930, 1932, 1934, 1936; see also Part II of this thesis). Hardy correlated the oliguria with the observed reduction of renal excretion of sodium which was in turn related by him to increased adrenocortical activity. However, in 1949, Cooper et al. had shown that the reduction in urine flow took place in the immediate post-operative period when sodium output was still maintained and that this oliguria persisted in spite of water loading by the intravenous route. To Ariel and Miller (1950) goes the credit for the first suggestion that the possible physiological mechanism involved was independent of the other metabolic changes and that the oliguria might be the result of a liberation of antidiuretic hormone from the posterior lobe of the pituitary gland. Additional support for this hypothesis /

hypothesis was provided by the experience of Hayes and Coller (1952) with a patient with established anterior and posterior pituitary insufficiency who was unable to produce an absolute oliguria after an operation of unstated magnitude under ether anaesthesia, although a considerable reduction in urine volume (from 11.5 ml./min. to 4 ml./min.) did occur. The situation was further clarified by Le Quesne and Lewis's (1953) study of a group of 21 patients who were submitted to partial gastrectomy for duodenal ulcer while on a controlled intake of 4 litres of water daily with or without the addition of 140-170 mEq. of sodium chloride (equivalent to a litre of 0.9% solution of this salt). All of their patients retained water and consequently gained weight (between 0.8 and 2.3 kg.) during the first twenty-four hours after operation and in all the urine volume remained low (600-880 ml./24 hrs.) and the specific quantity high (in excess of 1020-1025). Le Quesne and Lewis concluded that the evidence could best be interpreted as the operation of a physiological mechanism which favoured decreased renal excretion of water in the immediate post-operative period. The only known agent for such a reduction is posterior pituitary antidiuretic hormone.

Further Problems

After the completion of LeQuesne and Lewis's work five questions remained to be answered:

(1) /

(1) Is the diuretic response to the reduction of plasma tonicity by the administration of "electrolyte free" water (that is water without ions, for example 5-6% dextrose) absent when gross overloads of both water and salt such as were used by Coller et al. (1944), Berry et al. (1948) and by Le Quesne and Lewis (1953) are not employed?

(2) How long does the inhibition of a diuretic response to water persist?

(3) Are the volume and concentration of the urine produced immediately after injury compatible with the action of the known antidiuretic mechanisms of the posterior pituitary gland?

(4) Can other qualitative and quantitative similarities between the renal output of water and solutes after injury and that which occurs under the influence of posterior pituitary antidiuretic hormone be demonstrated?

(5) Is there any evidence to suggest increased circulating antidiuretic activity in the blood during the phase of oliguria after injury or operation in man?

Problem I. The response to intravenous water loads.- In an attempt to answer the first question six healthy patients who were to undergo partial gastrectomy for duodenal ulcer on the surgical service of the Peter Bent Brigham Hospital and in the Professorial charges of the Royal Infirmary of Edinburgh were studied.

Plan of investigation. A normal intake of liquid was allowed /

allowed until the day of operation; thereafter water losses were replaced by the intravenous administration of 6 per cent. glucose solution. Insensible loss was calculated on the basis of the figures obtained by direct weighing of patients in the environment under study and were found to amount to between 50-100 ml./hr. for an adult; the expected urinary output was regarded as 1 litre in the first 24 hours after injury. Thus the patients were maintained in approximately normal water balance throughout the experimental period.* On the day before each operation the patient was subjected to a water load test. This consisted of a rapid intravenous infusion of between 780 and 950 ml. of 6 per cent. dextrose in less than 40 minutes. Such an infusion fulfils the following criteria.

(a) It is not sufficiently large to bring about any gross distortion of total body water.

(b) It delivers a maximal osmotic stimulus to the hypothalamus by bringing about a considerable reduction of serum osmolarity.

(c) It is administered within the "lag period" before water diuresis begins as a result of a diminished output of posterior pituitary antidiuretic hormone.†

(d) /

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* No allowance was made for water of oxidation which in the post-traumatic patient may be considerable (Moore, 1953) but which would tend to increase the positive balance and thus compensate for any unmeasured loss by other routes.

† This lag period is most probably explained by the need to eliminate circulating antidiuretic hormone before changes in renal conservation of water can occur.

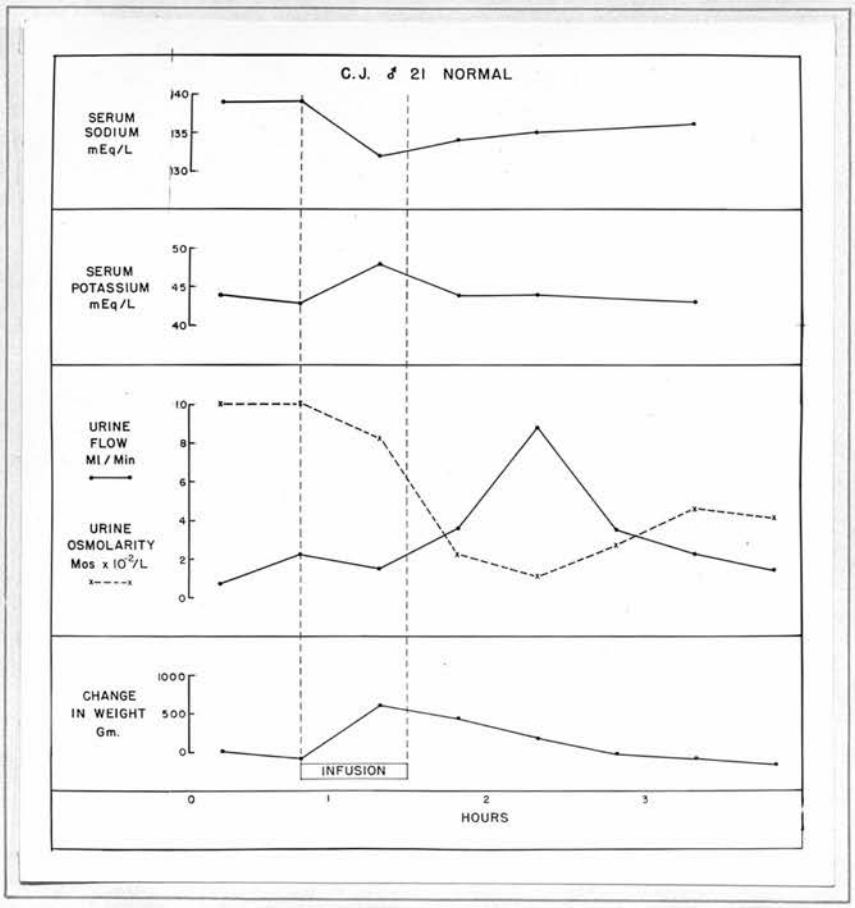

Fig. 3

Normal response to an intravenous water load of the type described in the text (Appendix II, Table II).

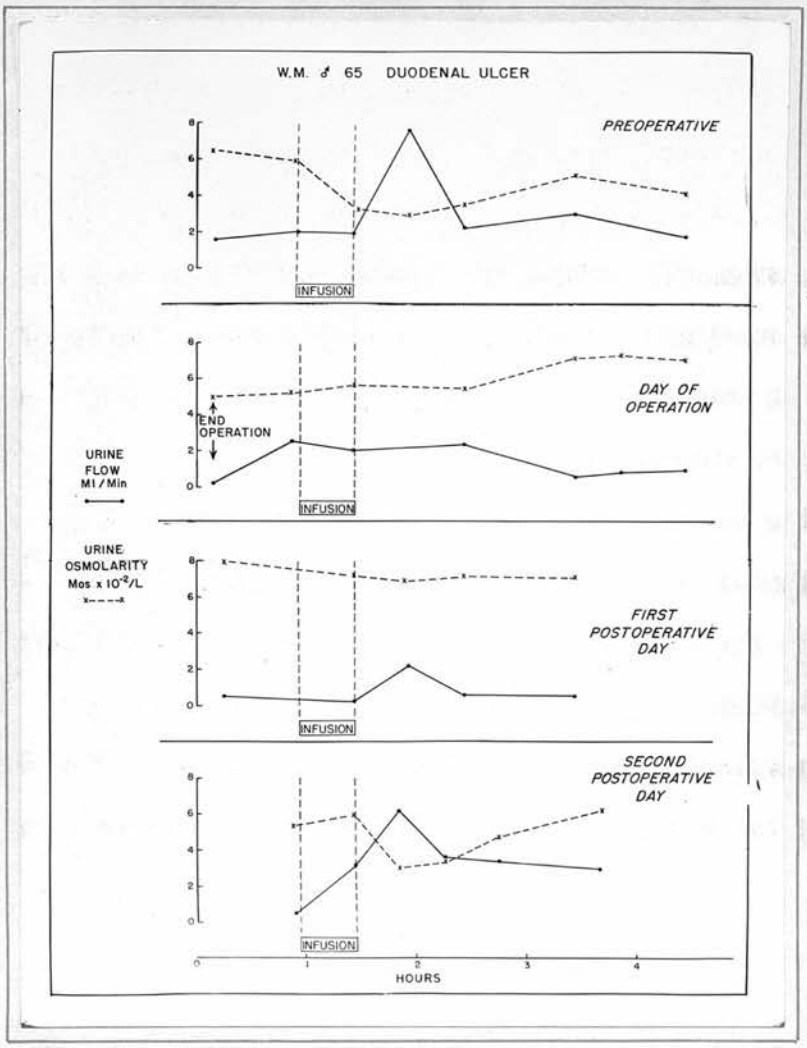

Fig. 4

Pre-operative and post-operative responses of urine flow and solute concentration to an intravenous water load (Appendix II, Table III).

(d) In the problem under study it has the additional advantage that it is independent of alimentary absorption.

In this and in subsequent studies on unconscious, seriously ill and post-operative patients the urine was collected through an indwelling Foley catheter. In the clinical cases gravity drainage alone was used but in most of the experimental studies the bladder was flushed with air at the conclusion of each experimental period. In experiments on conscious, experienced and co-operative subjects, voluntary voiding was used.

The normal response to an infusion of this kind is illustrated in Fig. 3 (Appendix II, Table II). There is a fall in the serum sodium during the period of the infusion; this implies an adequate stimulus, to the hypothalamic osmoreceptors. In the first specimen taken just after the end of the infusion the flow of urine rises, reaches a peak in the following specimen and falls off as the load is eliminated. As the rate of urine flow increases the osmolarity of the urine falls, to rise again, although not to its former levels, when the load has been eliminated.

In contrast to this rapid elimination of an administered load in the normal individual, the patients after the surgical operation showed a considerably different response (Appendix II, Tables III-VIII). A typical example is illustrated in Fig. 4 (Appendix II, Table III). Although a normal pattern was present before operation, only a very slight /

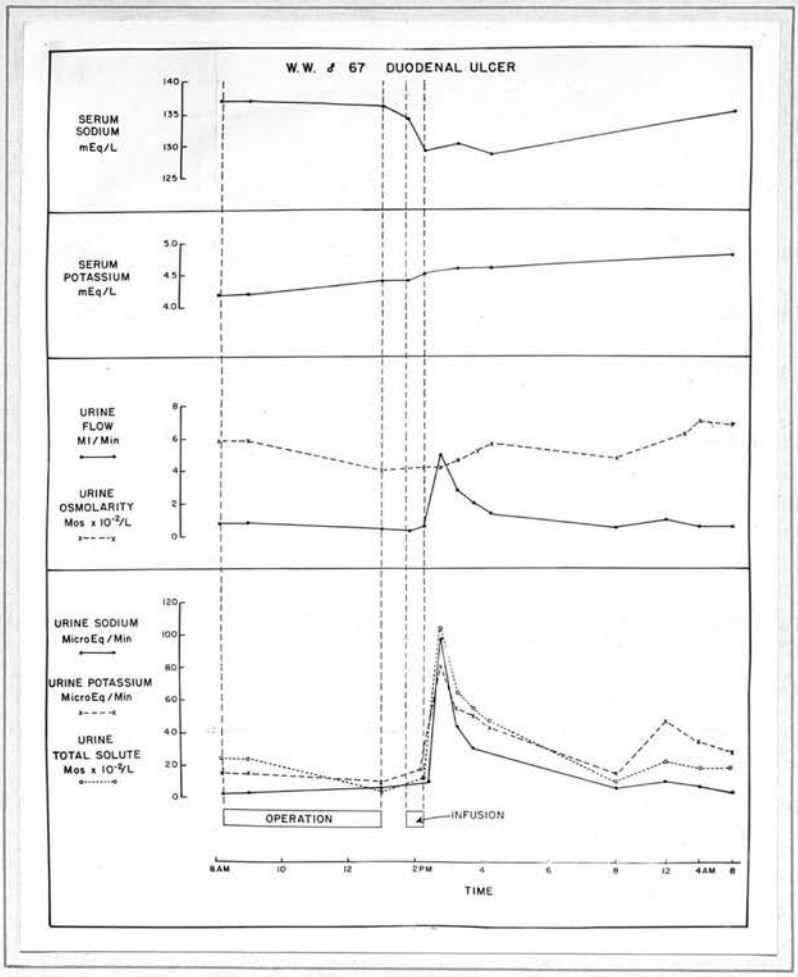

Fig. 5

Post-operative response to an intravenous water load. For full consideration see text. (Appendix II, Table IV.)

slight increase in the rate of flow of urine follows the surgical procedure and there is no marked change in the solute concentration of the urine. Not until the second post-operative day has the diuretic response to water begun to return to normal.

The explanation for the slight rise in urine flow that temporarily follows the infusion when a true water diuresis with reduction in urine osmolarity is not present, is apparent from Fig. 5 (Appendix II, Table IV). The solute load is suddenly and markedly increased by the infusion of glucose at rates which produce blood concentrations in excess of the renal threshold for glucose and accordingly the urinary output rises without marked change in solute concentration. It is of interest to note that electrolyte excretion is also temporarily increased, a fact in accord with the experience of others under conditions of the action of antidiuretic hormone (Rapoport et al., 1952).

The consistent absence after a major surgical operation of a normal diuretic response to the intravenous administration of water in the form of 6 per cent. dextrose suggests some form of antidiuretic activity but does not, of course, elucidate its nature. The considerable hypertonicity of the urine before the infusion suggests water absorption from the urine rather than any interference with renal function such as might be produced by a reduction in blood flow. However this observation requires confirmation.

Every /

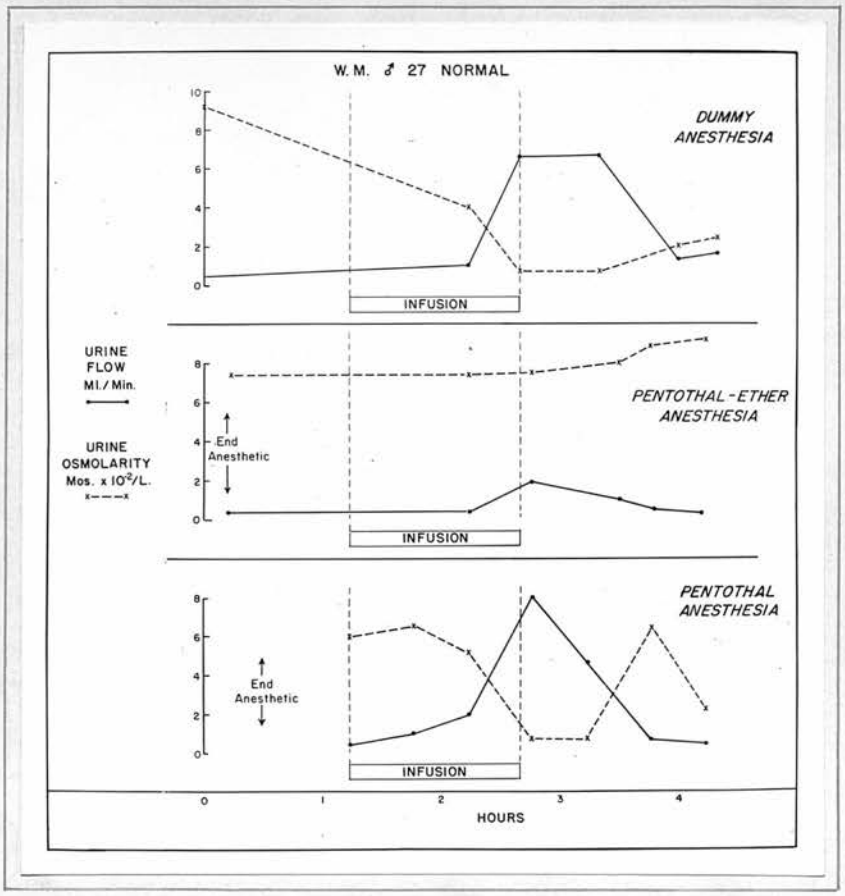

Fig. 6

The effects of Pentothal (thiopentone) and of ether anaesthesia on the response to an intravenous water load (Appendix II, Table X).

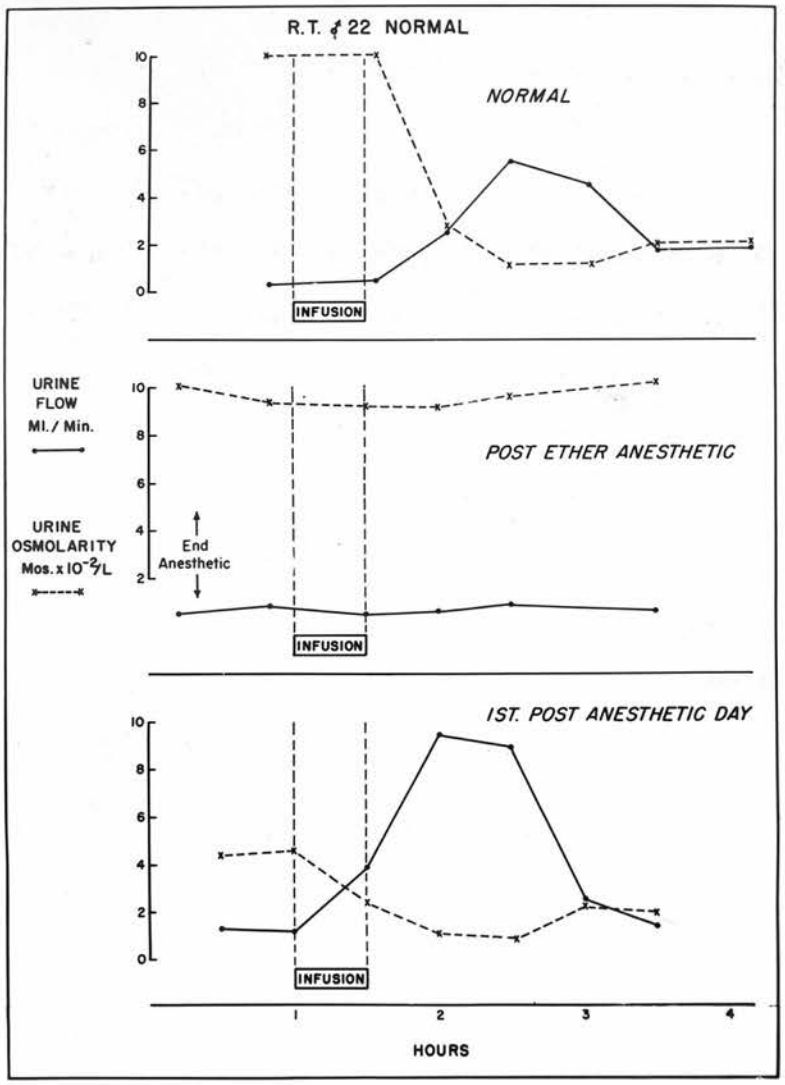

Fig. 7

The effects of an ether anaesthetic on the response to an intravenous water load (Appendix II, Table IX).

Every major surgical operation includes some form of anaesthesia and in the cases under study this was by induction with thiopentone (Pentothal, Abbott) and maintenance with ether. It is accordingly of interest to attempt to separate the influence of anaesthesia alone on the response to the intravenous infusion of 6 per cent. dextrose. For this purpose, and as part of a group of metabolic studies (Moore et al., 1956) two healthy male volunteers were subjected to control (6 per cent. dextrose) infusions and thereafter to similar infusions following either thiopentone (1 hour), or thiopentone and ether anaesthesia (3 hours). Before the control infusion in subject W.M. an attempt was made to simulate all the preparatory features of anaesthesia and he remained in ignorance of whether or not he was to be submitted to an anaesthetic on this occasion. Fig. 6 (Appendix II, Table X) illustrates that an ether anaesthetic in W.M. effectively inhibits the diuretic response, whereas thiopentone is ineffective. However, as is shown by subject R.T., the inhibition after ether is short-lived and a normal response occurs on the first day after ether anaesthesia (Fig. 7; Appendix II, Table IX).

Finally in one of the patients submitted to partial gastrectomy and in both the subjects who were anaesthetised the effect of these procedures on the response to dextrose infusion was compared with the effect of the administration of /

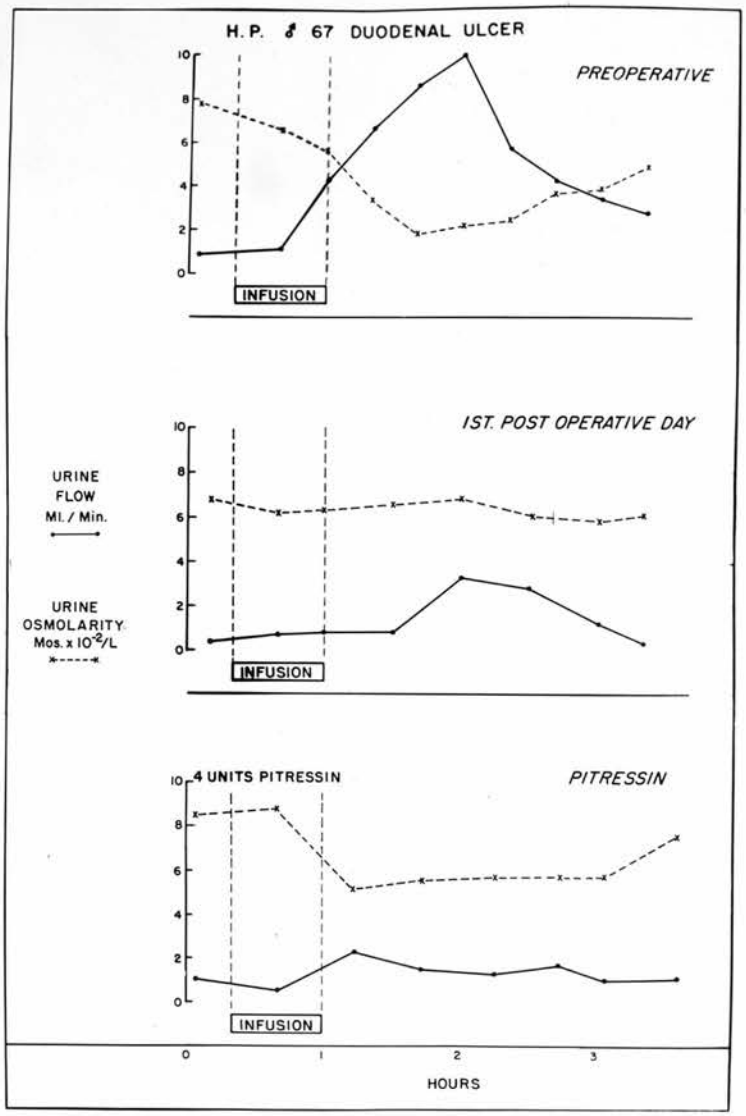

Fig. 8

Comparison of the effects of operation and of posterior pituitary antidiuretic hormone on the response to an intravenous water load (Appendix II, Table V).

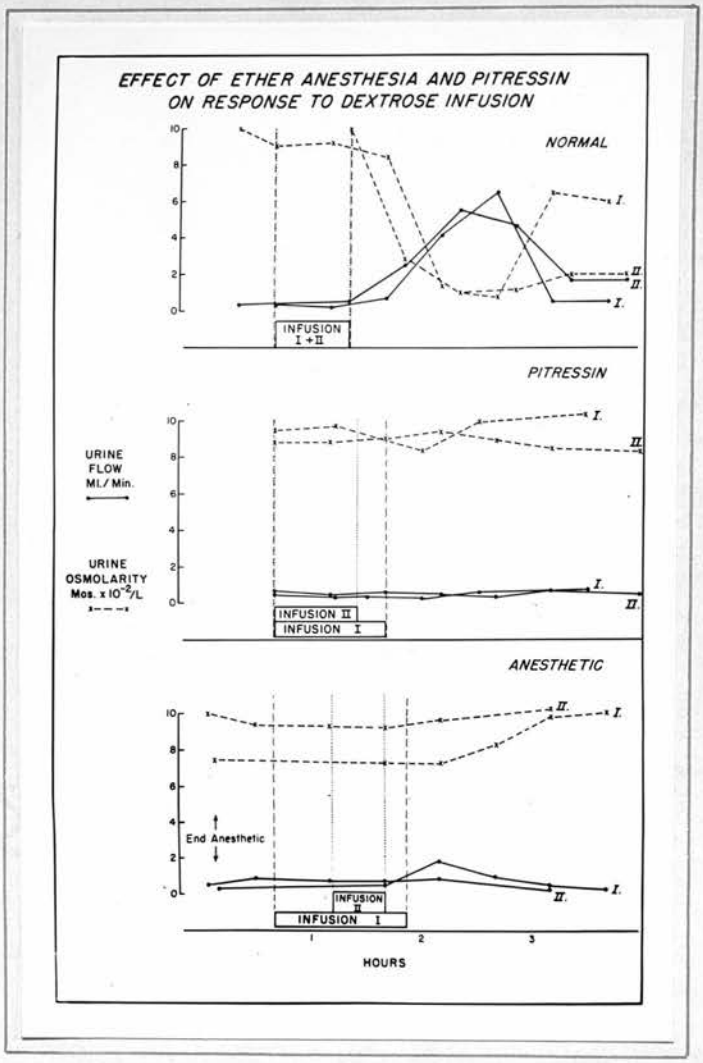

Fig. 9

Comparison of the effects of ether anaesthesia and of posterior pituitary antidiuretic hormone on the response to an intravenous water load (Appendix II, Table IX).

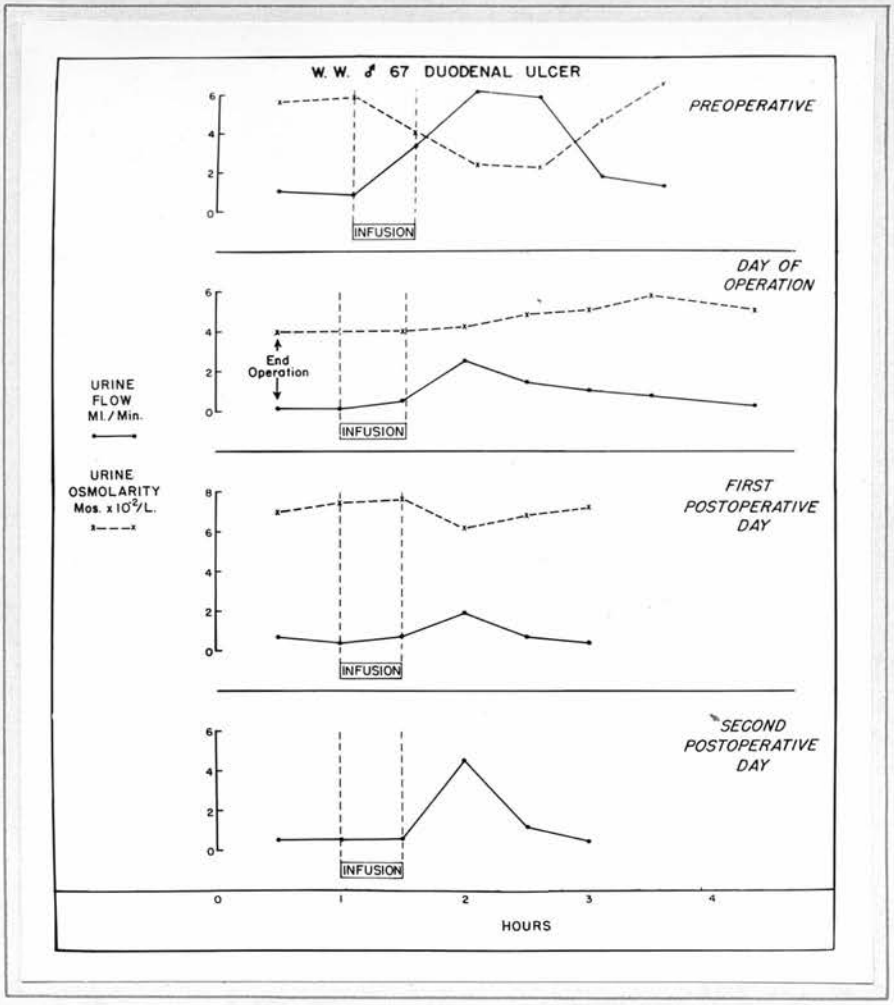

Fig. 10

Duration of antidiuresis after partial gastrectomy (Appendix II, Table IV). Fig. 4 shows the results of a similar experiment.

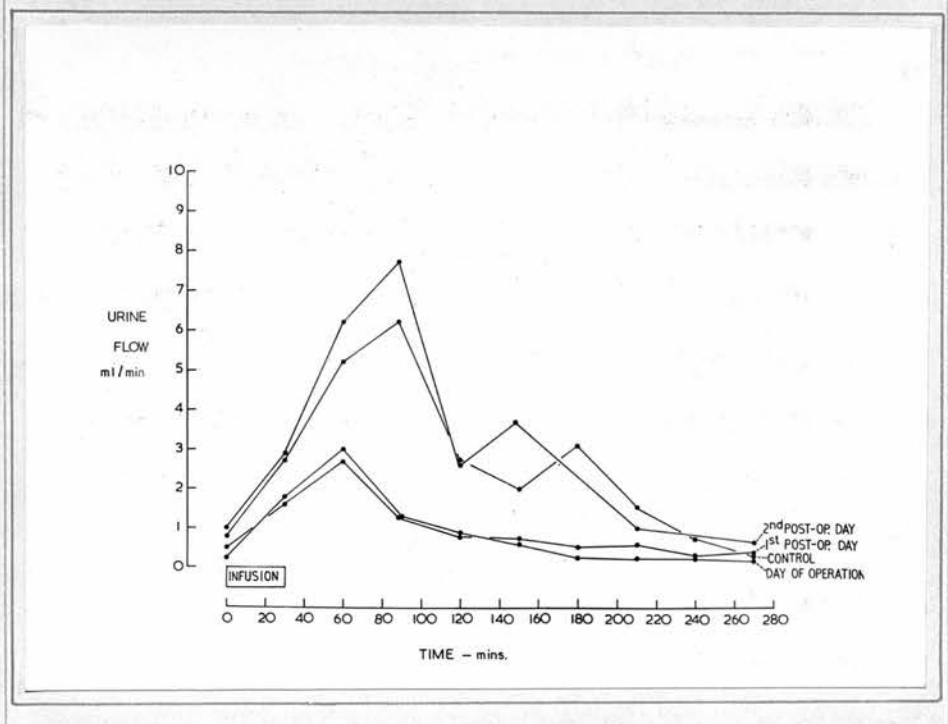

Fig. 11

Average rates of urine flow in response to an intravenous water load for four patients after partial gastrectomy. (Appendix II, Tables V-VIII.)

of commercial antidiuretic hormone (Pitressin, Parke Davis). In each of the three experiments four units of aqueous Pitressin were administered intramuscularly 20 minutes before the infusion was begun. The similarity between the effects of this agent and those of the operation and the anaesthetics is apparent from Figs. 8 and 9.

Problem II. Duration of antidiuresis after operation and after anaesthesia.- The experiments described in the previous section indicate that the inhibition of response to intravenous 6 per cent. dextrose persists for up to 48 hours after a major surgical procedure and for no more than 24 hours after anaesthesia alone. This was confirmed for the operative cases by the type of experiment illustrated in Fig. 4 and similarly in Fig. 10 which was undertaken in four of the six patients. Measurements of urinary osmolarity were not made in all these experiments; Fig. 11 shows the average maximum rate of flow of urine in response to dextrose infusion for the four examples (Appendix II, Tables V-VIII). A near normal diuretic response is present by the second post-operative day.

It is thus apparent that the inhibition of water diuresis that follows a major surgical procedure is a prolonged one and may be of considerable significance when replacement of losses of water is contemplated.

Problem III. Urinary volume and concentration after injury and after operation.- Although the studies so far described /

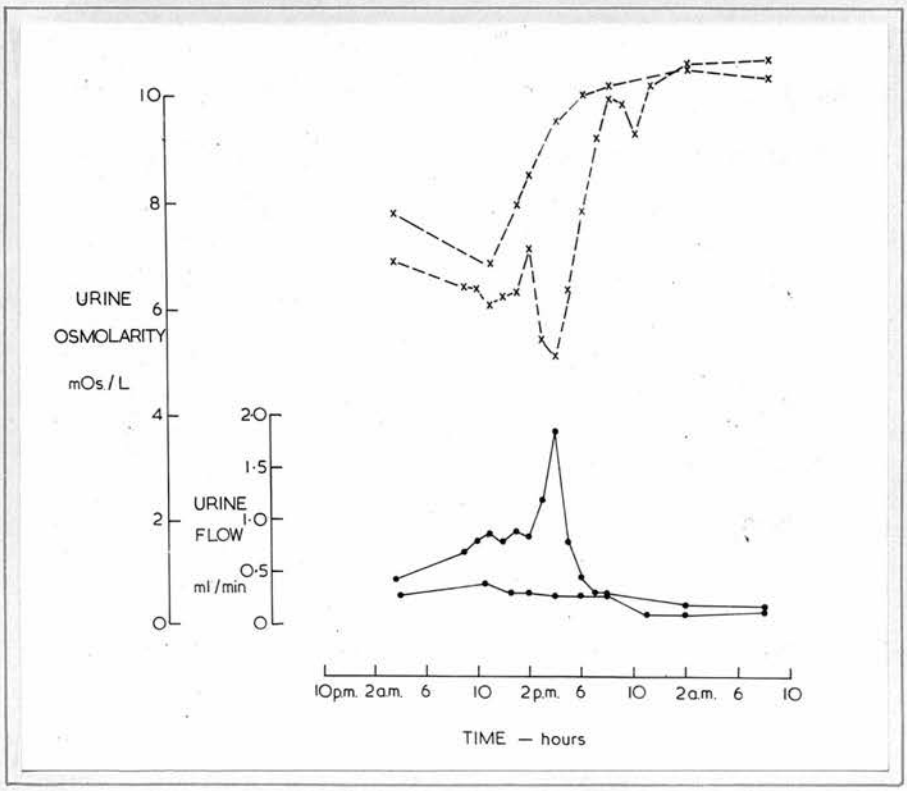

Fig. 12

The effect of a "dummy" operative procedure on urine volume and concentration. (Appendix II, Tables XI and XII.)

Urine osmolarity in Fig. 12 should read mOs/L. x 10^{-2}.

described indicate that a high urinary concentration and a low rate of urine flow may be expected after operation, they have not furnished any information on the pattern of urinary flow rate and solute concentration encountered in patients after major surgical procedures. For some years it has been the practice in the Professorial Units of the Royal Infirmary to manage patients undergoing major abdominal operations by a scheme which withholds all food and fluids for the first 48 hours after operation (Wilkinson, 1956, 1957). This provides a satisfactory clinical circumstance in which to observe the renal response to injury: there are no disturbing features such as intravenous infusions which may complicate the pattern of renal adjustment. In man, 48 hours' deprivation of water alone induces maximal urinary concentration (Jones and de Wardener, 1956; see p. 9). The pattern of emergence of renal water conservation during a period of a "dummy operation" with water and food deprivation is shown in Fig. 12 which is based on observations made on two volunteers (Appendix II, Tables XI and XII). The solute concentrations observed are in agreement with those found by Jones and de Wardener (1956) and by Boyarsky and Smith (1957), although others have observed much higher urinary concentrations during prolonged water and food deprivation (e.g. Gamble, 1947). The post-operative patient should develop a similar pattern of renal conservation merely because of deprivation of water and food

if /

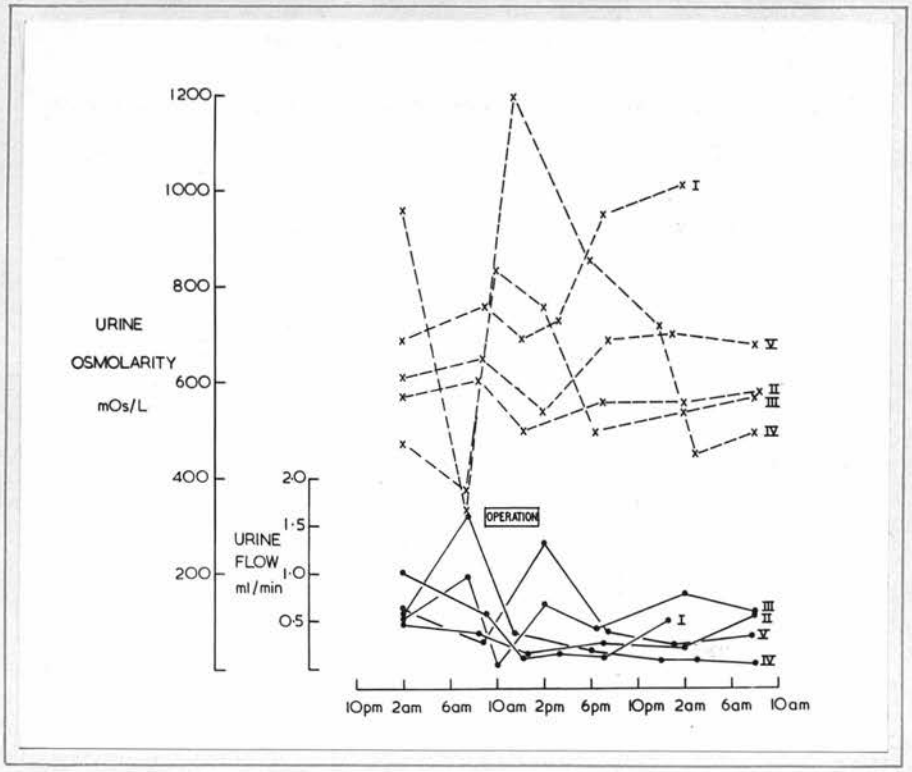

Fig. 13

Graphical representation of urine volume and concentration in 5 of the 10 subjects submitted to major surgical procedures and managed by the regime described in the text (Appendix II, Tables XIII-XVII). Data on the other 5 cases are contained in Appendix II, Tables XVIII-XXII).

if he does so it would not be justifiable to assume that any additional antidiuretic activity is in evidence because it has been clearly demonstrated that additional (exogenous) antidiuretic hormone cannot further reduce the urine volume or increase the urinary concentration in the subject who has already been deprived of water and food for more than 18 hours (Black et al., 1944; Jones and de Wardener, 1956). However, if the pattern of urinary flow and concentration in the post-operative or post-traumatic patient differs greatly from that seen in water deprivation alone, it would be reasonable to conclude that factors other than maximal tubular reabsorption of water are at work in determining urinary volume and concentration after injury or operation. The detailed analysis of the volume and concentration of the urine in the first 48 hours after operation or injury is therefore a critical investigation in the positive sense; should it show differences from that seen in water deprivation alone, other factors must immediately be invoked. A graphical representation of the urine volume and concentration in 5 patients undergoing major surgical procedures is shown in Fig. 13 (Tables XIII-XVII). It is clear that there is a considerable variation from the pattern previously illustrated in Fig. 12 for water deprivation alone.

Effects of reduction in renal blood flow. A healthy volunteer (H.A.F.D.) in normal water balance with a considerable /

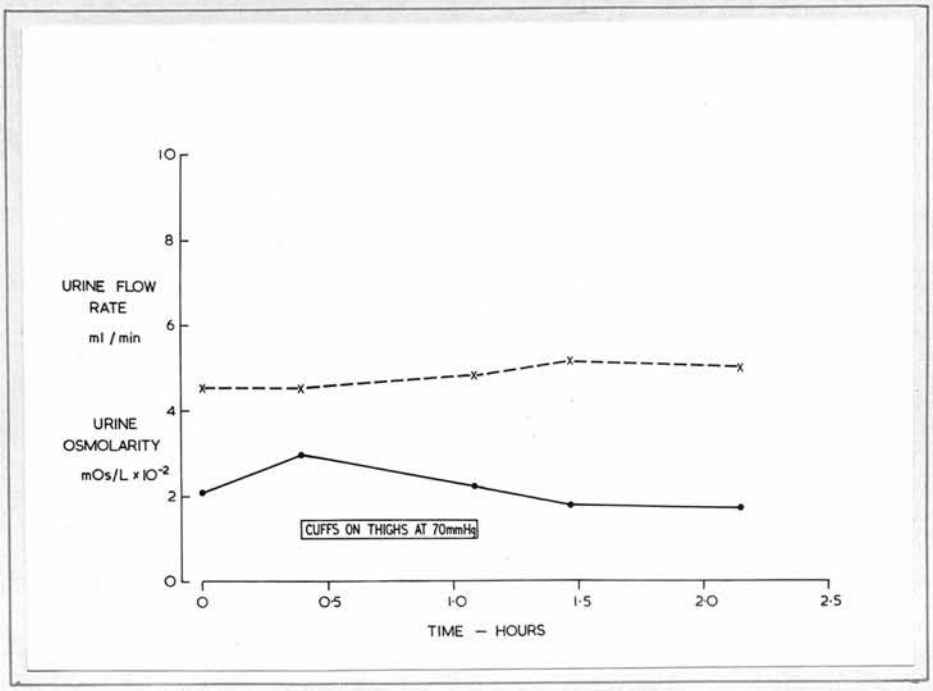

Fig. 14

Effects of cuffs applied to the thighs on the volume and concentration of the urine in a conscious volunteer (Appendix II, Table XXIII). Mean of two experiments.

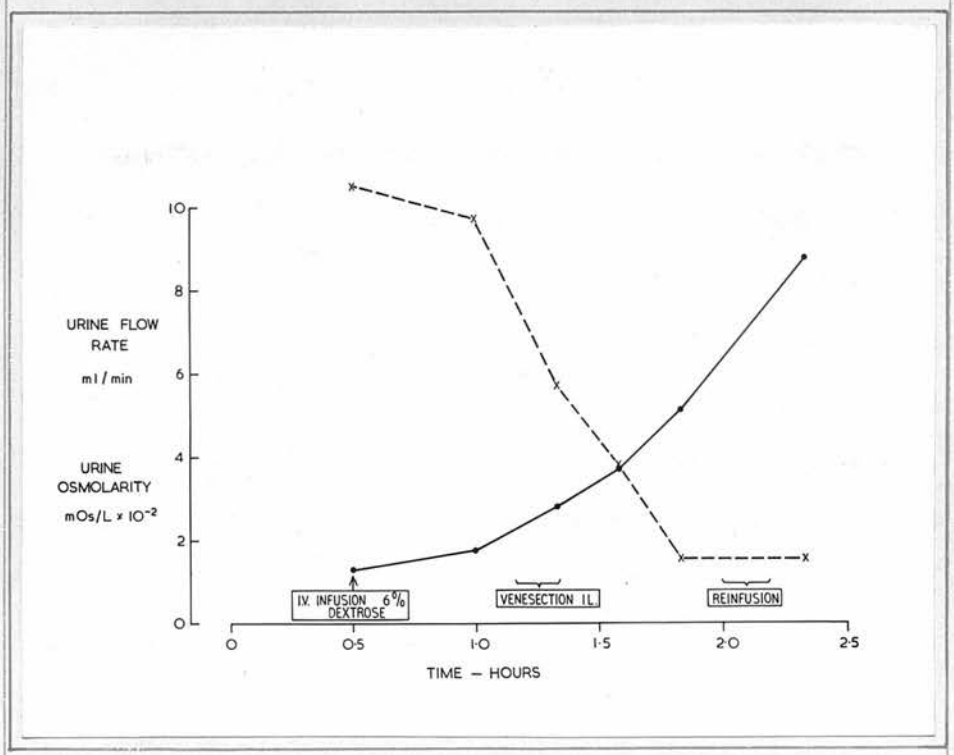

Fig. 15

Effect of a venesection of one litre on the volume and concentration of the urine in a conscious volunteer during water diuresis (Appendix II, Table XXIV). Mean of two experiments.

considerable experience of experimental procedures and therefore unlikely to be influenced by psychogenic stimuli was submitted to reduction in renal blood flow by (a) cuffs applied at diastolic pressure to the legs and (b) venesection of 1 litre. The reductions in renal blood flow produced by these techniques are comparable with those described during and after anaesthesia and operations. Urine volume before the reduction of renal blood flow was adjusted by water intake to equal approximately the osmolar clearance - that is to render the urine approximately isotonic. The results of two experiments of this nature are illustrated in Figs. 14 and 15 (Appendix II, Tables XXIII and XXIV). There is only a slight rise in urinary osmolarity which is not in any way as marked as is seen in injury or operation in spite of the comparable nature of the changes in renal blood flow.

These observations are supported by the levels of osmolarity encountered in patients with low renal blood flow as a result of hypovolaemia. Examples of such patients are given in the section on haemoglobinuria (p. 36). By chance also urine osmolarities were being made on a patient after abdominoperineal resection of the rectum who sustained a severe haemorrhage of at least 2 litres. Urine volume fell to very low levels but solute concentrations did not rise above 600 mOs/l. (Table XXV).

Problem IV. Similarities between post-operative oliguria and that seen in the "hydropenic state".- The nature /

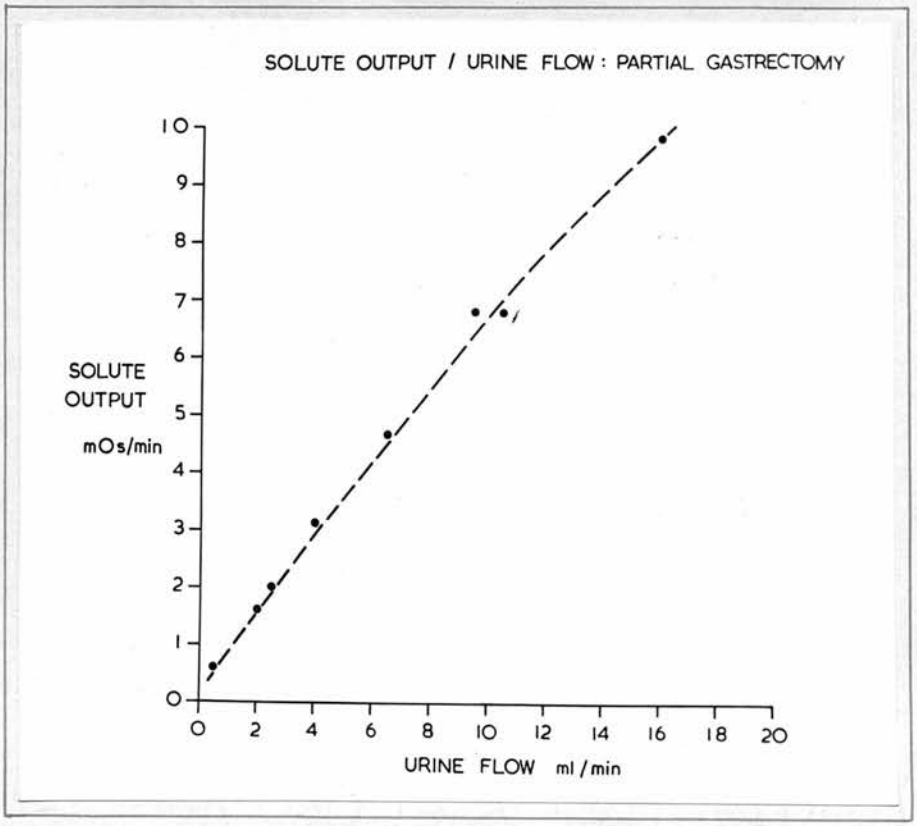

Fig. 16

Plot of urine flow against solute output in a patient after partial gastrectomy (Appendix II, Table XXVI).

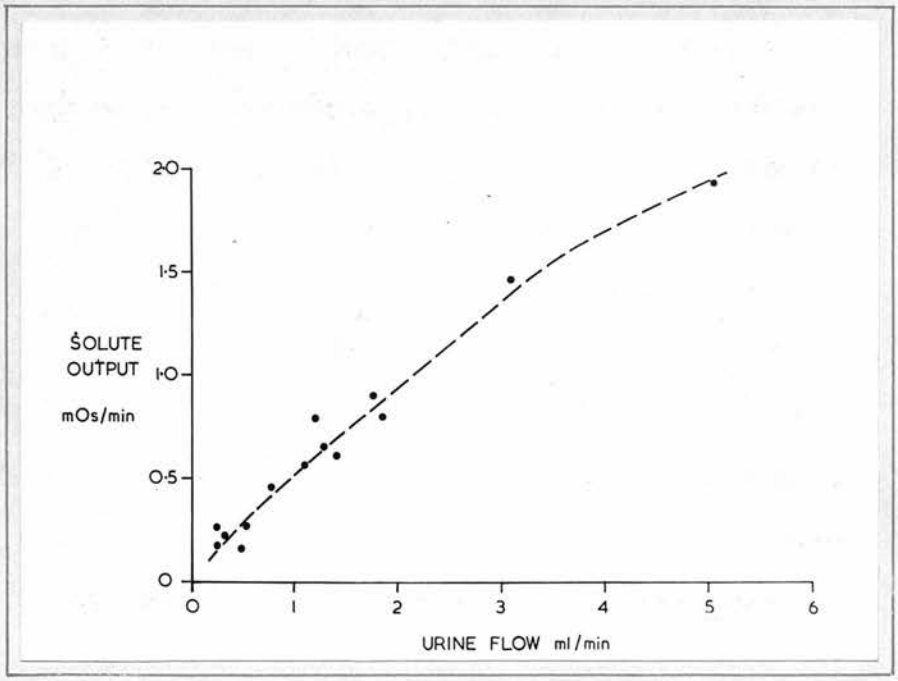

Fig. 17

Plot of urine flow against solute output in a patient with extensive burns (Appendix II, Table XXVII).

nature of the isosmotic parameter and the meaning of the term osmolar clearance have already been described on p. 8. Under conditions of hydropenia and of induced posterior pituitary antidiuresis the osmolar clearance at varying levels of solute load has been thoroughly explored by Zak et al. (1954). In these circumstances there is a non-linear relationship between solute load and urine flow and a linear relationship between osmolar clearance and urine flow above values of the latter 5 ml. per minute. It would be expected that similar relationships might be observed after injury or operation if post-operative and post-traumatic oliguria were produced by the same mechanism, that is by posterior pituitary antidiuretic hormone.

Relationship between solute load and urine flow. In two patients after partial gastrectomy and in three patients after extensive burns, hourly urine collections were made over the first 24 hour period after injury or operation. The results are presented graphically in Figs. 16 and 17 (Appendix II, Tables XXVI and XXVII).

In each instance the line drawn through the points has been fitted by eye but there is a reasonably clear correspondence which indicates a direct relationship similar to that described by Rapoport et al. (1949) and by Bull (1956).

These preliminary measurements suggested that the relationship between osmolar clearance and urine flow might be investigated in subjects undergoing a major surgical procedure /

procedure and in whom solute load was artificially varied by infusion of a substance such as mannitol. Therefore, in six patients who underwent either partial gastrectomy for duodenal ulcer or bilateral inguinal herniorrhaphy the osmolar clearance was measured during the course of a mannitol infusion.

Plan of Experiments. The procedure was standardised as far as possible. All operations were carried out in the morning under general anaesthesia, with or without supplementation by hexamethonium bromide or under spinal anaesthesia. Before operation the patients had been deprived of both food and water since 10 p.m. on the previous evening. After anaesthesia had been induced an intravenous infusion of 6 per cent. dextrose was begun and a volume of this solution administered to replace the known urinary and estimated insensible losses between 10 p.m. and the time of operation. Thereafter the infusion was continued at a rate of approximately 100 ml./hr. The bladder was emptied by an indwelling Foley catheter and at the end of each experimental period was flushed with air.

Some four hours after the operation and when the patient was conscious and with systolic blood pressure above 115 mm.Hg systolic, an intravenous infusion of 15 per cent. mannitol was begun at a rate of approximately 20 ml./min. No effort was made to keep the infusion rate constant from case to case but for any one experiment the rate of flow as judged /

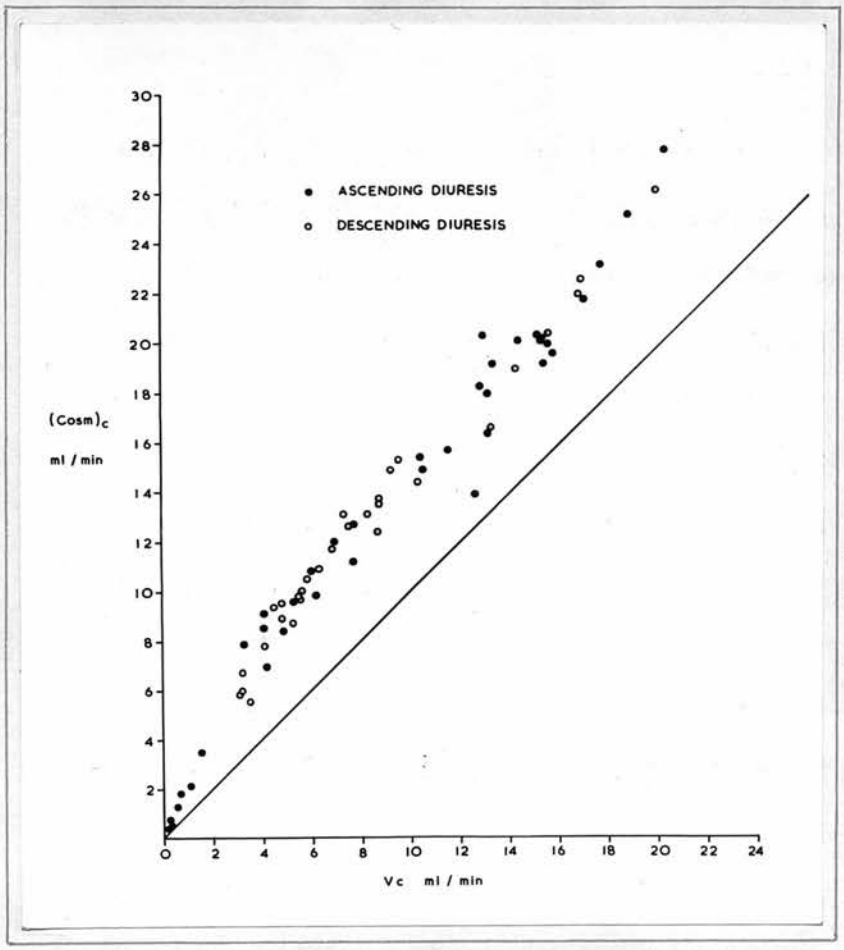

Fig. 18

Combined plot of osmolar clearance against urine flow of 6 patients undergoing mannitol diuresis after surgical procedures (Appendix II, Tables XXVIII-XXXIII).

judged by the drops passing through the standard dropper was the same. Because calculations of osmolar clearance were made for values of urine flow and solute concentration during the ascending and descending limbs of the diuresis and were extended beyond the termination of the infusion and because of the known errors introduced into clearance methods by changes in plasma levels and by the slow rate of equilibration between plasma and renal tubule (see Smith, 1956), the absolute values of clearance cannot be regarded as highly accurate. However, the purpose of the experiment was to demonstrate the form of the curve Cosm/V for the post-operative state rather than accurately to determine osmolar clearance. For this the experimental method adopted seems valid.

The combined results after correction to a surface area of 1.73 sq. m. are shown in Fig. 18* (Tables XXVIII-XXXIII give the full values). It is seen that the form of the curve is exactly similar to that seen in the hydropenic individual or in a subject under the influence of antidiuretic hormone. The values for Cosm and the derived value of free water clearance agree well with those of Zak et al. (1954), Boyarsky and Smith (1957) and Robson and Lambie (personal communication) for normal subjects infused at a constant rate with mannitol, an agreement which indicates that the errors already referred to are small at rates of flow above 5 ml./min. Therefore, it would seem reasonable /

* Individual values are charted. The calculation of a regression line is inadmissible because of the common term V in both parameters (Boyarsky and Smith, 1957).

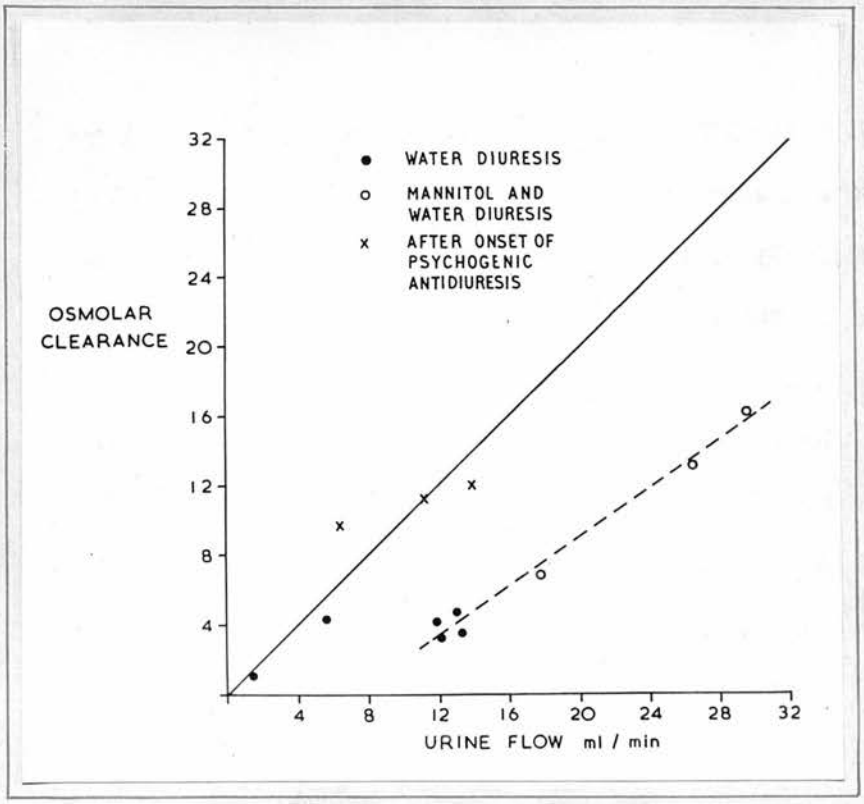

Fig. 19

Osmolar clearance/urine flow relationships for experiment on conscious volunteer described in text (Appendix II, Table XXXIV).

reasonable to assume that the mechanism involved in the post-operative restriction on urine volume is basically the same as that seen when antidiuretic hormone is released or administered.

There remains a possible alternative explanation for the effects of hypertonic mannitol, namely that the substance itself stimulates the production of antidiuretic hormone. It seemed essential to eliminate this possibility and accordingly an exactly similar infusion of mannitol was administered to a normal subject at the height of a water diuresis.

The result of this experiment is shown in Fig. 19 (Appendix II, Table XXXIV). With the increase in urine flow produced by the mannitol infusion, Cosm also rose in a linear manner indicating that an increased water reabsorption was not taking place (or alternatively in terms of renal physiology that free water clearance remained constant at a high positive value). This experiment proved of added interest because at the height of the combined water and mannitol diuresis the urine flow was so rapid that very severe and painful ureteric colic developed. This provoked a marked release of antidiuretic hormone as is evident from the reduced values of free water clearance obtained for the short time that it proved possible to continue the experiment.

Problem V. Antidiuretic activity in peripheral blood after /

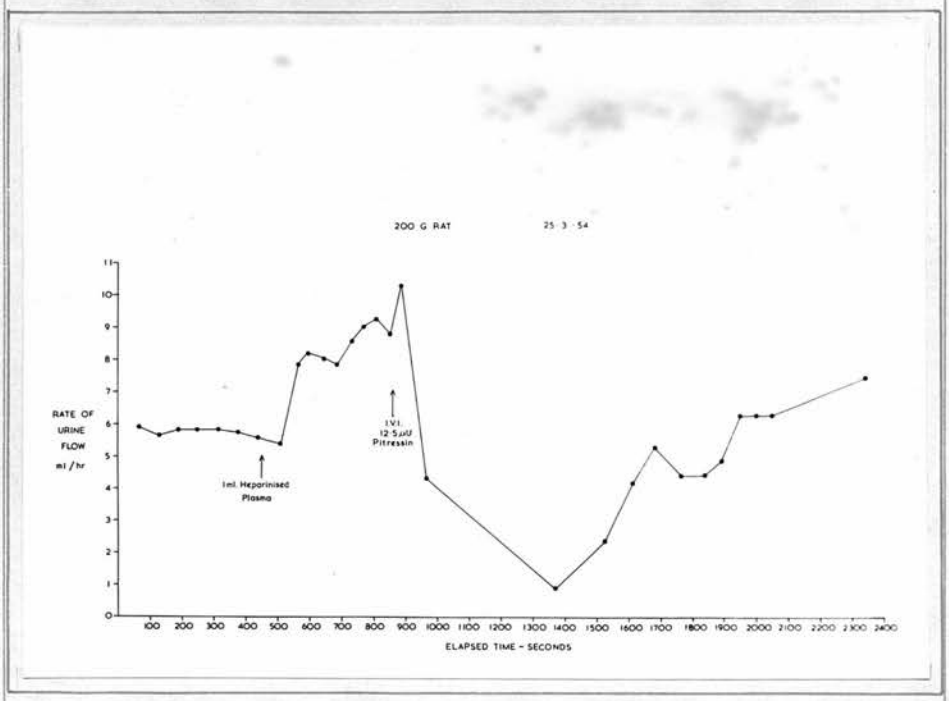

Fig. 20

Effect of 1 ml. heparinised plasma from a patient who had undergone prostatectomy one hour previously, on the urine flow rate of an alcohol-anaesthetised rat. The sensitivity of the preparation to Pitressin is also shown (Appendix II, Table XXXV).

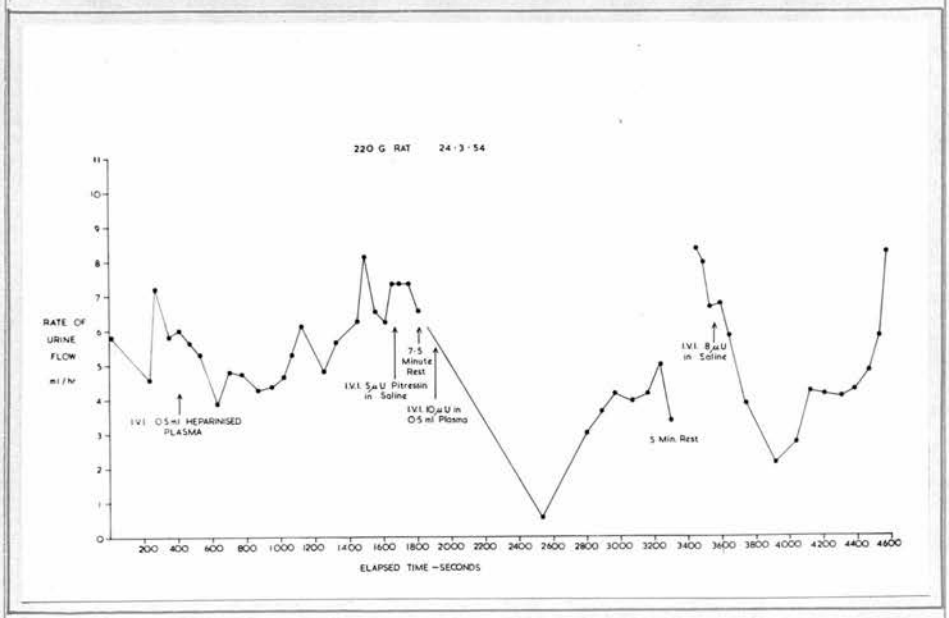

Fig. 21

The effect of 0.5 ml. heparinised plasma from a patient who had undergone mitral valvulotomy two hours previously, on the urine flow rate of an alcohol-anaesthetised rat. The sensitivity of the preparation to 8 micro-units but not to 5 micro-units of Pitressin is also shown, as is the efficacy of Pitressin in plasma from the same patient (Appendix II, Table XXXVII).

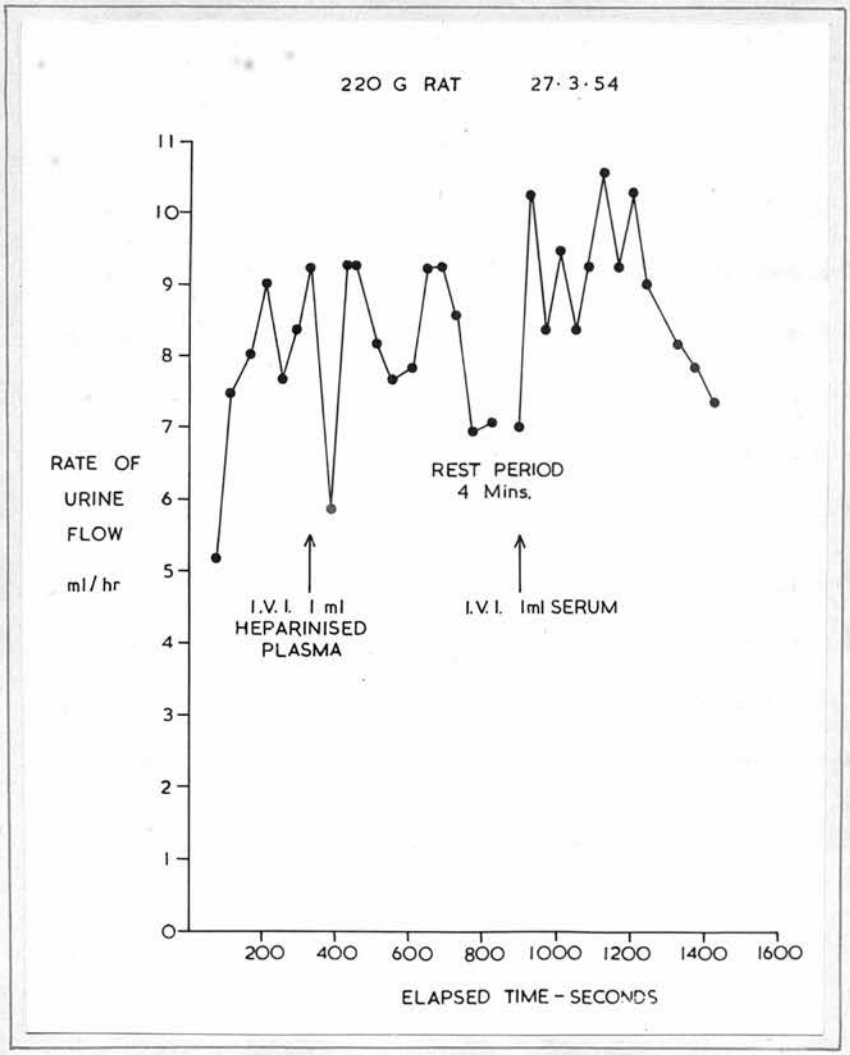

Fig. 22

(a) and (b) The failure of both heparinised plasma and of serum from a patient who had undergone gastrectomy one hour previously, to reduce urine flow rate in an alcohol-anaesthetised rat (Appendix II, Table XXXVIII).

after injury and after operation.- The logical method by which the presence of increased antidiuretic activity could be confirmed would be its demonstration in the circulating blood after injury or operation during the time when the changes in water excretion described in the previous sections are present. Because the chemical nature of pituitary antidiuretic hormone is complex and has only recently been elucidated (Du-Vigneaud, 1956) it is necessary to use a biological method for the detection or assay of such antidiuretic activity. For reasons that are given in Appendix I an intravenous method modified from that of Jeffers, Livezey and Austin (1942) was used. This technique was used for detection only, although by the choice of a suitable parameter it may be adapted for assay purposes (see Appendix I).

For purposes of detection the method is sensitive to a concentration of antidiuretic activity equivalent to five micro-units of commercial pituitary antidiuretic hormone (Pitressin) per millilitre. Three experiments were carried out with both serum and plasma from patients in the antidiuretic phase within 12 hours of operation and with the use of test injections at various times after withdrawal from the patient. These experiments are summarised in Figs. 20, 21 and 22 (Appendix II, Tables XXXV-XXXVIII). In none was any activity demonstrated. In order to assess the sensitivity of the method in another circumstance where antidiuresis is known to be produced, blood was withdrawn from /

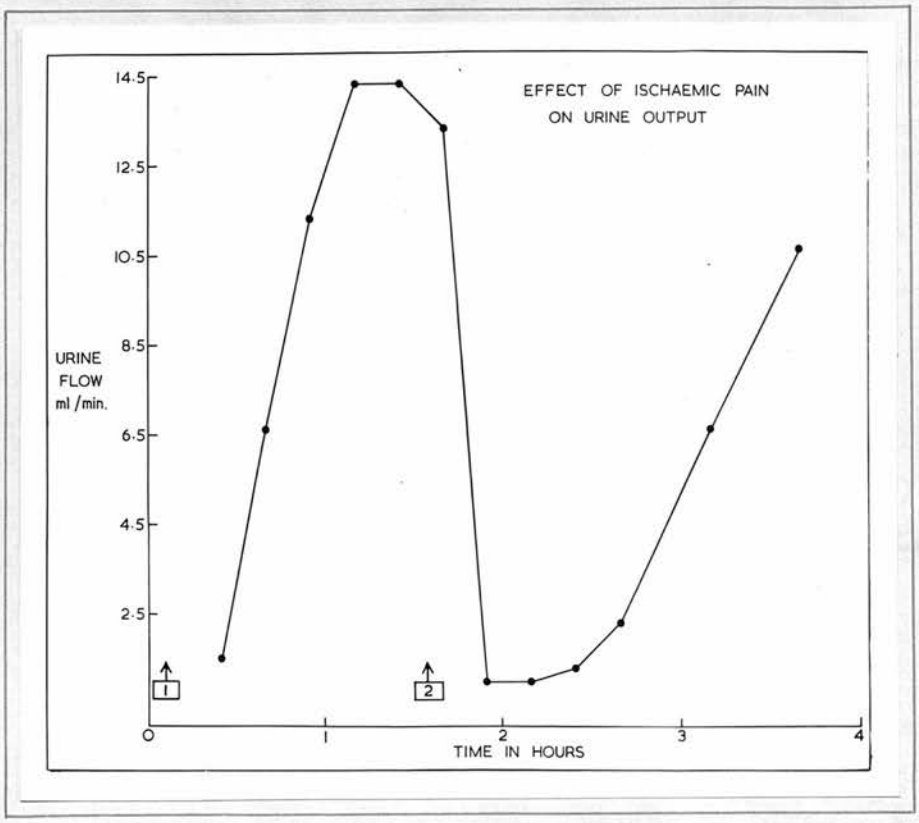

Fig. 23

The effect of ischaemic pain produced by an upper arm tourniquet on the rate of flow of urine in a conscious subject. Diuresis begins at 1. and ischaemic pain was produced for ten minutes at 2. (Appendix II, Table XXXIX).

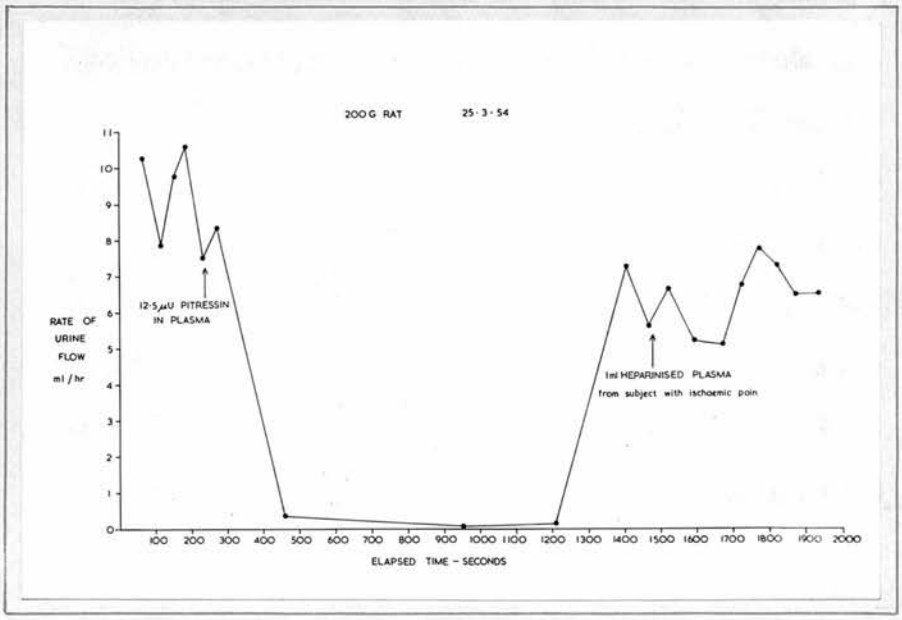

Fig. 24.

Absence of effect of plasma withdrawn at height of antidiuresis on the urine flow of an alcohol-anaesthetised rat (Appendix II, Table XL).

from three healthy volunteers who had had a tourniquet applied to the arm above systolic pressure for 10 minutes and in whom ischaemic pain had been induced by exercise of the forearm muscles. The effect of such a procedure on the rate of urine flow in one subject is shown in Fig. 23. A diuresis had been induced by free drinking before the application of the tourniquet (Appendix II, Table XXXIX). Fig. 24 shows the result of a typical experiment (Appendix II, Tables XL-XLII). Although physiological antidiuresis is produced, the level of antidiuretic activity in the serum is certainly less than 10 micro-units per millilitre and probably less than 5 micro-units per millilitre. Thus it is probably impossible even with the sensitive technique available to demonstrate antidiuretic activity in the plasma of the subject even when antidiuresis is known to exist.

Discussion and Conclusions

The evidence so far described lends considerable support to the concept that antidiuresis after injury or operation is caused by an enhanced activity of the posterior pituitary gland, an activity that resembles that known to be produced by fear or pain in the human and by trauma in the experimental animal. With the additional data provided by the studies of solute excretion and water clearance and the demonstration that changes in renal blood are insufficient to produce the small volume of highly concentrated urine which occurs /

occurs after injury or operation, it is justifiable to conclude, as did Le Quesne and Lewis (1953) on the basis of their early studies of post-operative water retention, that it is difficult to conceive of any physiological mechanism which would produce the observed effects other than a prolonged intense secretion of antidiuretic hormone. Direct measurements of antidiuretic activity in the blood have not proved possible. This is scarcely surprising because if Lauson's (1951) indirect estimate of 16 milli-units per hour (in terms of commercial antidiuretic hormone) for the rate of secretion of antidiuretic hormone is accepted, then assuming the most conservative volume of distribution in the plasma this could be taken to imply a maximum concentration of not more than 3 micro-units per millilitre in the plasma*. Increased antidiuretic activity in the urine post-operatively has been demonstrated both by Cline et al. (1952) who used a non-specific assay technique and by Lewis (1953) who employed the more selective intravenous method. Such antidiuretic activity cannot be assumed to be of posterior pituitary origin without further evidence but nevertheless it suggests that there may be a humoral basis for the observed post-operative oliguria. No known substance other than anti-diuretic /

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* This calculation can be at best only approximate but is based on the "lag period" already mentioned (p.). If an osmotic stimulus which inhibits antidiuresis is withdrawn it is approximately 40 minutes before diuresis begins. In this time if Lauson's figure is correct about 10 milli-units of activity will have been produced. With no allowances for destruction this would give a plasma concentration in a normal adult of 10/3000 milli-units per millilitre or 3 micro-units per millilitre.

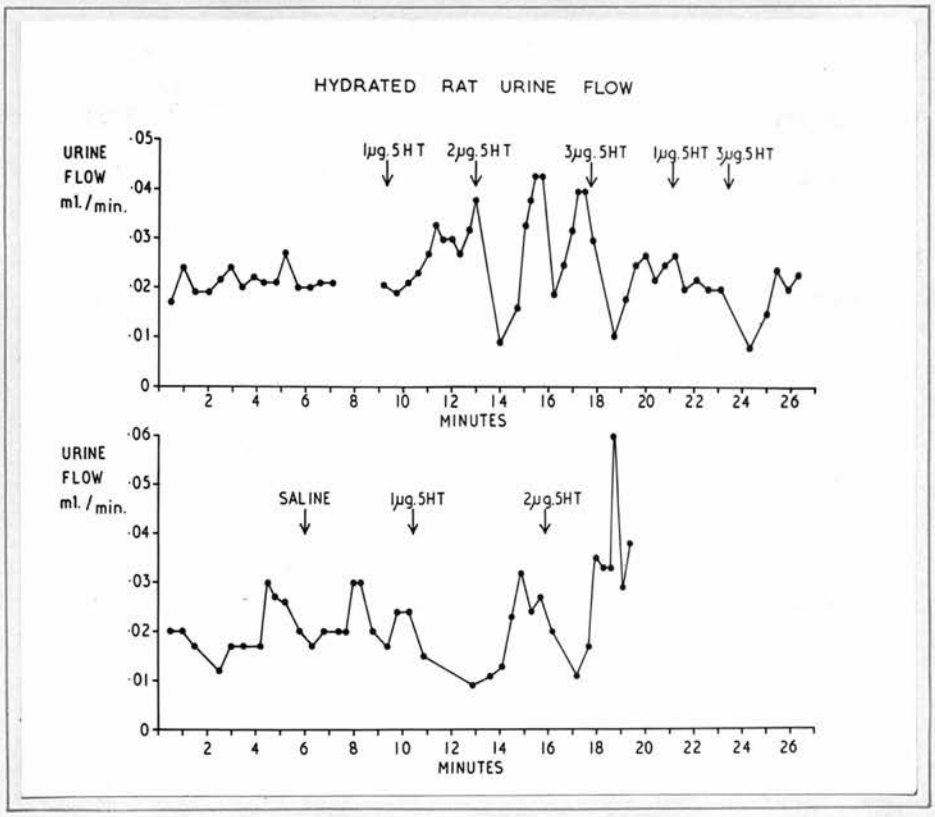

Fig. 25

Effect of serial injections of 5-hydroxytryptamine on the rate of urine flow of alcohol-anaesthetised rat (Appendix II, Tables XLIII and XLIV).

antidiuretic hormone can explain the restriction of renal water excretion after injury but it is of course possible that either some unknown hormone or a product of tissue destruction or altered metabolism after anaesthesia or injury might be responsible. The only other postulated antidiuretic hormone is 5-hydroxytryptamine (Espamer, 1954, 1955). Pickford (1956) found it to be only a weak antidiuretic agent in the dog but it is capable of inhibiting diuresis in the rat preparation of Jeffers, Livezey and Austin. Fig. 25 illustrates typical experiments (Appendix II, Tables XLIII and XLIV). Further confirmation of its possible role in the restriction of urine output is proved by Sinclair's (1957) observations that patients with carcinoid tumours and consequent increased rate of production of 5-hydroxytryptamine may have oliguria and an altered response to the intravenous administration of water. In an endeavour to confirm this the urine of six post-operative patients was analysed by Le Quesne (personal communication) for the presence of increased amounts of 5-hydroxy-indole acetic acid (the chief degradation product of 5-hydroxytryptamine), but with entirely negative results. Therefore it appears unlikely that increased production of 5-hydroxytryptamine is concerned in post-operative antidiuresis. There remains the possibility that some produce of tissue destruction may be involved, particularly in the prolonged intense antidiuresis that follows an extensive injury or a major /

major surgical procedure. There is as yet no evidence to support this hypothesis and Hayes and Coller's (1952) single case of operation on a aptient without a functioning hypophysis suggests that any contribution made by such an unknown substance is likely to be small. However, some reduction of urine output did occur in this patient and details were not given of the magnitude of the procedure; therefore firm conclusions cannot be drawn on the basis of this case alone.

In conclusion, the accumulated evidence is in favour of the posterior pituitary as the source of the antidiuresis or oliguria that follows an injury or a major surgical procedure. The stimulus to the secretion of antidiuretic hormone is not an osmotic one and is presumably compounded from the pain, fright and altered metabolism that are consequent upon the operative procedure. The duration of antidiuresis is usually 36-48 hours and attempts to stimulate an increased flow of dilute urine during this period by the administration of water are unlikely to be successful. Urine flow can be increased and the concentration of the urine somewhat reduced by the induction of a solute diuresis.

In spite of this accumulated evidence the conclusion cannot be regarded as certain, particularly in view of the observations on urine volume and concentration after operation in patients deprived of fluid. Other factors, humoral or haemodynamic, may be involved but their nature is still a matter for conjecture.

THE PRACTICAL SIGNIFICANCE OF THE NEUROHUMORAL ANTIDIURESIS AFTER INJURY OR OPERATION

(a) Prophylaxis of Renal Damage in the Burned Patient

Introduction.- The appearance of blood pigment in the urine of burned patients was first observed by Klebs in 1868. A considerable proportion of patients with burns involving more than 20 per cent. of the body surface excrete small quantities of pigment in the first three days after burning (Cope and Rhinelander, 1943), and the incidence and the degree of urinary pigmentation is approximately correlated with the extent and the depth of the burn. The pigment is derived from red cells damaged by heat in the capillaries at the periphery of the burned area (Shen et al., 1943, Brown, 1945). Its chemical nature has not been extensively investigated: most of it is probably methaemoglobin but in this account the term haemoglobinuria will be used. After crushing injuries of muscles, the urine may contain metmyohaemoglobin (Bywaters, 1944).

When renal function is normal the kidney can excrete large quantities of haemoglobin (Mueller et al., 1953). Two additional factors may result in damage to the renal tubules from pigment released from red cells or from ischaemic muscle: first, reduction in renal blood flow consequent upon reduced plasma volume; secondly, the high concentration of the urine which results from posterior pituitary antidiuresis and which in turn produces a high concentration /

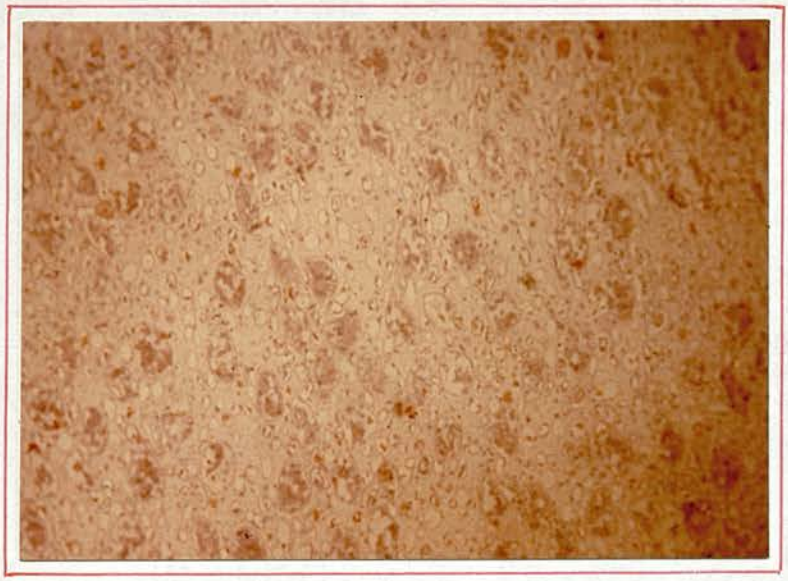

Fig. 26

Microscopic appearances of kidney in
Case 1 of series with haemoglobinuria.

concentration of pigment in contact with the cells of the tubule. The most important clinical feature of tubular damage is oliguria or anuria, although mechanical blockage of the tubules by pigment is certainly not the reason for the reduction of the volume of the urine (Bywaters and Dible, 1942; Goodpaster et al., 1946). Tubular necrosis is occasionally seen without oliguria (Sevitt, 1956) but severe oliguria or anuria is invariably accompanied by histopathological changes. The production of pathological oliguria in burns is well illustrated by the following two cases.

Case 1.- A man of 52, suffering from disseminated sclerosis, sustained extensive burns when he fell into an open fire and was unable either to lift himself out or to summon help. The burns involved about 40 per cent. of the body surface and included extensive charring of the right arm and shoulder. An initial catheter specimen of urine (obtained two hours after the injury and one hour after admission) was clear but in the next hour only a few millilitres of cherry coloured urine were withdrawn, and until death he remained anuric. A specimen of venous blood showed well-marked haemolysis. In spite of vigorous resuscitation with dextran and plasma and a well maintained blood pressure he died 10 hours after admission. Post-mortem examination confirmed the diagnosis of disseminated sclerosis. The kidneys were microscopically normal but showed deposits of acidophil granular and colloid material in the collecting tubules in the medulla and the early signs of tubular necrosis (Fig. 26).

Case 2.- A 14 year old girl was burned when lighting a fire with the aid of shoe polish. Resuscitation was undertaken at a peripheral hospital, and she was admitted to the Burns Unit of Bangour General Hospital four and a half hours later, having by that time received 1.5 litres of plasma. One hundred and eight millilitres of clear urine had been passed before transfer.

On examination, she was in shock. She had very deep flame burns of the trunk and of all four limbs to a total extent /

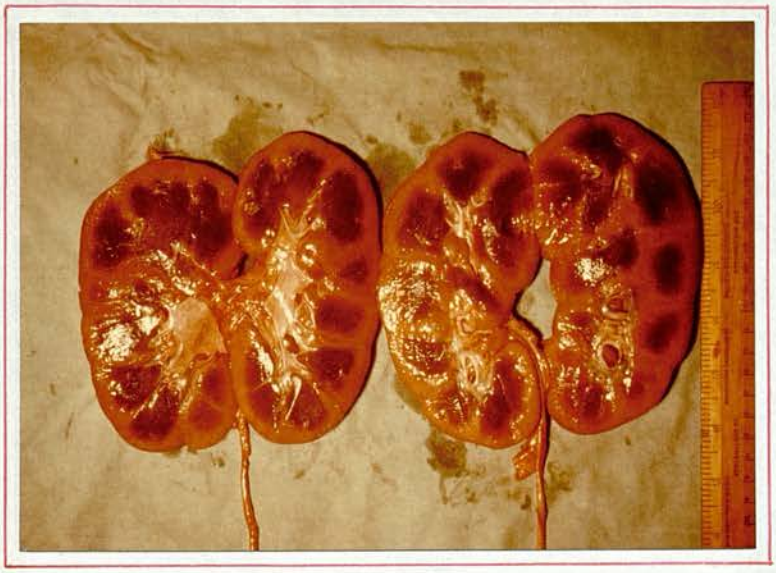

Fig. 27

Naked-eye appearances of kidney in Case 2 of series with haemoglobinuria.

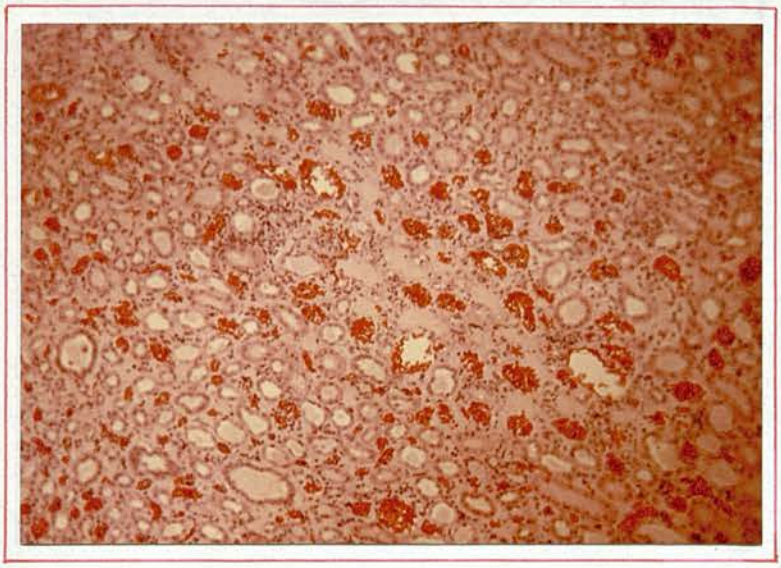

Fig. 28

Microscopic appearances of kidney in Case 2.

extent of 42 per cent. of the body surface. In the next hour, 30 ml. of heavily pigmented urine were obtained by catheter. Resuscitation was continued with plasma and whole blood, but because of technical difficulties, the rate of infusion was inadequate to maintain a normal blood pressure. A systolic pressure of over 100 mm. Hg was not attained until 12 hours after injury. Extreme oliguria persisted throughout this period, although the depth of pigmentation of the urine varied.

Thereafter, while her general state remained good, low volumes of urine were passed - 94, 91, 96 ml. on the first, second and third days. A modified Bull's regime was begun, to supply glucose and fat emulsion by nasogastric tube (Bull, Joekes and Lowe, 1949). From the fifth day onwards, 50 per cent. glucose and insulin were administered intravenously in an attempt to control the steadily rising serum potassium. She died of potassium intoxication on the tenth day after injury.

At autopsy the kidneys were enlarged. The cortex was pale, the medulla dark brown, with the vessels standing out as radial streaks (Fig. 27). Microscopical examination (Fig. 28) showed the typical appearance of tubular necrosis: patchy loss of cytoplasm in the tubular cells, peritubular round cell infiltration and hyperplasia and mitotic figures in the surviving tubular cells. Numerous casts covered with granular pigment were present in the tubules. The glomeruli were normal.

Correction of oliguria in the burned patient.- These cases illustrate that death may occur from the severity of the general injury or may follow later from the effects of oliguria. Even if recovery should take place, convalescence is likely to be complicated as a result of the biochemical disturbance that may accompany and follow the oliguric phase.

To prevent the development of renal failure in burns it is necessary to endeavour to control the two significant factors already mentioned: (a) reduction in renal blood flow and (b) the high concentration of the tubular urine. In shock after burning, renal blood flow can be returned to normal /

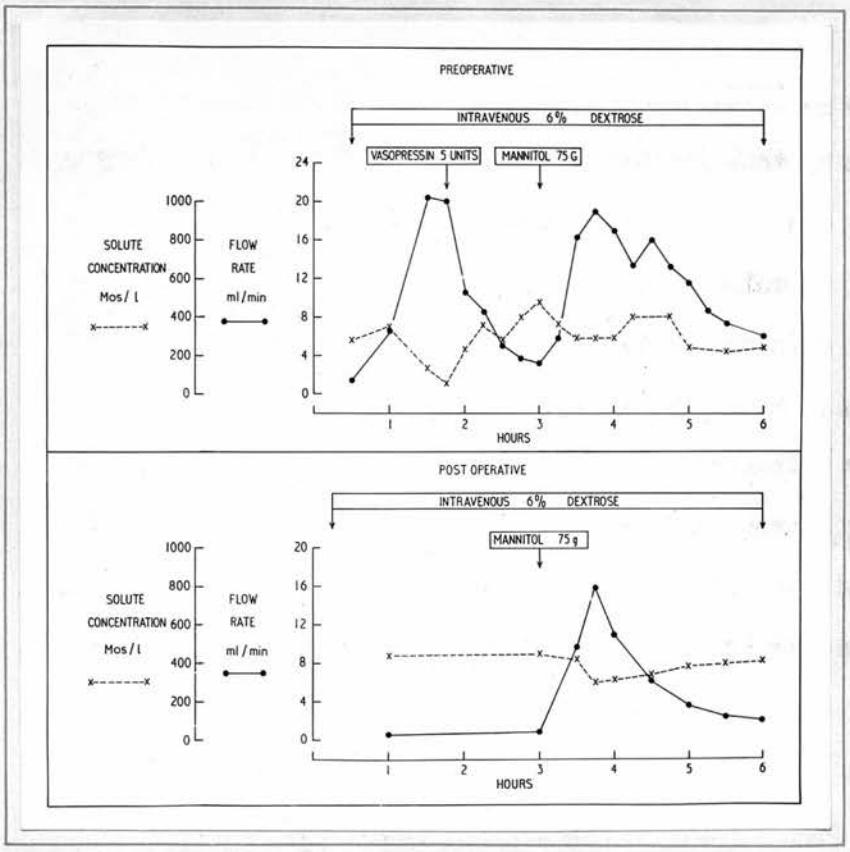

Fig. 29

Effect on urine flow rate of mannitol after the administration of antidiuretic hormone and after partial gastrectomy in the same patient (Appendix II, Table XXVI).

normal by the rapid transfusion of plasma or of a plasma expander but because of maximal antidiuresis a water diuresis cannot be produced. Apart from small fluctuations with changes in renal blood flow, increase in the rate of flow of urine after injury occurs only with increase in the total solute excretion. Making use of such a solute diuresis, Owen et al. (1954) were able to prevent the damage to the dog's kidney that follows injection of methaemoglobin under conditions of maximal antidiuresis and decreased renal blood flow. Sodium sulphate had already been suggested as a solute diuretic under similar circumstances in man (Wade and Dick, 1934; Maitland, 1941) and Olson and Necheles (1947) had shown that it is effective in promoting diuresis after extensive burns in dogs. There is no convincing clinical evidence of its success for this purpose in man and the possible toxic effects of the sulphate ion make it an undesirable choice as a diuretic. Solute diuretics with non-toxic molecules are preferable and in the case reports that follow both the plasma expander polyvinylpyrrolidone (the smaller molecules of which escape rapidly into the glomerular filtrate) and mannitol were used. Mannitol is probably the solute diuretic of choice and its effect on the rate of flow of urine under conditions of maximal antidiuresis and after major operation and injury has already been discussed and is also shown in Fig. 29 (Appendix II, Table XXVI). In this experiment, six per cent. dextrose was administered intravenously /

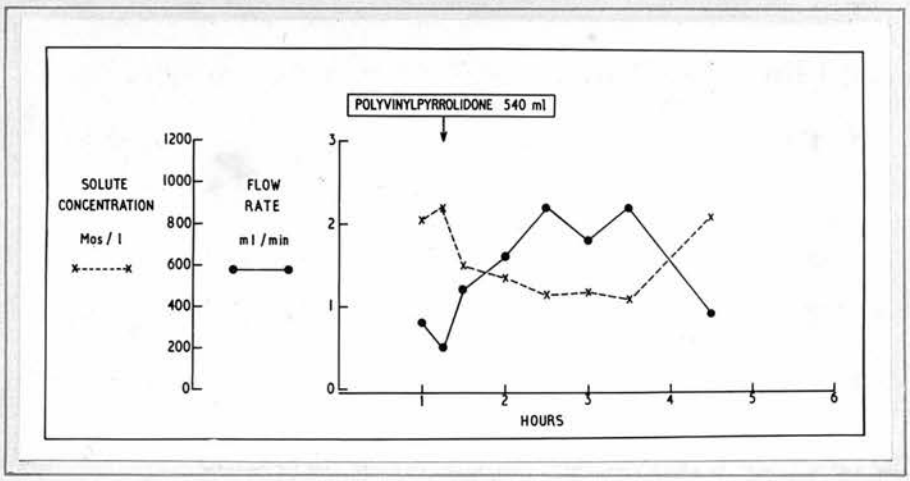

Fig. 30

Effect of polyvinylpyrrolidone on the rate of urine flow and solute concentration after partial gastrectomy (Appendix II, Table XLV).

intravenously to a normal subject before partial gastrectomy for duodenal ulcer: a water diuresis with a rapid rate of flow of dilute urine resulted. This diuresis can be prevented by the administration of posterior pituitary antidiuretic hormone. If mannitol is given intravenously while antidiuresis persists, the rate of flow of urine rises almost to the level seen at the peak of water diuresis, although the urine that is passed is much less dilute. After partial gastrectomy the intravenous administration of 6 per cent. dextrose does not, as has already been shown (p. 40), affect the rate of flow of urine. However, mannitol is again effective in increasing the rate of flow. Fig. 30 (Appendix II, Table XLV) shows that polyvinylpyrrolidone has a similar although less effective action. That such solute diuretics can also increase the rate of flow in burns is demonstrated by Table XXVII (Appendix II) which shows the result of the rapid intravenous administration of mannitol in a female patient with a 45 per cent. burn: the rate of flow of urine increases and the solute concentration is reduced. If such a solute diuresis could be induced early enough after injury it might be expected to reduce the risk of damage to the distal tubules by pigment. Four patients with haemoglobinuria have been treated in this way and subjected to complete study and in addition mannitol has been administered in six other instances where renal damage appeared likely. Renal failure has not been encountered in any burn treated in the /

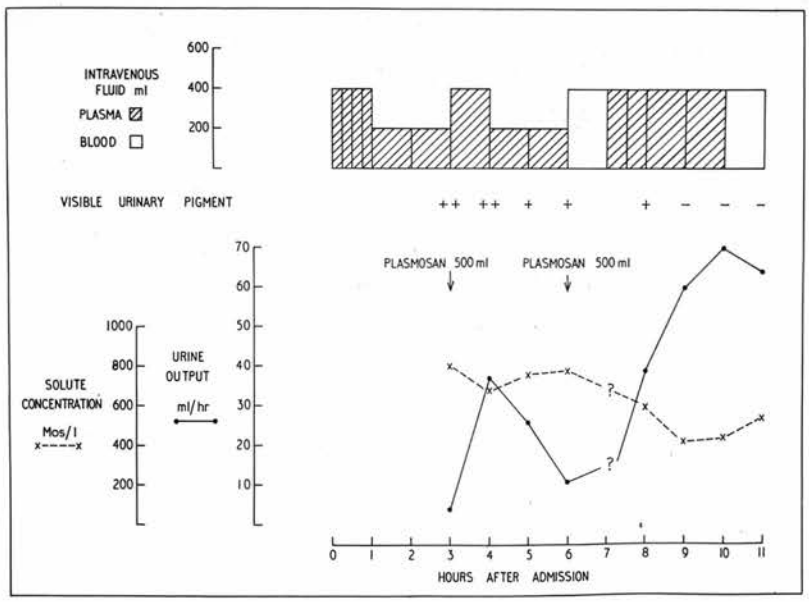

Fig. 31

Urine flow rate, solute concentration, resuscitation and visible urinary pigmentation in Case 3 (Appendix II, Table XLVI).

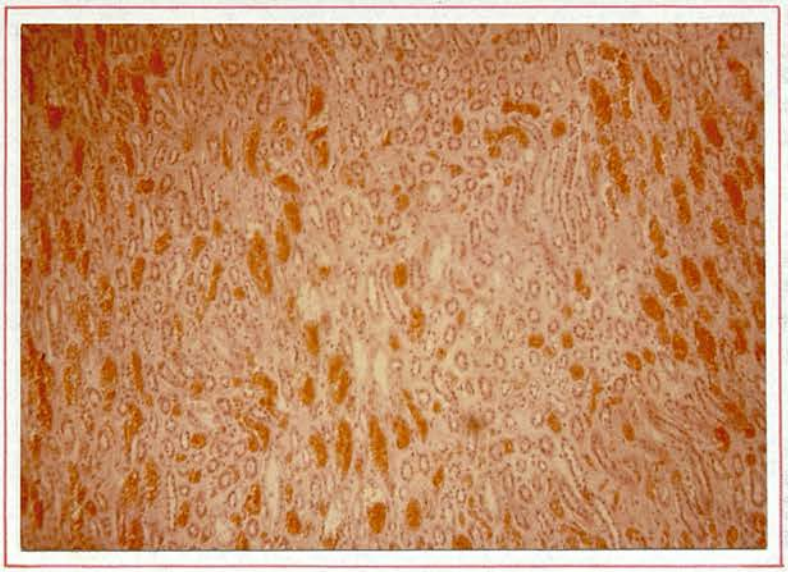

Fig. 32

Microscopic appearances of kidney in Case 3.

the Burns Unit of Bangour Hospital, in the Royal Hospital for Sick Children or in the Professorial Surgical Units of the Royal Infirmary since this regime was begun.

Case Reports. Case 3.- A healthy 28 year old foundry worker sustained deep burns (75 per cent. of his body surface) when a container of molten iron inverted over him. Although the outcome was considered hopeless a determined attempt at resuscitation was made. Within an hour of injury plasma transfusion had begun, and when first seen at the end of three hours he had received two litres of plasma. One hundred millilitres of clear urine were obtained by catheterisation. In the next hour only 4 ml. of heavily pigmented urine were passed, although he had received a further 500 ml. of plasma which had maintained his blood pressure at 120/70 mm. Hg. Renal failure from pigment deposition was regarded as imminent and 500 ml. of Plasmosan were administered in 10 minutes. In the next hour 37 ml. of pigmented urine were passed and thereafter (with continued plasma transfusion), apart from incomplete collection periods between the 8th and 9th hours caused by a leaking catheter, his recorded urine volume never fell below 30 ml. an hour and rose to 74 ml. an hour by 12 hours. By this time all trace of visible pigment in the urine had disappeared. Fig. 31 (Appendix II, Table XLVI) shows the volume of urine passed in relation to the intravenous fluids administered during the first 11 hours. His condition was well maintained for a further 36 hours, when he had received 15.5 litres of plasma and 1.5 litres of blood. On the morning of the fourth day, he suddenly collapsed and his urine output, previously adequate, fell to negligible volumes. Further plasma transfusion did not improve his condition and he died in coma some 11 hours later. Autopsy showed gross dilation of all the chambers of the heart and oedema of both lungs. The kidneys appeared congested but not otherwise abnormal to the naked eye. On histological examination (Fig. 32) congestion was confirmed, but although there were a few hyaline casts in the loops of Henle evidence of tubular necrosis could not be found.

Case 4.- A master butcher of 56 had been drinking heavily and fell on his back into an open fire. By the time he was extricated he had sustained a deep burn of the whole of his back (18 per cent.), which on subsequent excision was found to extend into sacrospinalis, trapezius and the spinal column. On admission his general condition was good and his blood pressure was 155/100 mm. Hg. A catheter was passed and clear urine withdrawn. In the first two hours he received 1,200 ml. of plasma intravenously and passed 88 ml. of /

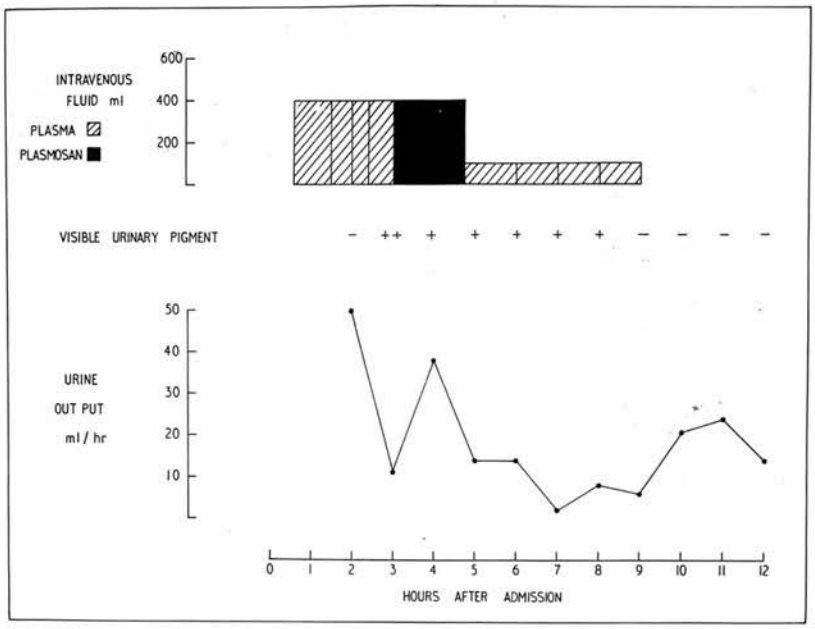

Fig. 33

Urine flow rate, resuscitation and visible urinary pigmentation in Case 4 (Appendix II, Table XLVII).

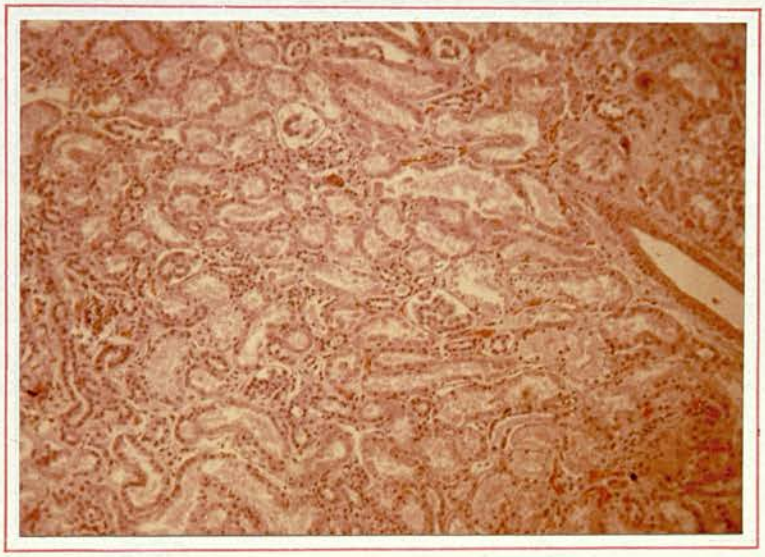

Fig. 34

Microscopic appearances of kidney
in Case 4.

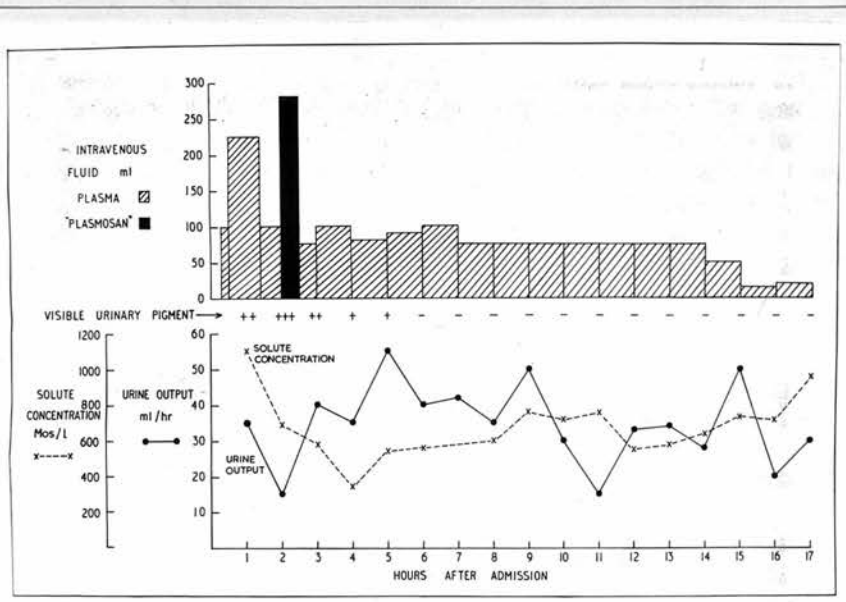

Fig. 35

Urine flow rate, solute concentration, resuscitation and visible urinary pigmentation in Case 5 (Appendix II, Table XLVIII).

of clear urine. Only 9 ml. of moderately pigmented urine were obtained in the next half hour and in the subsequent half hour only 4 ml. of similar colour. Five hundred and forty millilitres of polyvinylpyrrolidone were administered rapidly, and in the next half hour 30 ml. of less heavily stained urine were secreted. A further 560 ml. of polyvinylpyrrolidone were administered and, although the urine output remained persistently low for a further 11 hours, pigment staining decreased and had disappeared by the end of this period (Fig. 33; Appendix II, Table XLVII). His subsequent course was satisfactory until the fifth day, when the burn was excised. Thirty-six hours later he died, apparently of hypertensive cardiac failure. Autopsy showed dilatation of the right ventricle and frothy mucus in both main bronchi, with areas of collapse scattered throughout both lungs. There was marked fatty degeneration of the liver, consistent with his history of alcoholism. The cortex of each kidney was swollen and, on section, a moderate number of granular hyaline casts were found in the distal tubules and in the collecting ducts (Fig. 34). Otherwise the tubules were normal.

Case 5.- A 10 year old boy was transferred from another hospital four and a quarter hours after being burned when his clothes caught fire. Intravenous fluid had not been administered before his transfer.

Moderate shock was evident, and examination revealed deep flame burns of 35 per cent. of the body surface, involving the neck, trunk and lower limbs. Plasma infusion was begun and continued rapidly. Thirty-eight millilitres of heavily pigmented urine were obtained on catheterisation and 34 ml., showing similar staining, were passed in the next hour. Though resuscitation seemed adequate, only 15 ml. were excreted in the subsequent hour. Two hundred and seventy-five millilitres of polyvinylpyrrolidone were given intravenously, and 105 ml. of urine were excreted in the next hour. Pigment had disappeared at the end of two hours. Fig. 35 (Appendix II, Table XLVIII) demonstrates the decline in solute concentration in the urine and the rise in urine flow rate following the administration of polyvinylpyrrolidone.

Thereafter his general condition remained good, and 506 ml. of urine were passed in the first 14 hours after his admission.

The usual treatment by grafting was completed without further incident.

Case 6.- A four year old girl was admitted two and a half hours following injury. Her clothes had been completely charred and she had a very deep flame burn of trunk and extremities, /

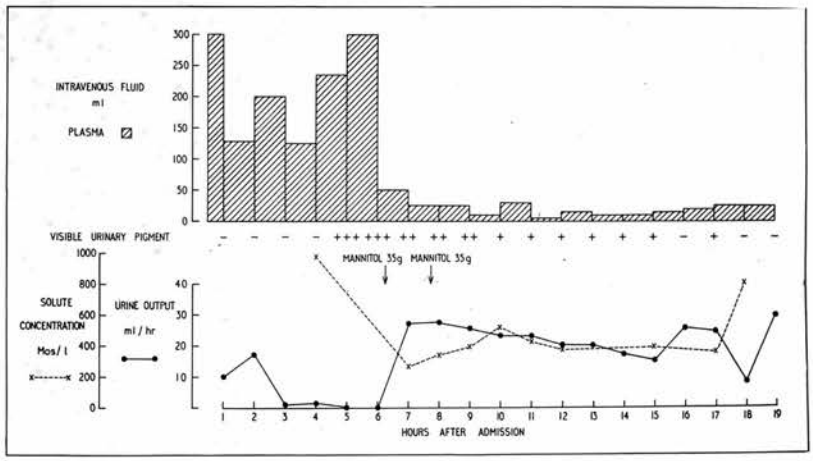

Fig. 36

Urine flow, solute concentration and resuscitation in Case 6 (Appendix II, Table XLIX).

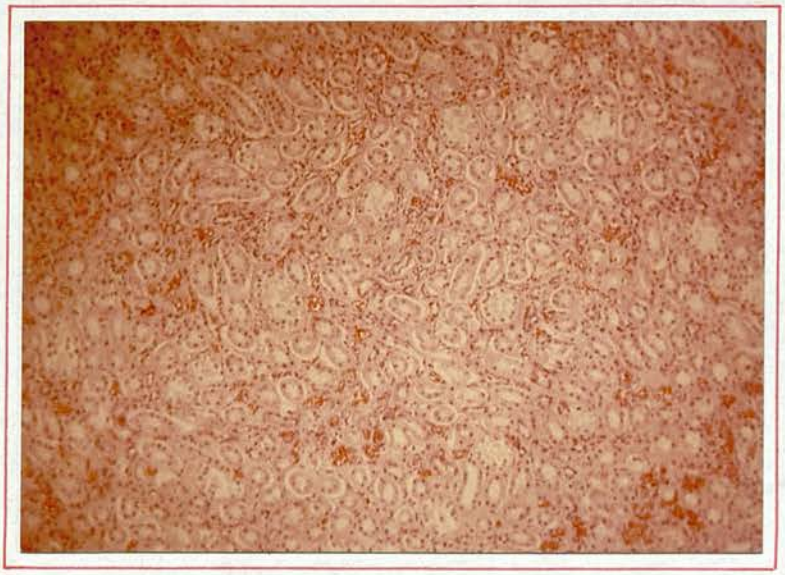

Fig. 37

Microscopic appearances of kidney
in Case 6.

extremities, totalling 42 per cent. of the body surface. Intravenous infusion of plasma had been begun one hour previously in a peripheral hospital.

On examination, she showed a moderate degree of shock, and catheterisation revealed that her bladder was empty. Further infusion of plasma and of whole blood restored a satisfactory blood pressure, palpable peripheral pulses, and resulted in hourly urine outputs of 10 and 17 ml. in the first two hours. Both these specimens were clear and free from macroscopic pigment. Without deterioration of her general state, her urine output fell to one millilitre per hour, and the urine became heavily pigmented. Following the rapid infusion of 150 ml. of 15 per cent. mannitol, 27 ml. of heavily pigmented urine were obtained. The next specimen of urine showed increased pigment and therefore a further 100 ml. of mannitol were administered. Thereafter the urine volume was maintained at about 20 ml. per hour, and the pigment slowly cleared over the next 24 hours (Fig. 36; Appendix II, Table XLIX). Urinary output was satisfactory from this time but in spite of an apparently normal water balance over the next five days, she showed progressive hypernatraemia from which she died on the eighth day after injury. At autopsy the only findings in the kidneys were a number of acidophil granular casts in the collecting tubules (Fig. 37).

Conclusions.- These cases confirm that after extensive burns satisfactory solute diuresis can be obtained by the administration of polyvinylpyrrolidone or mannitol. They suggest also that the declining hourly urine volume and increased pigment staining of the urine that are thought to be the precursors of actual physical damage to the tubular cell (Mueller et al., 1953) can be reversed by solute diuresis. It is much more difficult to establish that distal tubular necrosis was in fact prevented. A proportion of patients with severe burns have moderate haemoglobinuria without demonstrable effect on their renal functions, and during the period in which the patients recorded above were studied one such instance was seen in a man of 58 who sustained a deep flame /

flame burn of 20 per cent. of his body surface. He was transferred under the care of the Burns Unit 12 hours after injury having received two litres of plasma in a peripheral hospital, and was in shock when admitted. Catheterisation yielded 840 ml. of heavily pigmented urine. Vigorous resuscitation with plasma was carried out, 85 ml. clear urine were excreted in the next hour, and thereafter the urine volume was well maintained.

In spite of spontaneous recoveries such as this the clinical impression is that at least in the fourth and fifth cases of the treated series the infusions of polyvinyl-pyrrolidone and of mannitol increased urine flow rate and reduced solute concentration sufficiently to allow excretion of the pigment without renal tubular damage.

It remains to be decided whether solute diuresis is a necessary part of therapy or whether a similar effect could be produced solely by augmenting renal blood flow. Clinical experience with large transfusions (Flear and Clark, 1955) suggests that the relative oliguria seen after major injuries is caused in part by low renal blood flow and that a much higher urinary output occurs when transfusion is adequate. When renal blood flow is reduced in the dog, urine output decreases and solute concentration rises (Del Greco and de Wardener, 1956; and p. 12). Although similar consistent results are difficult to obtain in humans, in most cases of burning a marked increase in the hourly urine volume can be attained /

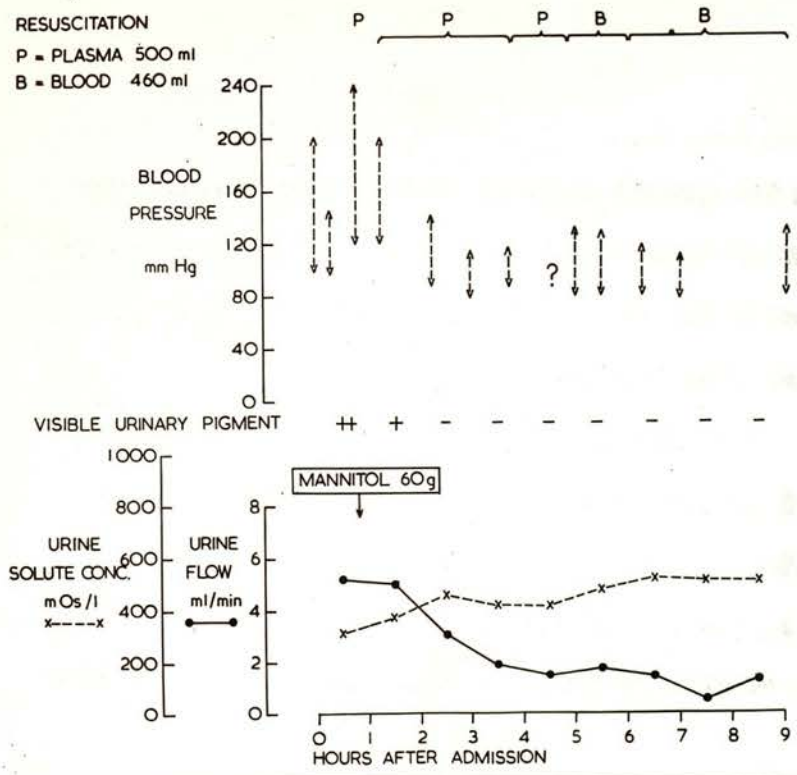

Fig. 38

The urine flow rate and resuscitation of a patient with severe burns (45% of body surface, Appendix II, Table XXVII). There is an initial period of hyperdynamic hypertension with a markedly raised urine output of low solute concentration. Mannitol was thereafter administered because of the depth of the burn and the appearance of visible urinary pigment.

attained by rapid plasma transfusion, which increases renal blood flow and consequently glomerular filtration rate and which, at the same time, corrects the hypoxia which favours the production of renal damage. Fig. 38 (Appendix II, Table XXVII) shows that hypertension alone in the post-injury phase may be responsible for a high rate of flow, an indication that the renal circulation does not necessarily share in the general vasoconstriction that produces the condition of "hypertensive shock". Therefore, there are some grounds for the belief that early restoration of renal blood flow alone might prevent pigment damage to the renal tubule. This conclusion was strengthened by Artz's (personal communication, 1955) observation that haemoglobinuria with renal failure was not seen in cases of burning during the Korean campaign when early adequate resuscitation was usually feasible, although because wide-fraction dextran was used the influence of a concomitant solute diuresis could not be excluded. However, the last case of the present series suggests that severe haemoglobinuria with impending renal failure can occur in spite of the adequate restoration of blood volume and an induced solute diuresis may be of value in such patients. Further, the last case treated with mannitol demonstrates that the onset of haemoglobinuria may be delayed until circulation is restored and the damaged red cells in the capillaries in the marginal zone of the burn are swept into the general circulation. In some instances /

instances this delay may allow time for the administration of a disposable solute if serial specimens of urine show increasing pigmentation and a decline in volume. Such a conclusion may have a significance beyond the management of renal damage in burns; in crushing injury in which the tubular necrosis is assumed to be related to the release of products of decomposition of muscle, the occurrence of renal damage is delayed until after release of the crushed limb and restoration of the circulatory state. In such cases if a solute diuresis can be induced while the circulation is improving it is likely that renal damage may be avoided. Attempts to produce a water diuresis (Bywaters, 1944) are unlikely to succeed because of the marked antidiuresis that accompanies such severe injury.

Because of the possibility of haemoglobinuria with renal failure in cases of deep burns of over 20 per cent. of the body surface, certain measures should be adopted in their management. As soon after admission as possible a catheter is inserted into the bladder. In deep burns, the initial shock is combatted in the usual manner by the transfusion of plasma or of blood, the clinical criteria being blood pressure, venous filling and peripheral capillary circulation. The deliberate administration of a certain volume in a certain time is avoided, the aim being to return blood volume and therefore renal blood flow to normal within two to three hours of admission. If there is heavy pigment staining /

staining in serial specimens of urine and if the volume of urine secreted shows a marked decline in two successive hours despite adequate restoration of the peripheral circulation, either 8 ml. of polyvinylpyrrolidone or 1 g. of mannitol per kg. body weight is administered. Because the effect of these solutions depends upon their concentration in the plasma reaching the kidney, it is essential that they be administered rapidly within 10-15 minuts.

(b) Effects of Water Loads in Surgical Patients

The injured or post-operative patient in whom there is marked antidiuresis is unable to respond to the administration of a water load by the production of a water diuresis. The normal mechanism for regulation of body tonicity and of the volume of total body water is overridden by the non-osmotic stimuli that have already been discussed (p. 32). Should water be administered in excess of the attainable urinary volume and the extrarenal loss by all routes (sweat, expired air and gastro-intestinal losses if these exist) then water retention will result. It is important to realise that retention is a secondary phenomenon because this emphasises that it is produced by incautious or incorrectly directed therapy and is not primarily a result of the body's physiological adjustments (Dudley, 1957).

The results of water retention are manifest in two ways. First, expansion of the total body water will lower the concentration of electrolytes dissolved in this water so that /

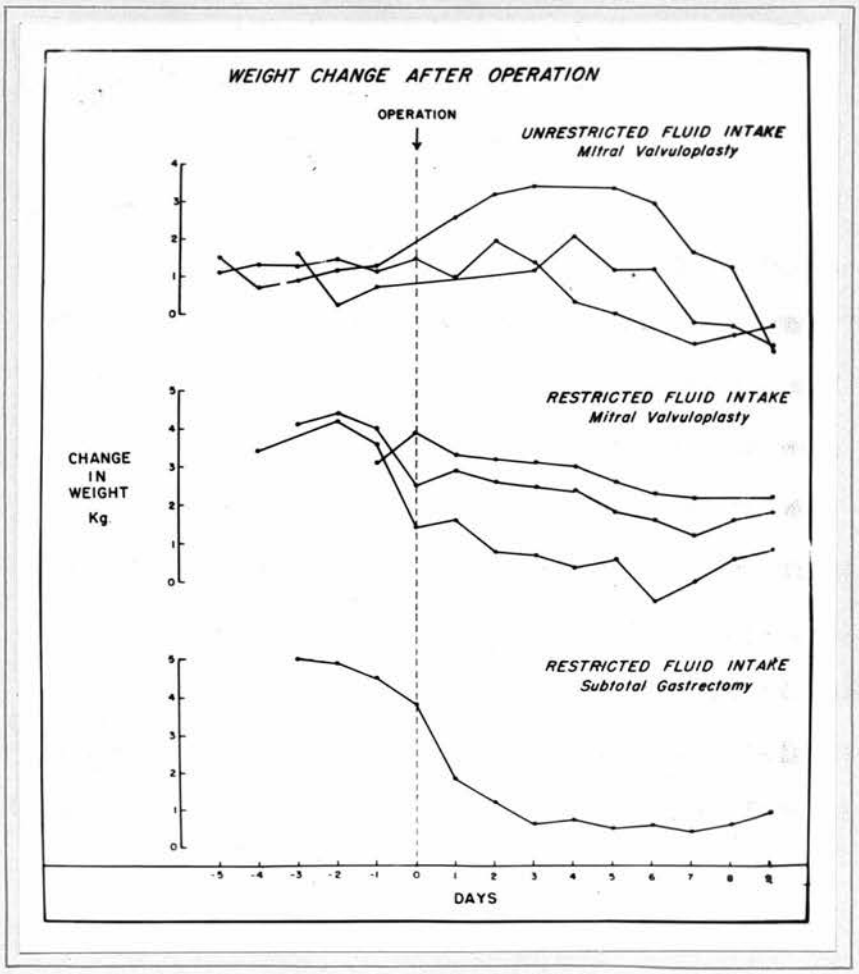

Fig. 39

The weights of three classes of patients submitted to surgical procedures. The data on those undergoing operations on the mitral valve are derived from Wilson et al. (1954) and on the patient submitted to partial gastrectomy from an unpublished study of the Department of Surgery, Peter Bent Brigham Hospital (Harvard Medical School).

that if serum electrolyte levels are studied they will be found to have decreased. Secondly, if carried to considerable excess the hypotonicity produced by the retention of administered water may cause the clinical syndrome loosely and probably incorrectly referred to as "water intoxication" (Green and Rowntree, 1927; Zimmermann and Wangensteen, 1952; Le Quesne, 1954; Wynn and Robb, 1954). The gross overloads that have occurred in the clinical cases of water intoxication are extremely rare and usually result only from errors of management. However, a lesser degree of overhydration is not uncommon in the early management of patients after injury or operation. Figure 39 (derived from the data of Wilson et al., 1954 and from unpublished observations of the Metabolic Research Laboratory of the Peter Bent Brigham Hospital) illustrates how if ordinary oral intake is not restricted in patients who undergo operations on the mitral valve, their weight remains stationary or may actually increase. This increment in, or failure to lose, weight indicates a retention of water because if fluid intake is restricted weight is lost by the normal processes of oxidation of fat and of lean tissues. Such a loss of weight is most marked when oral fluid intake is totally absent and intravenous therapy is controlled so that a net gain or loss of water does not take place. An example of such management is shown on the weight line (Fig. 39) of the subject undergoing partial gastrectomy (see also Wilkinson, 1956 /

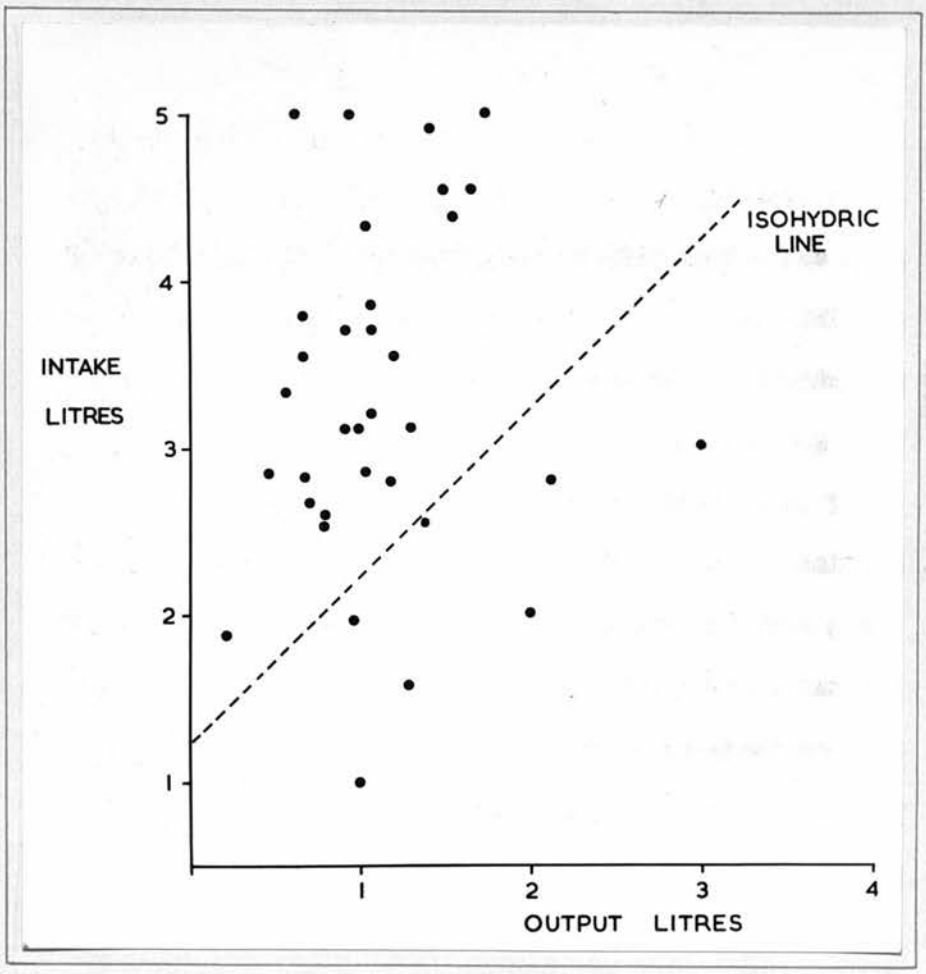

Fig. 40

Combined plot of fluid intake/output in 31 consecutive patients submitted to gastric surgery and managed by intravenous fluid therapy according to "standard" techniques. Points to the left of the isohydric line imply a positive fluid balance after allowance for insensible loss (Appendix II, Table L).

1956). Fig. 40 demonstrates that a similar overload of water can occur in the course of routine gastro-intestinal surgery. In this figure the fluid balance in the first 48 hours after operation of 31 consecutive patients submitted to gastrectomy for duodenal ulcer and managed by "routine replacement" with intravenous 6 per cent. dextrose is depicted as a scattergram (Appendix II, Table L). Equation of intake and output with an allowance of 1200 ml. per day for insensible loss, is indicated by the oblique line. Twenty five patients or 80 per cent. were in positive water balance at the end of this period.

If it is accepted that such minor degrees of overhydration are not uncommon it is of interest to determine (a) the effects of such overloads on the serum electrolyte loads and (b) the subjective effects, if any, of retention of small net loads of water within the body. Knowledge of (a) will assist in the interpretation of serum electrolyte concentrations when these determinations are used as part of the management of clinical cases and of (b) will aid in the decision whether such overloads are detrimental to the normal convalescence of the patient after injury or operation.

With these aims in view a study was made of overloads of water of amounts which ranged from 1.5 to 3.5 per cent. of total body water administered by mouth and 2 per cent. of total body water administered as 6 per cent. dextrose by the intravenous route. The water was ingested over 10 minutes in /

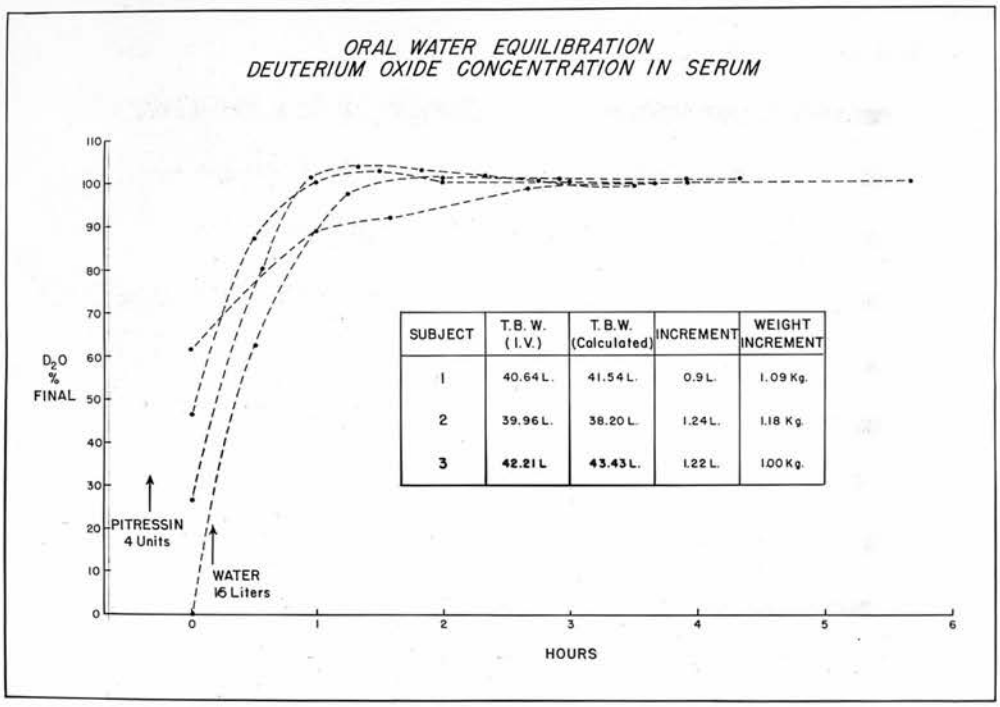

Fig. 41

Pattern of equilibration of deuterium oxide in serum after the oral ingestion of a tracer dose which formed part of a large water load. The inset table gives the derived figures for total body water calculated from this equilibration after allowance for water losses during equilibration and from a standard intravenous determination. (Reproduced from Dudley et al., 1954.)

in the oral experiments and administered in 40 minutes intravenously. Previous work (Schloerb et al., 1950) had shown that intravenously administered water is completely equilibrated with the total body water within two hours. To ascertain that a large oral water load was similarly equilibrated, total body water was estimated in three subjects by the intravenous method (see Appendix I). Thereafter urinary water excretion was reduced to a minimum by the subcutaneous administration of 4 units of commercial antidiuretic hormone; 1.5 litres of water which contained a tracer dose of deuterium oxide were then taken by mouth. Frequent determinations of weight and of deuterium oxide concentration in the serum were made over the next four hours. From these figures it was possible to calculate a new figure for total body water which represented the basic total body water plus the increment of the gross water load less the water losses by all routes (insensible loss + urine volume), that is

New total body water = Original total body water + gross load (1.5 litres) - (insensible loss + urinary loss).

The net load (gross load - total losses) is given by the weight increment.

Figure 41 (from Dudley et al., 1954) illustrates (a) the equilibration curves for four subjects and shows that the final values of deuterium oxide concentration are reached in two and a half hours after the administration of water by the oral route; (b) that the calculated values for the total /

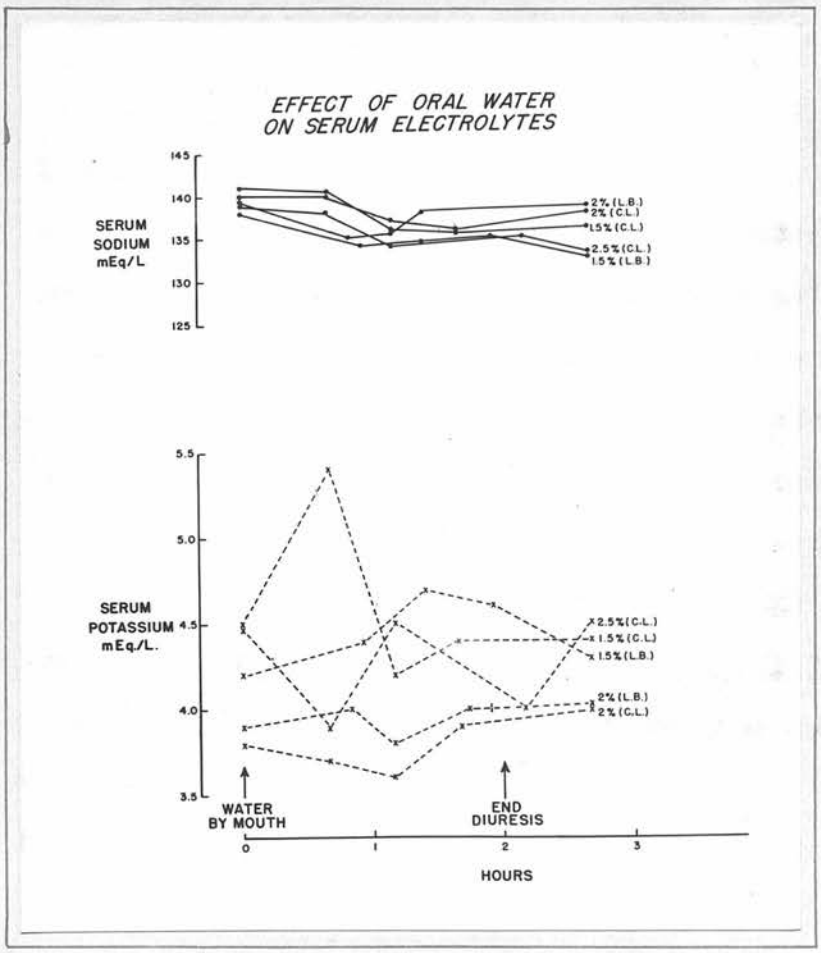

Fig. 42

Effect of the ingestion of water on the serum electrolytes (Appendix II, Table LI).

total body water from observed dilution on the second occasion agree closely with the expected total body water derived from the sum of the intravenous determination and the weight increment.

It can therefore be assumed that oral water loads are equilibrated within two hours of administration and that the water so administered is distributed throughout the total body water.

The percentage dilution of extracellular electrolytes at the end of this time should be proportional to the net load provided no "shifts" of electrolyte into or out of the extracellular phase have taken place during the course of equilibration.

Effects of Water Loads on Serum Electrolytes. (i) Oral water without diuresis.- The five experiments are presented in Fig. 42 (Appendix II, Table LI). The effect of oral water in amounts of 1.5-2.5 per cent. of total body water is to reduce serum sodium by about 5 mEq. at the end of one hour. It was a consistent finding that this depression persisted after the "clearing" of the water load (as indicated by cessation of diuresis and a return of weight to control levels or less) had been completed. Potassium levels do not show any such constant trend and may rise during absorption of the load. Only at the level of 2 per cent. of body water do the potassium figures suggest dilution alone.

(ii) Intravenous 5 per cent. dextrose without antidiuresis.- Four experiments were carried out and the results are /

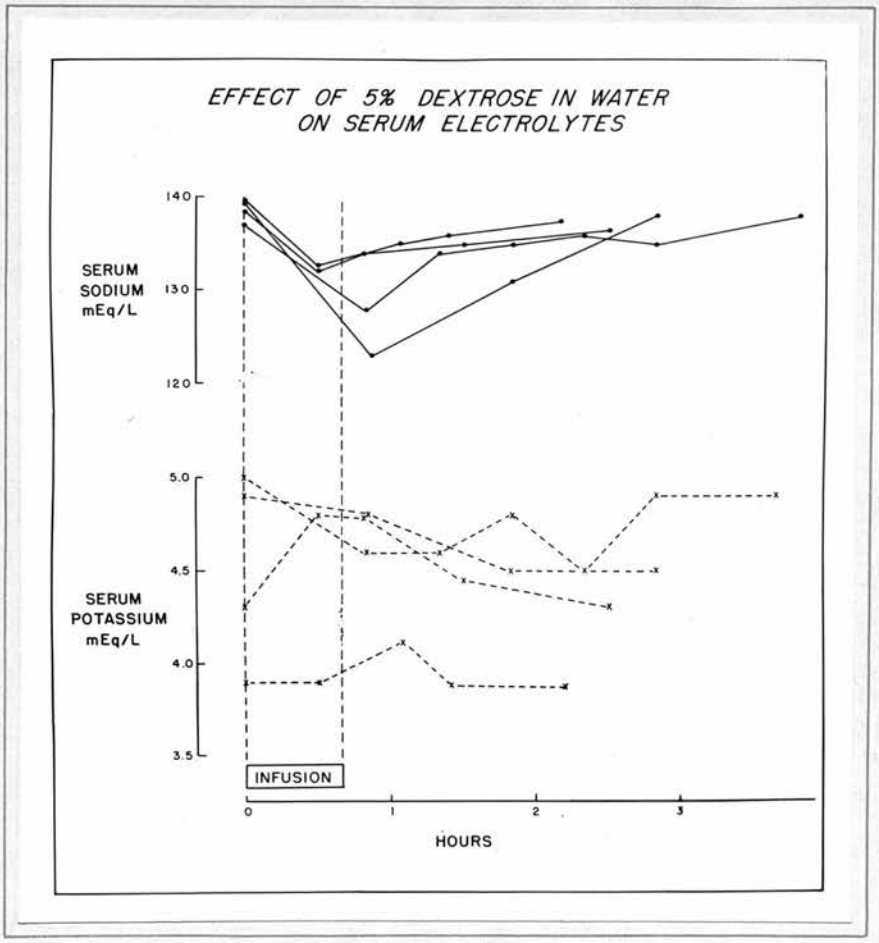

Fig. 43

Effect of the intravenous administration of a water load on the serum electrolytes (Appendix II, Table LII).

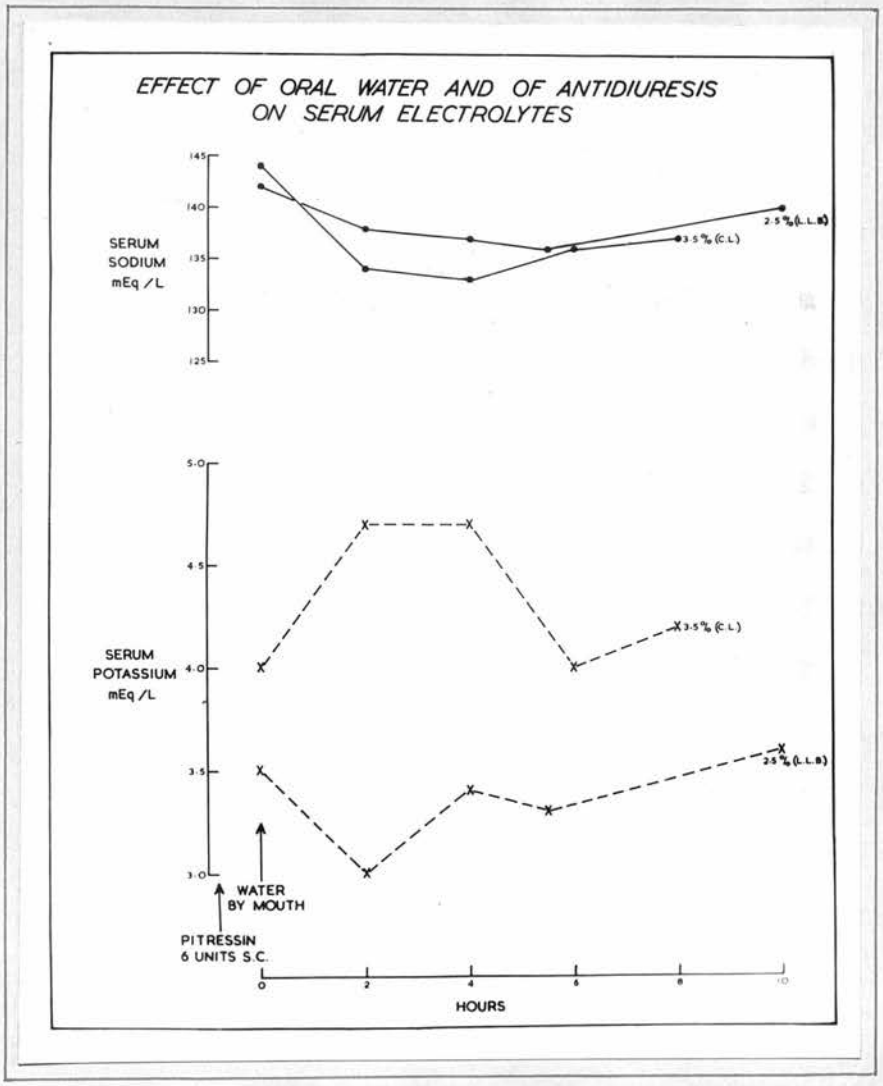

Fig. 44.

Effect of the oral administration of water to subjects in the antidiuretic state. (Appendix II, Table LIII.)

are shown in Fig. 43 (Appendix II, Table LII). The extent and rapidity of the fall in serum sodium concentration are both increased, as would be expected from the larger amount of water immediately available for expansion of the total body water and the dis-equilibrium between phases consequent upon rapid administration directly into the blood stream. Recovery is almost equally rapid and by completion of the diuresis the values for the serum sodium concentration have returned almost to pre-infusion levels. The end of this experiment is thus in slight contrast to the oral loads where depression persists beyond the end of diuresis. Changes in potassium concentration are again variable and elevations during the administration of the test dose are seen in two of the four instances. Lower values than the control also occur at the end of the experiment on two occasions - in one where elevation had accompanied the infusion.

(iii) Oral water with antidiuresis.- Two experiments were carried out at loads of 2.5-3.5 per cent. (approximately 1000-1500 ml.). The results are shown in Fig. 44 (Appendix II, Table LIII). The fall in the serum sodium at the time of equilibration (beyond 2.5-3 hours) equals or exceeds this figure. The fall is maintained as long as the determinations were continued (7-10 hours) by which time elimination of the load, as judged by weight, was complete. In one instance (C.L.) the potassium rises as sodium falls, in the other (L.L.B.) the changes in direction and magnitude are those /

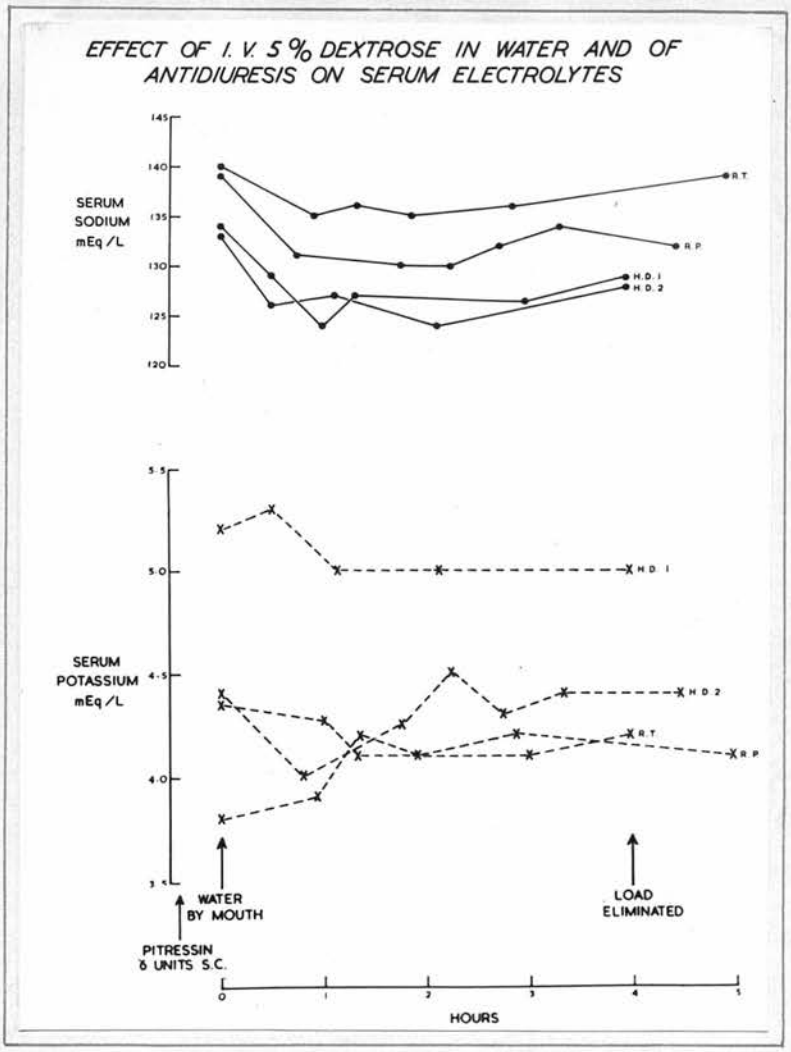

Fig. 45

Effect of the intravenous administration of 6% dextrose to subjects in the antidiuretic state (Appendix II, Table LIV).

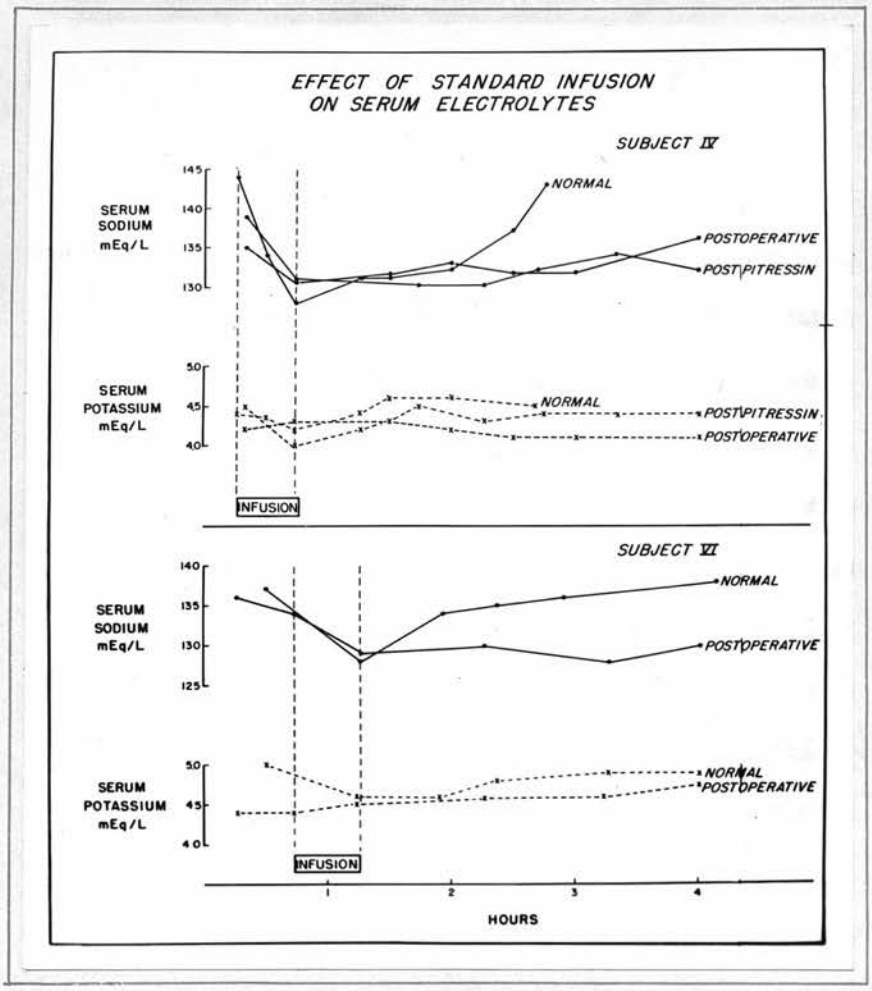

Fig. 46

Changes in serum electrolytes in two patients who received an intravenous water load before and shortly after partial gastrectomy (Appendix II, Tables III and V).

those that would be expected from dilution, although recovery to the control level of serum potassium takes place before the load is eliminated.

(iv) Intravenous 5 per cent. dextrose with antidiuresis.- Four experiments were made (Fig. 45; Appendix II, Table LIV contain the full data). As would be expected the changes seen with 5 per cent. dextrose infusions alone were prolonged. Elimination of the administered water was complete, using weight as an index, at the end of four hours. However, it is again worthy of note, that changes in the level of serum potassium are less marked than those of serum sodium and may be in the opposite direction (R.B., H.D.2); unlike the oral experiments serum sodium concentration returns to normal with the elimination of the load. Similar changes in electrolyte concentrations are seen if intravenous dextrose is administered to patients who have undergone partial gastrectomy. Fig. 46 (Appendix II, Tables III and IV) shows the electrolyte levels in two patients of the series of six already described (p. 18). It is clear that the levels are depressed (as could be expected) in a manner resembling that seen after posterior pituitary antidiuresis. It is again of interest that serum potassium concentration does not fall with the infusion.

Subjective effects.- None of the water loads described in the preceding sections produced the frank symptoms or signs of water intoxication such as vomiting, hypothermia, and /

and convulsions. Experimental production of such a condition in man would be unjustified, but Wynn's (1955) single experiment in which water overloading was combined with renal elimination of large quantities of sodium by mercurial diuresis indicates that water overloads of at least 2.5-3.0 litres or reduction of serum sodium to concentrations of not more than 115 mEq/litre are necessary before severe symptoms of water intoxication develop. The serum sodium concentrations recorded by Zimmermann and Wangensteen (1952) in their clinical cases give similar indications. Nevertheless, water loads of over 2.5 per cent. in the subjects under study consistently produced nausea, headache, lightheadedness and, if the upright posture was assumed, mild postural hypotension and dizziness. Therefore it is apparent that even mild overhydration should be avoided in surgical patients and this is in keeping with the findings of Wilson et al. (1954) that in patients already ill with valvular disease of the heart, mild post-operative water retention produces severe symptoms.

Significance of electrolyte changes in post-operative patients.- In the patients reported by Wilson et al. there was marked hyponatraemia and hyperkalaemia in spite of only slight water retention and in some instances even when total body water was not expanded. Similar changes in the concentration of serum sodium have been described in less seriously ill patients after surgical procedures (Wilson, 1955; /

1955; Wilkinson et al., 1951) and have led to the development of the hypothesis of a shift out of the extracellular phase after injury (Moore, 1954; Elkington, 1956) accompanied by a release of potassium from the intracellular water into the extracellular space. Confirmation of this hypothesis rests on the ability to measure total extracellular electrolytes, a figure which can be arrived at only if extracellular volume is accurately known. The latter parameter is probably indeterminate and the concept of extracellular space itself a convenient abstraction. Thus, demonstration of changes in distribution of electrolytes in the human must await more subtle methods of investigation of cellular processes.

In the published studies there has been some discrepancy of opinion whether the electrolyte changes are proportional to the increment in total body water. The data on man obtained by Leaf et al. (1953) suggest that this is not the case but Wynn's observations (1955) and the experience of Leaf et al. (1954) with dogs suggest an exact relationship. However, these apparent discrepancies may be explained by the complicated nature of Wynn's experiments both in man and in the dog, and by the fact that the animal experiments in the series of Leaf et al. were conducted with very gross overloads which could be expected to swamp any slight discrepancies in extracellular electrolyte concentrations. The investigations described here indicate that both sodium and potassium /

potassium changes are irregular and that they may be not directly related to the water load and its equilibration (see also Dudley et al., 1954). Further work on extracellular tonicity in response to large water loads is obviously required.

In spite of this lack of understanding of the processes that control the distribution and concentration of the chief body cations, certain practical conclusions can be drawn. The first is that such water loading should be avoided in the patient after injury because even small net loads may produce significant hyponatraemia. The second is that hyponatraemia and hyperkalaemia in the patient after injury cannot be regarded as an indication of sodium lack or potassium excess; far more frequently they are indications of some basic disturbance in fluid and electrolyte dynamics - excess of water, the metabolic processes of injury or a disturbed state of the body's chemical process.

CONCLUSIONS: PART I

From the first observation of Bernard and of Pringle et al. (1905) has grown a considerable body of knowledge of the limitation on renal excretion of water that follows injury or operation. This non-osmotic response of a neurohumoral mechanism adjusted normally to body tonicity might (teleologically) be regarded as a mechanism to be invoked when the normal intake of water is interrupted by inavailability /

WATER BALANCE AFTER MAJOR SURGERY

	INTAKE		OUTPUT		BALANCE
	BY MOUTH ml.	METABOLIC ml.	URINE ml.	INSENSIBLE ml.	
PREOPERATIVE	2400	300	1500	1200	0
DAY OF OPERATION	0	600-800	400-500	1200	900-1100
1st POSTOPERATIVE DAY	700	400-600	500-1200	1200	400-600
			CUMULATIVE DEFICIT 2 DAYS		1300-1700

= 32-42 % OF TOTAL BODY WATER

Fig. 47

Theoretical water balance in a patient submitted to partial gastrectomy.

inavailability or by inability of the organism to absorb water given by mouth, for example after gastro-intestinal injury or in circumstances of unconsciousness or of shock. Indeed a water balance constructed for the post-operative patient demonstrates that only a small net deficit in total body water results in the first 48 hours after a major operation (Fig. 47), largely because of the limited renal losses and the contribution made to total body water by the oxidation of fat which may be considerable after injury (Moore, 1953). Wilkinson (1956) has published an account of the successful application of this knowledge to the management of patients after major surgery such as partial gastrectomy by a regime which does not permit fluid in any form for the first 36-48 hours after operation, and this method is now routine also in our hands. In the absence of abnormal extrarenal losses of fluid from the body (by gastric suction, by fistula drainage or by diarrhoea) intravenous fluids are not required and may even be undesirable because it is easy to induce an expansion of total body water and resultant hyponatraemia. Water intoxication from this source is rare but minor symptoms have probably been common. In patients managed by this regime of water restriction, Wilkinson found thirst to be a constant and troublesome symptom not always relieved by sucking ice or even by drinking. In a recent series of 30 patients thirst has been complained of by only 14 and it has been a striking feature that even in the absence /

absence of intake both the subjective complaint of dryness and the cardinal physical sign of exsiccation, a dry tongue, may have disappeared by the second day. This clinical observation suggests that the contribution of "endogenous" water to body fluid resources may be greater than is at present thought. Further measurements of total body water after injury are required to confirm this supposition.

Studies on antidiuresis have also focussed attention on the causative factors of renal damage and have emphasised that maximal concentration of the urine may be of importance in localising the damage to the distal tubule when blood or muscle pigments are involved. Preliminary experiments indicate that manipulation of the urinary volume and concentration may provide effective prophylaxis for this condition.

PART II

THE NEURO-ENDOCRINE CONTROL OF NITROGEN, SODIUM AND POTASSIUM METABOLISM AFTER INJURY

Introduction

In the first part of this thesis the changes in renal excretion of water that follow injury were discussed. Many other events follow major trauma and the metabolic response to surgery includes by definition all these alterations in cellular and extracellular activity. However, in common use the term is confined to the changes in utilisation and in exchange of sodium, potassium and nitrogen. If an attempt is to be made to understand the control of such changes it is necessary to examine them critically to ascertain, first, their nature and secondly, whether or not they can be regarded as the result of injury itself. Should the latter be established it is then possible (a) to search for parallel occurrences which might throw light on causation and (b) to use the observed metabolic changes as indicators in circumstances when postulated controlling factors can be varied or eliminated.

Metabolic events may be studied in two ways: first, by direct observation of chemical or physiochemical changes in individual tissues or in the body as a whole, a method not often applicable to man except to measure changes in the plasma /

plasma concentrations; secondly, by computing a "balance" from the measurement of the rates of intake and output. Changes in the external balance give some indication of rates of utilisation and of the increase or decrease of total body stores. Nevertheless, such balance studies have some shortcomings both in execution and interpretation. First, they do not give any information about intermediate biochemical events or the origin of the end products that are excreted; secondly, the construction of a balance by direct addition and subtraction may well be unjustified, particularly in the case of nitrogen which is assimilated in a completely different form from that in which it is excreted. Thirdly, difficulties also arise in computing both intake and output: for example, some authors have regarded the nitrogen, sodium and potassium of whole blood as an increment on the intake side in spite of the known very slow utilisation of both plasma protein and intact red cells (Levenson et al., 1949). Further, although loss of whole protein from a raw surface is undoubtedly a debit to the body, it may have a different metabolic effect from nitrogen excreted in the urine as urea. Finally, most workers who have carried out balance studies are agreed that changes of less than 15 per cent. are always of doubtful significance.

However, it has been largely by the balance method that the current description of the changes in sodium, potassium and nitrogen metabolism associated with injury has been established. /

established. If this description is to be properly interpreted, it is necessary to have some conception of the extraneous factors which may alter a "balance". In the first place a spuriously positive balance may be induced by the excessive addition to the body of some substance in the absence of any diminution of renal excretion; in the second, negative balance may apparently be present if intake has been reduced, in spite of a constant renal excretion rate. Particularly in instances of continued stress such as peritonitis or burns, gross changes in the external balance may occur not only because of metabolic events but also as a result of treatment with fluid and electrolytes; balance sheets from such patients must be interpreted with great caution. These matters are of more than theoretical interest because they have resulted in much confusion of thought. Increase or decrease in body content of a substance may be a secondary phenomenon, the consequence of alterations in intake, rather than of a true metabolic event; the use of such terms as "retention" or "loss" should be abandoned in descriptions of normal metabolism after injury although "loss" is sometimes allowable in circumstances in which it is clearly shown that the body's stores are reduced and that the levels of the renal or extrarenal rate of excretion are largely independent of intake.

With these provisos in mind, the available evidence with respect to nitrogen, potassium and sodium can be considered.

Normal Nitrogen Metabolism

This subject has been exhaustively studied and its main features are so well known that they require little emphasis. Nitrogen constantly enters the body in the form of protein and leaves via the kidney as urea (80-85 per cent.) and other end products such as creatinine and uric acid (15-20 per cent.)

Keys et al. (1950) have pointed out that Voit (1887) was the first to make an estimate of the dietary requirements for health when he recommended 118 g. of protein as a daily intake. Since then this figure has been reduced to between 67 and 70 g. (10.7-11.2 g. nitrogen); although the protein content of diets is usually increased in those who undertake hard manual labour there is in fact little evidence which suggests that nitrogen metabolism is conditioned by the level of physical activity (Keys et al., 1950). If food intake is stopped in healthy men as in the classic experiments of Benedict (1916), nitrogen excretion continues at a rate which averages approximately 12 g. daily in all the published studies (Calloway and Spector, 1954). This rate of nitrogen excretion decreases if calories are supplied. Thus Lowe (1953) in studies on patients who received a high calorie, nitrogen-free diet found that nitrogen excretion fell rapidly from 9 g. daily to about 5 g. daily and then gradually to about 2.5 g. daily at the end of two weeks. (However, he did not record whether or not his patients lost /

lost weight.) Gamble (1947) found a similar nitrogen-sparing effect of carbohydrate in starving and thirsting men and established that 100 g. of dextrose (400 calories) were sufficient in starvation to reduce endogenous nitrogen metabolism and consequently nitrogen excretion to a minimum of 40 g. of protein daily. Carbohydrate is apparently more effective than fat in sparing nitrogen when calorie intake is reduced (Werner, 1948), although Munro (1951) could find little evidence for any difference between the two sources of nitrogen-free calories. Calloway and Spector (1954) came to approximately the same conclusion as Gamble but felt that an overall daily calorie intake of 900 per day was necessary to reduce nitrogen excretion to the minimum of about 7 g. daily. Below this level of calorie intake, any additional protein is entirely used for energy purposes and the nitrogen end products therefore increase urinary excretion rates. If the calorie intake is increased to between 900 and 1600, 3 g. of nitrogen are effective in reducing the deficit of nitrogen to 5 g. so that the urinary excretion rate becomes approximately 8 g.; at the same calorie intake 6 g. of nitrogen decreases the deficit to between 1.8 and 2.4 g. nitrogen per day. When the calorie intake is increased to a usual level of 3,300, equilibrium is achieved on 8.5 g. daily. As Calloway and Spector have emphasised, "on a fixed adequate nitrogen intake, energy level is the deciding factor in nitrogen balance".

This /

This brief review of normal metabolism of nitrogen emphasises that changes in excretion rates and balance after injury must be judged against a background of a normal nitrogen loss of between 8 and 12 g. daily on a usual dietary intake and of an excretion rate of between 7 and 12 g. daily in starvation and deprivation of water depending chiefly on the degree of calorie withdrawal. In surgical patients maintained for the first 24 hours on approximately 1500-2000 ml. of 5 per cent. or 6 per cent. dextrose the total calorie intake is less than 400 and thus nitrogen sparing is minimal or absent. To establish that nitrogen metabolism is fundamentally altered by injury would require the consistent demonstration of rates of excretion of more than 12 g. daily in the starved and injured patient and of the failure of an adequate nitrogen/calorie intake to influence the negativity of the balance.

Nitrogen Metabolism after Injury

With these facts relating to normal nitrogen metabolism in mind, it is possible to review the accepted basis for the observations which have led to the idea that the excretion of nitrogen after injury is increased and that a "catabolic phase" (Browne et al., 1944) takes place in which "whole lean tissue" is destroyed throughout the body as a whole (Moore and Ball, 1952). The initial review is necessarily extensive: facts are available in profusion but their correct /

correct interpretation is still a matter for conjecture. Many of the difficulties lie in an inadequate appreciation of the quantitative significance of the observed changes and in the neglect of some of the other factors that are inseparable from injury, for example, starvation, "exsiccation" and alterations in blood volume and blood flow. A critical analysis such as is attempted here may throw light upon the further experiments required to confirm or to confute the occurrence of a metabolic response to injury and to establish the possible factors which determine its neuro-humoral control.

The concept of a metabolic response which involves nitrogen has evolved from observations made upon the changes in excretion rate and intake-excretion ratio (i.e. the balance). Although "nitrogen wasting" and the destruction of the protein of muscles during fever was known at the end of the nineteenth century (Baur, 1872; Malcolm, 1893) and Pringle et al. (1905) had studied nitrogen excretion in the first 24 hours after operations under general anaesthesia, Cuthbertson (1934), who has made an exhaustive study of the history of nitrogen metabolism after injury, considers that the first deliberate observations after major injury were made by Wertheimer et al. in 1919. In a study of war wounded patients these workers observed an excretion rate of 16 g. of nitrogen in the first 24 hours after injury and established that even higher rates (up to 27 g. per 24 hours) /

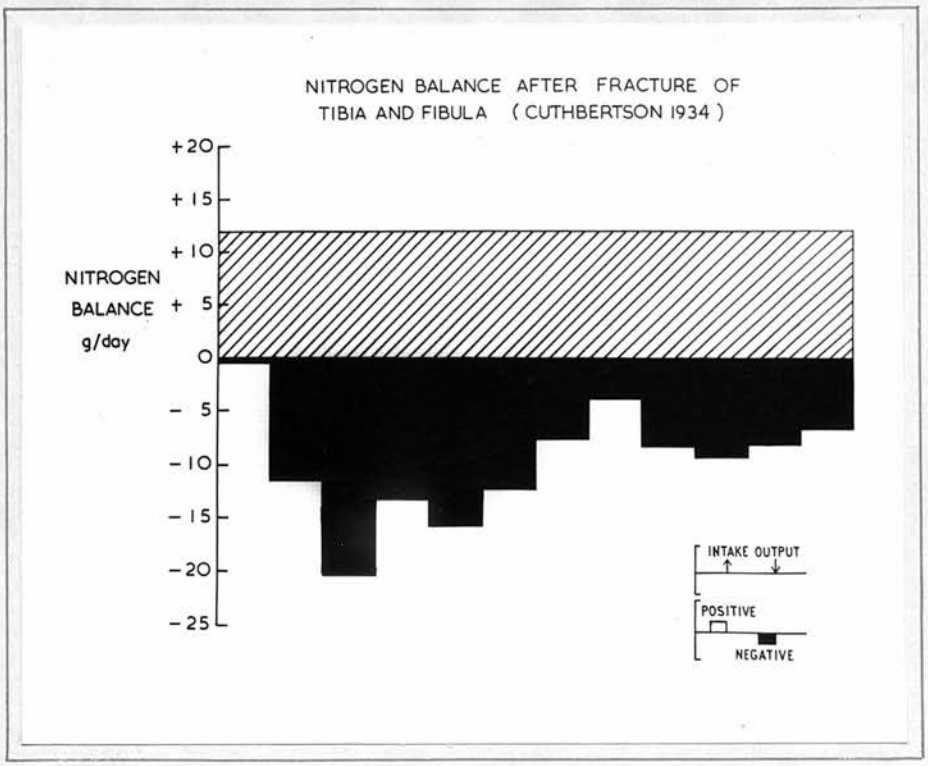

Fig. 48

The nitrogen balance of a patient who sustained a fracture of both bones of the leg. (Redrawn from Cuthbertson, 1934.)

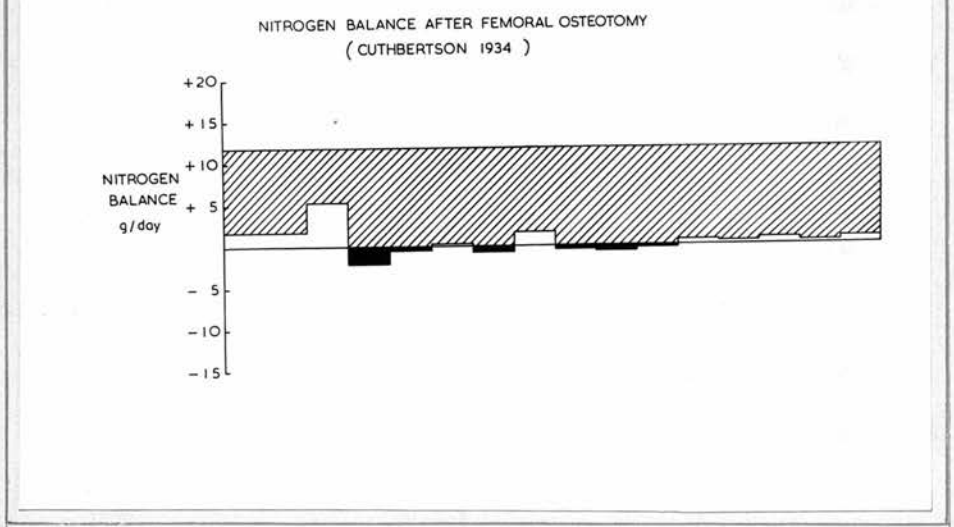

Fig. 49

The nitrogen balance of a patient who underwent osteotomy of the femur. (Redrawn from Cuthbertson, 1934). Contrast Fig. 48.

hours) were reached during the next few days, in marked contrast to the normal excretion of 8-10 g. daily by a healthy adult in nitrogen equilibrium.

Cuthbertson's own interest in the problem arose from a study of the effects of fracture on mineral metabolism (Cuthbertson, 1929). During the course of these investigations he noted that after a major injury to bones, nitrogen excretion was raised from the time of the beginning of study (3-7 days after injury), that nitrogen output after such trauma usually reached a maximum during the period of the 8-10th day after injury and that this excretion of nitrogen was sufficiently large to produce a marked negative balance (in spite of a "normal" intake of food). His most dramatic case of excess nitrogen excretion over intake (Cuthbertson, 1934) - a boy of 16 with a fracture of both bones of the leg - is illustrated in Fig. 48. On an intake of 11.7 g. nitrogen a day, excretion rates reached 27.6 g. per day on the eighth day after injury and were maintained at levels above the intake for the duration of the study (12 days). At this time Cuthbertson also observed that nitrogen excretion was less marked after a deliberate operation on bone, such as an osteotomy, and one case that he studied remained in nitrogen equilibrium during the period of such an operation (Fig. 49).

Further observations which confirmed these findings followed (Cuthbertson, 1936) and investigation of patients after /

after bony injury and operations on bones and on joints showed that the negative nitrogen balance persisted, although at a reduced level, in spite of an apparently adequate dietary intake of both protein and of calories (Cuthbertson, 1936). An increased excretion rate of sulphur and of phosphorus suggested the destruction of lean tissue during the post injury phase (Cuthbertson, 1931 and 1934) although low respiratory quotients described in some of the patients (Cuthbertson, 1932) pointed to the concurrent oxidation of fat. It seemed clear that a definite phase of increased tissue breakdown followed injury and that the quantitatively large excretions of nitrogen seemed to preclude a local effect at the site of fracture. Further, the amount of nitrogen lost in the urine bore a rough relationship to the extent of damage both to the bone and to the soft tissues (hence the less marked losses in cases of deliberate operations on bones) although Cuthbertson himself made the perhaps propnetic remark that "it may be that future work will indicate that our conception of the degree of severity of an injury is at fault" (Cuthbertson, 1932).

In 1939 Cuthbertson, McGirr and Robertson endeavoured to analyse the various possible sources of the nitrogen excreted in the urine after fractures in rats. The injured animals were compared with a control group in which the femur was exposed but not fractured. Both groups lost nitrogen but the fractured animals lost about twice as much nitrogen as /

as the controls and continued to have high nitrogen excretions for up to nine days as against four days for the controls. A further series of animals were given a carbohydrate supplement in the diet but still showed a negative nitrogen balance although by the tenth day this second group was in a positive balance. In all groups the loss of weight of the injured limb was compared with the contralateral leg and was found to be insufficient to account for the excess excretion of nitrogen in the urine*. Similar results were obtained by Munro and Cummings (1948) and both groups of workers concluded that the nitrogen lost from the body after fracture represented the end result of a generalised post-traumatic breakdown which in some way subserved the healing process. Cuthbertson's Arris and Gale Lecture (Cuthbertson, 1942), in which he reviewed his findings over the preceding thirteen years, summed up his views on this accelerated excretion of nitrogen by regarding it as a purposeful response which favoured the production - from the body's own resources - of the necessary materials for repair. He again emphasised that in soft tissue and deliberate surgical injury to bones the raised excretion rate of nitrogen was less in degree and occurred earlier in the clinical course after injury than in accidental bony trauma. Further, he drew attention to the fact that although the body /

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* "Whole lean tissue" is derived from nitrogen by multiplication by a factor of 30 (Moore and Ball, 1952).

body was able temporarily to store excess dietary nitrogen under normal circumstances (Cuthbertson et al., 1937; Cuthbertson and Munro, 1937) it was under conditions of only very minor injury and where soft tissue damage was slight that a similar retention could be produced after injury*.

The interest occasioned by Cuthbertson's work on fractures led numerous investigators to study the excretion of nitrogen after other forms of surgical trauma. Studies in nitrogen balance were also stimulated by the development during the late 1930's of protein digests suitable for parenteral administration to patients unable to absorb foodstuffs from the gastro-intestinal tract (Elman and Weiner, 1939). While engaged on this work, Elman (1940) noted nitrogen losses of up to 22 g. a day, two to five days after a major surgical procedure when the patient was maintained on a protein-free intake. Brunschwig et al. (1942) studied 41 patients undergoing major surgical procedures and demonstrated widely varying nitrogen losses of from 3.8 to 75.8 g. when protein was not administered in the first five days after operation. In a further series of patients who were submitted to cholecystectomy the same authors found excretion rates of from 3 to 28 g. per day when /

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* In the study of patients who are undergoing major surgical procedures it must be remembered as Peters (1948) has pointed out, that all such subjects may not be normal. Thus, undernourished individuals show a greater capacity to retain nitrogen while on low calorie intakes than do the well-nourished: frequently, patients submitted to such procedures as partial gastrectomy have had a preceding long or short period on an inadequate intake.

when the intake varied from 6 to 18 g. per day. Similar results were obtained by Browne and his co-workers (Browne et al., 1944; Browne et al., 1946). Howard's extensive studies on fractures and operations on bones (Howard et al., 1944a and b; Howard, 1945; Howard et al., 1947) confirmed the findings of Cuthbertson and emphasised that a nitrogen excretion in excess of intake might persist for up to 35 days. These investigators carried the analysis one stage further by the construction of a graph which related the expected negativity of the balance of nitrogen to the simultaneous intake rate of nitrogen and of calories; the traumatic cases did not conform to this relationship and lost more nitrogen than could be expected on the basis of partial starvation alone. On the other hand Mulholland et al. (1943) who studied patients submitted to partial gastrectomy, found that nitrogen excretion rates after operation were in the range of 11.7-18 g. per day for the first five days although if nitrogen and calories (in the form of glucose) were administered parenterally the output of nitrogen was in the range 9.7-21.8 g. per day. In spite of occasionally high nitrogen excretion rates the latter patients were in positive nitrogen balance. Further studies by the same group (Co Tui et al., 1944) on patients who underwent gastrectomy revealed post-operative nitrogen excretion rates in the range of 7.4 g. per day even when nitrogen intake was artificially increased; except for the day /

day of operation their patients were maintained in positive nitrogen balance with ease by nutritional supplements. Co Tui et al. concluded: "there is thus little evidence of a significant and sustained loss of urinary nitrogen following such a major surgical procedure as a partial gastrectomy", thereby stressing once again that, at least under the circumstances of major abdominal operations, care must be taken to distinguish the effects of starvation from those of operation. Studies on patients undergoing herniorrhaphy (Keeton et al., 1948) confirmed that the "disturbance" of nitrogen metabolism was over by the first post-operative day, that there was no evidence for an increased excretion rate of nitrogen after an operation of this type and that if nitrogen and calorie "starvation" was prevented by the intravenous administration of amino acids and of dextrose the patients remained in positive nitrogen balance. Werner (1947) found nitrogen losses of only 25 g. in the first five days after partial gastrectomy when carbohydrate was given alone; if nitrogen was also supplied by the administration of intravenous amino acids, the overall negative balance of half his patients was much reduced. Of considerable interest was his observation of a patient who sustained a fracture of the femur with extensive soft tissue injury but who was maintained in positive nitrogen balance, except on the day of injury, by the use of oral and intravenous nitrogen supplements and in spite of nitrogen excretion rates of between

21 /

21 and 49 g. per day for 22 days. This instance is in striking contrast to the results of Cuthbertson and Howard already mentioned. Werner concluded that in general "no excesses of nitrogen appear in the urine when nitrogen is withheld post-operatively and in fact the nitrogen excretion may be less than that of an uninjured patient on the same intake". The same author followed these observations with a detailed study of the effects on nitrogen excretion of the independent variation of the nitrogen and of the calorie composition of the diet (Werner, 1948), and observed that reduction in calories at a constant nitrogen intake produced a negative nitrogen balance in an analogous manner to trauma and that within limits already described (p. 63) restitution of nitrogen balance on a low calorie intake could be achieved by increasing the nitrogen intake.

Further studies on nitrogen excretion rates demonstrated that a negative balance in surgical patients was in large part the result of nitrogen and calorie deprivation rather than of increased nitrogen excretion after injury. Werner et al. (1949) observed that "operation or injury is generally accompanied by a serious deviation from the individual's customary habits of nutrition and activity. The effects of this change in routine must be considered before any conclusion can be drawn about physiologic alterations resulting from trauma itself". They studied patients who underwent herniorrhaphy and cholecystectomy under a variety of nutritional circumstances and found no evidence of increased /

increased nitrogen excretion after injury or of a negative nitrogen balance, provided an intake of nitrogen and of calories was maintained. Wilkinson et al. (1949) who investigated the metabolic response to gastrectomy found rates of loss of nitrogen of 12-28 g. daily when nitrogen intake was zero but Beal et al. (1954) did not find any increase in nitrogen output after a similar procedure nor after cholecystectomy. Analysis of the observations made by Moore and Ball (1952) on a variety of surgical procedures confirms that in an "uncomplicated" single surgical operation nitrogen loss is not usually in excess of that seen in starvation. Indeed, in their "dummy operation" on a healthy medical student, nitrogen excretion continued at a "rate fully as great as that exhibited after any but the most traumatic operative procedures" (Moore and Ball, 1952). The small quantitative significance of negative nitrogen balance after an operation such as partial gastrectomy appears to have been put beyond doubt by the careful and detailed studies of Abbott and his co-workers which have been summarised by Holden et al. (1957). These investigators made balance studies on patients undergoing partial gastrectomy, colectomy and appendicectomy and found that if nitrogen and calorie intake was completely maintained by a balanced intravenous intake of amino acids, fat emulsion and dextrose the average net loss of nitrogen from the body at the end of four days was 9 g. (range +2.8 g. -14 g.).

Personal /

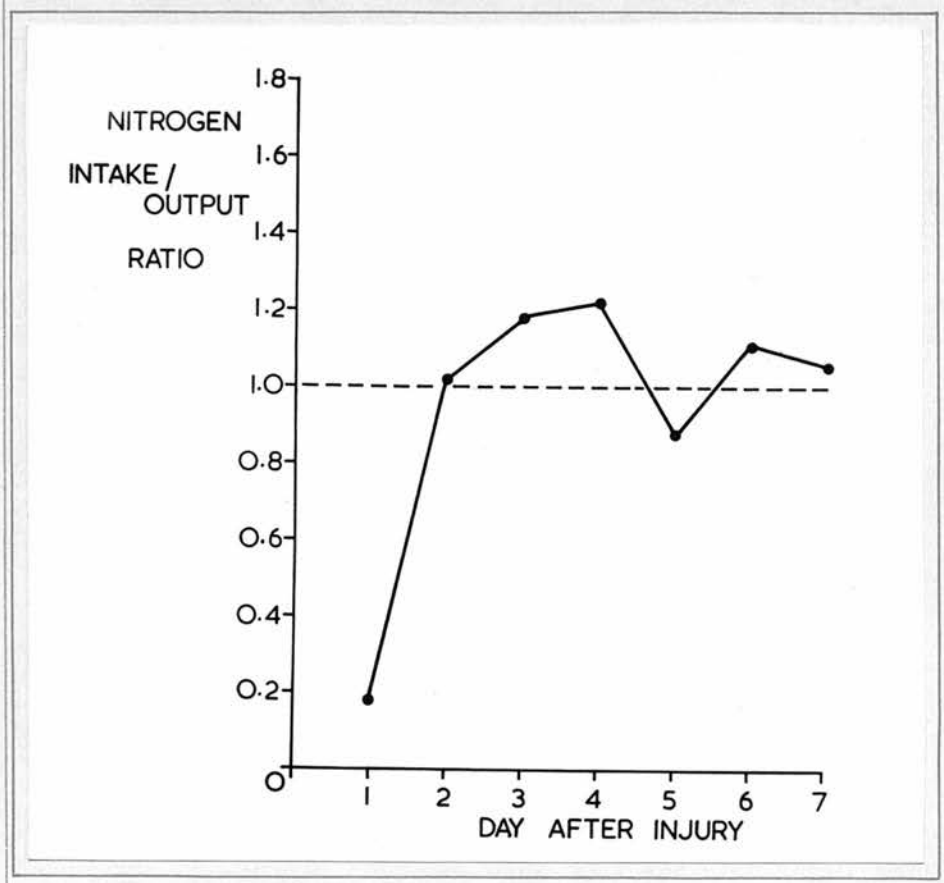

Fig. 50

Intake/output rates for a group of injured and burned patients (Appendix II, Table LV).

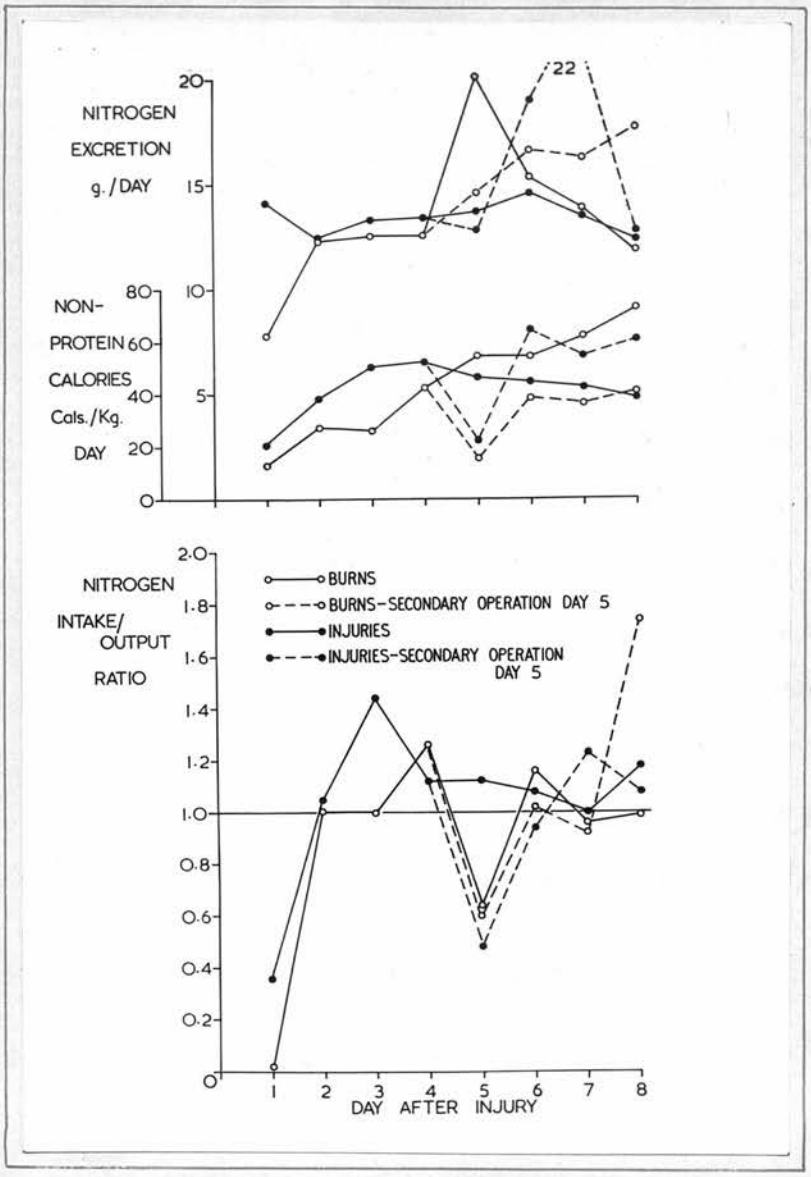

Fig. 51

Comparison of effect of burns and of injury on the intake/output ratio and the absolute excretion rate for nitrogen. The influence of a dressing on the fifth day on both caloric intake and nitrogen balance is well demonstrated (Appendix II, Table LV).

Personal studies on a variety of injured patients made in conjunction with Dr A.B. Sutherland and Mr A.D.R. Batchelor have confirmed these findings. In view of the weight of evidence already quoted these studies will not be described in detail. Fig. 50 shows a graph of nitrogen intake/output ratio for a consecutive series of cases of minor injury and burns (Appendix II, Table LV). It is seen that only on the day of injury does output exceed intake and that even in burns this intake/output ratio is below one on the day of injury only. Negative balance (ratio less than one) is produced in those patients who are subjected to a secondary procedure on the fifth day, and in patients with burns; in the former group this is a consequence of low intake rather than of increased excretion but in burns there is a rise in nitrogen excretion up to the fifth day which is maintained in the patients who are subjected to a dressing (Fig. 51). It is probable that the difference between burns and injury is the result of the continuing processes of inflammation and exudation present in the former; in this respect they resemble a fracture more closely than a soft tissue injury.

In all these cases a determined attempt was made to maintain not only a "reasonable" nitrogen intake but also, because of the influence of calorie intake on nitrogen metabolism, an adequate non-protein energy intake. The average intake obtained is shown graphically in Fig. 51 which demonstrates also the influence of secondary procedures on calorie /

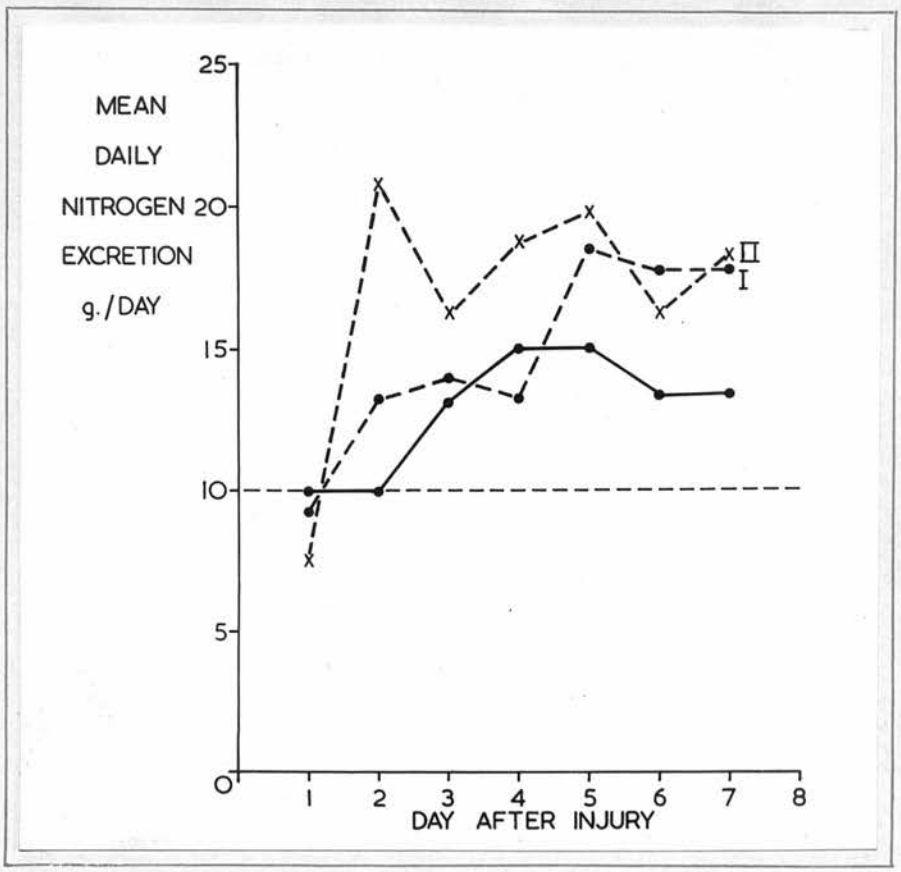

Fig. 52A

Intake/output ratios of the cases of Flear and Clarke (1956) contrasted with those of the cases in Table LV. Free intake of food results in a consistently negative balance, that is, a value of the ratio of less than unity. Group I were not transfused. Group II received massive transfusions.

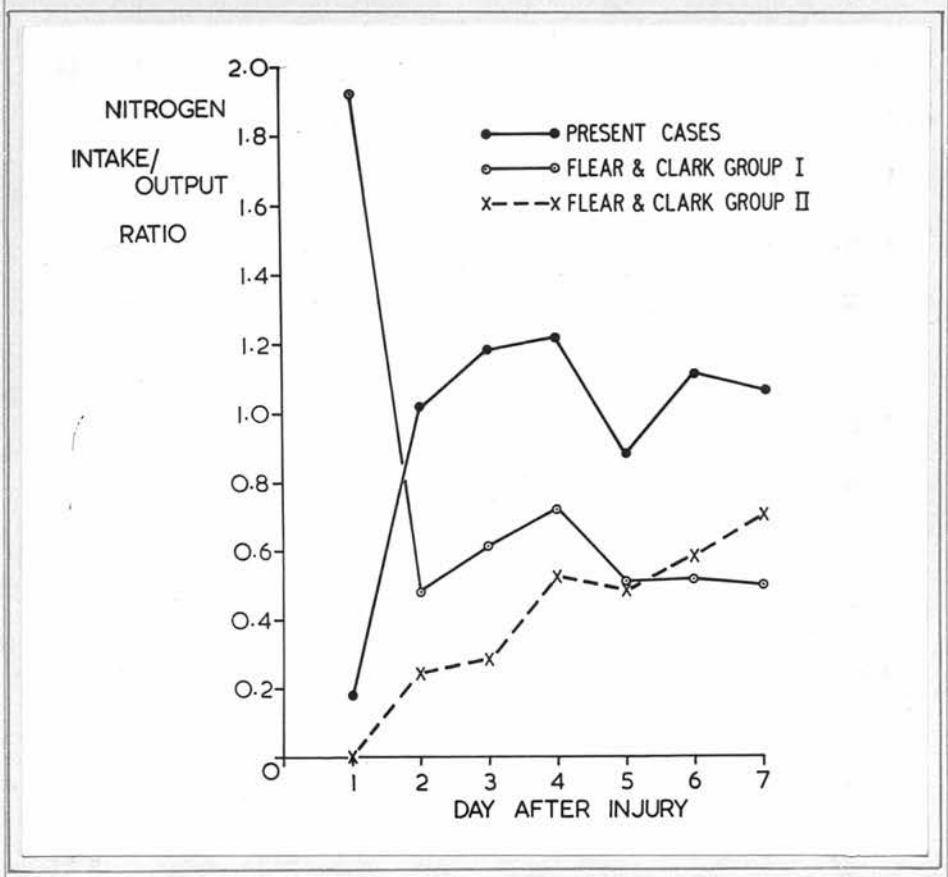

Fig. 52B

Absolute excretion rates of nitrogen in the cases of Flear and Clarke (1956) contrasted with those of the cases in Table LV. The difference is accounted for partly by the magnitude of the injury and partly by caloric intake.

calorie intake. It is clear that if calorie intake is not maintained nitrogen deficits are increased and the intake/output ratio tends to fall below one. In cases of injury and burns an adequate nutritional intake can be achieved only by a deliberate effort because unaided the patient will always fail to consume sufficient protein and calories: Fig. 52 A,B, contrasts the nitrogen intake/output ratios of the "well fed" cases with those in two groups of cases treated by Flear and Clark on a regime of self selection of food. Except when blood transfusions are given and included in the balance (Flear and Clark, Group II) there is a persistent ratio value of less than one indicating that intakes of calories and nitrogen are probably both inadequate.

All these studies lead to two conclusions. First, that there appears to be some marked quantitative differences in nitrogen excretion after accidental bony injury, after deliberate surgical operations on bones and after definitive operations on soft tissues. After bony injury, increased urinary nitrogen excretions are the rule and a negative balance is common even if nitrogen intake is maintained (although Werner's single case (p. 71) suggests that very energetic therapy might still produce a positive balance). After deliberate bony operations the nitrogen loss is less in amount and duration while in soft tissue injury there is only variable and fragmentary evidence of an increase in urinary nitrogen excretion. Secondly, any negative balance that /

that does develop apart from the special conditions of bony injury is largely a matter of nitrogen and calorie starvation.

Such conclusions inevitably pose two questions: first, the nature of the difference between the various types of injury, and secondly, whether the occurrence of a "negative nitrogen balance" can be regarded as a reliable indication of an increased rate of destruction of tissue protein - that is of a "catabolic phase" (Browne et al., 1944). Such a phase has been thought to serve the purpose of liberating large quantities of amino acid radicles for the synthesis of new tissue and also to provide energy during a period of deprivation of, or abstinence from, a normal intake of food. Experimental evidence for a selectively increased rate of protein catabolism is lacking and Madden's (1950) experiments on the incorporation of amino acids into tissues after injury suggests that the rate of anabolism is unaffected by injury. It would seem necessary, therefore, to find some explanation other than a general alteration of bodily metabolism for the increased nitrogen excretion which follows injury. From Cuthbertson's original work it appears necessary to postulate the destruction of "whole lean tissue" if the simultaneous increased excretion of phosphorus and of sulphur is to be explained and also if the occasional similarity between the rates of excretion of potassium and of nitrogen is to be accounted for (see p.). Breakdown of whole tissue, as distinct from the selective withdrawal of some substances such /

such as protein from the cell, seems unlikely in healthy tissues far from the site of injury and for this reason local sources should again be considered. In the experimental animal, actual destruction of intact tissues in the injured area during the processes of repair does not account for the high nitrogen excretions (Munro and Cummings, 1948) but recent studies by Prentice et al. (1954) and by Clark et al. (1956) have shown that a very large quantity of blood is extravasated at the site of any but the most minor soft tissue or bony injury. For example, the haematoma around a fracture of the shaft of the femur may contain up to 2 litres of blood, 48 hours after the injury has been inflicted. Crosby (1956) has shown that the red cells of such blood do not return intact to the circulation and histological studies reveal that they are subjected to the usual processes of destruction and phagocytosis (see Florey, 1957 for review). It is tempting to assume that this blood might be the source of at least some of the nitrogen excreted after injury: such a supposition is, of course, susceptible to experimental proof. Should this be forthcoming then it is no longer possible to regard nitrogen excretion rates and negative balance as an indication of any fundamental or widespread alteration in nitrogen metabolism consequent upon injury. Until the matter has been decided it would seem wise not to use rates of nitrogen excretion or nitrogen balance as a reliable indication of the body's overall response to injury.

Metabolism /

Sodium and Potassium Metabolism

Normal Electrolyte Metabolism and its Control

As with nitrogen only a most exhaustive review could completely encompass the known facts of sodium and potassium metabolism. In the present context an effort will be made only to single out those features which are of significance with respect to the metabolic response to injury and its control.

Both sodium and potassium enter the body in the food and to a less extent in drinking water and are excreted (if the small sodium losses in normal sweat are disregarded) predominantly in the urine. It follows that dietary and fluid intake will greatly influence the urinary content of both sodium and potassium but, on an average, in healthy adults the turnover rate varies between 70 and 100 mEq. per day for both ions. The available evidence suggests that the excreted sodium is a residue of the very large quantity of sodium filtered at the glomerulus after isosmotic proximal tubular reabsorption and selective distal tubular reabsorption have both "operated" on the glomerular filtrate (see Smith, 1956). However, filtered potassium is probably completely reabsorbed and that which appears in the urine is a product of tubular secretion (Mudge et al., 1948). Further, the detailed study of the composition of the urine in circumstances under which carbonic anhydrase inhibitors are in action suggests that the mechanisms for the tubular absorption /

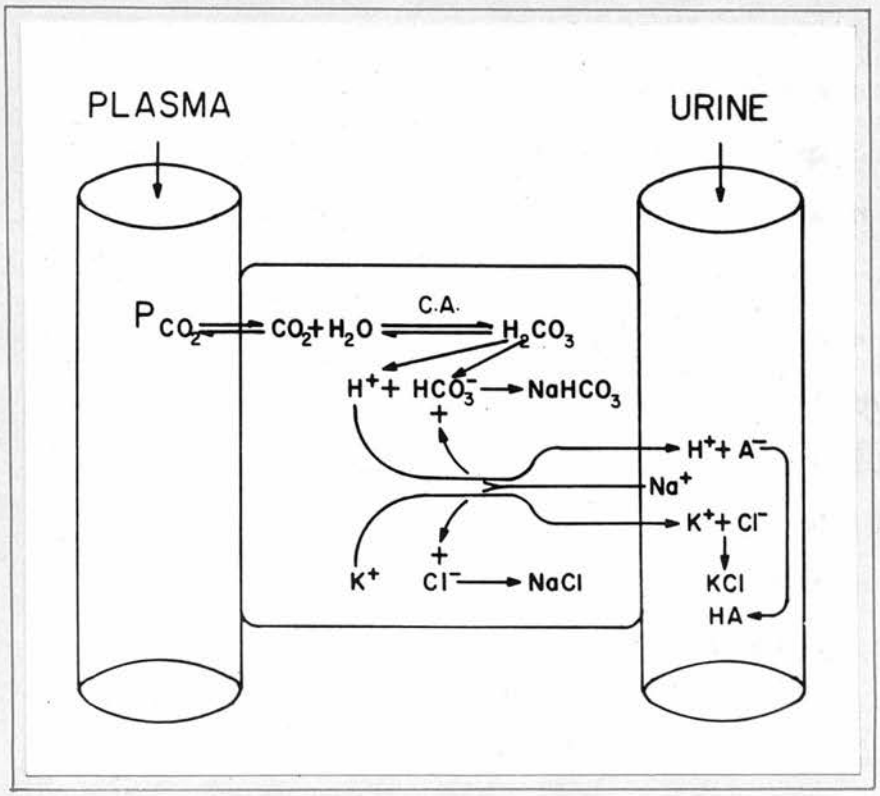

Fig. 53

Mechanisms of tubular absorption of sodium and excretion of potassium. (From Smith, 1956.) There is a common pathway for sodium reabsorption and potassium excretion so that when one is increased the other is reduced.

absorption and secretion of sodium and potassium are linked to a common competition for available hydrogen ions (see Smith, 1956 for review). This relationship is summarised in Fig. 53 and indicates that in circumstances where sodium excretion is reduced it is possible that potassium output may be increased and that the opposite may also be true. Tubular reabsorption and excretion seem to be influenced both experimentally and clinically by changes in blood flow. Reduction in renal blood flow diminishes the output of sodium and to a lesser extent that of potassium, and expansion of blood volume, for example by albumin infusion, increases renal sodium elimination. Detailed studies of these changes in man are lacking largely as a result of the difficulty of establishing the appropriate experimental circumstances in human beings.

The known, and possibly unknown, mechanisms for the adjustment of the renal elimination of sodium and potassium are further influenced by two factors. The first is load which may also be the final common pathway in the effects of alterations in blood flow. If load is increased so is excretion; reduction in load produces a reduction in output. Load is in turn a function of the product of concentration and flow and it has been repeatedly shown that changes in load too small to be derived from these measurements may account for the known range of sodium excretion (see Wesson, 1957 for review). Thus, many studies that attempt to elucidate /

elucidate the cause of changes in the rate of sodium excretion in a particular circumstance, for example after injury or operation, must be made with the knowledge that ~~indeterminate~~ unmeasurable changes in filtered load may be taking place. This is a serious drawback that has been insufficiently appreciated in the majority of clinical studies although its appreciation adds only to the degree of uncertainty of the interpretation of the results.

The second known factor which influences sodium and potassium excretion is the activity of the suprarenal cortex. Since the first experimental adrenalectomies were carried out and the first biochemical observations made on patients with chronic adreno-cortical destruction (Addison's disease), it has been known that the fine control of sodium excretion and metabolism is largely dependent upon this gland. In brief, reduction in adreno-cortical secretion favours the renal excretion of sodium* and the conservation of potassium whereas increase tends to produce sodium conservation and potassium loss. The effect is mainly on the facultative absorption of sodium in the distal tubule, although changes in the filtered load cannot be excluded in view of the known effects of adreno-cortical hormones on the overall physical processes of the body and thus on the dynamics of renal /

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* Not only are renal sodium losses increased but also flexibility of function is lost and the kidney adapts poorly or not at all to an increase in sodium load.

renal blood flow. When this relationship between adrenal cortex and renal electrolyte excretion was ~~first~~ established and after cortisone and hydrocortisone had been discovered, it was thought that they were the responsible hormones, ~~responsible hormone~~, but it was not clear why the synthetic substance desoxycorticosterone acetate was far more active than the naturally occurring hormones. The difficulty was resolved by the discovery of a further adreno-cortical secretory product with specific effects on renal sodium and potassium excretion (Simpson et al., 1954). This substance, aldosterone, appears to be the one mainly responsible for the normal control of sodium and potassium balance: in excess, as occurs in some instances of adreno-cortical adenoma (Conn, 1955), it produces an increased renal excretion of potassium and occasionally a degree of sodium excess within the body (Thorne et al., 1957); it is absent when Addison's disease is present and is often increased in the urine in physiological and pathological states of diminished sodium excretion. However, unlike most of the hormones of the adrenal cortex it is not totally subservient to the anterior pituitary gland and appears to be more closely associated, by a reflex arc which is at present undetermined, with the volume of the extracellular fluid and therefore with the body content of sodium (Barrter, 1956). This is not to say that changes in anterior pituitary activity do not result in changes in sodium and potassium excretion; administration of adreno-corticotrophic hormone (ACTH) results in a diminished renal excretion /

excretion of sodium and an increased (although variable) elimination of potassium (Forsham et al., 1948) but whether these effects are the consequence of a small change in aldosterone production or of the secretion, under the influence of ACTH, of sufficient cortisone-like substances to produce identical effects is not known. The overall effect of adreno-cortical activity on potassium excretion is probably made up of two components. First, changes in adreno-cortical secretion influence bodily metabolism so that increased activity may produce nitrogen catabolism which is associated with the liberation and excretion of intracellular potassium; secondly, as has already been described, renal potassium and sodium excretion are linked so that alterations in the excretion rate of the former under the influence of adrenal hormones may secondarily and reciprocally influence the urinary content of potassium.

When sodium and potassium are withdrawn from the diet, different effects occur for each ion. As befits its position as the main osmotic extracellular constituent, sodium is strictly conserved by the kidney so that renal excretion is progressively reduced to very low levels (5-10 mEq. daily). This reduction is stepwise over 2-3 days and is associated with increased amounts of aldosterone in the urine (an indication that the change in renal sodium excretion is probably dependent upon activation of the adrenal cortex (see Leaf and Couter, 1949 for additional evidence in this connection) /

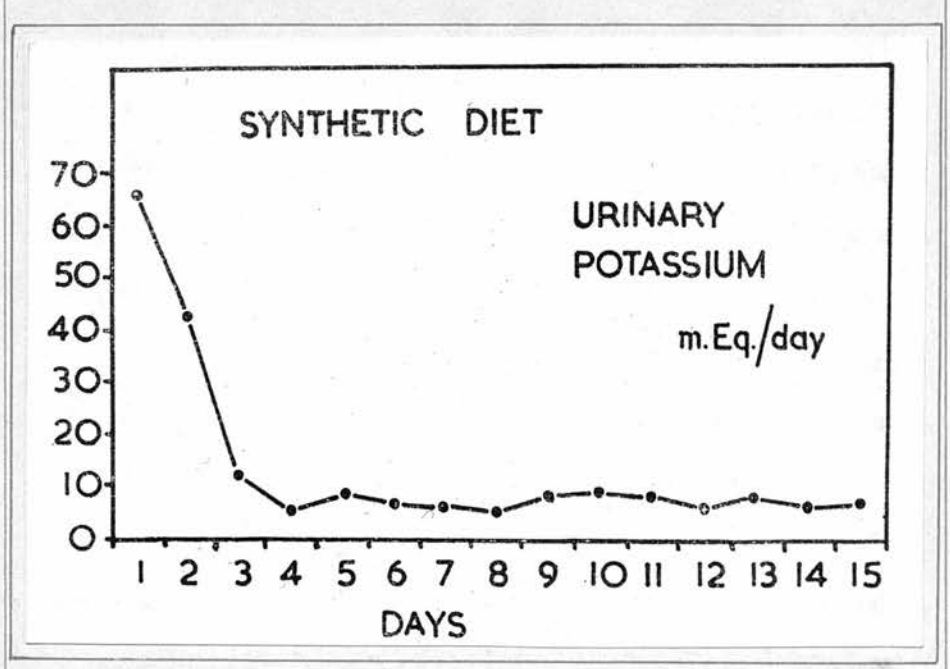

Fig. 54

Effect of nitrogen-free electrolyte-free diet on potassium excretion in man. Reproduced from Lowe (1953).

connection)). Renal sodium losses are more effectively reduced if a minimal 400 calories are provided from carbohydrate sources (Gamble, 1947). Potassium conservation in starvation is much less complete, although in one series of experiments in which adequate nitrogen-free calories were supplied, excretion was very rapidly reduced to insignificant levels (see Fig. 54; Lowe, 1953). If water deprivation accompanies starvation, potassium excretion is temporarily increased over the first 24-36 hours and thereafter returns to the levels seen in starvation (Elkington et al., 1942; Elkington and Winkler, 1944). The explanation of these potassium changes is thought to lie in the variable rates of the breakdown of protein and the mobilisation of intracellular water. If the potassium/nitrogen ratio (K/N ratio) of the urine is examined in starvation it is found to correspond closely to the K/N ratio of "wet lean tissue", a correspondence which suggests that in this circumstance, whole tissue is being broken down for energy purposes. The increased renal excretion of potassium over nitrogen which is a feature of water deprivation may represent a liberation of cell water separate from protein changes although the significance of this occurrence is not clear.

Sodium and Potassium Metabolism after Injury

The interest in the renal excretion of nitrogen occasioned by the work of Cuthbertson (see p.66) and the development /

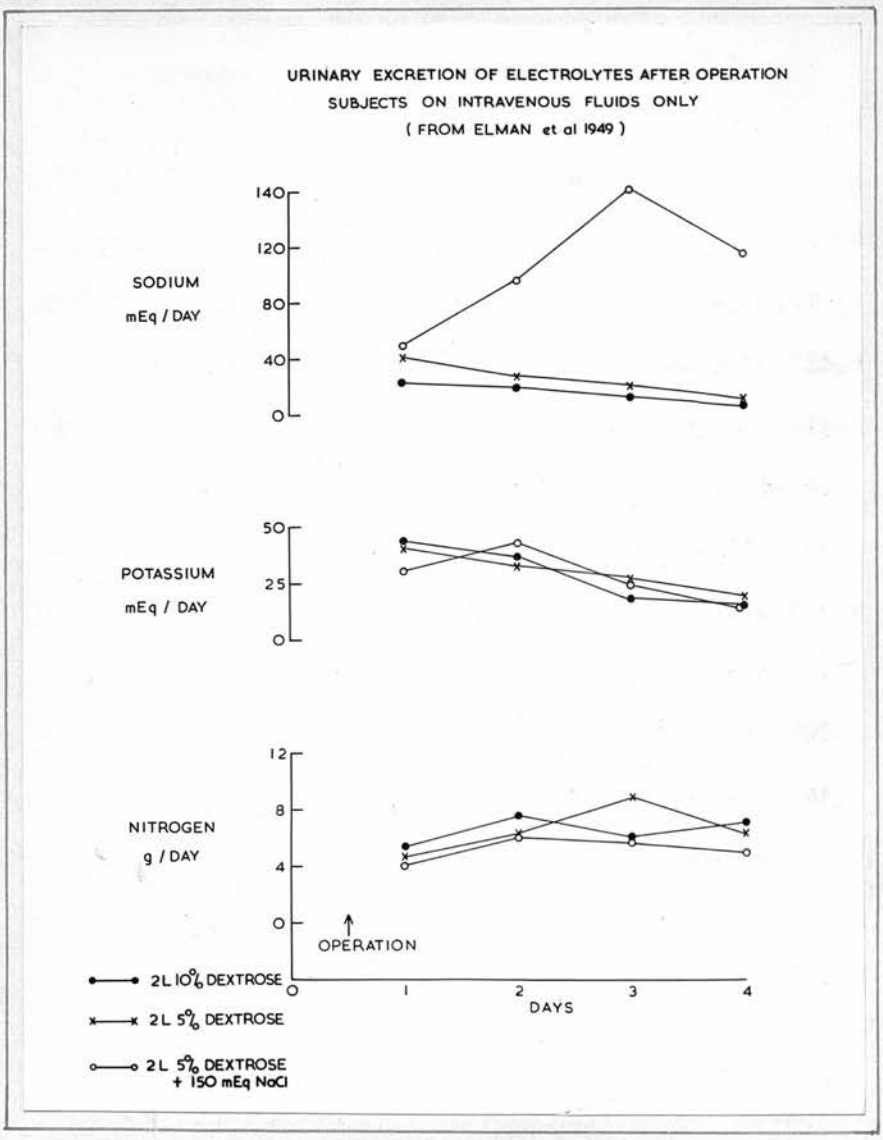

Fig. 55

Changes in renal sodium, potassium and nitrogen excretion after major operations in man. Redrawn from Elman et al. (1949).

development and application of techniques for intravenous fluid replacement has resulted in many advances in knowledge of changes in renal excretion of sodium and potassium after injury and operation. Coller et al. (1944) described a condition of "salt intolerance" after major operation in which administered isotonic saline was retained instead of being excreted; Berry et al. (1948) showed that potassium excretion was increased in the first 24 hours after operation and this was confirmed by Blixenkrone Møller (1949) who concluded that the excretion rate bore a rough relationship to the magnitude of the operation. These observations were confirmed and extended by Wilkinson et al. (1949, 1950 a & b) who also showed that the reduction in renal excretion of sodium took place irrespective of the level of intake. The quantitative changes in sodium and potassium elimination are a rapid reduction in sodium excretion from approximately 100 to 15-20 mEq./day in one day and a variable increase in potassium output to upwards of 120 mEq. on the day of operation, an effect which is usually over by the following day. The duration of restriction on the renal excretion of sodium may extend to 7 days but more usually is only 3 days and even by the second day a large proportion of an administered load of sodium chloride is eliminated. Fig. 55 redrawn from the data of Elman et al. (1949) shows in graphic form the changes for sodium and potassium described and indicates also that nitrogen excretion /

excretion does not always change in spite of alterations in potassium output. The onset of diminished sodium excretion is much more rapid than that found in simple sodium deprivation, although the change in renal potassium excretion is not often in excess of that seen in the early stages of starvation and water deprivation. The rapidity and intensity of the changes in sodium excretion led Wilkinson et al. (1949) to postulate an additional restrictive mechanism to that imposed by starvation and Wilkinson (1957) has recently emphasised this distinction again.

Of the two electrolyte changes that do occur, that for sodium is undoubtably the more constant. From what has already been concluded about the probable origin of the increased nitrogen excretion after injury and from the apparent correlation between the severity of injury and potassium excretion it seems likely the latter may also originate in damaged tissues and possibly in lysed blood at the site of injury. Therefore potassium excess in the urine probably represents a local consequence of trauma rather than any evidence of purposeful metabolic response.

Conclusions regarding the renal "indicators" of the metabolic response to injury

The foregoing discussion and results indicate that in the absence of firm conclusions regarding the significance of local tissue damage and the breakdown of accumulations of blood at the site of injury it would be unwise to attach

any /

any fundamental metabolic significance to changes in nitrogen and potassium excretion and balance as indications of a purposeful response to injury. However, reduction in sodium excretion seems to be an invariable occurrence, is not so closely related to the degree of trauma and is largely uninfluenced by variations in ionic or calorie intake. Therefore, it should be regarded as the most reliable indication of a fundamental alteration in metabolism and any explanation of post-operative metabolic changes should centre on this response rather than on that of nitrogen or of potassium. Without certain evidence on the cause and origin of increased potassium and nitrogen excretion it is, of course, desirable that any hypothesis of causation should also admit the inclusion of changes in the metabolism of these substances. Nevertheless, their incorporation in any logical structure should be regarded as secondary to the need to explain changes in sodium excretion.

Causative Factors in the Metabolic Response to Injury: Control by Neuro-humoral Responses

The purpose of the foregoing discussion was to test the foundations upon which the concept of a metabolic response to injury is based. It is now possible to turn to a consideration of the causation of changes described. Cuthbertson interpreted the nitrogen response as purposeful and it is certainly not difficult to conceive the necessity for the consumption /

consumption of endogenous protein after injury both to supply energy and to provide the necessary materials for wound healing. Similarly, changes in sodium excretion could serve the purpose of maintaining extracellular fluid volume and thus preserving the body's transport system. If such a change is purposeful it must have some mechanism, nervous, humoral or both, whereby it is brought about. Impressed by the similarity between the metabolic changes seen in pathological adreno-cortical hyperactivity (Cushing's disease) and those observed after injury and cognisant from the work of Selye (1950)* of the occurrence of adrenal hyperfunction as a general response to physiological situations that involved stress, Albright (1942) was the first to put forward the hypothesis that the observed changes were brought about by hyperactivity of the adrenal cortex. This interpretation could explain not only the changes in sodium excretion but also those that irregularly involve nitrogen and potassium because stimulation of the adrenal cortex by ACTH or the administration of exogenous adreno-cortical steroids produces a transient increase in the rate of excretion of both these substances. Albright's concept has gained considerable support as refinements in the chemical techniques of steroid hormone estimation have permitted more and more accurate identification of the substances of adreno-cortical /

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* See Sayers (1950) for review.

adreno-cortical origin excreted in the urine after injury. Although methods have differed greatly from investigation to investigation, most workers in this field are agreed that if a priori reliable indices of adreno-cortical activity are chosen* there is an increased urinary excretion of the end products of the metabolically active adreno-cortical steroids in the immediate post-injury phase. Such increased excretion usually lasts for from 24 to 48 hours in the urine but may be prolonged either in association with continued stress such as in a burn (Hardy, 1954; Hume et al., 1956), with complications, or without apparent reason (Moore et al., 1955). More recently it has been demonstrated that the concentration of free 17-hydroxysteroids of blood increases during and after operation (Sandberg et al., 1954; Tyler et al., 1954; Steenbert et al., 1956), an increase which is usually short-lived (16-24 hours) and which precedes or overlaps the alterations in urinary excretion of the end products of steroid metabolism. Other evidences of adrenal hyperactivity usually accompany these steroid changes: in man, eosinopenia, and alterations in glucose tolerance and fat oxidation; /

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* Urinary 17 ketosteroids are often increased in hyperplastic diseases of the adrenal cortex such as those associated with Cushing's syndrome (Albright, 1942), but in spite of this, these substances are not a reliable index of physiological adreno-cortical function in respect of electrolyte balance and probably of metabolic activity for nitrogen and carbohydrate. The spurious popularity they have enjoyed in this respect has led to some confusion because in fact they are the only group of commonly estimated urinary steroid substances of presumed adrenal origin that do not show consistent increases after surgery or injury (see Fig. below). Much more reliable information is derived from estimation of those substances or groups of substances which represent the end products of metabolism of cortisone-like substances: total formaldehydogenic steroids and 17-OH steroids.

oxidation; in the experimental animal, adrenal hyperplasia. Therefore, there is strong evidence that increased adrenocortical activity accompanies injury. It would appear reasonable to assume that it might therefore be the cause of the changes in sodium metabolism and possibly be concerned also in the alterations in excretion of potassium and of nitrogen. This hypothesis has been developed to the greatest extent by Moore and Ball (1952) and by Moore (1953).

The discovery of aldosterone already referred to (p. 81) suggested that the post-operative electrolyte changes might be specifically related to this substance. In agreement with this hypothesis several workers have found it to be present in increased amounts in the urine after major surgical procedures (Llaurado, 1955; Zimmermann et al., 1956; Llaurado and Woodruff, 1957). The absolute quantities present vary considerably, but this is hardly surprising in view of the small proportion of exogenous aldosterone that can be recovered from the urine after parenteral injections (Thorne et al., 1957) and of the chemical and biological difficulties involved in its extraction and assay. If it is indeed the case that increased adrenal function is a feature of injury and surgical operations then it would seem probable on the grounds of the available evidence that the complete neuro-endocrine reflex arc is made up by the hypothalamic pituitary connections postulated and partially demonstrated by Hume (1953) and by Harris (1955). In response to stimuli from the central nervous system, the anterior pituitary secretes /

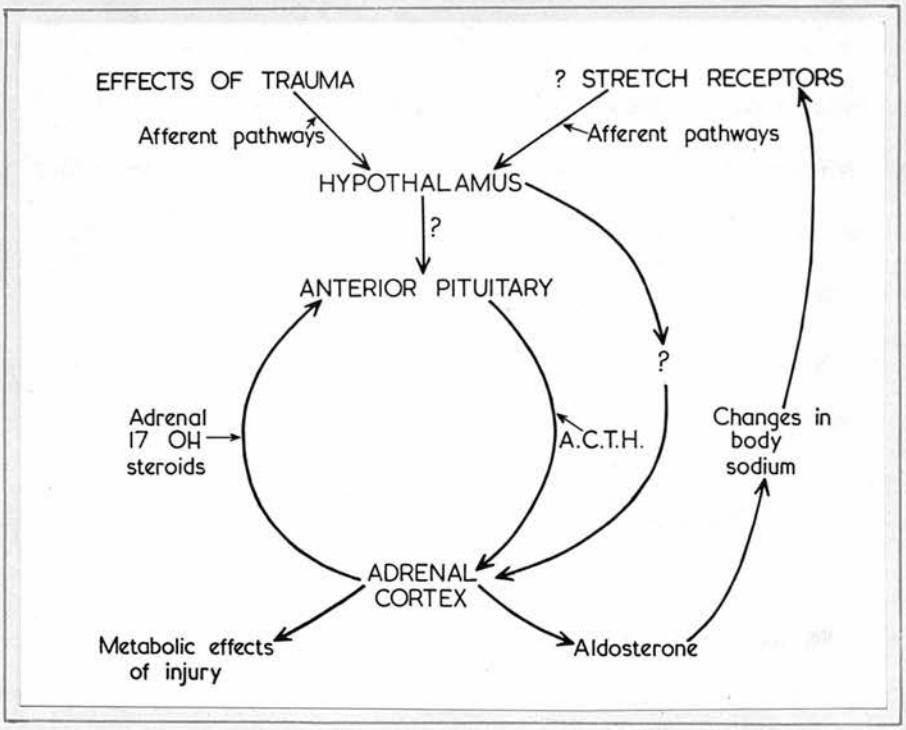

Fig. 56

The current concept of the neuro-endocrine control of the metabolic response to injury. Some of the pathways depicted - particularly that which controls aldosterone - are still conjectural. (See Barrter et al., 1958.)

secretes adrenocorticotrophic hormone (ACTH) which in turn increases the secretion of adrenal hormones. This hypothesis (summarised in Fig. 56) has the attraction of being based on known physiological pathways and of ascribing to a common origin in the pituitary not only the changes in metabolism at present under consideration but also those that involve water. However, the apparent independence of aldosterone from pituitary control suggests that the stimulus to an increased secretion of this substance must be sought elsewhere perhaps in direct hypothalamic-adrenal stimulation (Smith, 1957). A consideration of this matter is at present deferred (see p. 104).

Permissive Action of the Adrenal Cortex in Relation to Injury

In spite of these apparently incontrovertible experimental facts and the deductions that have been made from them, there is still nothing which logically requires the assumption that there is a causal association between adreno-cortical activity and the metabolic response to injury. The association in time is, of course, highly suggestive but for final proof it must be shown that the metabolic response to injury is absent when changes in the rate of secretion of adrenal cortical secretion can be excluded. This logical barrier and the gradual growth of experimental knowledge which indicated that the presence of adreno-cortical hormones /

hormones was permissive to the performance of a wide variety of intermediate metabolic processes (for summary see Ingle, 1953) suggested that the action of the adrenal cortex in relation to the metabolic response to injury might be merely "permissive" rather than "causative" in the exact sense of the latter term. Ingle et al. (1947) put this theory to the test by the production of femoral fractures in the forced-fed adrenalectomised rat maintained on a constant dose of adrenal cortical hormones. A typical increased nitrogen excretion followed although in view of the doubts relating to the validity of nitrogen excretion as an index of a true generalised tissue response (see p. 76) this finding must be treated with some caution. However, Ingle's group (Ingle et al., 1951) further demonstrated that fracture in the same preparation was followed by the characteristic reduction in sodium excretion (potassium excretion showed a reduction followed by an increase - an unfamiliar type of response in terms of human metabolism. The foundation of the permissive theory of adrenal activity in relation to the metabolic response to injury was thus laid in the experimental animal and both Engle and Ingle have developed this theory in greater detail in subsequent publications (Engle, 1951; Ingle, 1953).

The use of bilateral adrenalectomy in human subjects as a means of treatment for hypertension and for malignant disease of the breast has now provided the opportunity directly /

directly to explore the possibility of a permissive action of the adrenal cortex in man. Ideally it would be desirable to produce trauma in a previously adrenalectomised subject but because the opportunity for this rarely arises* it was felt that the metabolic response to the operation of adrenalectomy itself might be used to provide information of the type desired. A study of adrenalectomy is, of course, open to the criticism that metabolic events set in train by anaesthesia and the early stages of surgery may occur or be initiated through normal adreno-cortical pathways before the adrenal has been removed. However, it is difficult to see how such a long-standing phenomenon as reduction in the renal excretion of sodium for 3-4 days can be entirely determined by a stimulus that can act through the adrenal cortex for only some 30 minutes (this matter will be discussed again on p. 104).

PLAN OF INVESTIGATION OF THE PERMISSIVE ACTION OF THE ADRENAL CORTEX IN MAN

Three methods of investigation of the postulated permissive action are possible in patients who are submitted to adrenalectomy.

A. To study the overall metabolic response to surgery in a patient who undergoes adrenalectomy while on a constant dose of cortisone, that is, to measure changes in urinary excretion and in balance for sodium, potassium and nitrogen. Such /

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* See, however, investigations of Forrest et al. (1957) described on p.

Such an investigation should be combined with a measurement of urinary steroid excretion.

B. To measure aldosterone excretion under similar circumstances.

C. To investigate the levels of blood 17-hydroxy-corticoids in similar patients.

A. Metabolic Response to Surgery in Patients undergoing Adrenalectomy

Plan of observations.- Estimations were made of the 24-hour urinary excretion of sodium, potassium, nitrogen and corticosteroids in one patient subjected to bilateral adrenalectomy and splanchnicectomy carried out in two stages, in one subject subjected to second stage adrenalectomy and one patient undergoing bilateral adrenalectomy. With the exception of the day of operation and first three days thereafter, all the patients received a diet constant for each one and containing calories within the range 1400 to 2000. The basic diet contained 0.5 g. sodium chloride (8.6 mEq. each of sodium and chloride) and 1.2 to 2.0 g. potassium (30-50 mEq.). The greater part of the potassium was derived from canned fruit juice and each patient received a fixed daily allowance from a single batch. The diet was supplemented with 4.5 g. sodium chloride (77 mEq. each of sodium and chloride) per day given by mouth as cachets. The total sodium intake was thus 85.6 mEq. approximately. On the day of operation food was not eaten, and a slow intravenous infusion of 500 ml. of 0.9 /

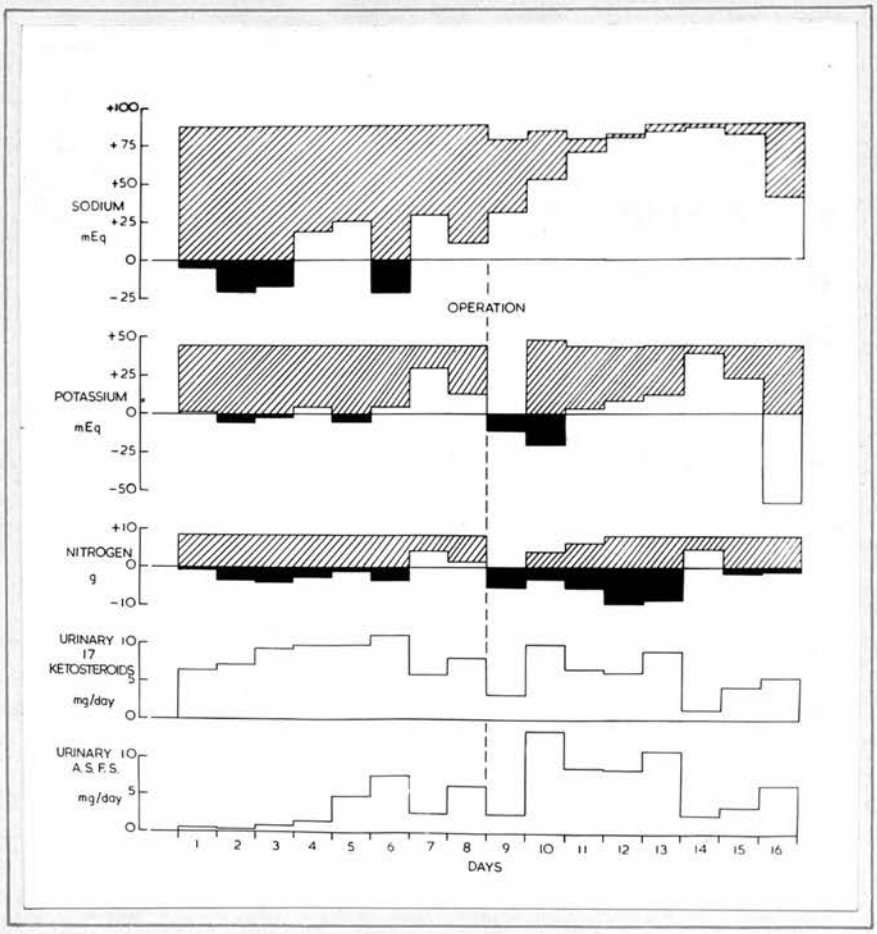

Fig. 57

Metabolic response to first stage adrenalectomy (Appendix II, Table LVI).

0.9 per cent. sodium chloride was given to ensure an intake of 77 mEq. sodium chloride. In some of the cases 400 to 1200 ml. of blood were transfused to replace measured operative blood losses but this blood was not included in the balance figures. On the first three post-operative days the intake of potassium and of nitrogen was estimated from the actual amount of the diet consumed, and the salt intake of 77 mEq. was maintained either by infusion or by oral administration. Thereafter the basic diet, supplemented by 77 mEq. sodium chloride, was once more given. The patients received 50 mg. of cortisone acetate four times per day by intramuscular injection. The cortisone was begun from five to twelve days before the operations, and the patients were in sodium, potassium and nitrogen equilibrium for some days before the operation. The dose of cortisone used is more than the minimum necessary for recovery from adrenalectomy*, and was considered ample to ensure the uncomplicated convalescence desirable for a satisfactory balance study. This indeed proved to be the case in these subjects.

Results.- The results of the studies are shown in terms of overall metabolic balance in Figs. 57-59. In Fig. 57 (Appendix II, Table LVI) are shown the typical changes in sodium, potassium and nitrogen balance that occur after a first /

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* This minimum is not established with certainty but is probably less than 100 mg. daily. Metabolic conclusions based on high dosages up to 600 mg. (e.g. Wilkinson, 1955) must be treated with caution.

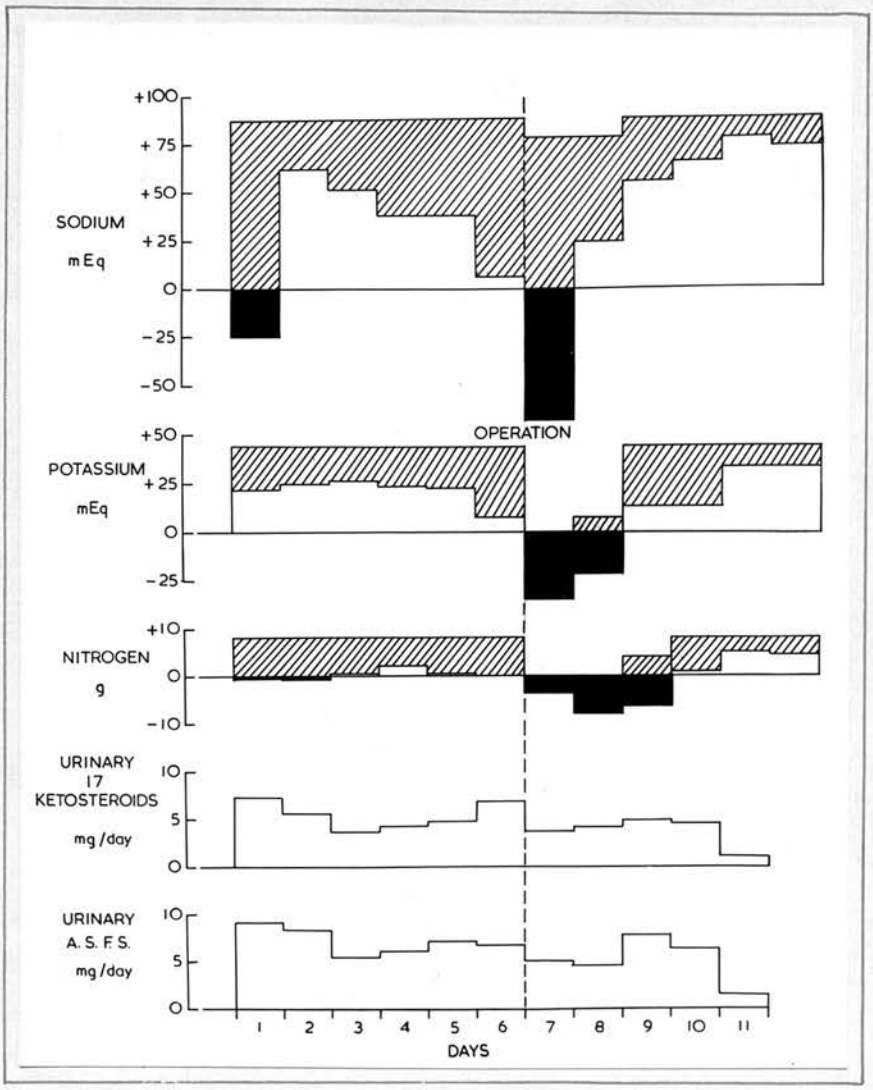

Fig. 58

Metabolic response to second stage adrenalectomy (Appendix II, Table LVI).

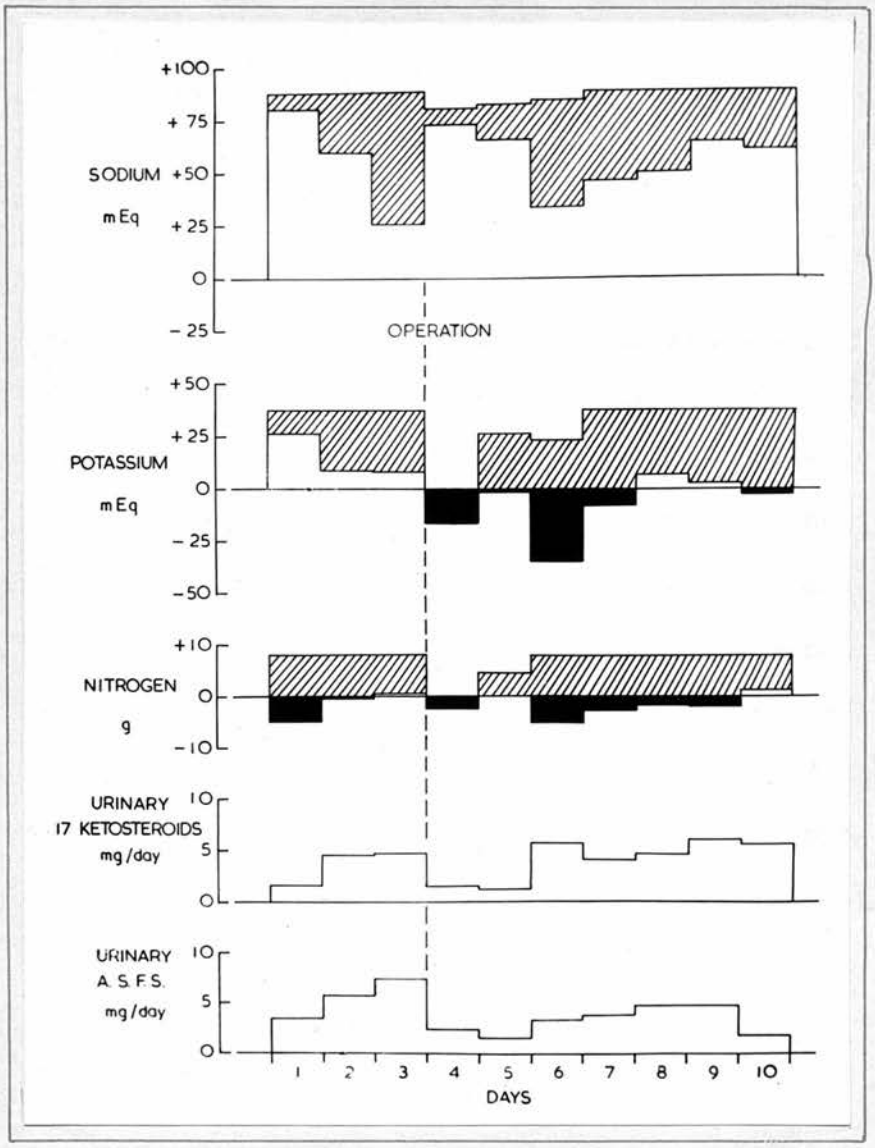

Fig. 59

Metabolic response to second stage adrenalectomy (Appendix II, Table LVII).

first stage adrenalectomy. There is a marked reduction in renal excretion of sodium which, in association with a continued intake, produces a considerable positive balance. Potassium output does not change greatly but a negative balance occurs as a consequence of reduced intake in the first three post-operative days. Nitrogen balance is negative for a similar reason but the excretion rates do not exceed those occasionally encountered in starvation and therefore no metabolic significance can be attached to them. Excretion of acid stable formaldehydogenic steroids (ASFS) also increases during the first four days although considerable variations occur from day to day. The second stage operation in the same patient is illustrated in Fig. 58 (Appendix II, Table LVI). Before operation there is a slightly positive balance of sodium presumably a consequence of the moderate exogenous dose of cortisone. Over the four day post-operative period of study there is a moderate retention of administered sodium slightly less in degree than that seen after the first operation but considerably greater than that present before operation. The absolute sodium excretion rate is significantly reduced. The nitrogen and potassium changes are similar to those in the first stage operation but there is no change in the rate of excretion of ASFS - a crude indication that an increase in the rate of production of adreno-cortical hormones comparable to that seen after the first stage operation has not taken place. Fig. 59 (Appendix /

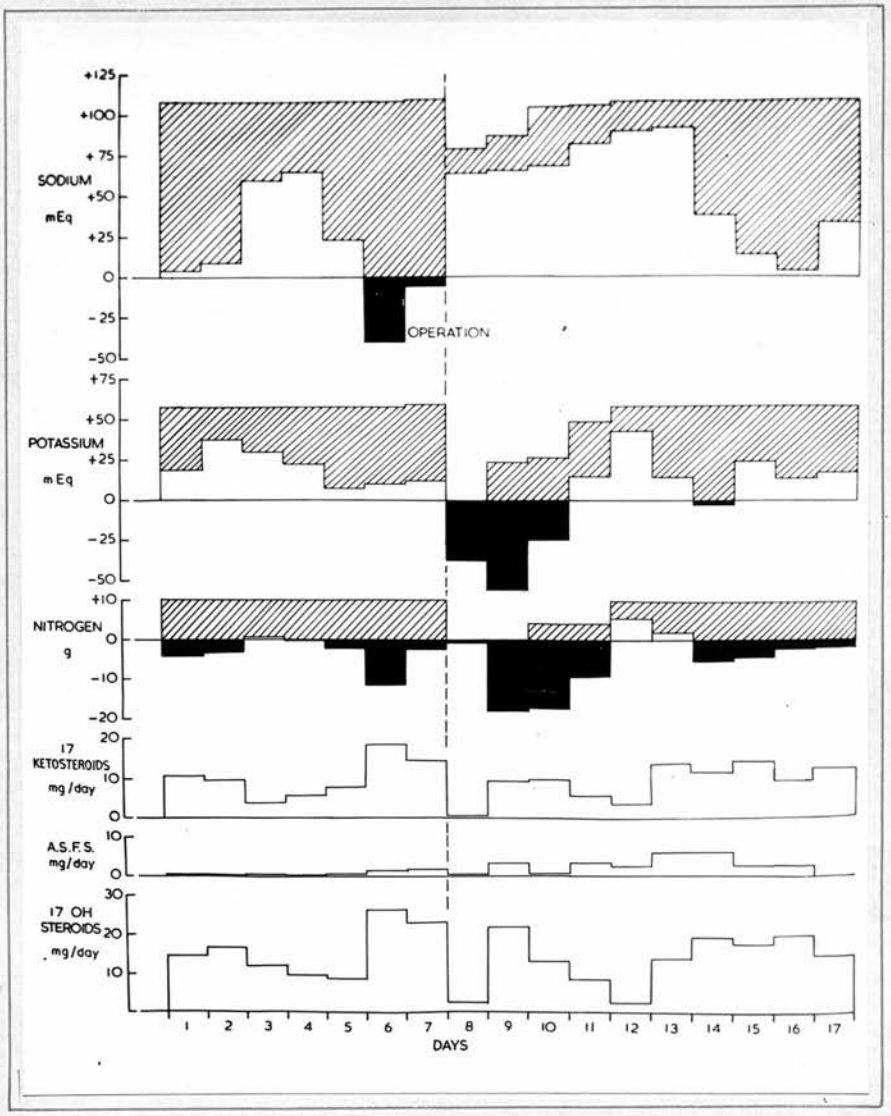

Fig. 60

Metabolic response to second stage adrenalectomy (Appendix II, Table LVIII).

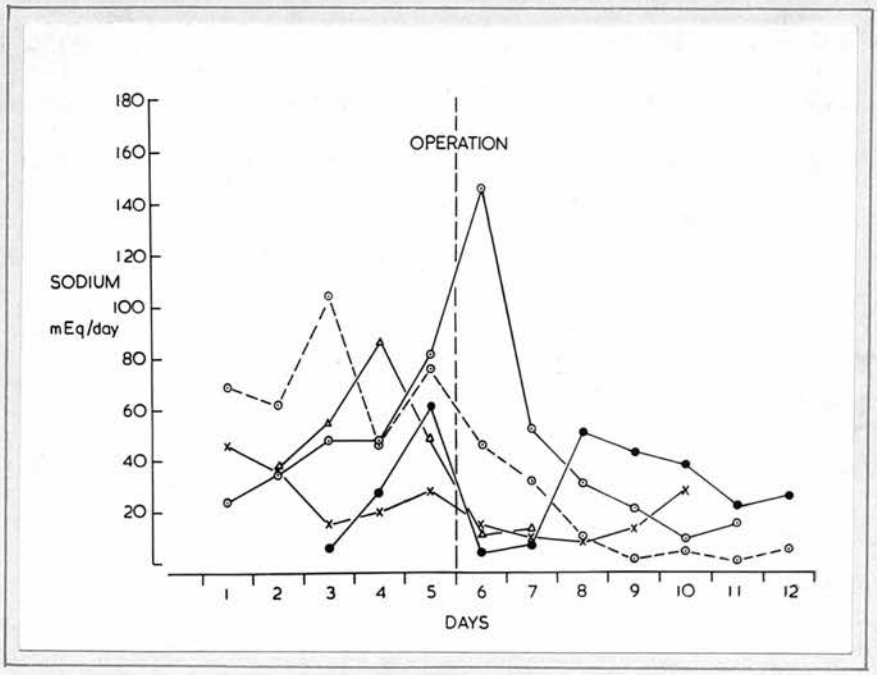

Fig. 61

Absolute excretion rates of sodium in three female patients before and after second-stage adrenalectomy. A first-stage adrenalectomy is shown by contrast. The first stage is shown by the dotted line which connects open circles.

(Appendix II, Table LVII) shows the overall balance results for a second stage adrenalectomy. In this instance blood loss occurred during the operation and approximately 1400 ml. of citrated blood were given at this time. Sodium and chloride balances are grossly positive on the day of operation and the first post-operative day but the nitrogen changes are again compatible with those seen in starvation. Finally, Fig. 60 (Appendix II, Table LVIII) shows the third example of a second stage adrenalectomy: in this, moderate sodium retention with considerable reduction in the rate of excretion of sodium occurs. In this healthy young man, nitrogen excretion rises to levels more often seen in bony injury (see p. 66). 17-hydroxycorticoids in urine were studied as an alternative and possibly slightly more specific indication of adreno-cortical activity of "metabolic" type. When 200 mg. of cortisone were given daily, high rates of excretion were found but operation did not increase the rate as it does in a patient with intact adrenals (Moore et al., 1955) and on the day of operation urinary output of these substances is in fact very small. The absolute excretion rates of sodium for the three patients after second stage adrenalectomy are shown in Fig. 61. In all, sodium excretion was reduced post-operatively although in one instance (Fig. 58) it remained strikingly high on the day of operatim.

Summary.- The results of these metabolic studies on patients undergoing adrenalectomy may be summarised as follows: /

follows:

(1) Reduction in the absolute excretion of sodium with the consequent development of a positive balance.

(2) Absence of an increase in the excretion of adreno-cortical steroids such as is usually associated with injury.

(3) Variable changes in the excretion of potassium and of nitrogen which correspond in duration and in magnitude with those regarded as part of the metabolic response to injury but which are for the most part of insufficient degree to permit their certain separation from those seen in starvation.

B. Urinary Excretion of Aldosterone in Patients submitted to Adrenalectomy

The evidence already referred to that aldosterone is in all probability the adreno-cortical hormone which is responsible for the normal control of sodium and potassium excretion by the kidney, and the observation of changes in sodium metabolism after adrenalectomy, suggested that it would be desirable to eliminate aldosterone as a cause of these post-operative changes. Although it seems unlikely that aldosterone produced in the short period prior to adrenalectomy could be responsible it is desirable to exclude it by direct measurement and also to establish that it is not being produced from some extra-adrenal or accessory adrenal source after operation. To this end, aldosterone was measured in the urine of three of the patients /

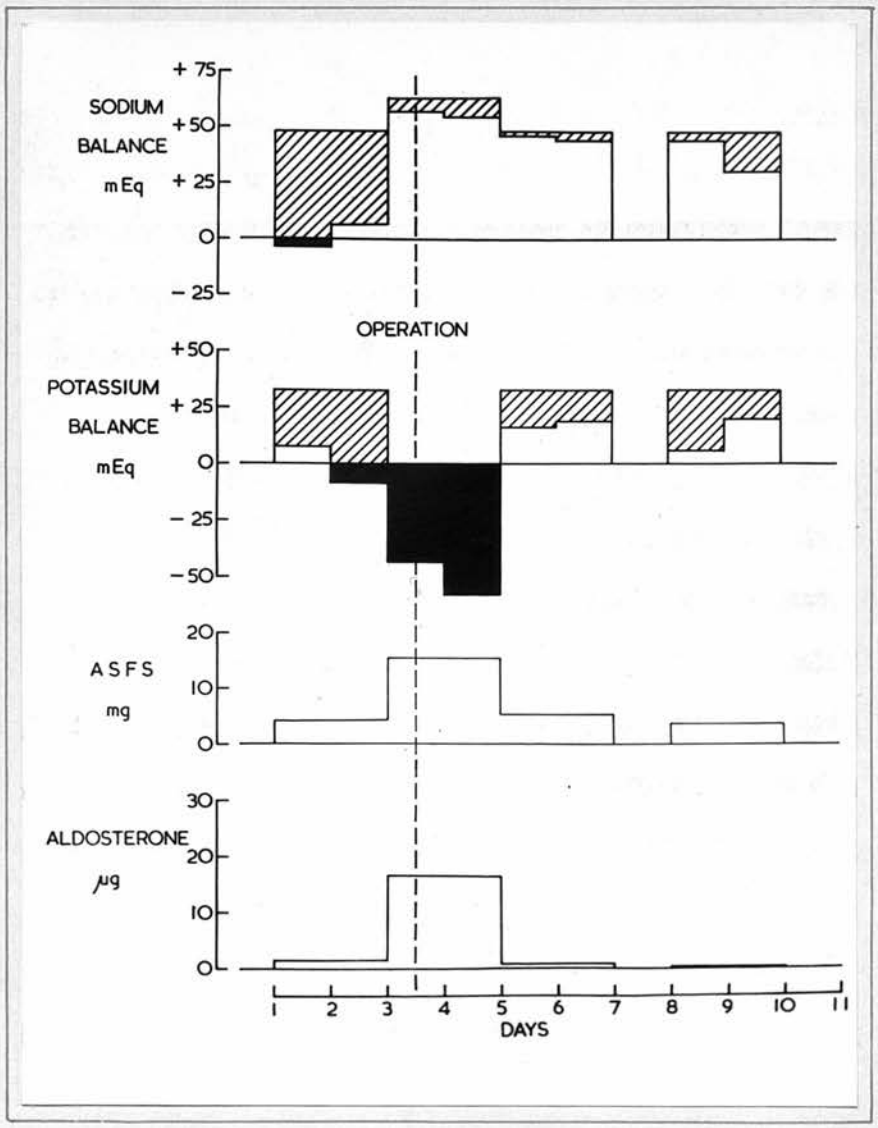

Fig. 62

Metabolic response to first-stage adrenalectomy (Appendix II, Table LIX).

patients who underwent adrenalectomy. One was the subject listed in Table LVIII already described and the other two were the subjects of the studies which will be described under section C below.

Results.- On the days before operation aldosterone was excreted in all patients, but post-operatively, in spite of the usual reduction in sodium excretion, aldosterone was absent from the urine. Fragmentary data are available on two other patients. The first showed a normal metabolic response in terms of sodium, 17-hydroxysteroids and aldosterone (Fig. 62; Appendix II, Table LIX) after a unilateral adrenalectomy: this can be taken to indicate that when one or other adrenal is intact such an operation is sufficient to produce a change in the rate of urinary excretion of aldosterone. She died of liver failure within a few hours of second stage adrenalectomy and therefore the presence or absence of aldosterone after both adrenals had been removed could not be confirmed. The last patient (Appendix II, Table LX) was submitted to an uneventful bilateral oophorectomy 10 days after bilateral adrenalectomy, but died two days later. Although aldosterone was absent from her urine for six days before oophorectomy and for the two days she survived thereafter, and although she demonstrated a reduction in urinary sodium and increase in urinary potassium, she cannot be regarded as a satisfactory study.

Summary.- /

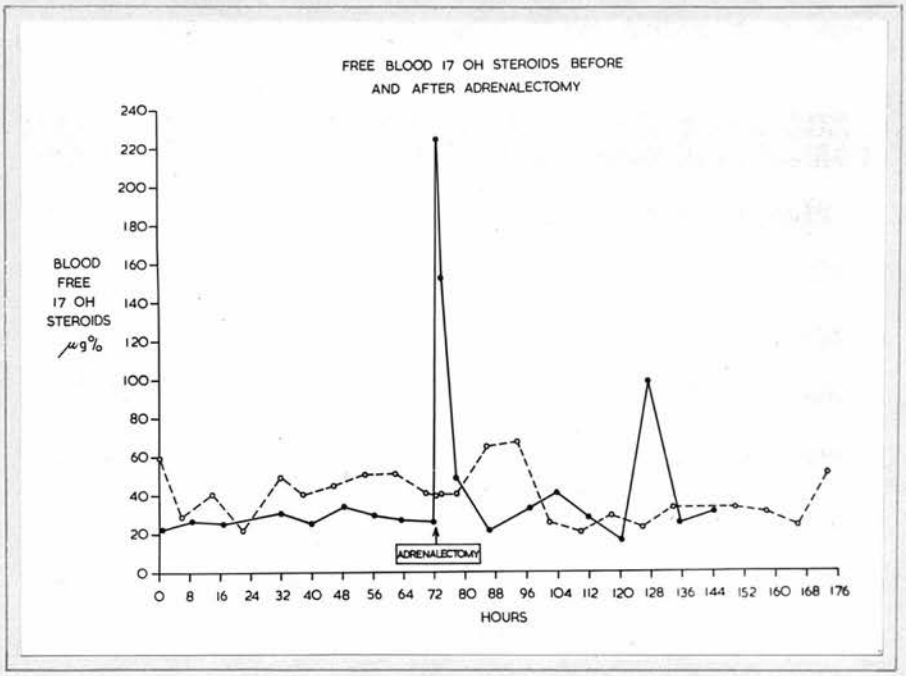

Fig. 63

Blood 17-OH corticoid concentrations in two patients submitted to adrenalectomy (Appendix II, Tables LXI and LXII).

Summary.- The available data on aldosterone do not suggest that a secretion of this substance comparable to that found after an operation of the magnitude of unilateral adrenalectomy takes place if both adrenal glands are removed and therefore it appears unlikely that changes in the secretion of aldosterone can explain the reduction in renal excretion of sodium after bilateral adrenalectomy.

C. Preliminary Observations on Levels of Blood 17-hydroxy-corticoids in Patients undergoing Bilateral Adrenalectomy

Plan of Observations.- A similar procedure to that described under A was adopted with two patients who were to undergo adrenalectomy for carcinoma of the breast with skeletal metastases and for Cushing's syndrome respectively. However, in these patients hydrocortisone (200 mg. in the first case and 150 mg. in the second case) was given by continuous intravenous infusion throughout the 24 hours. The hydrocortisone was dissolved in 1800 ml. of 6 per cent. dextrose and in the first case but not in the second was shielded from daylight at all times. Constancy of the rate of infusion was ensured as far as possible by frequent checks on the rate of the drip and by the use of a catheter of polyethylene inserted into the superior vena cava to ensure a continuous free flow. Sodium intake was adjusted for the day of operation and subsequently in the same way as for the cases described in paragraph A.

Results.- Blood 17-hydroxysteroid levels are shown in Fig. 63 /

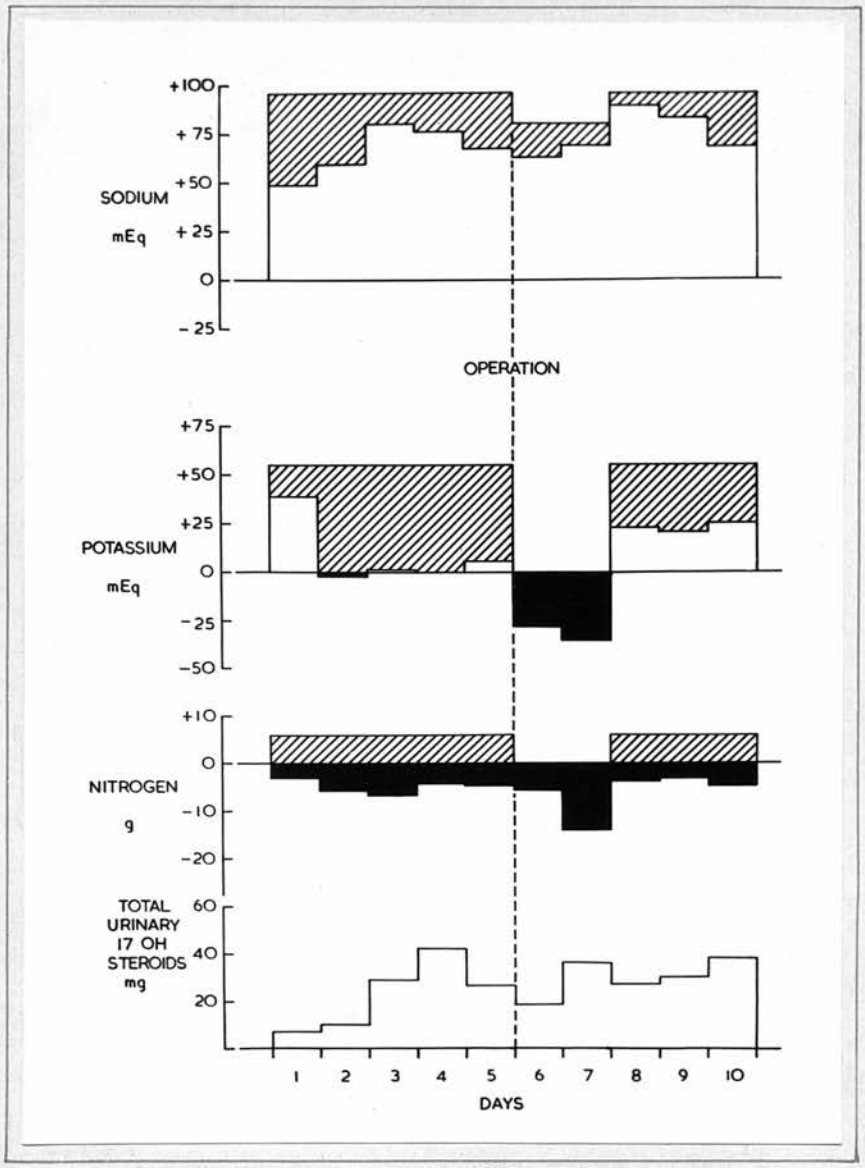

Fig. 64.

Metabolic response to second-stage adrenalectomy (Appendix II, Table LXI).

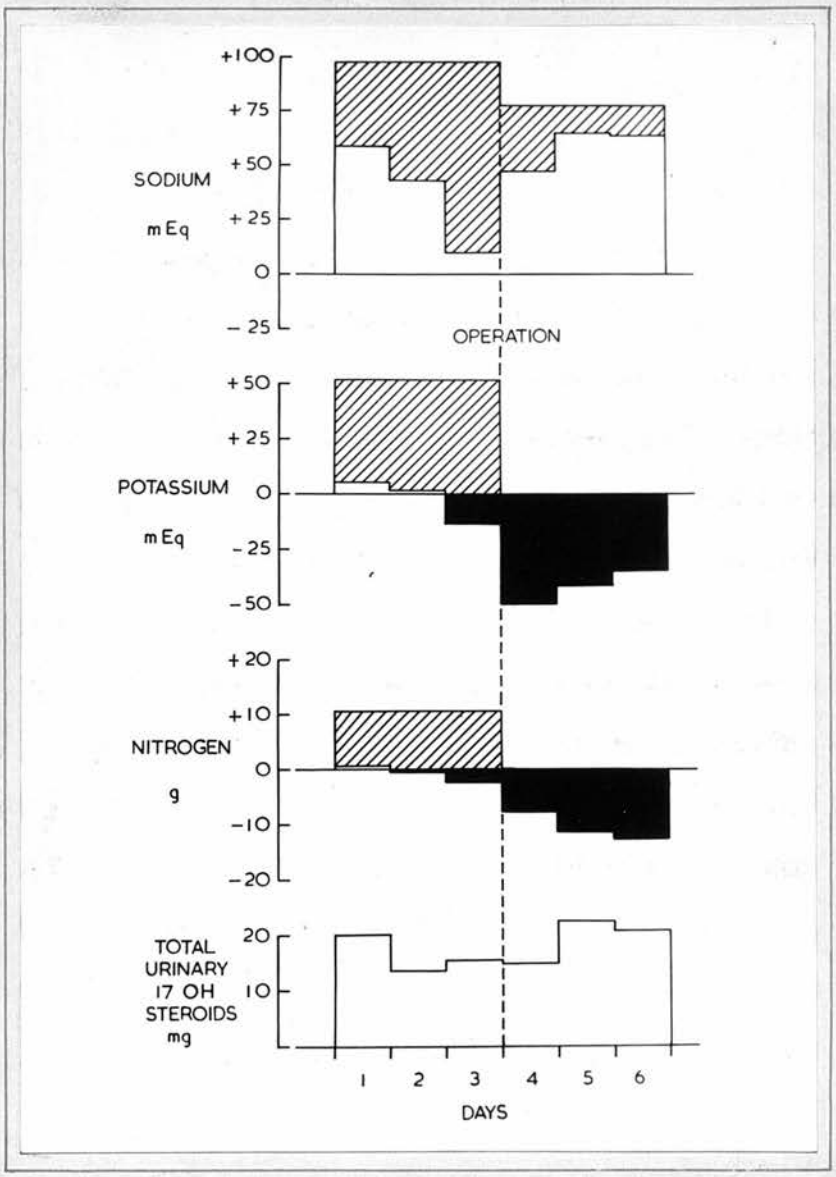

Fig. 65

Metabolic response to bilateral adrenalectomy (Appendix II, Table LXII).

Fig. 63 and the overall balance data in Figs. 64 and 65 (Appendix II, Tables LXI and LXII). The onset of anaesthesia is associated in the first case (Mrs D., Appendix II, Table LXII) with a rise in blood corticoid level but this is delayed until the operation has been completed in the second (Mrs L., Appendix II, Table LXI). Thereafter a moderate rise takes place which is, however, over by the following morning. The pattern of response is different in the two cases but in Mrs L. suggests that an increase in the level of blood corticoids may take place even after the adrenal cortex has been removed. The magnitude of the rise is not less than the normal range seen after major surgical procedures in patients with intact adrenal glands (Steenburg, et al., 1956). In Mrs D. it is considerably more, an observation in agreement with that of Christy et al. (1957), on the response to ACTH in Cushing's syndrome and indicative of the fact that the early peak is the result of the intact but pathologically hyperactive adrenal cortex. From the figures available it is not possible to say whether or not any secondary rise of blood corticoid concentration occurred in Mrs D., a rise that could be obscured by the initial concentrations produced by stimulation of the intact gland. It would be expected that on a constant intake such as was the case the decline in concentration of corticoids would follow the usual pattern of biological systems and be an exponential function of the initial concentration. Fig. 66 shows the semi-logarithmic plot /

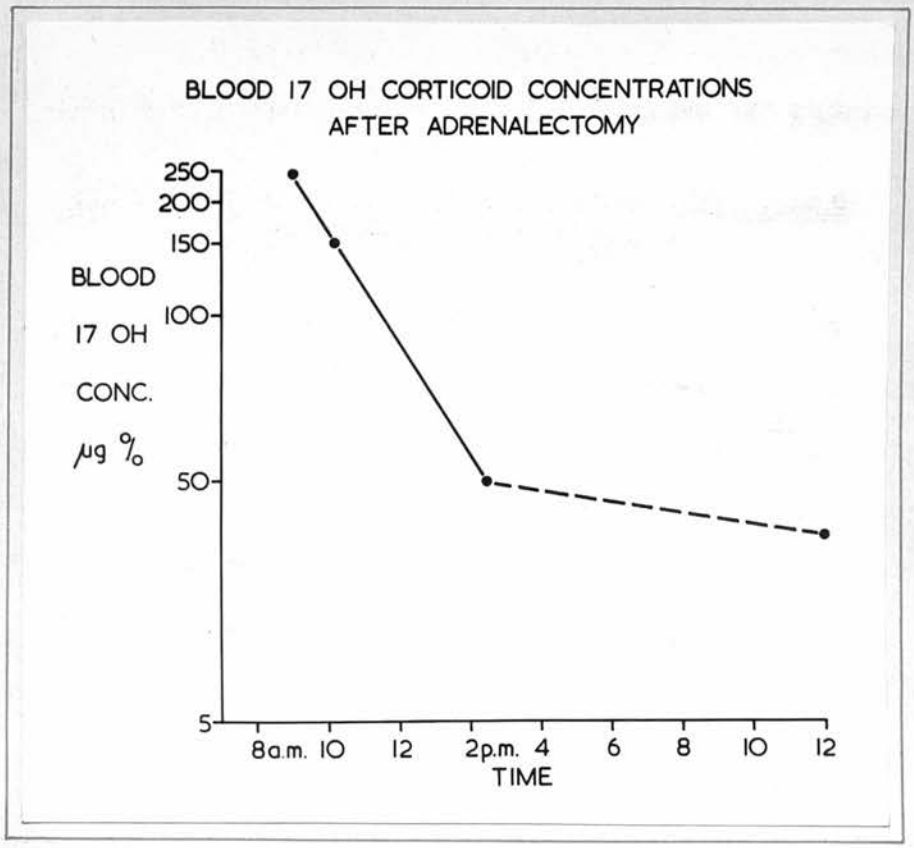

Fig. 66

Semilogarithmic plot of blood 17-OH corticosteroid data from patient undergoing second-stage adrenalectomy for Cushing's syndrome. The exponential relationship for the first three points is seen. The relationship does not apply for the fourth point but this may merely imply that the reading was taken too late when the fall in concentration had been completed (Appendix II, Table LXII).

plot of the first three post-operative values in Mrs D. against time and indicates that an exponential relationship does apply: accordingly it cannot be assumed that any alteration in the disposal rate of circulating 17-hydroxy-steroids after operation occurs which could account for the rise in concentrations found post-operatively in Mrs L. Therefore the matter remains open to further investigation.

General Conclusions regarding the Permissive Action of the Adrenal Cortex in Man

These three groups of results provide evidence which supports the contention that the group of metabolic changes that accompany injury or major surgical operation can take place under circumstances when increased secretion by the suprarenal gland plays no prolonged part. Since the majority of the studies described were made, Mason (1955) and Jepson et al. (1957) have reported similar changes in the metabolism of nitrogen, sodium and potassium (and in the cases of Jepson et al. without increase in renal steroid excretion) after adrenalectomy. Forrest et al. (1957) have described similar occurrences after oophorectomy in patients who have previously undergone adrenalectomy although it is of interest that in this group of cases as in those of Krieger et al. (1955) who were submitted to rib resection after adrenalectomy, there was no constancy of response in potassium and nitrogen excretion. Jepson et al. /

et al. (1957) assumed that the absence of changes in renal excretion of steroids indicated that there was unlikely to be any change in blood levels during the surgical procedure. The preliminary results obtained in the present studies indicate that such changes may occur and that they resemble qualitatively those found when the adrenal gland is intact. Therefore, although adrenal stimulation does occur during ordinary surgical procedures it does not appear to produce any greater change in blood corticoid levels than do the other factors operative after bilateral adrenalectomy. The changes in blood corticoids after bilateral adrenalectomy are unlikely to be the result of adreno-cortical activity unless it is assumed that the suprarenals have previously secreted these substances in some other form. This concept is an unlikely one in view of Hume and Nelson's (1954) analysis of adrenal vein steroids in the intact dog. Similar changes in blood steroid concentrations have been described during the first four hours after an operation in adrenalectomised dogs maintained on a constant hydrocortisone infusion throughout the experimental period (Steenburg and Ganong, 1955). Thus it seems necessary to postulate some extra-adrenal influence on blood corticoid levels. Two mechanisms appear likely: (a) a decreased rate of conjugation of free steroids by the liver and/or (b) a decreased rate of urinary secretion. A detailed analysis of these possible factors has not yet been undertaken in man or /

or in the experimental animal although it is well known that glomerular filtration rate is temporarily reduced after operation (see p. 15) and that changes in hepatic blood flow and function probably also occur. Whatever the cause, it is obvious that changes in the levels of circulating adrenal hormones may take place after injury or operation without adrenal activity being altered. It remains to be decided what part these changes play in the metabolic response to injury and whether or not increased adreno-cortical activity can be regarded as a necessary part of this response. Two slightly opposed lines of argument are possible from the available information on normal and adrenalectomised subjects. First, changes in blood corticoids are transient in both groups whereas metabolic events, particularly restriction on the renal excretion of sodium, are prolonged over several days: this suggests that some other factor is involved and the demonstration of changes in aldosterone activity in normal subjects would theoretically indicate that this substance might be responsible. However, the results described above indicate that sodium conservation takes place for several days after adrenalectomy in the absence of any renal excretion of aldosterone. (This cannot, of course, be taken as absolute proof that it is not present in smaller quantities in the blood.) It is therefore almost essential to assume either that (a) the transient changes in blood corticoid levels that follow injury or operation are sufficient /

sufficient to "trigger off" the metabolic events that follow over the next few days in both adrenalectomised and non-adrenalectomised patients or (b) that the adrenal cortex and its steroid products bear no relation to post-traumatic metabolic events other than the "permissive" one described by Ingle. From this second conclusion it would then follow that the observed changes in steroid levels and, in the non-adrenalectomised subject, in renal excretion of steroid degradation products, bears only a casual rather than a causal relationship to the metabolic response to injury. The former theory although an unattractive one on the grounds that it has no known analogue in other fields of endocrine activity in all of which a discrete stimulus produces a discrete and temporally limited effect, has recently received considerable support from the observations of Barrter et al. (1958) and of Wolff (1958) that transient reductions in blood volume may be associated with a diminished excretion of sodium that lasts for 3-4 days and that aldosterone activity remains high for a similar length of time. However, the absence of aldosterone from the post-operative urine of adrenalectomised patients implies that this mechanism cannot be directly responsible in all circumstances. Nevertheless, this is one of the first examples of a prolonged response from a single stimulus, in this instance a short-lived contraction of blood volume. Further evidence against the causal association of changes in blood /

blood corticoid concentrations and in sodium excretion is provided by the knowledge that a dose of pituitary adreno-corticotrophic hormone (ACTH) which is sufficient to produce changes in blood levels of 17-hydroxysteroids of the order and duration seen after major surgery (Steenburg et al., 1956), is associated with only a transient reduction in renal sodium excretion (Forsham et al., 1948). Therefore it would seem probable that the origin of the changes that are observed after operation and injury must be sought not only in alterations in pituitary adreno-cortical activity but also in other physiological adjustments, the nature of which is as yet unknown. Mechanisms of this kind would also explain the poor correlation between the renal excretions of sodium and of steroids that have repeatedly been observed (Moore et al., 1955).

The search for other factors of endocrine nature might reasonably lead to the pituitary. In this connection it is of interest to observe that the metabolic response to operation in a hypophysectomised patient is normal both with and without the administration of cortisone (Mason, 1955; Robson et al., 1955). Robson et al. noted further that in such patients the post-operative output of 17-hydroxy-steroids is increased, an indication either that the supra-renal has been normally stimulated by the hypophysis before removal of the latter or that other pathways can produce such stimulation. These findings are in contrast to the low /

low steroid excretions seen after adrenalectomy. This suggests that after hypophysectomy other factors are responsible for continued stimulation of the adrenal cortex and that the metabolic events are independent at least in part of pituitary stimulation. A prolonged intense secretion of aldosterone after hypophysectomy cannot be excluded because as has already been discussed (p. 81), it is well established that the secretion of aldosterone is partially independent of the anterior pituitary. However, the results on adrenalectomised patients make it unlikely that aldosterone is necessary for the post-operative sodium changes and the conclusion to be drawn from the studies on hypophysectomised patients and those reported here in adrenalectomised patients is that changes in the rate of secretion either of hypophysis or of suprarenal are unnecessary for a normal metabolic response to injury.

If these conclusions are confirmed by further investigations it becomes apparent that some modification must be made to the currently held views on the initiation of the metabolic response to injury. First, it will be necessary to continue a search for other endocrine or neural reflex arcs which initiate or maintain the changes in sodium excretion. Secondly, until this search has proved negative or been completed it will be desirable to avoid didactic descriptions of phases of metabolism after injury based upon a groundwork of changes in endocrine secretion, particularly /

particularly that of the adrenal cortex (see, for example, Moore and Ball, 1952; Moore, 1953; Hardy, 1954). Thirdly, if adrenocortical hyperactivity is to be regarded as a side issue in the metabolism of the convalescent surgical patient it is justifiable to speculate whether on occasion it can be actively harmful rather than a purposeful supportive phenomenon. Hyperfunction, or relative over-activity, the result of reduction in steroid inactivation and excretion, might well produce on occasion some of the changes described by Selye (1950) in the experimental animal or the features of the clinical picture that has occasionally resulted from the prolonged therapeutic use of adreno-cortical steroids in high dosage. Such a "hyperfunction syndrome" should also show some of the features of Cushing's disease - loss of lean tissue, diabetes mellitus, inhibition of ovarian function in the female, poor wound healing and vascular disease with thrombosis. Such a hypothetical condition would be most likely to occur in individuals in whom stress was prolonged and therefore in whom the factors that favour a persistent elevation of blood corticoids are most likely to be found. An example of such circumstances is the extensive burn many of the victims of which are now successfully brought through the phase of shock and circulatory imbalance. Blood corticoid levels are known to be raised for up to 15 days in extensive burns (Hume et al., 1956) and particularly high levels are reached in patients who are very ill or about to die. /

die. Extensively burnt patients may develop transient or permanent diabetes, usually lose lean tissue stores rapidly in spite of a reasonably maintained intake of nitrogen and calories and there may be a remarkable lack of granulation tissue when slough separates from the burnt area. In some instances granulations appear to form and then to fade away to expose the underlying structures such as fat which then becomes infected or necrotic. At autopsy in such patients there are occasionally multiple thrombi in small vessels and microscopic areas of infarction. It is tempting to assume that some or all of these changes might have a basis in pathologically raised blood levels of adrenocortical hormones. Adrenal hyperfunction need not necessarily be present because it is now clear that such changes could result from alterations in rates of inactivation or of excretion of the active steroids. A careful study of future cases will be required to yield a certain answer to this problem.

It is as yet difficult to appreciate how renal sodium conservation is brought about when there is no apparent possibility of variation in the concentration of suprarenal hormones. Two possibilities exist: (a) that unmeasurable changes in renal blood flow, the result perhaps of a small post-operative reduction in blood volume, persist for several days after operation, a possibility that cannot be denied when it is recalled that all the physiological changes /

changes in sodium excretion can be accounted for by changes in glomerular filtration rate that cannot be measured (see p. 79); (b) that the kidney has in some way a "memory" in its cells which results in persistence of sodium conservation even after withdrawal of the initial stimulus. (a) The possible significance of changes in blood flow is supported by Flear and Clarke (1955) who found atypical changes in sodium excretion in patients who were "adequately" transfused after extensive soft tissue injuries and fractures. However, careful analysis of their data does not at the moment support any conclusion that the metabolic response to injury is greatly modified by vigorous blood volume expansion. (b) The operation of a similar "delayed response system" is implicit in the observations of Chalmers et al. (1952) on sodium excretion during reduction in glomerular filtration rate in which it was demonstrated that sodium excretion was still diminishing when glomerular filtration rate had returned to normal. The work of Barrter et al. (1958) on aldosterone and sodium excretion after haemorrhage that has already been discussed supports a similar mechanism but cannot be the operative factor in adrenalectomised patients. Further work on renal sodium excretion after major surgery or injury in man will be required before such a theory can be entertained other than on a speculative basis.

Conclusions /

GENERAL CONCLUSIONS TO THESIS

Dissection of the metabolic response to injury with the object of determining the factors which produce and control it has suggested a number of tentative conclusions. In brief these may be stated as follows:-

(1) Activation of the neurohypophysis by non-osmotic stimuli is a normal accompaniment of trauma although the renal response to this increased secretion of antidiuretic hormone is different from that seen when the osmotic stimulus of water deprivation is applied. This activation must be borne in mind when the administration of water to the post-operative patient is under consideration. Concentration of the urine in the distal tubule may be of significance in the causation of renal damage after the release ob blood pigment into the circulation, and in favourable circumstances renal injury can be prevented if the distal tubular urine is diluted by the induction of a solute diuresis.

(2) The changes in the renal excretion of potassium and of nitrogen bear a closer relationship to the extent of tissue injury and the size of the wound haematoma than they do to any other factor. The available evidence suggests that the magnitude of nitrogen loss is not determined by endocrine forces although the presence of the adrenal cortex is permissive to its occurrence in the experimental animal and /

and probably also in man. The changes in renal sodium excretion are associated with increased adreno-cortical secretion but the time relationships are not exact and identical changes take place when the adrenal cortex and the hypophysis have been removed.

(3) Extra-adrenal factors may influence or be responsible for the raised blood levels of free 17-hydroxy-steroids measurable after injury or operation. The concept of a neuro-endocrine reflex arc in which increased pituitary adreno-corticotrophic hormone stimulates an increased production of suprarenal steroids which in turn produce the metabolic changes after injury can no longer be held in its simple form. Rather it would appear that the suprarenal exercises a permissive action in respect to changes in sodium excretion after injury, and that the observed evidences of hyperfunction after operation in patients or animals with intact adrenals may represent a casual, not a causal, association.

(4) If adrenal hyperfunction occurs to excess either as a result of increased secretion or reduced disposal of the hormones, pathological effects may be manifest.

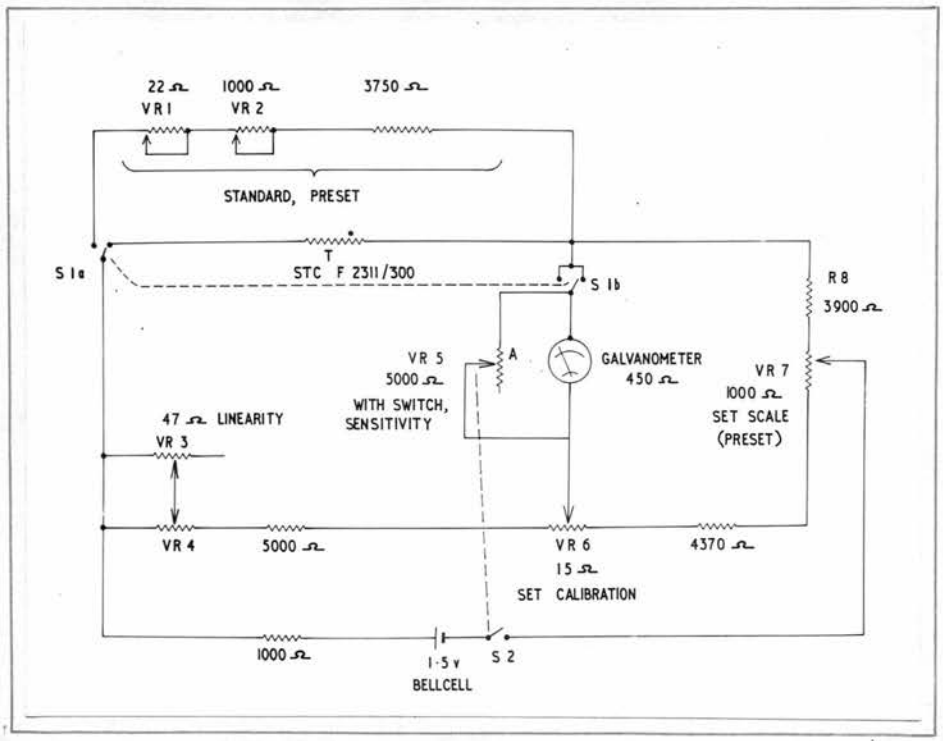

Fig. 67

Electrical circuit of the osmometer described in the text.

APPENDIX I - METHODS

Sodium and potassium in body fluids

Lithium internal standard flame photometry was used for all the determinations of potassium and sodium in serum and in urine described in Part I. Instruments with electronic circuits and amplification (Perkin-Elmer and Barclay) and simple Wheatstone Bridge arrangements (Baird) were employed. The reproducibility of determinations with all instruments was shown to be within 1 per cent. and the accuracy of determinations of a single reading within 2 per cent. For the studies described in Part II an EEL flame photometer was used.

Total solute concentration of serum and urine

The advent of the thermister has enabled accurate measurement of the temperature of liquid to be carried out in terms of electrical resistance. For those determinations carried out in the U.S.A. a commercial instrument (Fiske Assoc., Boston, Mass.) which employed a Wheatstone Bridge circuit was used. In Edinburgh an instrument was designed and constructed for this purpose with the co-operation of Dr D.C. Simpson*.

In this instrument the thermister (T) is connected to a Wheatstone Bridge circuit as shown in Fig. 67 and is cemented /

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* Medical Physics Department, University of Edinburgh.

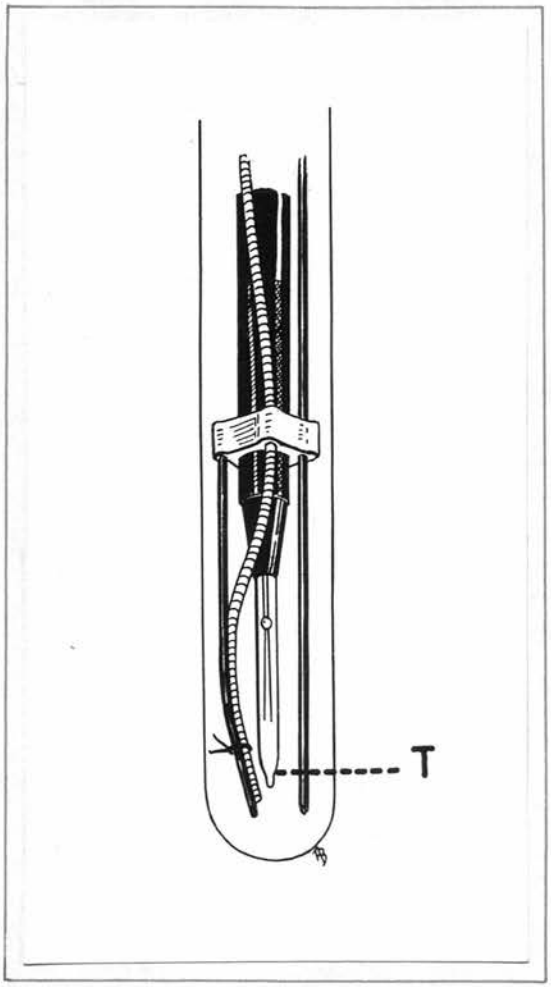

Fig. 68

Probe assembly for the osmometer described in the text.

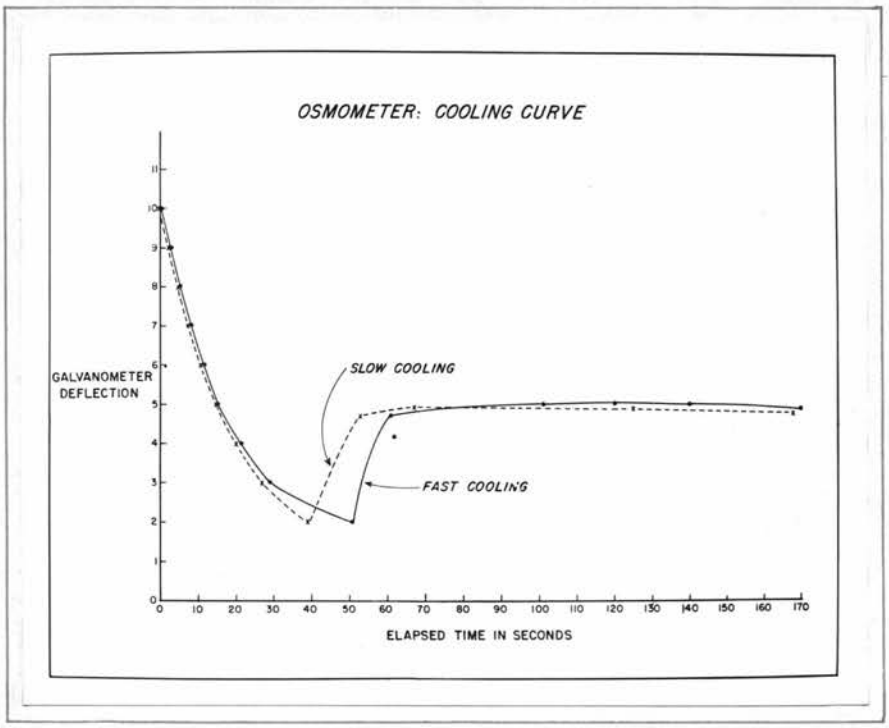

Fig. 69

Cooling cycle of osmometer

cemented into a length of fine glass tubing in such a manner (Fig. 68) that it is held at a constant distance from the bottom of the 90 mm. Pyrex test tube which contains the sample. This is stirred by a fine stream of air introduced through a length of 0.5 mm. polyethylene tubing. Cooling is brought about by immersion of the tube in an ice/salt mixture at $-8^{\circ}C$.

In operation some of the liquid is slightly supercooled, and then suddenly frozen. The change of temperature which occurs alters the resistance of the thermister and the galvanometer spot is deflected across the scale. The degree of supercooling is controlled by stopping the air supply when the deflection has reached a pre-determined value: a full scale deflection is convenient and the liquid is then frozen by a sharp tap from a stainless steel rod which rests in the test tube. Conversion to the solid state releases latent heat so that the galvanometer spot swings in the opposite direction. This deflection is maintained during the evolution of heat and thereafter the spot once more moves in the direction of cooling as the test liquid approaches the temperature of the bath. A typical cooling cycle is illustrated in Fig. 69. The freezing point of the liquid is obtained by adjusting resistance VR_4 so that there is a null point reading on the galvanometer when all the latent heat has been emitted.

The pattern of the galvanometer deflection for any individual /

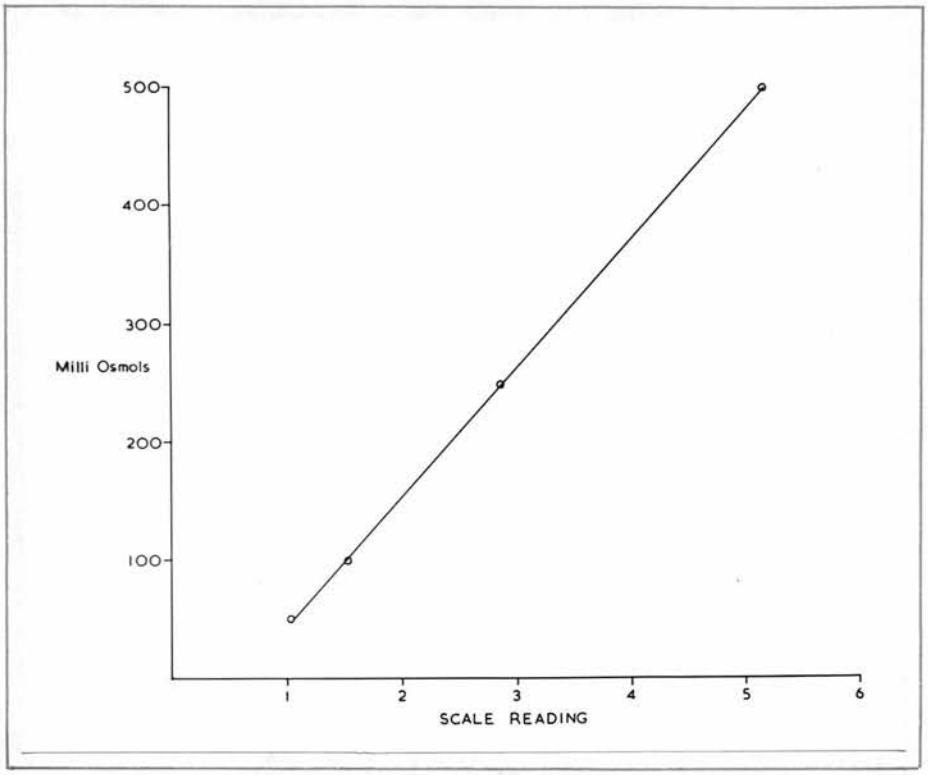

Fig. 70

Typical calibration response of
Scottish osmometer.

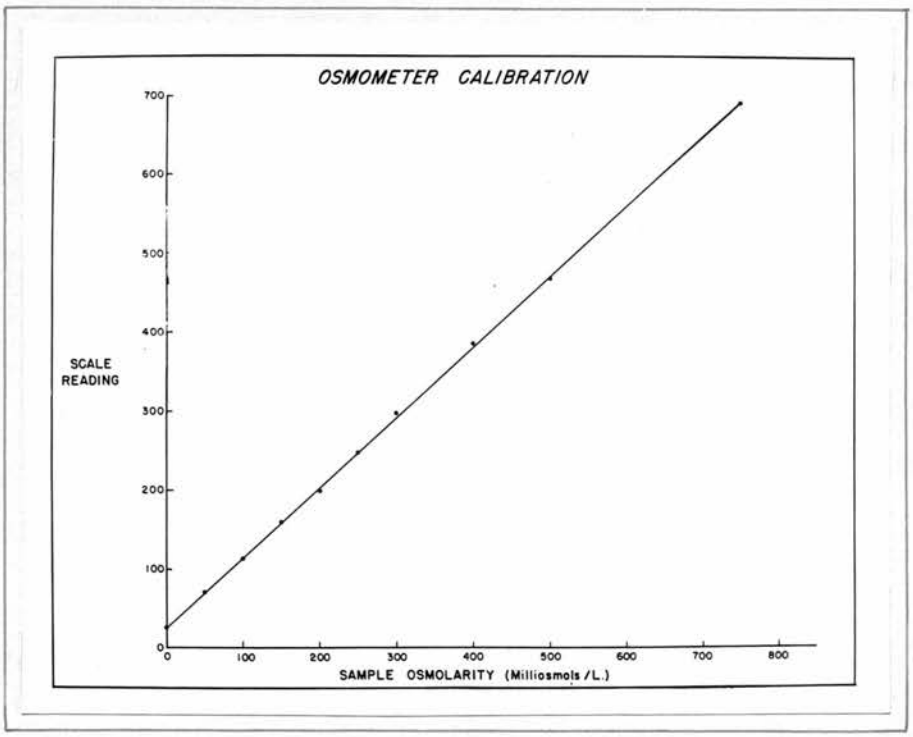

Fig. 71

Typical calibration response of American osmometer.

individual determination is influenced by (a) the initial setting of the variable resistance VR_4 which will affect the galvanometer deflection during the cooling cycle, (b) the rate of cooling which is in turn determined by the temperature gradient between the sample and the mixture of ice and salt water in the bath, and (c) the amount of supercooling that is produced before the sample is frozen. Therefore these conditions must be standardised as far as possible. The initial determination of the freezing point of a test liquid should be regarded as a means of adjusting resistance VR_4 so that it has approximately the correct value for the production of a null point reading without major alteration during the next freezing point.

With these precautions the instrument produced a linear response between 0 and 500 mOs/litre (Fig. 70) and the reproducibility of readings of standard salt solutions, urine and plasma is within 5 scale divisions or 2.7 mOs/litre. In both the American and Scottish instruments the dial reading was by a double scale calibrated in 10 complete revolutions. Each revolution was subdivided into 100 (America) and 200 (Scottish) divisions. Fig. 71 shows the similar linear calibration of the American instrument.

Weight.- Accurate weighing of surgical patients is often a matter of considerable difficulty. In spite of developments in bed weighing instruments the only satisfactory method by which a valid figure can be obtained is to weigh /

weigh the patient nude or to make a direct allowance for "tare" by weighing separately all items of clothing, dressings and bedclothes. In the American studies this was done on a Toledo litter scale with dial recording which allowed discrimination of 25 g. changes. In Scotland a bar scale manufactured for the purpose by Messrs White of Auchtermuchty was used (Sutherland, 1955). Direct reading to 100 g. can be made on this machine but the discrimination can be increased by including a measuring flask in the tare and adjusting the beam to swing at the midpoint (with the rider at the nearest 100 g. interval) by the addition of water. Changes in weight of 25 g. can be detected in this manner.

Total body water

This was determined by isotope dilution with deuterium oxide (heavy water). The concentration of deuterium oxide in body water was obtained by vacuum distillation of serum and assessment of the rate of fall of a drop of the pure water so obtained through an orthotoluene column at constant temperature. The principle of isotope dilution has been described by Moore (1946) and the application of the method to deuterium oxide by Scloerb et al. (1950) and by Scloerb et al. (1951). From their work it is thought that the technique is capable of measuring changes of 1 litre (2 per cent.) of total body water.

Antidiuretic /

Antidiuretic activity

The technique of Jeffers et al. (1942) was used with modifications designed to increase its sensitivity. The principle of the method is that alcohol induces a state of physiological diabetes insipidus and also a sufficient depth of anaesthesia to render intravenous administration of the test substance possible in the rat. The use of an intravenous method is absolutely essential to a satisfactory evaluation of antidiuretic activity. Innumerable studies have been made with intraperitoneal and intramuscular injection but although such a technique which is usually based on the methods of Burn (1937) can be made to give a linear response with aqueous solutions of Pitressin there is little doubt that non-specific effects become predominant once serum, urine or tissue extracts are used. Support is given to such a conclusion by the reduced or absent antidiuretic activity of the same substances when administered intravenously. Further reports of the antidiuretic titre of serum based on the intraperitoneal method (Stein et al., 1952) give results so far outside the probable physiological range (see p. and Lauson, 1951) as to render them at once suspect. The inability in the present study to demonstrate any antidiuretic activity in human serum when administered in 1 ml. doses suggests that in fact the responses found, by Stein et al. were non-specific. Finally, an intravenous assay or method of detection should on first principles be of greater /

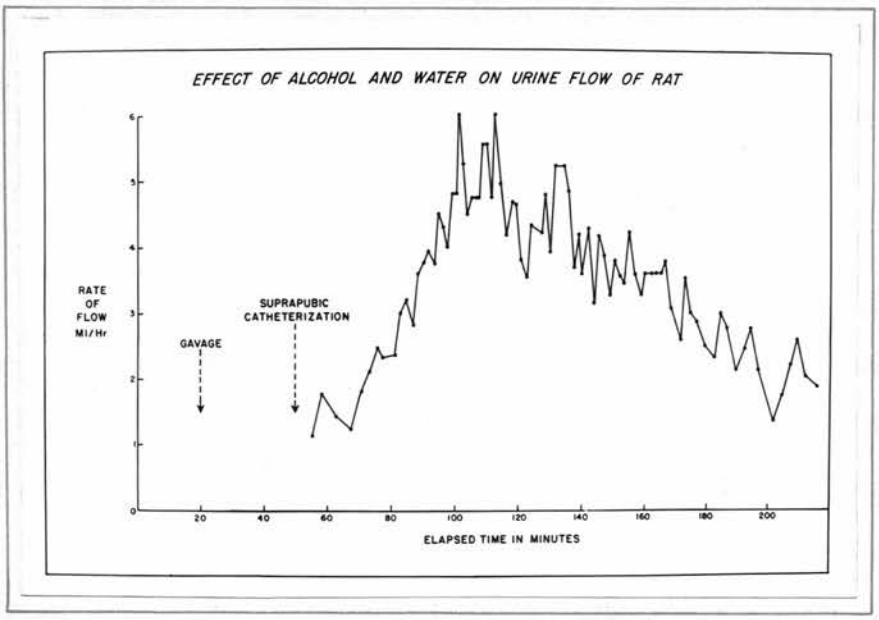

Fig. 72

Diuretic response of rat to the ingestion of a water/Ethanol mixture.

greater precision and sensitivity than one which uses an intraperitoneal or intramuscular injection. In their original technique of Jeffers et al. doses of alcohol and water were administered to a rat which weighed between 150-200 g. and the rate of flow of urine recorded by counting the drops that issued from a suprapubic cannula. One undesirable feature of this technique is that the rate of flow of urine follows the normal course of diuresis, reaches a peak and thereafter declines (Fig. 72) so that as Dicker (1953) has pointed out the assay may be carried out against a background of changing rate of flow. To avoid this drawback, complex methods of maintaining a constant water load have been devised (Dicker, 1951) but for relatively short-term experiments it has been found sufficient to inject through an indwelling stomach tube a volume of water equivalent to the urine passed in every 15 minute period.

In the search for greater sensitivity (although this cannot necessarily be taken to mean greater precision) the collecting system was modified so that a record of the time taken to pass very small quantities of urine could be obtained. The most simple method of achieving this was found to be by connecting the suprapubic drainage tube to a 1 ml. graduated pipette mounted horizontally; the rate of flow of urine is then measured by timing the advance of the meniscus. A syringe and side take are attached to the suprapubic tube to empty the pipette when the meniscus has reached /

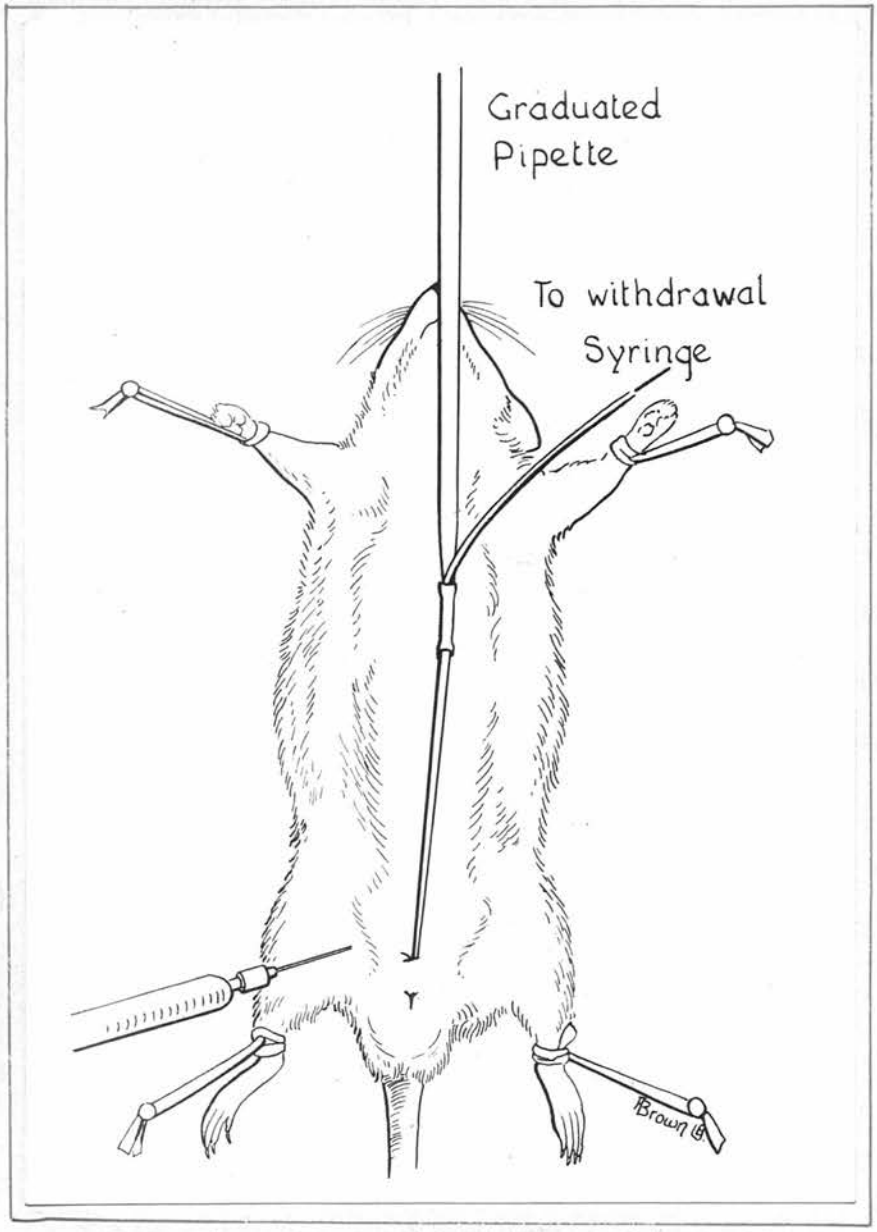

Fig. 73

Diagrammatic representation of rat technique for detection of antidiuretic activity.

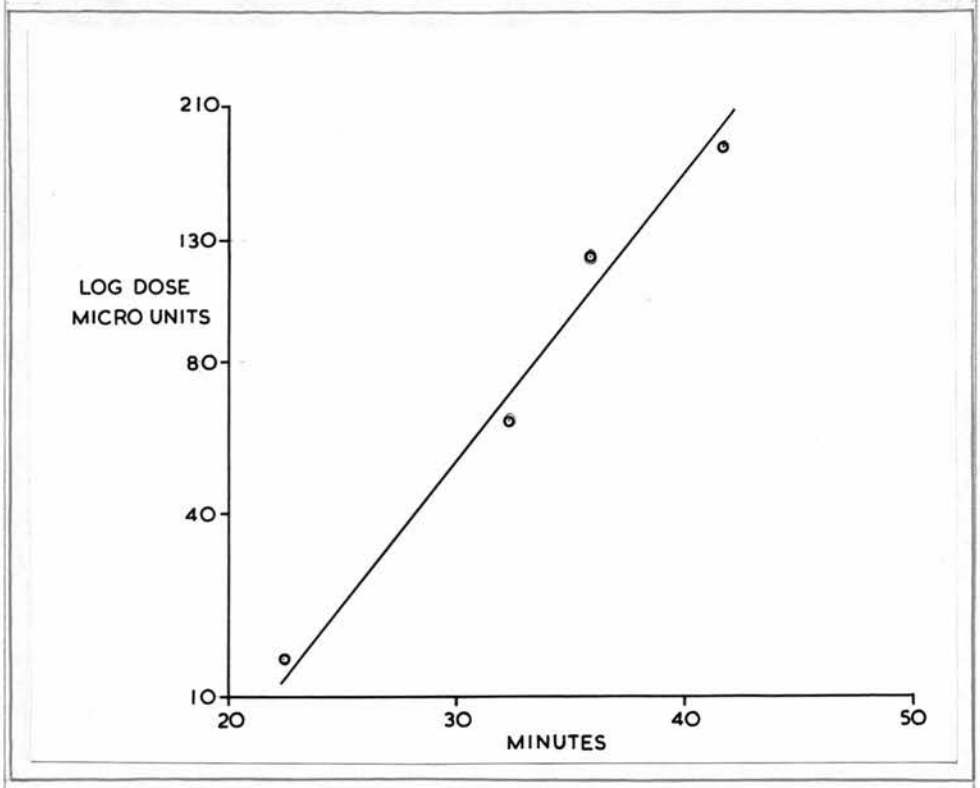

Fig. 74

Log-dose response to graded injections of commercial antidiuretic hormone.

reached the end of the graduated section. The experimental arrangement is shown diagrammatically in Fig. 73. With this method of recording it is possible to detect the presence of 5 micro-units of Pitressin in 1 ml. of solution. The method can be adapted for assay purposes by the use either of the duration of antidiuresis from any given dose or by measuring the amount of urine passed in an arbitrary period before and after the injection of the test substance. However, for this purpose it has little to commend it over the simpler method of Jeffers et al. and although linear responses were obtained from individual animals over a range of dosage of Pitressin (Fig. 74) the method was not used for this purpose.

The complete technique of application was as follows:-

(1) A 200-300 g. rat was allowed free access to water but was starved for 18 hours before the experiment.

(2) Six per cent. of body weight of 12 per cent. alcohol in 0.25 per cent. sodium chloride solution were given by stomach tube.

(3) At the end of 45 minutes the rat was immobilised on a board, the bladder exposed by a short vertical suprapubic incision and a glass or polyethylene cannula inserted and attached to a 1 ml. pipette. A circumferential ligature was passed around the base of the penis to eliminate urethral losses.

(4) The femoral vein was cannulated either by a short length /

length of polyethylene or more commonly and simply with a child's lumbar puncture needle. Removal and reinsertion of the stillete permitted repeated intravenous injections.

(5) A stomach tube was reinserted for intermittent gavage. The rate of flow of urine achieved by this technique varied from 6-12 ml./hr. but was reasonably constant for any single animal. Difficulties were often encountered with partial aspiration of the gavage solution and such animals invariably failed to show diuresis and had to be discarded. Further, the airway of an animal with gavage tube in situ is precarious and great care must be used to avoid obstruction which immediately inhibits diuresis and is rapidly fatal. The advance of the meniscus was timed with two stop watches so that it would prove easier to start a time interval exactly at the completion of an injection or at the start of a "flow" up the meniscus.

The procedures required for separation of the cells cannot easily be completed in under 10 minutes and it is possible that some antidiuretic activity may have been lost during the lapse of this time. However, knowledge of the "lag period" of water diuresis and the work of Ginsburg on destruction of antidiuretic activity would have been dissipated at the end of this relatively short period. In early experiments with collection of the blood in glass, serum from blood frequently resulted in death of the animal and at autopsy massive pulmonary and cardiac thrombi were found. This is probably attributable /

attributable to uncombined thrombin in such rapidly separated serum and for this reason serum was usually allowed to "age" for 12 minutes before injection. Both serum and heparinised plasma (100 u/ml. of whole blood) gave negative results in the series of experiments described on p. 31 and although it is conceivable that heparin could have destroyed the antidiuretic activity of the plasma, this is most unlikely as it was also used in all the control injections of plasma which contained commercial antidiuretic hormone. Further experiments with the use of siliconed equipment would be required to clinch this point but the consistent negativity of the results obtained in post-operative patients suggested that this was unlikely to be worth while.

Injections of 1 ml. of plasma into a 200 g. rat consistently slightly increased the rate of flow of urine unless antidiuretic activity was present. The explanation of this phenomenon is open to discussion but is most probably related to the slight plethora and consequent increase in renal blood flow consequent upon an injection of this volume into a total blood volume of approximately 10 ml.

Methods (cont'd)

Nitrogen

Micro-Kjeldehl.

Urinary 17-ketesteroids

Method of Zimmermann (1943).

Acid Stable Formaldehydogenic Steroids in Urine

Method of Tompsett and Smith (1954).

17-hydroxysteroids in Urine

Method modified from that of Forsham (1955).

Free 17-hydroxysteroids in Blood

Modified from the method of Nelson and Samuels (1952) to eliminate the use of fractionating columns.

REFERENCES

Albright, F. (1943). Harvey Lectures, 38, 123.

Ariel, I.M. (1951). Arch. Surg. Chicago, 62, 303.

Ariel, I.M. and Miller, F. (1950). Surgery, 28, 716.

Artz, C.P. (1955). Personal communication.

Barrter, F.C. (1956). Metabolism, 5, 369.

Barrter, F.C., Biglieri, E.F., Pronove, P. and Delea, C.S. (1958). Effects of Changes in Intravascular Volume on Aldosterone Secretion in Man. In "Aldosterone," ed. F. Muller and C.M. O'Connor. London: J. & A. Churchill.

Baur, J. (1872). Z. Biol., 8, 567.

Beal, J.M., Cornell, G.N. and Gilder, H. (1954). Surgery, 36, 468.

Benedict, F.G. (1915). "A Study of Prolonged Fasting." Carnegie Institution of Washington: Pub. 203.

Berliner, R.W. and Davidson, D.G. (1957). J. clin. Invest., 36, 1416.

Bernard, C. (1859). "Lecons sur les Propriétés physiologiques et les Altérations pathologiques des Liquides de l'Organisme," Vol. I, p. 297. Paris: J.B. Baillière et fils.

Berry, R.E.L., Iob, V. and Campbell, K.N. (1948). Arch Surg. Chicago, 57, 470.

Black, D.A.K., McCance, R.A. and Young, W.F. (1944). J. Physiol., 102, 406.

Bliss, E.L., Sandberg, A.A., Nelson, D.H. and Eixnes, K. (1953). J. clin. Invest., 32, 818.

Blixenkrone-Møller, N. (1949). Acta chir. scand., 97, 300.

Boyarsky, S. and Smith, H.W. (1957). J. Urol., 78, 511.

Brodsky, W.A., Rapoport, S., Graubarth, H.N. and Levkoff, A.H. (1952). J. appl. Physiol., 5, 62.

Brown, /

Brown, A. (1945). Special Report Series, Medical Research Council, No. 249, Part IV.

Brown, J.S.L., Schenker, V. and Stevenson, J.A.F. (1944). J. clin. Invest., 23, 932.

Brown, J.S.L., Schenker, V. and Venning, E.H. (1946). Trans. Ass. Amer. Phycns, 59, 235.

Brunschwig, Z., Clark, D.E. and Corbin, N. (1942). Ann. Surg., 115, 1091.

Bull, G.M. (1956). "Modern Views on the Secretion of Urine." London: J. & A. Churchill.

Bull, G.M., Joekes, A.M. and Lowe, K.G. (1949). Lancet, 2, 229.

Burn, J.H. (1937). "Biological Standardisation." London: Oxford University Press.

Bywaters, E.G.L. (1944). J. Amer. med. Ass., 124, 1103.

Bywaters, E.G.L. and Dible, H.J. (1942). J. Path. Bact., 54, 111.

Calloway, H. and Spector, H. (1954). Amer. J. clin. Nutr., 2, 405.

Chalmers, T.M., Lewis, A.A.G. and Pawan, G.L.S. (1952). J. Physiol., 117, 218.

Christy, L.P., Langson, D. and Jailer, J.W. (1957). Amer. J. Med., 23, 910.

Clark, W.E. Le Gros, Beattie, J., Riddoch, G. and Dott, N.M. (1938). "The Hypothalamus: Morphological, Functional, Clinical and Surgical Aspects." Edinburgh: Oliver & Boyd.

Clarke, R., Topley, E. and Flear, C.T.G. (1955). Lancet, 1, 629.

Cline, T.M., Cole, J.W. and Holden, W.D. (1953). Surg. Gynec. Obstet., 96, 674.

Coller, F.A., Campbell, H.N.V., Vaughan, H.H., Iob, L.V. and Moyer, C.A. (1944). Ann. Surg., 119, 533.

Coller, F.A., Rees, V.L., Campbell, K.N., Iob, V.L. and Moyer, C.A. (1943). Ann. Surg., 118, 717.

Conn, J.W. (1955). J. Lab. clin. Med., 45, 3.

Cooper /

Cooper, D.R., Iob, L.V. and Coller, F.A. (1949). Ann. Surg., 129, 1.

Cope, O. and Rhinelander, F.W. (1943). Ann. Surg., 117, 915.

Co Tui, Wright, M., Mulholland, J.H., Carabba, V., Barcham, I. and Vinci, V.J. (1944). Ann. Surg., 120, 99.

Crosby, W.H. (1956). "Peaceful Uses of Atomic Energy," Vol. 10, p. 378. New York: United Nations.

Cuthbertson, D.P. (1929). Biochem. J., 23, 1328.

Cuthbertson, D.P. (1930). Biochem. J., 24, 1244.

Cuthbertson, D.P. (1931). Biochem. J., 25, 236.

Cuthbertson, D.P. (1932). Quart. J. Med., 1, 233.

Cuthbertson, D.P. (1934). Glas. med. J., 121, 41.

Cuthbertson, D.P. (1936). Brit. J. Surg., 23, 505.

Cuthbertson, D.P. (1942). Lancet, 1, 433.

Cuthbertson, D.P., McCutcheon, A. and Munro, H.W. (1937). Biochem. J., 31, 681.

Cuthbertson, D.P., McGirr, J.L. and Robertson, G.S.M. (1939). Quart. J. exp. Physiol., 29, 13.

Cuthbertson, D.P. and Munro, H.W. (1937). Biochem. J., 31, 694.

Dale, H.H. (1957). Evidence concerning the Endocrine Function of the Hypophysis and its Nervous Control. In "The Neurohypophysis." Ed. H. Heller. London: Butterworth.

Del Greco, F. and de Wardener, H.E. (1956). J. Physiol., 131, 307.

Dicker, S.E. (1953). J. Physiol., 122, 149.

Dicker, S.E. (1957). J. Physiol., 139, 108.

Dreser, H. (1892). Arch. exp. Path. Pharmacol., 29, 303.

Dudley, H.A.F. (1957). Postgrad. med. J., 33, 585.

Dudley, H.A., Boling, E.A., Le Quesne, L.P. and Moore, F.D., Ann. Surg., 140, 354.

Elkington, /

Elkington, J.R. (1956). Circulation, 14, 1027.

Elkington, J.R. and Winkler, A.W. (1944). J. clin. Invest., 23, 93.

Elman, R. (1940). Ann. Surg., 112, 594.

Elman, R., Lemner, R.A., Weichselbaum, T.E., Owen, T.G. and Yore, R.I.N. (1949). Ann. Surg., 130, 703.

Elman, R. and Weiner, D.O. (1939). J. Amer. med. Ass., 112, 716.

Engel, F.L. (1951). Endocrinology, 49, 127.

Erspamer, V. (1954). Pharmacol. Rev., 6, 425.

Erspamer, V. (1955). J. Physiol., 127, 118.

Farmi, F. (1913). Wien. klin. Wschr., 26, 1867.

Fisher, C.W., Ingram, W.R. and Ranson, S.W. (1938). "Diabetes Insipidus and the Neuro-hormonal Control of Water Balance: A Contribution to the Structure and Function of the Hypothalamico-Hypophyseal System." Ann Arbor: Edwards Bros. Inc.

Flear, C.T.G. and Clarke, R. (1955). Clin. Sci., 14, 375.

Florey, H. (1957). "General Pathology." London: Lloyd-Luke.

Forsham, P.H. (1955). Ciba Foundation Colloquium on Endocrinology, VIII, 282. London: J. & A. Churchill.

Forsham, P.H., Thorn, G.W., Prunty, F.T.G. and Hills, A.G. (1948). J. clin. Endocrin., 8, 15.

Forrest, A.P.M., Brown, D.A., Morris, S.A. and Hendry, E.B. (1957). J. R. Coll. Surg. Edinb., 3, 33.

Frank, J.E. (1912). Klin. Wschr., 49, 393.

Frank, M.N., Dreifus, L.S., Rarrick, F. and Bellet, S. (1957). Clin. Res. Proc., 5, 24.

Gamble, J.L. (1944). Amer. Philos. Soc. Proc., 88, 151.

Gamble, J.L. (1947). Harvey Lectures, 42, 247.

Gamble, J.L. (1954). "Chemical Anatomy, Physiology and Pathology of Extracellular Fluid." 6th edn. London: Geoffrey Cumberlege.

Goodpaster, /

Goodpaster, W.E., Levensen, S.M., Tagnon, H.J., Lund, C.C. and Taylor, F.H.E. (1946). Surg. Gynec. Obstet., 82, 652.

Green, C.H. and Rowntree, L.G. (1927). Amer. J. Physiol., 80, 209.

Hamburger, H.J. (1902). "Osmotische Druck und Ionenlehr in den medicinischen Wissenschaften," II, 6, 247. Wiesbaden: Bergmann.

Hardy, J.D. (1950). Ann. Surg., 132, 189.

Hardy, J.D. (1954). "Surgical Physiology of the Adrenal Cortex." Springfield, Ill.: C.C. Thomas.

Harris, G.W. (1955). "Neural Control of the Pituitary Gland." London: Edward Arnold.

Hayes, M.A. and Coller, F.A. (1952). Surg. Gynec. Obstet., 95, 142.

Holden, W.D., Krieger, H., Levey, S. and Abbott, W.E. (1957). Ann. Surg., 146, 563.

Howard, J.E. (1945). Arch. Surg. Chicago, 50, 166.

Howard, J.E., Parson, W., Stein, I.C.E., Eisenberg, H. and Reidt, V. (1944). Bull. Johns Hopk. Hosp., 75, 156.

Howard, J.E., Winternitz, J., Parson, W., Bigham, R.S., Jr. and Eisenberg, H. (1944). Bull. Johns Hopk. Hosp., 75, 209.

Howard, J.E., Bigham, R.S., Jr. and Mason, R.E. (1947). Trans. Ass. Amer. Phycns, 89, 242.

Howell, W.H. (1898). J. exp. Med., 3, 245.

Hume, D.M. (1953). Ann. Surg., 138, 548.

Hume, D.M. and Nelson, D.H. (1954). Fed. Proc., 13, 73.

Hume, D.M., Nelson, D.H. and Miller, D.W. (1956). Ann. Surg., 143, 316.

Ingle, D.J. (1953). In "The Suprarenal Cortex." Ed. J.M. Yoffey. London: Butterworth.

Ingle, D.J., Meeks, R.C. and Thomas, K.E. (1951). Endocrinology, 49, 703.

Ingle, D.J., Ward, E.O. and Kuizenga, M.H. (1947). Amer. J. Physiol., 149, 510.

Jeffers, /

Jeffers, W.A., Livezey, M.A. and Austin, J.H. (1942). Proc. Soc. exp. Biol., N.Y., 50, 184.

Jepson, R.P., Jordan, A., Levek, M.J. and Wilson, G.M. (1957). Ann. Surg., 145, 1.

Joekes, A.M., Mowbray, T.F. and Dormandy, K. (1957). Lancet, 2, 864.

Jones, R.V.H. and de Wardener, H.E. (1956). Brit. med. J., 1, 271.

Keeton, R.W., Cole, W.H., Calloway, N., Glickman, N., Mitchell, H.H., Dyniewicz, J. and Howes, D. (1948). Ann. intern. Med., 28, 521.

Keys, A., Brozek, J., Henschel, A., Mickelsen, O. and Taylor, H.L. (1950). "The Biology of Human Starvation." London: Geoffrey Cumberlege.

Klebs, J. (1868). "Handbuch der Pathologie und Anatomie." (Quoted by Harkins, H.H. (1942). "The Treatment of Burns." Springfield, Ill.: C.C. Thomas.)

Krieger, H., Benson, J.W., Rayburn, C.J., Abbott, W.E., Levey, S. and Holden, W.D. (1955). Surgical Forum, 6, 391. Philadelphia: W.B. Saunders.

Lauson, H.D. (1951). Amer. J. Med., 11, 153.

Leaf, A. and Couter, W.T. (1949). J. clin. Invest., 28,1067.

Leaf, A., Barrter, F.C., Santos, A.F. and Wrong, O. (1953). J. clin. Invest., 32, 868.

Leaf, A., Chatillon, J.Y., Wrong, O. and Tuttle, E.P. (1954). J. clin. Invest., 33, 1261.

Leaf, A., Kerr, W.S., Wrong, O. and Chatillon, J.Y. (1954). Amer. J. Physiol., 179, 191.

Le Quesne, L.P. (1954). Lancet, 1, 172.

Le Quesne, L.P. (1957). Personal communication.

Le Quesne, L.P. and Lewis, A.A.G. (1953). Lancet, 1, 153.

Levenson, S.F., Birkhill, F.R., Maloney, M.A. and Bell, J.A. (1949). Ann. Surg., 130, 723.

Lewis, A.A.G. and Eisen, V.D. (1953). Proc. Physiol. Soc., 122, 33.

Limbert, /

Limbert, E.M., Power, M.H., Pemberton, de J. and Wakefield, E.G. (1945). Surg. Gynec. Obstet., 80, 609.

Llaurado, J.G. (1955). Lancet, 1, 1295.

Llaurado, J.G. and Woodruff, M.F.A. (1957). Surgery, 42,313.

Lowe, K.G. (1953). Clin. Sci., 12, 57.

McCance, R.A. (1945). J. Physiol., 104, 196.

Madden, S.C. (1950). In "Plasma Proteins," Vol. 2. Ed. J.B. Youmans. Springfield, Ill.: C.C. Thomas.

Maitland, A.I.L. (1941). Lancet, 2, 446.

Malcolm, J.D. (1893). "The Physiology of Death from Traumatic Fever; A Study in Abdominal Surgery." London: J. & A. Churchill.

Mason, A.S. (1955). Lancet, 2, 632.

Matas, R. (1924). Ann. Surg., 79, 643.

Miles, B.E., Paton, A. and de Wardener, H.E. (1954). Brit. med. J., 2, 901.

Moore, F.D. (1946). Science, 104, 157.

Moore, F.D. (1953). Ann. Surg., 137, 289.

Moore, F.D. (1954). J. Amer. med. Ass., 154, 379.

Moore, F.D. and Ball, M.R. (1952). "The Metabolic Response to Surgery." Springfield, Ill.: C.C. Thomas.

Moore, F.D., Steenburg, R.W., Ball, M.R., Wilson, G.M. and Myrden, J.A. (1955). Ann. Surg., 141, 145.

Moyer, C.A. (1950). Surgery, 27, 198.

Mudge, G.H., Foulks, J. and Gilman, A. (1948). Proc. Soc. exp. Biol., N.Y., 67, 545.

Mueller, C.B., Eiseman, B., Mason, A.D. and Norman, P.T. (1953). Surgical Forum, 4, 460. Philadelphia: W.B. Saunders.

Mulholland, J.H., Co Tui, Wright, A.M. and Vinci, V.J. (1942). Ann. Surg., 117, 512.

Munro, H.N. (1951). Physiol. Rev., 31, 449.

Munro /

Munro, H.N. and Cummings, M.C. (1948). Nature, Lond., 161, 560.

Naunton-Morgan, C. and Avery-Jones, F. (1938). St. Bart's Hosp. Rep., 71, 83.

Nelson, D.H. and Samuels, L.T. (1952). J. clin. Endocrinol., 12, 519.

Olson, W.H. and Necheles, H. (1947). Surg. Gynec. Obstet., 84, 283.

Owen, K., Desautels, P. and Walter, C.W. (1953). Surgical Forum, 4, 459. Philadelphia: W.B. Saunders.

Peters, J.P. (1948). Amer. J. Med., 5, 100.

Pickford, M. (1956). Antidiuresis. In "Modern Views on the Secretion of Urine." Ed. F.R. Winton. London: J. & A. Churchill.

Prentice, T.C., Olney, J.M., Artz, C.P. and Howard, J.M. (1954). Surg. Gynec. Obstet., 99, 542.

Pringle, H.R., Maunsell, C.B. and Pringle, S. (1905). Brit. med. J., 2, 542.

Randall, H.T., Habif, D.V., Lockwood, J.S. and Werner, S.C. (1949). Surgery, 26, 341.

Rapoport, S., Brodsky, W.A., West, C.D. and Mackler, B. (1949). Amer. J. Physiol., 156, 433.

Reddy, W.J. (1954). Metabolism, 3, 489.

Reddy, W.J., Jenkins, D. and Thorne, G.W. (1952). Metabolism, 1, 511.

Reiss, E., Pearson, E. and Artz, C.P. (1956). J. clin. Invest., 35, 62.

Riegel, C., Koop, C.E., Drew, J., Stevens, L.W. and Rhoads, J.E. (1947). J. clin. Invest., 26, 18.

Robinson, J.R. (1954). "Reflections on Renal Function." Oxford: Blackwell Medical Books.

Robson, J.S., Dudley, H.A.F., Horn, D.B. and Stewart, C.P. (1956). Clin. chim. Acta, 1, 533.

Sandberg, A.A., Eiknes, I.L., Samors, L.T. and Tyler, F.H. (1954). J. clin. Invest., 331, 509.

Sayers, G. (1950). Physiol. Rev., 30, 261.

Schloerb /

Schloerb, P.R., Friis-Hansen, B.J., Edelman, I.S., Solomon, A.K. and Moore, F.D. (1950). J. clin. Invest., 29, 1296.

Schloerb, P.R., Friis-Hansen, B.J., Edelman, I.S., Sheldon, D.B. and Moore, F.D. (1951). J. lab. clin. Med., 37, 653.

Selye, H. (1950). "The Physiology and Pathology of Exposure to Stress." Montreal: Acta Inc.

Sevitt, S. (1956). J. clin. Path., 9, 279.

Shen, S.C., Ham, J.H. and Fleming, E.M. (1943). New Engl. J. Med., 229, 701.

Simpson, S.A., Tait, J.F., Wettstein, A., Neher, R., von Euw, J., Schindler, O. and Reichstein, T. (1954). Experentia, 10, 132.

Sinclair, I.S.R. (1957). Proc. R. Soc. Med., 50, 443.

Smith, H.W. (1940). "The Physiology of the Renal Circulation." Harvey Lectures, 35, 166.

Smith, H.W. (1951). "The Kidney. Structure and Function in Health and Disease." New York: Oxford University Press.

Smith, H.W. (1956). "Principles of Renal Physiology." New York: Oxford University Press.

Smith, H.W. (1957). Amer. J. Med., 23, 623.

Smith, H.W., Rovenstine, E.A., Goldring, W., Chasis, H. and Ranges, H.A. (1939). J. clin. Invest., 18, 319.

Steenburg, R.W. and Ganong, W.F. (1955). Surgery, 38, 92.

Steenburg, R.W., Lennihan, R. and Moore, F.D. (1956). Ann. Surg., 143, 180.

Stein, M., Jinks, R. and Mirsky, I.A. (1952). Endocrinology, 51, 492.

Stewart, J.D. and O'Rourke, G.M. (1942). J. clin. Invest., 21, 197.

Strauss, M.B., Rosenbaum, T.D. and Nelson, W.P., III. (1949). J. clin. Invest., 28, 813.

Sutherland, A.B. (1954). Brit. J. plast. Surg., 8, 68.

Thorne, /

Thorne, G.W., Ross, E.J., Crabbé, J., Van 'T. Hoff, W. (1957). Brit. med. J., 2, 955.

Tompsett, S.L. and Smith, D.C. (1954). J. clin. Endocrin., 14, 922.

Van Dyke, H.B. (1955). Recent Progress in Hormone Research, 11, 1.

Van Dyke, H.B., Ames, R.G. and Plough, I.C. (1950). Trans. Ass. Amer. Phycns, 63, 35.

Van den Velden, R. (1913). Klin. Wschr., 50, 2083.

Verney, E.B. (1926). Proc. roy. Soc. B., 99, 487.

Verney, E.B. (1947). Proc. roy. Soc. B., 135, 25.

du Vigneaud, V. (1956). "Hormones of the Posterior Pituitary Gland: Oxytocin and Vasopressin." Harvey Lectures, 50, 1.

Voit, C. (1881). In Hermann's "Handbuch der Physiologie." Vol. 6. Leipzig.

Wade, H. and Dick, I.L. (1934). Trans. med.-chir. Soc. Edinb., Session XCIII, p. 103.

Werner, S.C. (1947). Ann. Surg., 126, 169.

Werner, S.C. (1948). J. clin. Invest., 27, 561.

Werner, S.C., Habif, D.V., Randall, H.T. and Lockwood, J.S. (1949). Ann. Surg., 130, 688.

Wertheimer, Fabre, and Clogne, R. (1919). Bull. Soc. Chirurgiens Paris, 45, 8.

Wesson, L.G. (1957). Medicine, 36, 281.

Wilkinson, A.W. (1955). "Body Fluids in Surgery." Edinburgh: E. & S. Livingstone.

Wilkinson, A.W. (1956). Lancet, 2, 429.

Wilkinson, A.W. (1957). Unpublished.

Wilkinson, A.W., Billing, B.H., Nagy, G. and Stewart, C.P. (1949). Lancet, 1, 640.

Wilkinson, A.W., Billing, B.H., Nagy, G. and Stewart, C.P. (1950a). Lancet, 1, 523.

Wilkinson, /

Wilkinson, A.W., Billing, B.H., Nagy, G. and Stewart, C.P. (1950b). Lancet, 2, 135.

Wilkinson, A.W., Billing, B.H., Nagy, G. and Stewart, C.P. (1951). Lancet, 1, 315.

Wilson, G.M. (1955). Proc. R. Soc. Med., 48, 817.

Wilson, G.M., Edelman, I.S., Brooks, L., Myrden, J.A., Harken, D.E. and Moore, F.D. (1954). Circulation, 9, 199.

Wirz, H. (1957). The Location of Antidiuretic Action in the Mammalian Kidney. In "The Neurohypophysis." Ed. H. Heller. London: Butterworth.

Wolff, H.P. (1958). Discussion of paper by Barrter et al. in "Aldosterone". Ed. A.F. Muller and C.M. O'Connor. London: J. & A. Churchill.

Wynn, V. (1955). Clin. Sci., 14, 669.

Wynn, V. and Rob, C.G. (1954). Lancet, 1, 587.

Zak, G.A., Brun, C. and Smith, H.W. (1954). J. clin. Invest., 33, 1064.

Zimmermann, B. (1943). Clin. J. Endocrin., 3, 195.

Zimmermann, B., Casey, J.H., Bloch, H.S., Bickel, E.Y. and Govrik, K. (1956). Surgical Forum, 6, 3.

Zimmermann, B. and Wangensteen, O.W. (1952). Surgery, 31, 654.

APPENDIX II

TABLE II

NORMAL SUBJECT: C.J., Male, age 21; Medical Student

Intravenous Water Load 6% Dextrose: 2.11.53

Time mins.	Serum Sodium mEq/l.	Serum Potassium mEq/l.	Urine flow ml./min.	Urine osm. mOs/l.	Change in weight g.
15	139.0	4.4	0.7	1000	0
45	139.0	4.3	2.1	1000	- 60
45	Dextrose infusion begins				
80	132.5	4.8	1.6	840	+ 650
90	Dextrose infusion ends - total 750 ml.				
110	134.0	4.4	3.5	250	+ 500
140	135.5	4.45	9.0	150	+ 350
165	-	-	3.5	260	+ 60
200	136.0	4.4	2.2	440	+ 30
225	-	-	1.4	400	- 60

TABLE III

W.M., Male, age 58; Duodenal Ulcer: Operation - gastrectomy;

Approximately 820 ml. 6% dextrose infused 45-85 mins. of each experimental period.

Time mins.	15.0	30.0	45.0	90.0	105.0	130.0	150.0	165.0	180.0	210.0	225.0	240.0	270.0
Pre-operative 9 a.m.													
Urine flow ml./min.	1.7	-	2.0	1.9	7.7	-	2.1	-	-	3.0	-	-	1.8
Urine osmolarity mOs/l.	640.0	-	610.0	320.0	280.0	-	350.0	-	-	570.0	-	-	420.0
Serum sodium mEq/l.	-	137.0	-	127.5	-	134.0	135.5	-	136.0	-	-	138.0	-
Serum potassium mEq/l.	-	5.0	-	4.6	-	4.6	4.75	-	-	4.8	-	4.78	-
Day of operation 2.30 p.m.													
Urine flow ml./min.	0.2	-	2.5	2.0	-	-	2.5	-	-	0.3	0.5	-	1.0
Urine osmolarity mOs/l.	500.0	-	520.0	550.0	-	-	540.0	-	-	700.0	710.0	-	690.0
Serum sodium mEq/l.	136.0	-	134.5	129.0	-	-	129.5	-	-	127.0	129.0	-	-
Serum potassium mEq/l.	4.4	-	4.4	4.5	-	-	4.55	-	-	4.55	4.65	-	-
First post-operative day 9 a.m.													
Urine flow ml./min.	0.6	-	-	0.3	2.1	-	0.6	-	-	0.6	-	-	-
Urine osmolarity	800.0	-	-	720.0	750.0	-	720.0	-	-	720.0	-	-	-
Second post-operative day 9.15 a.m.													
Urine flow ml./min.	-	-	0.3	3.1	6.1	3.5	-	3.3	-	-	-	-	3.0
Urine osmolarity mOs/l.	-	-	450.0	580.0	300.0	330.0	-	450.0	-	-	-	-	610.0

TABLE IV

W.W., Male, age 58; Duodenal Ulcer; Operation - gastrectomy; 10.12.53

Detailed study of effect of 6% dextrose infusion in immediate post-operative period

Time	Serum Sodium mEq/l.	Serum Potassium mEq/l.	Urine flow ml./min.	Urine osm. mOs/l.	Urine sodium mEq/min.	Urine potassium mEq/min.	Urine total solute mOs/min.
8.15 a.m.	137	4.2	0.8	580	3	17	24
8.15 a.m.	Operation begins						
9 a.m.	137	4.25	0.8	580	4	16	23
1 p.m.	Operation ends						
1 p.m.	136.5	4.4	0.6	420	4	4	6
1.45 p.m.	Infusion begins						
1.50 p.m.	134	4.4	0.5	-	-	-	-
2.15 p.m.	Infusion ends - total 890 ml.						
2.15 p.m.	130	4.55	0.8	430	9	18	16
2.45 p.m.	-	-	5.0	430	95	80	103
3.15 p.m.	131	4.6	2.7	470	42	55	63
4.15 p.m.	128	4.6	1.2	560	-	42	49
8 p.m.	-	-	0.8	500	6	19	16
12 m.n.	-	-	1.2	610	9	45	20
4 a.m.	-	-	0.8	680	6	33	18
8 a.m.	135	4.8	0.8	670	4	25	20

TABLE V

H.P., Male, age 67; Duodenal Ulcer; 7.2.54

Pre-operative study

Time mins.	Urine Flow ml./min.	Urine Osmolarity mOs/l.
10	0.8	782
20	6% dextrose infusion begins approx. 2 ml./min.	
40	1.0	694
60	6% dextrose infusion ends - 850 ml. administered	
	4.2	560
80	6.8	354
100	8.7	203
120	1.0	231
140	5.8	247
160	4.2	379
180	3.2	390
200	2.6	461

(Over)

TABLE V (cont'd)

Effect of Pitressin on response to water load

Time mins.	Urine Flow ml./min.	Urine Osmolarity mOs/l.
0	4 units of Pitressin by intramuscular injection	
10	1.0	840
20	6% dextrose infusion begins	
40	0.5	882
60	6% dextrose infusion ends - 850 ml. administered	
80	2.2	524
100	1.4	548
140	1.2	563
160	1.8	565
190	1.0	560
220	1.1	762

(Over)

TABLE V (cont'd)

Water load on day after operation

Time mins.	Urine Flow ml./min.	Urine Osmolarity mOs/l.
10	0.4	660
20	6% dextrose infusion begins approx. 2 ml./min.	
40	0.8	610
60	6% dextrose infusion ends - 865 ml. administered	
100	0.9	643
120	3.2	658
150	2.7	600
180	1.1	591
200	0.5	603

(Over)

TABLE V (cont'd)

Time mins.	Serum Sodium mEq/l.	Serum Potassium mEq/l.
	Serum electrolytes after intravenous water load	
20	Infusion begins	
	144.5	4.4
40	134.5	4.36
60	Infusion ends	
	126.5	4.2
90	131.0	4.4
105	131.0	4.6
130	132.0	4.57
160	136.5	-
180	143.0	4.5
	Serum electrolytes during potassium experiment	
0	4 units Pitressin intramuscularly	
20	Infusion begins	
25	139.0	4.52
60	Infusion ends	
	131.0	4.0
120	130.5	4.45
150	130.0	4.3
180	131.5	4.4
210	134.0	4.4
240	131.0	4.4

(Over)

TABLE V (cont'd)

Time mins.	Serum Sodium mEq/l.	Serum Potassium mEq/l.
Serum electrolytes during administration of water load 1 day post-operatively		
20	Infusion begins	
25	135.0	4.25
60	Infusion ends	
	131.0	4.4
105	132.0	4.4
135	133.0	4.25
160	131.0	4.08
190	130.5	4.06
240	135.5	4.05

TABLE VI

J.K., Male, age 54; Duodenal Ulcer; Operation - gastrectomy; 4.11.55

Serial water loads administered intravenously as 6% dextrose between 0-30 minutes

Pre-operative (9 a.m.)										
Time (mins.)	0	30	60	90	120	150	180	210	240	270
Urine flow (ml./min.)	1.2	3.3	3.1	8.0	3.0	2.8	-	1.4	-	0.8
Urine osmolarity (mOs/l.)	690	411	225	89	240	372	-	521	-	605
Day of operation (water load administered at 2 p.m.; operation 8.30-11.30 a.m.)										
Urine flow (ml./min.)	0.35	2.8	0.3	1.2	1.1	-	0.4	-	0.2	-
Urine osmolarity (mOs/l.)	680	672	644	711	749	-	791	-	813	-
First post-operative day (9 a.m.)										
Urine flow (ml./min.)	0.75	2.1	2.9	1.4	0.8	-	0.4	-	0.25	-
Urine osmolarity (mOs/l.)	840	861	837	816	892	-	894	-	917	-
Second post-operative day (9 a.m.)										
Urine flow (ml./min.)	0.4	2.9	3.6	5.9	4.0	3.2	-	2.3	-	0.3
Urine osmolarity (mOs/l.)	682	418	385	220	368	404	-	429	-	640

TABLE VII

R.L., Male, age 59; Duodenal Ulcer; Operation - gastrectomy; 7.12.55.

Serial water loads administered intravenously as 6% dextrose between 0-30 minutes

Pre-operative (9.30 a.m.)										
Time (mins.)	0	30	60	90	120	150	180	210	240	270
Urine flow (ml./min.)	0.9	2.8	6.4	8.3	3.0	3.0	-	0.7	-	0.65
Urine osmolarity (mOs/l.)	580	390	148	102	367	374	-	604	-	628
Day of operation (water load 1.45 p.m.; operation 9-11.30 a.m.)										
Urine flow (ml./min.)	0.2	1.4	3.2	2.0	0.7	-	0.35	-	0.3	-
Urine osmolarity (mOs/l.)	810	815	780	806	822	-	861	-	858	-
First post-operative day (9 a.m.)										
Urine flow (ml./min.)	0.4	0.9	2.8	1.8	0.9	-	0.65	-	0.3	-
Urine osmolarity (mOs/l.)	748	722	760	715	728	-	751	-	779	-
Second post-operative day (9 a.m.)										
Urine flow (ml./min.)	0.8	2.9	5.0	7.2	2.4	-	3.1	-	0.75	-
Urine osmolarity (mOs/l.)	629	601	172	108	470	-	412	-	592	-

TABLE VIII

G.W., Male, age 49; Stomal Ulcer; Operation - gastrectomy; 18.12.55.

Serial water loads administered intravenously as 6% dextrose between 0-30 minutes

Pre-operative (9 a.m.)										
Time (mins.)	0	30	60	90	120	150	180	210	240	270
Urine flow (ml./min.)	0.9	2.7	9.0	5.8	2.0	1.5	-	1.0	-	0.6
Urine osmolarity (mOs/l.)	745	527	98	178	573	640	-	711	-	772
Day of operation (2.45 p.m.; operation 10-1 p.m.)										
Urine flow (ml./min.)	0.2	2.2	2.9	1.0	0.9	0.6	-	0.25	-	0.2
Urine osmolarity (mOs/l.)	921	864	818	892	910	916	-	945	-	938
First post-operative day (9 a.m.)										
Urine flow (ml./min.)	0.25	2.8	3.4	0.9	0.8	0.75	-	0.6	-	0.4
Urine osmolarity (mOs/l.)	860	848	829	872	862	861	-	875	-	892
Second post-operative day (9 a.m.)										
Urine flow (ml./min.)	1.2	2.9	7.0	5.6	1.8	0.8	-	0.6	-	0.4
Urine osmolarity (mOs/l.)	629	640	118	212	576	680	-	721	-	729

TABLE IX

R.T., Male, age 22; Normal University student.
Effect of administration of an ether anaesthetic in response to 6% dextrose infusion.
Infusion administered between 60-90 minutes in each instance except in Pitressin experiment.
Catheter inserted at 0 minutes.

Time (mins.)	0	30	45	60	90	120	150	180	210	240
Control										
Urine flow (ml./min.)	-	-	0.2	-	0.5	2.4	5.5	4.3	1.8	2.0
Urine osmolarity (mOs/l.)	-	-	1008	-	1004	262	104	105	207	217
After Ether Anaesthesia										
Urine flow (ml./min.)	0.15	-	2.25	-	0.15	0.2	0.25	-	0.2	-
Urine osmolarity (mOs/l.)	1021	-	947	-	921	918	975	-	1038	-
First post-anaesthetic day										
Urine flow (ml./min.)	-	1.3	1.1	4.0	9.3	9.0	2.7	1.8	-	
Urine osmolarity (mOs/l.)	-	430	452	229	130	98	218	208	-	
Effect of Pitressin 4 units intramuscularly before intravenous water loading. Infusion between 0-45 minutes.										
Time	0	30	45	60	75	105	120	165	210	
Urine flow (ml./min.)	0.2	-	0.15	0.2	-	0.15	0.6	0.8	0.7	
Urine osmolarity (mOs/l.)	902	-	898	926	954	897	868	834		

TABLE X

W.M., Male, age 27; Normal subject; Responses to anaesthesia

Infusion of 6% dextrose after "dummy" anaesthesia - patient prepared as for anaesthesia but anaesthetic not given

Time mins.	Urine Flow ml./min.	Urine Osmolarity mOs/l.
0	End of dummy anaesthetic period	
	0.6	924
80	6% dextrose infusion begins 2 ml./min.	
120	1.0	
160	6% dextrose infusion ends	
	6.3	78
200	6.4	79
240	1.3	204
260	1.5	227

Infusion of 6% dextrose after a pentothal-ether anaesthetic of 2 hour duration

0	Anaesthetic ends	
10	0.4	747
80	6% dextrose infusion begins approx. 2 ml./min.	
120	0.4	730
160	6% dextrose infusion ends - 1050 ml. administered	
165	2.0	752
210	1.0	809
225	0.75	872
255	0.4	911

(Over)

TABLE X (cont'd)

Infusion of 6% dextrose after a pentothal anaesthetic of 50 minutes duration

Time mins	Urine flow ml./min.	Urine Osmolarity mOs/l.
0	Anaesthetic ends	
50	6% dextrose infusion begins approx. 2 ml./min.	
	0.45	6.05
70	1.1	6.27
110	2.0	534
120	6% dextrose infusion ends - 1100 ml. administered	
130	8.2	78
160	4.4	75
190	0.8	625
220	0.5	224

TABLE XI

Subject J.D., age 30; normal female. 12th July, 1954. Water deprivation from 10.00 p.m. 11th July, 1954.

Time and Date	Urine Flow Rate ml./min.	Urine Osmolarity mOs/l.
10.00 p.m. 11.7.54 - 9.00 a.m. 12.7.54	0.29	780
11.00 a.m.	0.4	682
1.00 p.m.	0.31	790
3.00 p.m.	0.31	845
5.00 p.m.	0.28	947
7.00 p.m.	0.28	998
9.00 p.m.	0.28	1021
10.00 p.m. - 6.00 a.m. 13.7.54	0.2	1046
6.00 a.m. - 10.00 a.m.	0.18	1022

TABLE XII

Subject I.T., age 24; normal male. 15th July, 1954. Water deprivation from 11 p.m.

Time and Date	Urine Flow Rate ml./min.	Urine Osmolarity mOs/l.
11.00 p.m. 14.7.54 - 8.30 a.m. 15.7.54	0.44	690
9.30 a.m.	0.7	640
10.30 a.m.	0.81	638
11.30 a.m.	0.88	602
12.30 p.m.	0.8	621
1.30 p.m.	0.9	630
2.30 p.m.	0.85	711
3.30 p.m.	1.2	542
4.30 p.m.	1.8	510
5.30 p.m.	0.81	634
6.30 p.m.	0.46	780
7.30 p.m.	0.31	927
8.30 p.m.	0.28	983
9.30 p.m.	0.23	975
10.30 p.m.	0.25	921
11.00 p.m.	0.2	1024
11.00 p.m. - 6 a.m. 16.7.54	0.1	1050
6 a.m. - 10 a.m. 16.7.54	0.13	1034

TABLE XIII

Subject - Garrigan; Duodenal ulcer; Operation - gastrectomy; General anaesthetic; 13.11.57

Time	Urine Volume ml.	Rate of Flow ml./min.	Osmolarity mOs/l.
10 p.m. - 6 a.m.	597	1.04	688
6 a.m. - 11 a.m.	191	0.64	760
11 a.m. - 12.52 p.m.	24	0.21	690
12.52 p.m. - 4 p.m.	90	0.31	730
4 p.m. - 10 p.m.	100	0.28	955
10 p.m. - 4 p.m.	182	0.5	1025

TABLE XIV

Subject - McClurg; Duodenal ulcer; Operation - gastrectomy; General anaesthetic; 20.11.57

Time	Urine Volume ml.	Rate of Flow ml./min.	Osmolarity mOs/l.
10 p.m. - 6 a.m.	218	0.45	573
6 a.m. - 11.20 a.m.	116	0.36	605
11.20 a.m. - 1.45 p.m.	160	0.31	502
4 p.m. - 10 p.m.	194	0.54	543
10 p.m. - 6 a.m.	200	0.42	562
6 a.m. - 10 a.m.	256	1.1	581

TABLE XV

Subject - Riddell: Duodenal ulcer: Operation - gastrectomy;
General anaesthetic: 29.11.57

Time	Urine Volume ml.	Rate of flow ml./min.	Osmolarity mOs/l.
10 p.m. - 6 a.m.	229	0.48	472
6 a.m. - 9.20 a.m.	186	0.93	382
9.20 a.m. - 11.15 a.m.	10	0.09	832
11.15 a.m. - 3 p.m.	154	0.68	756
3 p.m. - 10 p.m.	176	0.42	497
10 p.m. - 6 a.m.	378	0.79	540
6 a.m. - 10 a.m.	156	0.23	571

TABLE XVI

Subject - Mitchell; Duodenal ulcer; Operation - gastrectomy; General anaesthetic: 2.12.57

Time	Urine Volume ml.	Rate of flow ml./min.	Osmolarity mOs/l.
10 p.m. - 6 a.m.	241	0.5	960
6 a.m. - 9 a.m.	291	1.6	690
9 a.m. - 2 p.m.	115	0.38	330
2 p.m. - 6 p.m.	8	0.00	1215
6 p.m. - 10 p.m.	49	0.2	855
10 p.m. - 2 a.m.	21	0.09	720
2 a.m. - 6 a.m.	33	0.07	450
6 a.m. - 10 a.m.	8		495

TABLE XVII

Subject - Gallie, Female, age 46; Partial gastrectomy for duodenal ulcer: 20/1/58: Anaesthetic - general: Operation - 11.15 a.m. - 12.00 mid-day

Time and Date	Urine Volume ml.	Urine Flow Rate ml./min.	Urine Osmolarity mOs/l.
10.00 p.m., 19/1/58 - 6.00 a.m., 20/1/58	272	0.57	610
6.00 a.m. - 11.15 a.m., 20/1/58	94	0.3	648
11.15 a.m. - 4.00 p.m., 20/1/58	248	0.87	540
4.00 p.m. - 4.00 a.m., 20/1/58	140	0.39	686
10.00 p.m. - 4.00 a.m., 21/1/58	84	0.23	702
4.00 a.m. - 10.00 a.m., 21/1/58	114	0.32	680

TABLE XVIII

Subject - Craig, Female, age 34; Gastroenterostomy - Vagotomy for duodenal ulcer; 30/12/57; Operation - 11.00 a.m. - 12.00 mid-day

Time and Date	Urine Volume ml.	Urine Flow Rate ml./min.	Urine Osmolarity mOs/l.
10.00 p.m., 29/11/57 - 6.00 a.m., 30/12/57	291	0.61	830
6.00 a.m. - 12.00 mid-day, 30/12/57	84	0.23	652
12.00 - 2.00 p.m., 30/12/57	76	0.63	660
2.00 p.m. - 6.00 p.m., 30/12/57	115	0.48	648
6.00 p.m. - 12 midnight, 30/12/57	63	0.25	
12 midnight - 6.00 a.m., 31/12/57	108	0.3	
6.00 a.m. - 10.00 a.m., 31/12/57	86	0.36	

TABLE XIX

Subject - McKenzie, Male, age 48: Partial gastrectomy for duodenal ulcer: 9/1/58; Operation - 11.40 a.m. - 12.25 p.m.

Time and Date	Urine Volume ml.	Urine Flow Rate ml./min.	Urine Osmolarity mOs/l.
10.00 p.m., 8/1/58 - 6.00 a.m., 9/1/58	340	0.71	580
6.00 a.m. - 11.40 a.m., 9/1/58	211	0.62	612
11.40 a.m. - 12.25 p.m., 9/1/58	3	-	670
12.25 p.m. - 2.30 p.m., 9/1/58	24	0.19	660
2.30 p.m. - 6.00 p.m., 9/1/58	85	0.4	720
6.00 p.m. - 12 midnight, 9/1/58	227	0.63	788
12 midnight - 6.00 a.m., 10/1/58	110	0.3	860
6.00 a.m. - 10.00 a.m., 10/1/58	67	0.28	925

TABLE XX

Subject - Semple, Male, age 54; Gastroenterostomy - Vagotomy for duodenal ulcer; 14/1/58; Operation - 10.00 a.m. - 10.45 a.m.

Time and Date	Urine Volume ml.	Urine Flow Rate ml./min.	Urine Osmolarity mOs/l.
10.00 p.m., 15/1/58 - 6.00 a.m., 14/1/58	576	1.2	565
6.00 a.m. - 10.00 a.m., 14/1/58	103	0.43	622
10.00 a.m. - 4.00 p.m., 14/1/58	130	0.29	590
4.00 p.m. - 12 midnight, 14/1/58	141	0.4	598
12 midnight - 6.00 a.m., 15/1/58	115	0.32	610
6.00 a.m. - 10.00 a.m., 15/1/58	144	0.6	640

TABLE XXI

Subject - Scott, Male, age 47; Partial gastrectomy for duodenal ulcer: 23/1/58; Operation - 10.00 a.m. - 12.00 mid-day

Time and Date	Urine Volume ml.	Urine Flow Rate ml./min.	Urine Osmolarity mOs/l.
10.00 p.m., 22/1/58 - 6.00 a.m., 23/1/58	310	0.64	780
6.00 a.m. - 10.00 a.m., 23/1/58	130	0.54	711
10.00 a.m. - 4.00 p.m., 23/1/58	115	0.32	540
4.00 p.m. - 10.00 p.m., 23/1/58	90	0.25	825
10.00 p.m. - 6.00 a.m., 24/1/58	154	0.32	860
6.00 a.m. - 10.00 a.m., 24/1/58	97	0.4	517

TABLE XXII

Subject - Ripley, Female, age 52; Right hemicolectomy for carcinoma colon; 18/1/58; Anaesthetic - spinal; Operation - 11.00 a.m. - 12.00 mid-day

Time and Date	Urine Volume ml.	Urine Flow Rate ml./min.	Urine Osmolarity mOs/l.
10.00 p.m., 22/1/58 - 6.00 a.m., 23/1/58	210	0.44	580
6.00 a.m. - 11.00 a.m., 23/1/58	49	0.16	792
11.00 a.m. - 4.00 p.m., 23/1/58	98	0.33	764
4.00 p.m. - 10.00 p.m., 23/1/58	56	0.16	890
10.00 p.m. - 6.00 a.m., 23/1/58	73	0.15	1012
6.00 a.m. - 10.00 a.m., 23/1/58	51	0.21	1125

TABLE XXIII

Conscious volunteer - H.A.F.D., Male, age 32
Venesection of 1 litre of blood in 10 minutes to reduce renal blood flow
Water diuresis induced by constant rate infusion of 6% dextrose at approximately 5 ml./min.

Experiment 1 - 15/3/58

Time	Urine Volume ml.	Urine Flow Rate ml./min.	Urine Osmolarity mOs/l.
2.07	Empty Bladder		
2.37	32	1.1	1150
3.02	34	1.36	1000
3.19	Venesection begun		
3.18	Venesection completed		
3.20	47	2.6	560
3.35	60	4.0	390
3.50	110	6.3	164
3.51	Reinfusion begun		
4.00	Reinfusion completed		
4.15	265	9.4	200

Experiment 2 - 18/3/58

2.00	Empty Bladder		
2.30	46	1.5	1015
3.00	64	2.1	970
3.01	Venesection begun		
3.10	Venesection completed		
3.15	44	3.0	570
3.30	53	3.5	370
3.45	76	5.0	154
3.46	Reinfusion begun		
3.55	Reinfusion completed		
4.10	240	8.0	154

TABLE XXIV

Conscious volunteer - H.A.F.D., Male, age 32
Cuffs on thighs at 70 mm.Hg for 39 minutes to reduce renal blood flow
Water intake maintained by consumption of equal amount of water to volume of urine passed

Experiment 1 - 11/11/57

Date	Urine Volume ml.	Urine Flow Rate ml./min.	Urine Osmolarity mOs/l.
2.08	Bladder emptied		
2.37	52	1.8	490
3.01	56	2.34	530
3.02	Cuffs applied		
3.41	Cuffs released		
3.44	70	1.62	540
4.05	38	1.8	515
4.46	64	1.46	495

Experiment 2 - 13/11/57

2.00	Bladder emptied		
2.30	72	2.4	420
2.59	101	3.5	380
3.00	Cuffs applied		
3.40	Cuffs released		
3.43	123	2.8	411
4.03	36	1.8	525
4.43	85	2.1	509

TABLE XXV

W.P. Synchronous-combined abdomino-perineal excision of rectum. High spinal anaesthetic.

Operation complete 11 a.m.

Time	Urine Volume ml.	Urine Flow ml./min.	Osmolarity mOs/l.	Blood Pressure mm.Hg
	Bladder emptied			
2.20 p.m.	50	0.6	-	120/90
3.05	32	0.7	540	
3.41	32	1.12	675	80/58
3.45	Mannitol infusion begins			
4.00	66	3.48	505	
4.55	Experiment terminated			76/50

TABLE XXVI

D.G.: Duodenal ulcer: 28.4.55: Pre-operative study

Continuous infusion of 6% dextrose at 10 ml./min., begun at 11.30 a.m.

Time	Urine Flow Rate ml./min.	Osmolarity mOs/l.	Solute output mOs/min.
12.30 p.m.	1.5	260	0.390
1.00	6.5	320	2.14
1.30	21.0	120	2.52
1.45	Vasopressin 5 units intramuscularly		
	20.0	75	1.50
2.00	10.0	210	2.1
2.15	9.0	318	2.862
2.30	5.5	255	1.4
2.45	3.5	375	1.3
3.00	Mannitol 75 g. in 15% solution in 10 minutes		
	3.0	440	1.32
3.15	6.0	324	1.944
3.30	16.0	262	4.19
3.45	19.0	265	5.05
4.00	17.0	267	4.55
4.15	14.0	380	4.9
4.30	16.0	-	-
4.45	13.5	400	5.40
5.00	11.0	210	2.31
5.15	9.0	-	-
5.30	7.5	195	1.46
6.00	6.0	265	1.230

(Over)

TABLE XXVI (cont'd)

D.G.: Partial gastrectomy for Duodenal ulcer: General anaesthesia: Operation - 9 - 11 a.m.: 29.4.55

Mannitol 75 g. in 15% solution by rapid intravenous injection at 3 - 3.10 p.m.

Time	Urine Flow Rate ml./min.	Osmolarity mOs/l.	Solute output mOs/min.
1.00 p.m.	0.4	900	0.36
3.00	0.6	910	0.546
3.30	8.5	800	7.640
3.45	16.0	612	9.792
4.00	10.5	640	6.760
4.30	6.5	690	4.665
5.00	4.0	780	3.120
5.30	2.5	800	2.000
6.00	2.0	830	1.660

TABLE XXVII

Jane Brown: Age 36; 45% surface burns; 9.12.57 - 11.12.57

Time	Urine Volume ml.	Rate of Flow ml./min.	Osmolarity mOs/l.	Solute Output mOs/min.	Visible Pigment
6.10 - 6.30 p.m.	104	5.2	312	1.6	-
6.30 - 7.30	304	5.06	374	1.9	+
7.30 - 8.30	190	3.11	465	1.45	+
8.30 - 9.30	112	1.86	426	0.79	-
9.30 - 10.30	86	1.43	423	0.60	-
10.30 - 11.30	106	1.76	480	0.89	-
11.30 - 12.30 a.m.	78	1.3	517	0.67	-
12.30 - 1.30	32	0.53	512	0.27	-
1.30 - 2.30	66	1.1	513	0.56	-
2.30 - 10.30	492	1.2	660	0.97	-
10.30 - 6.30 p.m.	252	0.52	786	0.41	-
6.30 - 2.30 a.m.	126	0.26	1080	0.28	-
2.30 - 10.30	150	0.31	696	0.22	-
10.30 - 6.30 p.m.	120	0.25	705	0.18	-
6.30 - 2.30 a.m.	324	0.78	585	0.46	-

Urine was collected hourly for the first 9 hours and thereafter 8 hourly. Sixty g. of mannitol in 15% solution were administered between 6.30 and 6.50 p.m. after the first urine specimen had been collected because of the occurrence of heavy pigment staining in the urine.

TABLE XXVIII

Subject - Telford; Carcinoma of stomach; Operation - gastrectomy; 19.11.57; Anaesthetic - hypotensive; Height - 165 cm.; Surface area - 1.62 sq.m.; Weight - 60 kg.; Correction factor - 1.07

Time	Specimen	Volume ml.	Rate of Flow ml./min.	Vc	Osmolarity mOs/l.	$\frac{UV}{P}$	$\frac{(UV)}{(P)C}$
2.29 p.m.	U1	24	0.19	0.2	660	0.396	0.425
2.30	Mannitol infusion begins						
2.30	P1				317		
2.51	U2	32	1.0	1.07	643	2.01	2.15
3.00	P2				320		
3.12	U3	169	5.8	6.2	507	9.2	9.85
3.22	Mannitol infusion ends						
3.32	U4	268	13.4	14.3	470	19.7	20.12
3.35	P3				332		
3.52	U5	164	8.2	8.77	512	12.7	13.6
4.15	U6	177	7.7	8.22	526	12.2	13.1
4.18	P4				335		
4.39	U7	124	5.2	5.55	585	9.1	9.7
5.05	U8	118	4.5	4.8	620	8.3	8.9
5.32	P5				332		
5.35	P9	86	2.9	3.1	642	5.5	5.95

TABLE XXIX

Subject - Jeffs; Duodenal ulcer; Operation - gastrectomy; 12.11.57; Anaesthetic - spinal; Height - 175 cm.; Surface area - 1.73 sq.m.; Weight - 63.6 kg.; Correction factor - 1

Time	Specimen	Volume ml.	Rate of Flow ml./min.	Osmolarity mOs/l.	UV / P
2.01 p.m.	P1			302	
2.03	U1	76	0.59	660	1.3
2.07		Mannitol infusion begins			
2.25	U2	35	1.59	685	3.46
2.42	P2			315	
2.45	U3	97	4.85	545	8.4
2.59	U4	108	7.7	470	11.2
3.04		Mannitol infusion ends			
3.11	P3			325	
3.14	U5	176	11.7	435	15.7
3.29	U6	156	10.4	481	15.4
3.44	U7	116	7.75	510	12.7
4.06	P4			312	
4.04	U8	138	6.9	543	12.0
4.30	U9	156	6.0	560	10.8
4.58	U10	132	5.3	590	9.6
5.02	P5			325	

TABLE XXX

Subject - Vaughan: Recurrent inguinal hernia: Operation - bilateral inguinal hernia: 7.11.57.
Anaesthetic - general: Height - 175 cm.: Surface area - 1.73 sq.m.:
Weight - 63 kg.: Correction factor - 1

Time	Specimen	Volume ml.	Rate of Flow ml./min.	Osmolarity mOs/l.	UV P
12.00 p.m.	P1			310	
1.53	U1	88	0.77	752	1.18
1.55		Mannitol infusion begins			
2.13	U2	84	4.2	530	6.95
2.15	P2			321	
2.29	U3	184	13.1	417	16.4
2.42	U4	164	12.6	365	13.9
2.43	P3			332	
2.59	U5	227	15.3	405	19.2
3.00		Mannitol infusion ends			
3.23½	U6	323	13.2	418	16.5
3.35	U7	118	10.3	450	14.4
3.37	P5			321	
3.53	U8	94	5.23	523	8.7
4.18	U9	183	7.3	557	13.1
4.42	U10	80	3.1	595	5.75
5.11	U11	115	4.35	663	9.3

TABLE XXXI

Subject - Anderson; Bilateral inguinal hernia; Operation - bilateral inguinal herniotomy; 5.11.57; Anaesthetic - general; Height - 156 cm.; Surface area - 1.76 sq.m.; Weight - 68 kg.; Correction factor - 0.98

Time	Specimen	Volume ml.	Rate of Flow ml./min.	Vc	Osmolarity mOs/l.	$\frac{UV}{P}$	$\frac{(UV)}{(P)C}$
1.41 p.m.	U1	42	0.26	0.27	835	0.64	0.65
1.42			Mannitol infusion begins				
1.42	P1				300		
2.01	U2	80	4.0	4.1	665	8.4	8.5
2.02	P2				315		
2.11	U3	131	13.1	13.3	456	18.9	19.2
2.15			Mannitol infusion ends				
2.17	P3				318		
2.22	U4	190	17.3	17.6	423	23.0	23.2
2.32	U5	164	16.4	16.7	420	21.6	22.0
2.45	U6	187	15.2	15.5	430	20.3	20.4
2.48	P4				317		
3.06	U7	182	8.6	8.75	490	13.3	13.5
3.26	U8	134	6.7	6.8	546	11.5	11.7
3.57	U9	146	4.7	4.8	610	9.3	9.5
3.59	P5				307		
4.34	U10	120	3.1	3.2	654	6.6	6.7

TABLE XXXII

Subject - McMahon; Duodenal ulcer; Operation - gastrectomy; 17.10.57; Anaesthetic - general; Height 170.5 cm.; Surface area - 1.85 sq.m.; Weight - 76.5 kg.; Correction factor - 0.934

Time	Specimen	Volume ml.	Rate of Flow ml./min.	Vc	Osmolarity mOs/l.	$\frac{UV}{P}$	$\frac{(UV)}{(P)C}$
2.01 p.m.	P1				262		
2.51	U3	764	15.3	14.3	512	26.8	25.1
3.01	U4	112	11.2	10.5	432	16.0	14.9
3.09	P2				292		
3.11	U5	168	16.8		Specimen discarded		
3.19	U6	110	13.75	12.8	417	19.6	16.3
3.27	U7	130	16.25	15.2	417	21.5	20.1
3.31	P3				315		
3.35	U8	160	20.0	18.7	425	27.0	25.2
3.43	U9	128	16.0	14.9	420	21.9	20.25
3.47½	P4				317		
3.51	U10	114	14.0	13.1	437	19.3	18.0
3.52			Mannitol infusion ends				
3.58	U11	152	21.7	20.1	438	29.8	27.8
4.10	U12	110	9.25	8.65	455	13.3	12.4
4.3¾	U13	224	9.75	9.21	527	16.0	14.9
4.53	U14	120	6.0	5.6	580	10.6	10.0
5.12	U15	118	6.2	5.8	597	11.3	10.5
5.25	P6				327		
5.29	U16	75	4.4	4.1	608	8.35	7.8
5.55	U7	100	3.84	3.58	517	5.95	5.5

TABLE XXXIII

Subject - Wigley; Duodenal ulcer; Operation - gastrectomy; 24.10.57; Anaesthetic - general; Height - 154 cm.; Surface area - 1.43 sq.m.; Weight - 49 kg.; Correction factor - 1.21

Time	Specimen	Volume ml.	Rate of Flow ml./min.	Vc	Osmolarity mOs/l.	$\frac{UV}{P}$	$\frac{(UV)}{(P)C}$
1.50 p.m.	P1				320		
1.57	U1	38	0.19	0.23	755	0.45	0.54
1.59			Mannitol infusion begins				
2.10	U2	33	2.5	3.08	830	6.49	7.85
2.20	U3	34	3.4	4.11	725	7.55	9.15
2.27	P2				326		
2.30	U4	82	8.2	11.1	560	14.1	17.1
2.40	U5	86	8.6	10.4	425	10.9	13.2
2.48	P3				335		
2.51	U6	138	12.5	15.1	456	17.0	20.3
3.01	U7	126	12.6	15.2	450	16.9	20.2
3.11	U8	140	14.0	16.9	442	18.0	21.8
3.20	P4				344		
3.22	U9	142	13.0	15.7	430	16.2	19.6
3.32	U10	128	12.8	15.5	445	16.6	20.0
3.42½			Mannitol infusions ends				
3.42½	U11	172	16.4	19.8	455	21.6	26.2
3.54	P5				344		
3.54	U12	134	11.7	14.2	460	15.7	19.0
4.18	U13	194	13.9	16.8	482	19.5	23.6
4.28	U14	156	7.8	9.5	542	12.6	15.3
4.40	P6				337		
4.49	U15	130	6.2	7.5	565	10.4	12.6
5.18	U16	152	5.25	6.35	577	9.0	10.9
5.47	U17	136	4.7	5.7	582	8.1	9.8

TABLE XXXIV

Subject - Dudley: Conscious volunteer:

Corrections for surface area not applied.

Time	Specimen	Volume ml.	Rate of Flow ml./min.	Osmolarity mOs/l.	$\frac{U}{P}$
12.45 p.m.	U1	51	1.7	190	1.05
1.05	U2	112	5.6	225	4.08
1.20½	U3	184	11.9	105	4.05
1.35	U4	190	13.1	110	4.65
1.35	P1			319	
1.42	6% Dextrose infusion begins				
1.51	U5	194	12.1	80	3.12
2.04	U6	192	13.3	75	3.23
2.06	Mannitol infusion begins				
2.18	P2			296	
2.21	U7	302	17.8	105	6.3
2.35	U8	398	26.6	147	13.2
2.55	U9	590	29.5	165	16.2
2.56	Severe ureteric colic. Mannitol infusion ends				
3.00	P3			300	
3.11	U10	220	13.8	258	11.9
3.26½	U11	172	11.1	310	11.4
3.55	U12	182	6.4	440	9.4

TABLE XXXV

Rat, 200 g., 25.3.54

Elapsed Time secs.	Urine produced ml.	Time to pass 0.1 ml.	Flow Rate ml./hr.
61	0.1	61	5.9
125	0.2	64	5.62
187	0.3	62	5.8
249	0.4	62	5.8
311	0.5	62	5.8
374	0.6	63	5.71
439	0.7	65	5.54
Intravenous injection 1 ml. heparinised serum from patient who had undergone prostatectomy 1 hr. previously			
Time count restarted			
67	0.1	67	5.37
113	0.2	46	7.82
157	0.3	44	8.18
202	0.4	45	8.0
248	0.5	46	7.82
290	0.6	42	8.57
330	0.7	40	9.0
369	0.8	39	9.23
410	0.9	41	8.78

(Over)

TABLE XXV (cont'd)

Elapsed Time secs.	Urine produced ml.	Time to pass 0.1 ml.	Flow Rate ml./hr.
Intravenous injection 12.5 micro-units Pitressin in 1 ml. saline			
Time count restarted			
35	0.1	35	10.29
119	0.2	84	4.28
520	0.3	401	0.9
675	0.4	155	2.33
762	0.5	87	4.14
831	0.6	69	5.22
913	0.7	82	4.39
980	0.8	67	5.37
1042	0.9	62	5.8

TABLE XXXVI

Rat. 220 g., 24.3.54

Elapsed Time secs.	Urine produced ml.	Time to pass 0.1 ml.	Flow Rate ml./hr.
605	0.9	62	5.8
Time count restarted			
238	0.3	79	4.55
288	0.4	50	7.2
350	0.5	62	5.8
410	0.6	60	6.0
Intravenous injection 0.5 ml. heparinised plasma 10 mins. after withdrawal from patient who had undergone mitral valvulotomy 2 hrs. previously			
Time count restarted			
64	0.1	64	5.63
132	0.2	68	5.3
225	0.3	93	3.87
300	0.4	75	4.8
378	0.5	78	4.62
462	0.6	84	4.28
544	0.7	82	4.39
621	0.8	77	4.68

(Over)

TABLE XXXVI (cont'd)

Elapsed Time secs.	Urine produced ml.	Time to pass 0.1 ml.	Flow Rate ml./hr.
Intravenous injection 8 micro-units Pitressin in 0.5 ml. saline			
195	0.4	53	6.79
257	0.5	62	5.81
350	0.6	93	3.87
520	0.7	170	2.12
645	0.8	125	2.72
730	0.1	85	4.23
817	0.2	87	4.14
905	0.3	88	4.09
990	0.4	85	4.23
1065	0.5	75	4.8
1127	0.6	62	5.81
1170	0.7	43	8.38

(Over)

TABLE XXXVI (cont'd)

Elapsed Time secs.	Urine produced ml.	Time to pass 0.1 ml.	Flow rate ml./hr.
Intravenous injection 10 micro-units Pitressin in 0.5 ml. heparinised plasma			
Time count restarted			
660	0.1	660	0.56
900	0.3	120	3.00
998	0.4	98	3.66
1083	0.5	85	4.13
1175	0.6	92	3.91
1262	0.7	87	4.14
1334	0.8	72	5.0
1440	0.9	106	3.39
	Rest period 5 mins.		
43	0.1	43	8.38
88	0.2	45	7.99

(Over)

TABLE XXXVI (cont'd)

Elapsed Time secs.	Urine produced ml.	Time to pass 0.1 ml.	Flow Rate ml./hr.
Time count restarted			
68	0.1	68	5.3
127	0.2	59	6.1
257	0.4	75	4.8
449	0.7	172	6.27
493	0.8	44	8.17
558	0.9	55	6.54
616	1.0	58	6.21
Time count restarted			
49	2.1	49	7.34
Intravenous injection 5 micro-units Pitressin in 0.5 ml. saline			
98	0.2	49	7.34
147	0.3	49	7.34
202	0.4	55	6.56
	Rest 7.5 minutes		

TABLE XXXVII

Rat, 220 g., 27.3.54

Elapsed Time secs.	Urine produced ml.	Time to pass 0.1 ml.	Flow Rate ml./hr.
70	0.1	70	5.14
118	0.2	48	7.49
163	0.3	45	8.00
203	0.4	40	9.00
250	0.5	47	7.67
293	0.6	43	8.39
329	0.7	39	9.22
Intravenous injection 1 ml. heparinised plasma from patient who had undergone splenectomy 1 hr. previously			
391	0.8	62	5.8
430	0.9	39	9.22
469	1.0	39	9.22
511	0.1	44	8.17
558	0.2	47	7.67
604	0.3	46	7.81
643	0.4	39	9.22
682	0.5	39	9.22
724	0.6	42	8.57
775	0.7	52	6.91
827	0.8	51	7.06
Rest period 4 mins.			

(Over)

TABLE XXXVII (cont'd)

Elapsed Time secs.	Urine produced ml.	Time to pass 0.1 ml.	Flow Rate ml./hr.
Intravenous injection 1 ml. clotted serum from same case			
35	0.1	35	10.26
78	0.2	43	8.39
114	0.3	38	9.47
157	0.4	43	8.39
196	0.5	39	9.22
230	0.6	34	10.58
269	0.7	39	9.22
304	0.8	35	10.26
344	0.9	40	9.0
428	1.0	44	8.17
474	0.1	46	7.81
523	0.2	49	7.34

TABLE XXXVIII

Rat, 230 g., 21.3.54

Elapsed Time secs.	Urine produced ml.	Time to pass 0.1 ml.	Flow Rate ml./hr.
718	0.9	980	45.0
Time count restarted			
120	0.2	60	6.0
179	0.3	59	6.1
240	0.4	61	5.9
304	0.5	64	5.62
365	0.6	61	5.9
427	0.7	62	5.8
480	0.8	53	6.79
Intravenous injection 1 ml. heparinised plasma 9 minutes after withdrawal from patient with 45% surface burns			
Time count restarted			
62	0.1	62	5.8
122	0.2	60	6.0
173	0.3	56	6.43
226	0.4	48	7.5
318	0.6	46	7.81
367	0.7	49	7.34

(Over)

TABLE XXXVIII (cont'd)

Elapsed Time secs.	Urine produced ml.	Time to pass 0.1 ml.	Flow Rate ml./hr.
Intravenous injection 25 micro-units plasma in 1 ml. heparinised plasma from patient with 40% surface burns			
35	0.1	35	10.29
98	0.2	63	8.71
218	0.3	120	3.00
507	0.4	289	1.2
677	0.5	170	2.1
810	0.6	133	2.7
930	0.7	120	3.0
998	0.8	68	5.3
1090	0.9	82	49.0
1225	1.1	68	5.3
1278	0.1	53	6.79
1333	0.2	55	6.54

TABLE XXXIX

Effect of Ischaemic Pain on Urine Flow.

H.A.F.D., male, age 31, normal; 30.3.55.

Water diuresis induced by a free consumption of tap water at rate of approx. 300 ml. every 15 mins.

Time	Urine Volume ml.	Urine Flow ml./min.
2.00 p.m.	Bladder emptied. Begins to drink	
2.30	54	1.8
2.45	100	6.6
3.00	176	11.7
3.15	215	14.3
3.30	214	14.3
3.30)		
3.40)	10 minutes of ischaemic pain	
3.45	204	13.6
3.55	17	1.1
4.10	18	1.2
4.25	22	1.5
4.40	34	2.2
5.10	190	6.6
5.45	371	10.6

TABLE XL

Rat, 200 g., 25.3.54

Elapsed Time secs.	Urine produced ml.	Time to pass 0.1 ml.	Flow Rate ml./hr.
50	0.1	50	7.2
100	0.2	50	7.2
150	0.3	50	7.2
445	0.9	49	7.34
Time count restarted			
69	0.2	35	10.29
115	0.3	46	7.82
152	0.4	37	9.73
186	0.5	34	10.59
234	0.6	48	7.5
Intravenous injection 12.5 micro-units in 1 ml. heparinised plasma			
Time count restarted			
43	0.1	43	8.37
230	0.2	197	0.37
723	0.3	593	0.06
980	0.4	257	0.14
1130	0.5	150	0.24
1180	0.6	50	7.2
1245	0.7	65	5.54

(Over)

TABLE XL (cont'd)

Elapsed Time secs.	Urine produced ml.	Time to pass 0.1 ml.	Flow Rate ml./hr.
Time count restarted			
55	0.1	55	6.54
125	0.2	70	5.14
Intravenous injection 1 ml. heparinised plasma after induction of ischaemic pain			
202	0.3	77	5.03
255	0.4	53	6.79
302	0.5	47	7.66
352	0.6	50	7.2
408	0.7	56	6.43
464	0.8	56	6.43

TABLE XLI

Rat. 270 g., 10.7.54

Elapsed Time	Volume passed ml.	Time to pass 0.1 ml. secs.	Flow Rate ml./hr.
min.sec.			
1.52	0.1	112	3.21
3.42	0.2	110	3.27
5.53	0.3	131	2.75
11.22	0.6	117	3.08
13.29	0.7	127	2.84
15.24	0.8	115	3.13
17.25	0.9	121	2.98
Time count restarted			
2.5	0.1	125	2.88
1 ml. of heparinised plasma from subject immediately after 10 mins. of ischaemic pain			
4.4	0.2	119	3.03
6.53	0.4	169	4.28
8.10	0.5	77	4.67
9.31	0.6	81	4.44
10.50	0.7	79	4.56
11.45	0.8	55	6.54
12.43	0.9	58	6.21

TABLE XLII

Rat. 210 g., 14.7.54

Elapsed Time	Volume passed ml.	Time to pass 0.1 ml. secs.	Flow Rate ml./hr.
min.sec.			
1.35	0.1	95	3.89
3.10	0.2	95	3.89
4.42	0.3	92	3.91
6.15	0.4	93	3.87
7.53	0.5	98	3.67
9.33	0.6	100	3.60
11.25	0.7	112	3.22
14.55	0.8	260	1.38
19.25	0.9	270	1.33
Time count restarted			
3.28	0.1	208	1.76
6.36	0.2	188	1.42
1 ml. serum from subject immediately after 10 min. of ischaemic pain			
8.44	0.3	128	2.82
10.20	0.4	96	3.75
11.18	0.5	88	4.08
13.15	0.6	87	4.13
14.58	0.7	103	3.50
16.00	0.8	62	5.80
17.21	0.9	81	4.45

(Over)

TABLE XLII (Continued)

Elapsed Time	Volume passed ml.	Time to pass 0.1 ml. secs.	Flow Rate ml./hr.
min.sec.			
1 ml. of heparinised plasma from subject immediately after 10 mins. of ischaemic pain.			
Time count restarted			
2.40	0.1	160	2.26
3.55	0.2	75	4.80
4.48	0.3	53	6.80
5.38	0.4	50	7.20
6.28	0.5	50	7.20
7.25	0.6	57	6.30
8.25	0.7	60	6.00
9.53	0.8	88	4.10
11.30	0.9	97	3.72

TABLE XLIII

Effects of 5-Hydroxytryptamine on Urine Flow of Alcohol-Anaesthetised Rat.

In this and in the experiment in Table XLI the amount of urine flow at specified intervals was recorded from the pipette (see Appendix I) as giving a more convenient set of data for graphical purposes without conversion.

Elapsed Time min.	Flow Rate ml./min.
0.5	0.016
1.0	0.024
1.5	0.019
2.0	0.019
2.5	0.027
3.0	0.024
3.5	0.02
4.0	0.022
4.5	0.021
5.0	0.021
5.5	0.027
6.0	0.02
6.25	0.02
6.5	0.021
7.0	0.021
9.25	0.02
1 microgrm. 5 H.T. intravenously	
9.5	0.019
10.25	0.021
10.5	0.022
11.0	0.027
11.5	0.032
11.75	0.03
12.0	0.03
12.25	0.027
12.5	0.031
13.0	0.038
2 microgrm. 5 H.T. intravenously	
14.0	0.009
14.75	0.015
15.0	0.032
15.25	0.038
15.5	0.041
15.75	0.041
16.25	0.019
16.75	0.024
17.0	0.031
17.25	0.04
17.5	0.04

(Over)

TABLE XLIII (Continued)

Elapsed Time min.	Flow Rate ml./min.
3 microgrm. 5 H.T. intravenously	
17.75	0.03
18.75	0.01
19.25	0.016
19.75	0.024
20.00	0.025
20.25	0.021
20.75	0.024
21.25	0.025
1 microgrm. 5 H.T. intravenously	
21.75	0.019
22.00	0.02
22.5	0.019
23.0	0.019
3 microgrm. 5 H.T. intravenously	
24.25	0.006
25.0	0.014
25.5	0.023
26.0	0.019
26.25	0.022

TABLE XLIV

Effects of 5-Hydroxytryptamine on Urine Flow of Alcohol-Anaesthetised Rat.

In this and in the experiment in Table XLIII the amount of urine flow at specified intervals was recorded from the pipette (see Appendix I) as giving a more convenient set of data for graphical purposes without conversion.

Elapsed Time min.	Flow Rate ml./min.
0.5	0.02
1.0	0.02
1.5	0.017
2.5	0.012
3.0	0.017
3.5	0.017
4.25	0.017
4.5	0.03
4.75	0.028
5.25	0.027
5.75	0.02
1 ml. saline intravenously	
6.25	0.017
6.75	0.02
7.5	0.02
7.75	0.02
8.0	0.03
8.25	0.03
8.75	0.02
9.5	0.017
9.75	0.024
10.25	0.024
1 microgrm. 5 H.T. intravenously	
10.75	0.014
12.75	0.01
13.5	0.011
14.25	0.012
14.5	0.023
14.75	0.032
15.25	0.024
15.5	0.027
2 microgrm. 5 H.T. intravenously	
16.25	0.02
17.25	0.011
17.75	0.017
18.00	0.035
18.25	0.034
18.5	0.06
18.75	0.06
19.50	0.029
19.25	0.038

TABLE XLV

Effect of Polyvinylpyrrolidone on Urine Flow and Concentration

M.L., Male, age 45; Operation - partial gastrectomy;

Time of beginning of experiment - 3 hours postoperative.

Time mins	Urine Flow ml./min.	Urine Osmolarity mOs/l.
50	0.75	810
75	0.5	860
	540 ml. polyvinylpyrrolidone intravenous infusion in 20 mins.	
90	1.2	610
120	1.6	550
150	2.2	460
180	1.8	465
210	2.1	455
270	0.8	800

TABLE XLVI

Case 3 section on haemoglobinuria

Time hrs. after admission	Intravenous Therapy ml.	Urine Output ml.	Urine Osmolarity mOs/l.	Visible Urinary Pigment
1	1600 ml. Plasma			
2	200 ml. Plasma			++
3	200 ml. Plasma 500 ml. Polyvinylpyrrolidone	4	800	++
4	400 ml. Plasma	37	690	++
5	200 ml. Plasma	26	740	++
6	200 ml. Plasma	11	770	++
7	400 ml. Blood 500 ml. Polyvinylpyrrolidone			
8	800 ml. Plasma	40	580	+
9	400 ml. Plasma	60	430	
10	400 ml. Plasma	70	440	
11	400 ml. Blood	65	550	

TABLE XLVII

Case 4 section on haemoglobinuria

Time	Intravenous Therapy ml.	Urine Volume ml.	Visible Urinary Pigment
5.20 p.m.	200 6% dextrose		-
5.30		20	
5.45	400 plasma		
6.35	400 plasma		
6.55			-
7.00		88	++
7.15	250 dextran		
7.30		9	++
8.00	540 polyvinylpyrrolidone	4	+
8.30	540 polyvinylpyrrolidone	30	+
9.00		8	+
9.30		7	+
9.45	400 plasma		+
11.00		20	+
11.30		1	+
12.00		1	+
12.30		1	
1.00 a.m.		7	
1.30		2	
2.00	540 6% dextrose	4	
2.30		9	
3.00		12	
3.30		22	
4.00	540 6% dextrose	2	
4.30		4	
5.00		10	
5.30		3	
6.00		6	
6.30	500 plasma	3	
7.00		1	
8.00		3	
9.00		17	

TABLE XLVIII

Case 5 section on haemoglobinuria

Time hrs. after admission	Intravenous Therapy ml.	Urine Output ml.	Urine Osmolarity mOs/l.	Visible Urinary Pigment
0	225 Plasma	35	1100	++
1	225 Plasma	15	700	+++
2	275 Polyvinylpyrrolidone			
3	75 Plasma	41	600	++
4	100 Plasma	35	350	+
5	80 Plasma	55	520	+
6	90 Plasma	41	530	-
7	100 Plasma	42	-	-
8	75 Plasma	35	580	-
9	75 Plasma	50	730	-
10	75 Plasma	30	710	-
11	75 Plasma	15	730	-
12	75 Plasma	33	550	-
13	75 Plasma	34	560	-
14	75 Plasma	28	610	-
15	60 Plasma	50	700	-
16	20 Plasma	20	690	-
17	25 Plasma	30	920	-

TABLE XLIX

Case 6 section on haemoglobinuria

Time hrs. after admission	Intravenous Therapy ml.	Urine Output ml.	Urine Osmolarity mOs/l.	Visible Urinary Pigment
0	300 Plasma	10	-	-
1	125 Plasma	17	-	-
2	200 Plasma	1	-	-
3	120 Plasma	2	1000	-
4	230 Plasma	1	-	+++
5	300 Plasma	1	-	+++
6	150 Plasma Mannitol 35 g.			
7	25 Plasma	27	280	++
8	25 Plasma	28	310	++
9	10 Plasma	26	380	++
10	25 Plasma	22	500	+
11	5 Plasma	22	410	+
12	15 Plasma	20	360	+
13	10 Plasma	20	-	+
14	10 Plasma	17	-	+
15	15 Plasma	14	380	+
16	20 Plasma	23	-	-
17	25 Plasma	22	310	+
18	25 Plasma	5	720	-
19	25 Plasma	29	-	-

TABLE L

Fluid intake/output data for 31 consecutive patients who underwent major gastric surgery and received intravenous fluids.

Case	Intake for first 12 hours		Intake for second 12 hours		Urine for first 24 hours ml.	"Balance" not allowing for insensible loss ml.
	Intravenous (excluding blood transfused) ml.	Oral ml.	Intravenous ml.	Oral (less gastric aspirate) ml.		
1	2200	-	400	200	700	2100
2	1600	-	-	2120	890	1830
3	1300	-	-	1830	995	2135
4	2394	-	1600	1230	630	4694
5	1600	-	2000	200	1100	2700
6	800	-	980	780	1300	1260
7	1600	-	800	450	1400	1450
8	1200	-	1600	-	1190	1630
9	800	-	1600	270	780	1990
10	800	-	800	260	240	1620
11	1200	-	2000	1380	1630	2950
12	1200	-	400	2790	1600	2990
13	1200	-	1600	900	1080	2620
14	1200	-	2600	330	1300	2830
15	1400	-	100	1830	940	3290
16	800	-	1400	690	1040	1850
17	1440	-	2400	1650	940	3550
18	1200	-	2000	570	640	3130

(Over)

TABLE L (Continued)

Case	Intake for first 12 hours		Intake for second 12 hours		Urine for first 24 hours ml.	"Balance" not allowing for insensible loss ml.
	Intravenous (excluding blood transfused) ml.	Oral ml.	Intravenous ml.	Oral (less gastric aspirate) ml.		
19	1200	-	1600	180	980	2000
20	700	-	1200	960	480	2420
21	1900	-	800	820	1210	2310
22	1200	-	800	635	730	1905
23	800	-	-	780	1270	310
24	2000	-	2000	360	1050	3310
25	2000	-	2400	120	1500	3020
26	1600	-	1600	-	1100	2100
27	980	-	3600	300	1450	3430
28	800	-	2000	600	300	3100
29	1600	-	-	1000	800	1800
30	1200	-	2400	-	390	3210
31	1800	-	3200	-	1750	3250

TABLE LI

Effect of Oral Water on Serum Electrolytes

Total Body Water derived from D_2O equilibration. Load administered as single oral dose by mouth at zero time. Diuresis complete in all cases by 2 hours.

Subject L.B. T.B.W. = 40.8 l. Load 2% = 800 ml.							
Time mins.	-	40.0	50.0	70.0	90.0	105	160.0
Serum Sodium mEq/l	139.0	135.0	138.5	-	137.5	-	138.0
Serum Potassium mEq/l	3.85	40.0	40.0	3.75	-	40	4.02
Subject L.B. T.B.W. = 40.8 l. Load 1.5% = 610 ml.							
Time mins.	-	55.0	80.0	110.0	160.0	-	-
Serum Sodium mEq/l	137.5	134.0	134.5	135.0	132.5	-	-
Serum Potassium mEq/l	4.2	4.38	4.65	4.55	4.3	-	-
Subject C.L. T.B.W. = 43.5 l. Load 1.5% = 650 ml.							
Time mins.	-	40.0	70.0	105.0	160.0	-	-
Serum Sodium mEq/l	141.0	140.5	135.5.	135.0	135.5	-	-
Serum Potassium mEq/l	45.0	5.4	4.15	4.35	4.35	-	-
Subject C.L. T.B.W. = 43.5 l. Load 2% = 870 ml.							
Time mins.	-	40.0	70.0	105.0	160.0	-	-
Serum Sodium mEq/l	140.0	140.0	136.5	135.5	137.5	-	-
Serum Potassium mEq/l	3.78	3.65	3.59	3.85	3.96	-	-
Subject C.L. T.B.W. = 43.5 l. Load 2.5% = 1090 ml.							
Time mins.	-	40.0	70.0	130.0	160.0	-	-
Serum Sodium mEq/l	138.0	137.5	134.0	135.0	133.0	-	-
Serum Potassium mEq/l	4.45	3.9	4.5	4.0	4.5	-	-

TABLE LII

Effect of standard infusion of 5% Dextrose (800 - 900 ml) in 45 minutes on serum electrolytes in four normal subjects. Infusion between 0 and 45 minutes in each instance.

Time mins.	0	30	50	55	65	80	85	90	110	130	140	150	160	240
						Subject I								
Serum Sodium mEq/l.	140.0	-	-	122.0	-	-	-	-	130.0	-	-	-	138.0	-
Serum Potassium mEq/l.	4.86	-	-	4.8	-	-	-	-	4.5	-	-	-	4.5	-
						Subject II								
Serum Sodium mEq/l.	138.0	-	127.5	-	-	134.0	-	-	135.0	-	136.0	-	135.0	138.0
Serum Potassium mEq/l.	5.0	-	46.0	-	-	4.6	-	-	4.8	-	4.52	-	49.0	4.87
						Subject III								
Serum Sodium mEq/l.	140.0	132.5	134.5	-	-	-	-	135.0	-	-	-	136.0	-	-
Serum Potassium mEq/l.	4.32	4.81	4.8	-	-	-	-	4.45	-	-	-	4.35	-	-
						Subject IV								
Serum Sodium mEq/l.	139.0	132.0	-	-	135.0	-	135.5	-	-	137.5	-	-	-	-
Serum Potassium mEq/l.	3.9	3.9	-	-	4.15	-	3.86	-	-	3.85	-	-	-	-

TABLE LIII

Effect of Oral Water and of Antidiuresis on Serum Electrolytes

Total Body Water derived from D_2O equilibration. Load administered as a single dose by mouth at zero time. 6 units of "pitressin" administered by subcutaneous injection 15 minutes before administration of water. Load eliminated at 8 hours in both instances.

Subject L.L.B. T.B.W. = 40.8 l. Load 2.5% = 1020 ml.					
Time hours	-	2.0	4.0	5.5	10.0
Serum Sodium mEq/l	142.0	138.0	137.0	136.0	140.0
Serum Potassium mEq/l	3.5	3.0	3.4	3.36	3.6
Subject C.L. T.B.W. = 43.5 l. Load 3.5% = 1520 ml.					
Time hours	-	2.0	4.0	5.0	8.0
Serum Sodium mEq/l	144.5	134.0	132.5	135.5	136.0
Serum Potassium mEq/l	4.0	4.69	4.69	4.0	4.2

TABLE LIV

Effect of Intravenous 5% Dextrose in Water on Serum Electrolytes during Antidiuresis

5 Units of Pitressin by subcutaneous injection 15 minutes before experiment begun; in each instance 800 ml. of 5% dextrose administered in first 40 minutes of experiment. All subjects healthy adult males between 28 and 34 years. Weights in all cases preinfusion level at end of 4 hours.

Subject H.A.F.D. (1)										
Time mins.	-	3.0	60.0	75.0	130.0	180.0	240.0	-	-	-
Serum Sodium mEq/l	134.0	129.5	124.0	126.5	-	126.0	128.0	-	-	-
Serum Potassium mEq/l	5.2	5.3	5.0	-	5.0	-	5.0	-	-	-
Subject H.A.F.D. (2)										
Time mins.	-	30.0	70.0	105.0	125.0	135.0	165.0	195.0	240.0	270.0
Serum Sodium mEq/l	133.0	126.0	127.0	-	124.0	-	-	-	127.5	-
Serum Potassium mEq/l	4.4	4.0	4.25	4.5	4.3	-	-	4.4	-	4.4
Subject R.P.										
Time mins.	-	45.0	55.0	80.0	105.0	130.0	160.0	195.0	260.0	290.0
Serum Sodium mEq/l	139.0	131.0	-	-	130.5	130.0	132.0	134.0	133.0	-
Serum Potassium mEq/l	3.8	-	3.9	4.2	4.1	-	4.2	-	-	4.1
Subject R.T.										
Time mins.	-	60.0	80.0	105.0	160.0	290.0	-	-	-	-
Serum Sodium mEq/l	140.5	135.5	136.0	135.5	136.0	139.5	-	-	-	-
Serum Potassium mEq/l	4.35	4.28	4.1	4.1	4.55	4.18	-	-	-	-

TABLE LV

Case	Nitrogen Intake g.	Nitrogen Output (Urine) g.	Non-protein Calories Kg. Body Weight	Intake/Output Ratio (Nitrogen)
		Day 1 (Injuries)		
Compound fracture of Mandible (1)	1.6	19.5	12.0	0.08
Fracture of Mandible	7.2	12.7	62.0	0.57
Compound fracture of Mandible (2)	12.2	18.5	12.0	0.65
Multiple fractures	0.3	9.4	4.8	0.04
Surgical fracture of Mandible	4.8	10.6	11.2	0.45
Total	26.1	70.7	105.0	1.79
Avg.	5.2	14.1	21.0	0.36
		Day 2 (Injuries)		
Compound fracture of Mandible (1)	12.6	14.8	11.2	0.85
Fracture of Mandible	12.5	7.8	70.5	1.6
Compound fracture of Mandible (2)	4.5	9.8	26.2	0.46
Multiple fractures	14.4	16.7	42.5	0.86
Surgical fracture of Mandible	7.0	8.9	28.7	0.79
Multiple fractures	27.3	16.0	49.6	1.7
Total	78.3	74.0	228.7	6.26
Avg.	15.1	12.3	38.1	1.04

(Over)

TABLE LV (cont'd)

Case	Nitrogen Intake g.	Nitrogen Output (Urine) g.	Non-protein Calories Kg. Body Weight	Intake/Output Ratio (Nitrogen)
Day 3 (Injuries)				
Compound fracture of Mandible (1)	4.8	9.8	25.0	0.49
Fracture of Mandible	16.0	10.7	25.8	1.5
Compound fracture of Mandible (2)	25.9	26.9	50.0	0.96
Multiple fractures	13.8	4.0	62.8	3.45
Surgical fracture of Mandible	13.8	11.2	93.0	1.23
Multiple fractures	15.5	17.4	50.0	0.89
Total	89.8	80.0	306.6	8.52
Avg.	14.9	13.3	51.1	1.42
Day 4 (Injuries)				
Compound fracture of Mandible (1)	12.6	11.6	92.5	1.09
Fracture of Mandible	24.2	17.2	62.5	1.41
Compound fracture of Mandible (2)	4.6	5.5	23.2	0.84
Multiple fractures	14.9	12.0	50.0	1.24
Surgical fracture of Mandible	15.0	17.1	35.8	0.88
Multiple fractures	23.4	16.9	55.0	1.23
Total	94.7	80.3	319.0	6.69
Avg.	15.8	13.4	53.0	1.12

(Over)

TABLE LV (cont'd)

Case	Nitrogen Intake g.	Nitrogen Output (Urine) g.	Non-protein Calories Kg. Body-Weight	Intake/Output Ratio (Nitrogen)
	Day 5 (Injuries) (No secondary procedure)			
Compound fracture of Mandible (1)	10.2	17.8	16.9	0.57
Compound fracture of Mandible (2)	13.3	9.8	77.0	1.38
Surgical fracture of Mandible	15.7	15.3	38.6	1.0
Multiple fractures	18.7	11.8	54.0	1.59
Total	57.9	54.7	186.5	4.54
Avg.	14.5	15.7	46.6	1.13
	Day 5 (Injuries) (Secondary procedure)			
Multiple fractures	3.8	13.8	17.2	0.28
Fracture of Mandible	8.5	12.8	25.2	0.68
Total	12.3	26.6	42.4	0.96
Avg.	6.2	13.3	21.2	0.48

(Over)

TABLE LV (cont'd)

Case	Nitrogen Intake g.	Nitrogen Output (Urine) g.	Non-protein Calories Kg. Body Weight	Intake/Output Ratio (Nitrogen)
	Day 6 (Injuries) (No secondary procedure)			
Compound fracture of Mandible (1)	19.8	20.6	39.8	0.96
Compound fracture of Mandible (2)	12.0	14.2	27.0	0.85
Surgical fracture of Mandible	9.3	9.6	63.0	0.97
Multiple fractures	22.6	14.7	55.5	1.54
Total	63.7	59.1	184.8	4.32
Avg.	15.9	14.8	46.2	1.08
	Day 6 (Injuries) (Secondary procedure)			
Multiple fractures	16.3	13.0	58.0	1.25
Fracture of Mandible	22.2	25.1	63.0	0.88
Total	38.5	38.1	21.0	2.15
Avg.	19.2	19.0	60.5	1.06

(Over)

TABLE LV (cont'd)

Case	Nitrogen Intake g.	Nitrogen Output (Urine) g.	Non-protein Calories Kg. Body Weight	Intake/Output Ratio (Nitrogen)
Day 7 (Injuries) (No secondary procedure)				
Compound fracture of Mandible (1)	6.2	9.9	16.5	0.63
Compound fracture of Mandible (2)	11.8	9.6	72.8	1.24
Surgical fracture of Mandible	17.1	16.7	40.0	1.02
Multiple fractures	20.3	18.3	44.6	1.11
Total	55.4	54.5	175.9	4.00
Avg.	13.9	13.6	43.5	1.00
Day 7 (Injuries) (Secondary procedure)				
Multiple fractures	15.5	22.3	44.7	0.69
Fracture of Mandible	26.0	22.1	66.0	1.18
Total	41.5	44.4	110.7	1.87
A Avg.	20.75	22.2	55.4	0.93

(Over)

TABLE LV (cont'd)

Case	Nitrogen Intake g.	Nitrogen Output (Urine) g.	Non-protein Calories Kg. Body Weight	Intake/Output Ratio (Nitrogen)
	Day 8 (Injuries) (No Secondary procedure)			
Compound fracture of Mandible (1)	13.3	9.6	69.4	1.38
Compound fracture of Mandible (2)	12.0	12.6	13.7	0.95
Surgical fracture of Mandible	15.4	14.2	29.4	1.08
Multiple fractures	19.4	14.9	42.7	1.30
Total	60.1	51.3	155.2	4.71
Avg.	15.0	12.8	38.8	1.18
	Day 8 (Injuries) (Secondary procedure)			
Multiple fractures	19.4	10.5	45.5	1.85
Fracture of Mandible	24.5	15.0	72.5	1.63
Total	43.9	25.5	118.0	3.48
Avg.	21.9	12.7	59.0	1.74

(Over)

TABLE LV (cont'd)

Case	Nitrogen Intake g.	Nitrogen Output (Urine) g.	Non-protein Calories Kg. Body Weight	Intake/Output Ratio (Nitrogen)
		Day 1 (Burns)		
Burn 1	-	8.6	15.8	-
Burn 2	-	7.9	5.8	-
Burn 3	-	8.8	5.8	-
Burn 4	-	7.7	6.9	-
Burn 5	-	7.2	14.4	-
Burn 6	-	6.2	10.0	-
Burn 7	-	9.3	23.0	-
Total		55.7	81.9	
Avg.		7.9	11.7	

(Over)

TABLE LV (cont'd)

Case	Nitrogen Intake g.	Nitrogen Output (Urine) g.	Non-protein Calories Kg. Body Weight	Intake/Output Ratio (Nitrogen)
		Day 2 (Burns)		
Burn 1	12.8	9.8	35.0	1.31
Burn 2	10.2	16.0	32.4	0.64
Burn 3	8.0	11.4	32.0	0.7
Burn 4	4.5	7.8	17.4	0.58
Burn 5	9.4	17.9	24.0	0.53
Burn 6	6.9	14.3	20.6	0.48
Burn 7	4.6	3.4	8.3	1.35
Burn 8	3.2	5.3	24.0	0.61
Burn 9	4.2	13.2	23.0	0.32
Burn 10	1.3	6.3		2.1
Burn 11	5.0	6.5	19.0	0.77
Burn 12	36.3	11.3	60.5	3.25
Total	105.4	123.2	297.2	12.32
Avg.	8.8	10.3	27.0	1.03

(Over)

TABLE LV (cont'd)

Case	Nitrogen Intake g.	Nitrogen Output (Urine) g.	Non-protein Calories Kg. Body Weight	Intake/Output Ratio (Nitrogen)
Day 3 (Burns)				
Burn 1	14.6	8.8	20.6	1.66
Burn 2	14.1	16.2	26.4	0.87
Burn 3	21.6	22.3	28.6	0.97
Burn 4	14.4	12.2	41.5	1.18
Burn 5	16.6	6.6	38.0	2.5
Burn 6	17.0	17.1	41.5	1.00
Burn 7	11.8	16.5	17.0	0.71
Burn 8	3.0	3.4	35.6	0.88
Burn 9	12.0	23.6	27.0	0.51
Burn 10	6.7	9.8		0.68
Burn 11	6.9	15.0	28.8	0.46
Burn 12	5.9	7.4	15.5	0.8
Burn 13 (Not included in overall data)	10.1	7.4	18.2	1.37
Total	156.7	166.3	338.7	13.61
Avg.	12.1	12.8	26.6	1.00

(Over)

TABLE LV (cont'd)

Case	Nitrogen Intake g.	Nitrogen Output (Urine) g.	Non-protein Calories Kg. Body Weight	Intake/Output Ratio (Nitrogen)
Day 4 (Burns)				
Burn 1	22.6	9.5	63.5	2.38
Burn 2	19.4	14.9	53.6	1.30
Burn 3	19.0	13.4	48.8	1.42
Burn 4	21.6	22.3	28.0	0.97
Burn 5	18.4	7.7	57.6	2.39
Burn 6	16.8	7.9	30.1	1.34
Burn 7	10.4	18.3	39.0	0.57
Burn 8	8.2	12.0		0.68
Burn 9	24.3	25.0	40.8	0.97
Burn 10	24.2	12.7	45.5	1.90
Burn 11	4.5	5.9	45.0	0.76
Burn 12	5.4	17.3	25.0	0.30
Burn 13	10.1	7.4	18.7	1.37
Total	205.9	174.3	495.6	16.35
Avg.	15.8	12.6	41.3	1.26

(Over)

TABLE LV (cont'd)

Case	Nitrogen Intake g.	Nitrogen Output (Urine) g.	Non-protein Calories Kg. Body Weight	Intake/Output Ratio (Nitrogen)
Day 5 (Burns) (No secondary procedure)				
Burn 4	18.6	26.3	38.8	0.71
Burn 7	15.4	17.2	61.5	0.9
Burn 10	5.9	16.7	40.8	0.35
Total	39.9	60.2	141.1	1.96
Avg.	13.3	20.1	47.0	0.65
Day 5 (Burns) Secondary procedure (dressings)				
Burn 1	6.9	14.0	22.0	0.49
Burn 2	7.5	9.7	31.1	0.77
Burn 3	7.8	16.4	25.0	0.48
Burn 5	10.1	19.9	15.7	0.51
Burn 6	6.2	13.1	7.6	0.47
Burn 8	10.4	12.7	19.0	1.32
Burn 9	7.8	17.1	8.1	0.5
Burn 11	6.6	17.1	25.0	0.39
Total	63.3	120.0	153.5	4.93
Avg.	7.9	14.7	17.2	0.62

(Over)

TABLE LV (cont'd)

Case	Nitrogen Intake g.	Nitrogen Output (Urine) g.	Non-protein Calories Kg. Body Weight	Intake/Output Ratio (Nitrogen)
Day 6 (Burns) (No secondary procedure)				
Burn 4	8.3	5.6	33.0	1.48
Burn 7	6.4	11.5	39.4	0.56
Burn 10	30.2	21.2	66.0	1.42
Total	44.9	38.3	138.4	3.46
Avg.	17.9	12.7	52.8	1.15
Day 6 (Burns) (Secondary procedure)				
Burn 1	18.1	24.5	31.0	0.74
Burn 2	12.2	22.7	45.2	0.54
Burn 3	15.8	11.9	34.0	1.33
Burn 5	14.7	12.2	46.5	1.2
Burn 6	16.6	21.0	34.2	0.79
Burn 8	15.5	18.0	42.0	0.86
Burn 9	13.0	13.1	44.5	1.50
Burn 11	16.8	15.6	34.5	1.06
Total	122.7	139.0	281.9	8.52
Avg.	15.3	17.4	38.9	0.94

(Over)

TABLE LV (cont'd)

Case	Nitrogen Intake g.	Nitrogen Output (Urine) g.	Non-protein Calories Kg. Body Weight	Intake/Output Ratio (Nitrogen)
Day 7 (Burns) (No secondary procedure)				
Burn 4	9.9	6.5	82.8	1.52
Burn 7	18.2	23.5		0.77
Burn 10	7.0	11.4	39.0	0.61
Total	35.1	41.4	121.8	2.90
Avg.	11.7	13.8	60.9	0.96
Day 7 (Burns) (Secondary procedure)				
Burn 1	14.1	13.9	47.0	1.02
Burn 6	26.2	8.2	47.0	3.04
Burn 8	13.1	12.2	25.4	1.07
Burn 9	15.4	23.5	37.2	0.66
Burn 11	13.4	26.5	23.8	0.51
Burn	14.7	13.2	26.7	1.11
Total	96.9	97.5	207.1	7.41
Avg.	16.2	16.2	34.5	1.23

TABLE LVI

Mrs G.; Age 42; Two-stage adrenalectomy for carcinoma of breast with metastases; September-October 1955

200 mg. of cortisone daily by divided intramuscular dosage - 25 mg. 5 hourly begun on 5/10/55

Date	Urine Output ml.	Urine Sodium mEq.	Urine Potassium mEq.	Urine Nitrogen g.	17-ketosteroids mg.	A.S.F.S. mg.
30th - 1st	2680	133.0	49.3	10.96	7.8	0.82
1st - 2nd	2360	97.0	44.9	10.66	7.02	0.95
2nd - 3rd	2960	89.0	52.5	11.82	7.58	0.59
3rd - 4th	1910	92.5	43.3	8.79	6.47	0.55
4th - 5th	2380	108.5	50.6	110.67	7.15	0.48
5th - 6th	2060	104.8	46.4	12.19	9.26	0.86
6th - 7th	2080	69.2	40.4	10.99	9.74	1.47
7th - 8th	2100	62.2	49.9	9.3	9.78	4.78
8th - 9th	3290	104.6	39.3	12.55	11.19	7.51
9th - 10th	1080	48.0	14.9	3.76	5.94	2.70
10th - 11th	2080	76.0	30.8	6.51	8.02	6.13
11th - 12th	510	46.4	11.7	5.21	3.2	2.75
12th - 13th	850	32.4	68.3	7.04	9.91	13.89
13th - 14th	640	8.1	36.2	11.52	6.66	8.67
14th - 15th	750	1.95	35.4	17.5	6.15	8.59
15th - 16th	2030	4.2	31.7	16.65	8.98	10.87
16th - 17th	260	4.5	5.3	3.11	1.17	2.39

(Over)

TABLE LVI (cont'd)

Date	Urine Output ml.	Urine Sodium mEq.	Urine Potassium mEq.	Urine Nitrogen g.	17-ketosteroids mg.	A.S.F.S. mg.
17th - 18th	3540	5.6	21.9	10.31	4.21	3.58
18th - 19th	2460	47.2	102.3	10.17	5.58	6.29
19th - 20th	2080	112.0	22.4	8.48	7.32	9.23
20th - 21st	1670	24.8	18.9	8.86	5.78	8.40
21st - 22nd	1640	35.0	17.6	7.62	3.93	5.39
22nd - 23rd	1650	48.5	19.3	6.02	4.24	6.07
23rd - 24th	2110	48.1	20.4	8.47	4.97	7.17
24th - 25th	1520	81.0	36.8	7.96	6.89	6.72
25th - 26th	1200	145.3	35.0	3.89	3.81	5.05
26th - 27th	620	52.6	29.3	8.16	4.17	4.65
27th - 28th	1170	31.3	30.6	10.57	4.95	7.71
28th - 29th	1610	21.7	21.5	7.04	4.63	6.44
29th - 30th	500	9.4	10.4	2.46	1.08	1.5
30th - 31st	730	15.2	10.9	3.12		

Diet	11/10/55	12/10/55	13/10/55	14/10/55	25/10/55	26/10/55	27/10/55
Na = 87 mEq.	77.0	83.7	77.6	81.2	77.0	77.0	87.0
K = 44 mEq.	0.0	47.7	43.8	43.6	0.0	7.5	44.0
N = 8.04 g.	0.0	4.0	6.2	8.04	0.0	0.0	42.0

Operations - $\frac{11/10/55)}{25/10/55)}$ - 500 ml. of 0.9% sodium chloride given by intravenous infusion = 77 mEq.

TABLE LVII

Mrs B.; Age 47; Bilateral adrenalectomy for malignant hypertension; July 1955

200 mg. of cortisone daily by divided intramuscular dosage - 25 mg. 6 hourly

Date	Urine Volume ml.	Urine Sodium mEq.	Urine Potassium mEq.	Urine Nitrogen g.	17-ketosteroids mg.	A.S.F.S. mg.
1st - 2nd	770	6.9	11.6	3.1	1.57	2.98
2nd - 3rd	2270	27.2	27.5	7.52	4.65	5.76
3rd - 4th	2300	61.1	27.7	8.2	4.77	7.44
4th - 5th	560	4.7	16.3	2.02	1.4	2.49
5th - 6th	390	7.3	26.9	2.3	1.11	1.53
6th - 7th	2290	51.3	73.9	13.2	5.79	3.24
7th - 8th	1730	43.2	45.4	10.04	4.01	3.72
8th - 9th	1920	38.1	31.4	9.8	4.80	4.83
9th - 10th	2030	22.3	34.2	9.88	6.14	4.85
10th - 11th	1530	26.4	39.3	6.93	5.63	1.83

Diet	4/7/55	5/7/55	6/7/55
Na = 87 mEq.	77.0	82.0	84.6
K = 37 mEq.	0.0	26.4	25.5
N = 8.1 g.	0.0	4.9	8.1

Operation - 9 a.m., 4/7/55 - 500 ml. of 0.9% NaCl given by intravenous infusion = 77 mE_q.

TABLE LVIII

D.McK.: Second stage adrenalectomy for hypertension; April 1956; Operation - 24/4/56; Cortisone 150 mg./day by divided intramuscular administration

Date	Urine Volume ml.	Sodium mEq.	Potassium mEq.	Nitrogen g.	17-ketosteroids mg.	A.S.F.S. mg.	17 O.H.	Aldosterone mg./day
17th - 18th	1420	103.0	80.0	14.7	10.65	0.43	14.6	
18th - 19th	1160	97.5	37.9	13.1	9.74	0.35	16.7	
19th - 20th	630	48.0	21.9	9.1	3.78	0.38	12.0	
20th - 21st	935	42.0	26.9	10.0	5.61	0.28	9.6	
21st - 22nd	1190	84.0	35.4	11.9	7.74	0.36	8.8	0
22nd - 23rd	1710	147.0	67.8	21.5	18.47	1.2	26.5	
23rd - 24th	1360	114.0	46.2	12.2	14.14	1.63	23.0	1.58
24th - 25th	88	14.1	137.6	0.9	0.44	0.26	2.2	
25th - 26th	1170	71.5	81.1	15.1	9.13	3.28	21.9	0
26th - 27th	1030	36.0	56.7	21.5	9.94	0.21	13.0	
27th - 28th	660	23.4	32.5	13.5	5.74	3.30	8.4	
28th - 29th	580	16.8	10.2	4.3	3.31	2.20	2.4	0
29th - 30th	1690	70.0	43.5	11.9	13.86	6.08	13.7	
30th - 1st	1580	93.4	61.3	15.0	11.85	6.00	19.1	
1st - 2nd	1120	104.0	32.9	14.5	14.00	2.69	17.3	
2nd - 3rd	1040	74.0	44.1	12.0	9.36	2.87	19.7	
3rd - 4th	1270	124.0	39.7	11.8	12.45	-	14.4	

(Over)

TABLE LVIII (cont'd)

Dietary intake during operative period

Date	Nature of diet	K. mEq.	Na. mEq.	N. g.
23rd	Normal	59.0	108.5	9.74
24th	-	-	77.0 (I.V.)	-
25th	Fluids	24.3	86.8 (77 I.V.)	-
26th	Light	31.4	103.2	4.2
27th	Light	46.9	104.7	4.2
28th	Normal	59.0	108.1	9.74

TABLE LIX

M.G.: Age 39: First-stage adrenalectomy for carcinoma of breast with metastases: 13/5/57; Death after second stage

75 mg. cortisone by divided intramuscular injection begun on 16/5/57

Date	Urine Volume ml.	Urine Sodium mEq.	Urine Potassium mEq.	A.S.F.S. mg.	Aldosterone mg.
11th - 12th	650	51.0	25.0	8.27	3.2
12th - 13th	1035	42.0	40.5		
13th - 14th	305	5.7	44.5	30.79	33.2
14th - 15th	590	7.4	59.0		
15th - 16th	615	0.9	16.0	10.36	1.32
16th - 17th	680	2.6	14.0		
17th - 18th	-	-	-		
18th - 19th	540	3.5	26.0		
19th - 20th	285	3.5	12.5	10.79	0.0
20th - 21st	460	17.5	18.0		

Dietary sodium - 48 mEq. 400 ml. 0.9% sodium chloride (62 mEq.) of sodium) administered on 13th and 14th.
Dietary potassium - 32 mEq.

TABLE LX

Mrs R.; Age 42; May-June 1957; Bilateral adrenalectomy 31/5/57;
Cortisone 150 mg. daily by divided intramuscular dosage;
Bilateral oophorectomy 11/6/57

Date	Urine Volume ml.	Urine Sodium mEq.	Urine Potassium mEq.	Urine Nitrogen g.	A.S.F.S. mg.	17-OH. mg.	Sodium Intake mEq.	Potassium Intake mEq.	Aldosterone mg.
5th - 6th	1320	27.5	36.1	14.4	8.45	16.1	55	44	0
6th - 7th	1340	43.0	34.5	11.4	6.03	13.8	46.5	40	0
7th - 8th	1660	57.0	32.4	11.6	7.97	8.96	55	52	0
8th - 9th	2120	88.0	48.3	14.2	8.06	6.78	61	42	0
9th - 10th	1180	37.0	27.9	10.0	5.31	7.67	61	42	0
10th - 11th	1740	76.0	23.5	9.5	7.48	12.18	61	40	0
11th - 12th	590	36.0	29.5	5.6	6.02	10.38			
12th - 13th	680	20.5	28.0	6.4	5.98	11.02			

Diet - 3 g. of added sodium chloride (33 mEq.)

TABLE LXI

Mrs L.; Second stage adrenalectomy for carcinoma of breast with metastases: December 1957; Hydrocortisone 200 mg. by continuous intravenous infusion; Operation - 17/12/57

Date	Urine Volume ml.	Urine Sodium mEq.	Urine Potassium mEq.	Urine Nitrogen g.	Urine 17-ketosteroids g.	Urine Free 17-OH. Steroids g.	Urine Total 17-OH. Steroids g.	Urine Aldosterone ug.
12th - 13th	600	46.4	15.4	8.9	5.58	0.24	7.56	
13th - 14th	965	35.7	55.3	11.7	4.8	1.32	10.07	2.4
14th - 15th	1225	15.7	53.4	12.7	4.04	3.64	29.33	
15th - 16th	990	20.2	53.8	10.2	13.86	6.55	42.77	
16th - 17th	905	28.6	48.4	10.4	6.34	6.01	26.55	0.0
17th - 18th	470	15.5	28.5	5.8	4.98	3.96	19.37	
18th - 19th	920	10.7	35.6	14.2	9.75	4.42	35.60	0.0
19th - 20th	640	8.5	30.1	9.9	6.46	3.30	27.19	
20th - 21st	620	13.7	27.8	9.1	9.1	2.75	30.36	0.0
21st - 22nd	805	28.7	23.8	10.8	13.1	3.84	38.83	

(Over)

Diet: Sodium 96 mEq.
Potassium 54 mEq.
Nitrogen 6 g.

500 ml. 0.9% sodium chloride on day of operation.

TABLE LXI (cont'd)

Mrs L.: Carcinoma of breast with metastases; Second stage adrenalectomy; December 1957; 200 mg. hydrocortisone by continuous intravenous infusion

Time and Date	Free 17-OH. Steroids mg.%	Time and Date	Free 17-OH. Steroids mg.%
8 a.m., 14th	58.8		
4.15 p.m.	28.5		
12 midnight	40.9		
8 a.m., 15th	21.5	12 midnight	20.0
6 p.m.	49.2	8 a.m., 19th	28.8
12 midnight	40.0	4 p.m.	22.3
8 a.m., 16th	44.5	12 midnight	33.6
4 p.m.	50.2	8 a.m., 20th	-
12 midnight	50.8	4 p.m.	32.8
8 a.m., 17th	40.1	12 midnight	28.3
10.38 a.m. (post-anaesthetic)	39.6	8 a.m., 21st	23.8
11.45 a.m. (post-operative)	40.0	4 p.m.	43.3
4 p.m.	40.0	8 a.m.	27.3
12 midnight	64.5		
8 a.m., 18th	66.9		
4 p.m.	25.8		

TABLE LXII

Mrs D.: Second stage adrenalectomy for Cushing's syndrome: December 1957;
150 mg. hydrocortisone by continuous intravenous infusion: Operation - 30/12/57

Date	Urine Volume ml.	Urine Sodium mEq.	Urine Potassium mEq.	Urine Nitrogen g.	Urine 17-ketosteroids g.	Urine Free 17-OH. Steroids g.	Urine Total 17-OH. Steroids g.	Urine Aldosterone ug.
27th - 28th	2660	38.6	56.4	10.6	19.7	10.10	20.46	4.2
28th - 29th	2660	55.6	48.9	11.0	13.3	6.86	13.41	
29th - 30th	2430	86.3	64.9	12.6	13.6	4.76	15.34	0.0
30th - 31st	640	49.8	51.9	7.8	7.4	1.60	14.98	
31st - 1st	860	11.1	41.3	11.5	9.7	1.29	22.38	0.0
1st - 2nd	1800	13.9	35.4	12.7	17.4	2.20	20.74	

Diet: Sodium 97.0 mEq.
Potassium 50.7 mEq.
Nitrogen 10.4 g.

500 ml. 0.9% sodium chloride on 30th and 31st December.

(Over)

TABLE LXII (cont'd)

Mrs D.: Cushing's syndrome: Free blood 17-hydroxy steroids: December - January 1957; 150 mg. hydrocortisone daily by intravenous infusion

Time and Date	Free 17-OH. Steroids mg.%	Time and Date	Free 17-OH. Steroids mg.%
9 a.m., 27th	22.3		
4.15 p.m.	26.4		
1 a.m., 25th	24.6		
9 a.m.	-		
4.20 p.m.	30.3		
12.15 a.m., 24th	25.5		
8.40 a.m.	34.1		
4.25 p.m.	29.6	12 midnight	27.9
11.45 p.m.	26.9	8.30 a.m., 1st	15.9
8.45 a.m., 30th (post-anaesthetic)	25.0	4.45 p.m.	97.8
		11.45 p.m.	24.8
9 a.m. (Beginning of operation)	224.1	8.30 a.m.	30.8
10.15 a.m. (end of operation)	152.5		
3.00 p.m.	48.5		
11.45 p.m.	21.8		
9 a.m., 31st	33.3		
4.45 p.m.	40.5		