THE RESPONSE TO TRAUMA

being

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By

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This work is Dedicated

To

My Mother and Father

"Does the harmony which the human intelligence thinks it discovers in Nature exist apart from such intelligence? Assuredly no. A reality completely independent of the spirit that conceives it, sees it or feels it, is an impossibility. A world so external as that, even if it existed, would be for ever inacessible to us."

Poincaré. "The Value of Science"

CONTENTS

PREFACE

This work has developed out of observations made by chance on certain biochemical changes which follow uncomplicated operation. These observations were extended to include a variety of factors which might have some bearing on the response of living tissue to this injury.

The object of the work has been to relate these biochemical changes following operation to the wider field of the response of the organism to trauma. An effort has been made to synthesise observations from various fields of medical investigation with the results of the present enquiry into an organic unity. Although the number of patients under investigation has been small, some of the results obtained are too constant to be invalid.

The writer believes he has been able to demonstrate that:-

(1). Certain biochemical changes in the organism are a part of the pattern of the response to trauma.

(2). That these changes are a feature of the "stress" phenomenon more widely experienced in nature.

It has been said that the physical sciences have advanced so rapidly because they early ceased to enumerate and began to measure. The writer believes that the biological sciences, so long absorbed in classification and contemplation of the minutiae of dissimilitude, have, in general, failed to measure, to appreciate similarity of pattern other than by analogy, and to integrate their observations into general laws.

In very recent years, concepts such as these have stirred the world of medical science. Just when the physical sciences find themselves burdened by a Principle of Indeterminacy in a self-limiting Universe, new portals are being thrown open in medicine. We seem to be on the verge of great and exciting discoveries. The air has quickened with new ideas and the promise of fresh opportunity. With the poet we may agree:-

"Bliss was it in that dawn to be alive,
But to be young was very heaven."

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To Professor Charles Wells of the University of Liverpool sincere thanks are extended for his permission to continue the researches. Time has been allowed the author for the completion of this work which should have been spent on the problems currently being studied at Liverpool University.

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Finally, there remains one other who, by tolerance and forebearance, has contributed in an imponderable way to the performance of this work.

INTRODUCTION

This work was suggested as a result of the observation by the writer three years ago, that chloride excretion in the urine was diminished following an operation. As this fact was previously unknown to him, the observation was confirmed repeatedly. To ensure that this was not a reflection of chloride loss due to haemorrhage and tissue fluid loss at the time of operation, observations were made following simple operations. It was found that repeated estimations of urinary chloride demonstrated this diminished output after operations such as inguinal herniorrhaphy. This diminished output appeared to be out of all proportion to blood loss and tissue fluid loss at operation, and even to the diminished chloride intake which occurs at this time.

It seemed logical to compare the urinary chloride excretion with the plasma chloride concentration under the same circumstances. Repeated estimations of the plasma chloride content before and after similar operations frequently disclosed a sudden fall immediately after

operation. This concurred with the period when urinary chloride excretion was diminished. At the time it was not possible to account for the apparent chloride loss in the plasma, as it seemed in excess of anything that could be caused by blood loss, and by all the accompanying features of an operation.

It was decided that a new series of experiments should be commenced to investigate this phenomenon further. It was also decided to observe any changes in the blood and urine cation content to detect any correlation between the chloride and sodium or potassium changes. Such changes were indeed observed, and the investigation was accordingly broadened in the light of these findings until the present series of observations were finally instituted.

The second series of observations showed an apparent retention of sodium, with an increased excretion of potassium following operation. This suggested a comparison with the effects of deoxycorticosterone. Attempts were therefore made in the present investigation to measure adrenocortical activity by estimating the 17-ketosteroids in the urine, by circulating eosinophil counts, and by fasting blood sugar levels. If such adrenocortical activity could be demonstrated, it was thought that this might be the cause of the electrolyte changes considered

in Part I. It is believed that such evidence of adrenal cortical function as a result of the trauma of operation has been demonstrated.

Because these observations grew into the present work in such a way, the results and the discussion are presented in the same step-by-step fashion. It has not the merit of brevity, but it does show how one series of results suggested the next, and how the final investigation was planned. For this reason, also, the literature bearing on the different aspects of this work is considered in the appropriate sections.

As will be demonstrated, the changes detected in body metabolism appeared to result from the operation with all its attendant circumstances, this being the only factor common to all patients. The attendant circumstances, namely the expectation and apprehension, the inhalation anaesthetic, and exposure to heat, though varying in degree in each patient, must also be considered as a part of the integral stress of the operation. The word 'stress' is becoming so widely used in so many different contexts that it is now difficult to define. Such lack of clarity on the part of many writers allows a specious reasoning beyond the strict limits of their results.

'Stress' now amounts to no more than what the physiologist calls a stimulus, and usually a noxious one. Injury and operation can certainly be included within such a wide definition.

In 1794, John Hunter wrote: "There is a circumstance attending accidental injury which does not belong to disease - namely, that the injury done has in all cases a tendency to produce both the disposition and the means of cure." From the earliest times man has busied himself in making wounds in his fellows and must have been astonished by the amazing recuperative powers possessed by some of his victims. That the recovery from uncomplicated injury followed a recognised pattern is clearly shown from Hunter's words. The discussion of all the important factors that influence this recovery lies beyond the scope of this work. As the final results of the investigation herein described indicated evidence of an adrenocortical response to injury, only evidence of a metabolic nature can be reviewed here briefly. Such evidence as is noteworthy and presents a real advance in knowledge is considered again in more detail in the appropriate section of the work.

In 1872 Bauer observed that an increased elimination of nitrogen followed upon haemorrhage. In 1904

Hawk and Gies confirmed this, and showed also that the actual operation of venesection without withdrawal of blood was sufficient, in the dog, to cause increased urinary output of nitrogen and sulphur. Since that time, many observers have noted this increased nitrogen catabolism as a result of injury, associated with increased phosphorus, sulphur and potassium loss (Cuthbertson et al. 1939; Cuthbertson, 1942). This "negative" nitrogen metabolism was also noticed by Benedict (1915) during prolonged starvation. This evidence again emphasised that something inherent in the trauma, or some underlying response, might be common to many and various injuries done to the body. In more severe injury, when shock results, circulatory collapse occurs, partly due to a loss of circulating fluid at the site of injury (Blalock, 1931), and partly due to a more widespread capillary permeability, resulting in loss of fluid from the circulation. However, changes of lesser magnitude in electrolyte and water metabolism began to be noted following injury, being features in addition to the fluid loss of shock. Wilson and Stewart (1939) noted that, in burns, sodium was lost from the extracellular fluids into the cells of the damaged tissues, and also into the erythrocytes of the general circulation.

They noted that deoxycorticosterone rapidly restored the normal sodium level of the extracellular fluids and corrected other blood abnormalities. Weil and Browne (1939) showed that "cortin" - a crude extract of the adrenal cortex - appeared in the urine during the convalescence from acute influenza. It had been known from the work of Cannon (1929) that the secretion of the adrenal medulla had a very considerable part to play in the conditioning of the animal to fear, rage and to injury. It now began to be evident that the adrenal cortex, the part of the gland shown by Houssay and Lewis (1923) to be essential to life, exerted a different type of influence on the body following injury.

The literature which has developed on the function of the adrenal cortex in relation to injury has grown rapidly in recent years. Such evidence as is appropriate has been discussed in the various sections and in relation to the different aspects studied. The concept of the place of the adrenal cortex in the adjustment to the environment has, however, owed such a debt to the work of Hans Selye that a summary of the main features of his hypothesis must be considered before the details of the present investigation are presented.

The Hypothesis of Hans Selye.

"The General Adaptation Syndrome" (Selye, 1949, 1950).

Selye has made his work unnecessarily difficult to follow by his own erudition, and by his tendency to use words in a way not used by others. His extensive writings contain a great many definitions which are not clear to the ordinary reader, and the connecting links in his reasoning are not so apparent as he seems to suggest. In spite of these many valid objections, his work warrants close study and careful evaluation.

The general outline of his hypothesis is that, under the influence of a "stressor" agent the body modifies itself. This modification he terms the "General Adaptation Syndrome". He envisages three clear stages in this syndrome - the "alarm reaction", the stage of resistance, and the stage of exhaustion. The "alarm reaction" has two phases, "shock" representing the initial submission of the organism to the injury or stress factor, and counter-shock, representing the mobilisation of the body's defences to resist and overcome the continued attack. Counter-shock may merge gradually into the continued stage of resistance, which is the state of defence against long-continued struggle. If the onslaught be too vigorous,

or the body defences weaken, the stage of exhaustion may finally develop. The symptoms and signs of each stage are supposed to be typical but will vary with the degree of the stress factor, its duration and intensity, and whether it be associated with other stress effects. The picture is further confused by the overlap of the various phases, so that features of one phase may be intermingled with those of another. Further, the picture of a phase may be complicated by features which are especially inherent in the particular stressor agent.

The resistance to the stressor agent is reduced during the "shock" phase, but rises during the counter-shock period. Thus the production of the alarm reaction by one agent supplies a non-specific resistance during that phase which protects against any other stressor. This "cross-resistance" is supposed to explain such phenomena as protein-shock therapy, insulin-shock therapy, non-specific therapy and electrical convulsive therapy. Though the phase of counter-shock merges gradually into the period of resistance, this non-specific resistance does not; only a specific resistance to the original stressor being maintained in the resistance phase. For this reason the organism in the stage of resistance to

one stressor is vulnerable to others.

The list of stressor agents is enormous, and includes all forms of trauma, some drugs, radiation sickness and, of course, various disease factors. Each agent produces its own specific response in addition to the non-specific response of the Adaptation Syndrome.

Not only does the stress factor produce shock but it stimulates the pituitary in such a way that there is a diminished secretion of the growth, gonadotropic and thyrotropic hormones, and an increased production of the adrenotropic hormone (ACTH). This, in turn, stimulates the production of the adrenal cortical hormones, which Selye divides into two groups, the "glucocorticoids" and the "mineralocorticoids". The glucocorticoids, which include cortisone, produce such various effects as gluconeogenesis, eosinopenia, and involution of lymphatic tissue. They also decrease fibroplasia, increase granulocytes and antibody formation, reduce the sedimentation rate of the erythrocytes, and prevent the production of arteriosclerosis and the deposition of intercellular protein. These actions are antagonistic to those of the mineralosteroids. These latter cause retention of sodium chloride and water with increased elimination of potassium from the body,

and produce hyalising changes in the renal glomeruli. These changes are supposed to lead to nephrosclerosis with the release of renal pressor agents. Selye believes that the two main groups of corticoids are stimulated by different pituitary hormones. ACTH in pure form is mainly glucocorticotropic, whereas the mineralocorticoids are stimulated by an "X-factor" in addition to ACTH.

The many changes which the body may undergo during the action of many stressor agents may lead to certain pathological changes which Selye considers as the "disease of adaptation". By using deoxycorticosterone Selye claims to have produced many of these diseases, such as nephrosclerosis, arteriosclerosis, periarteritis nodosa, rheumatoid arthritis and various less specific forms of joint lesions.

As the knowledge of the adrenal steroids has developed, Selye has been forced to modify many of his statements and to alter some of his concepts. This brief summary detailed here does, however, include those features of his theory which Selye has incorporated in his recent work. That there is much disagreement with his work cannot be doubted, and that he has made it so elastic that it is possible to account for any discrepancy has also

been claimed. That it will need to be greatly modified in the light of new knowledge is clear. That the formalin-arthritis produced by Selye has not been consistently produced by others has become apparent. Yet the value of his contribution cannot yet be fully estimated, and may be much greater than many critics believe. Hench has compared the effect of cortisone to that of an asbestos suit, protecting a man against a surrounding fire. This protection of the organism against the changes in its environment finds a large place in the work of Hans Selye.

The present study does not attempt to elucidate the Selyian hypothesis, but merely to emphasise an aspect of the body's response to injury. During the time that the observations were being made, many of the results appeared in the current literature. It is believed, however, that very few investigations show such a comprehensive proof of the place of the adrenal cortex in the injury response, and that some of the clinical results of this response have not been considered before in medical practice.

METHOD

Observations were made before and after various operations. As far as possible, simple operations were chosen, where there would be little fluid or blood loss, and where there would be a minimal interference with normal food, fluid and electrolyte intake. In almost all the cases, it was possible to account for all the fluid or electrolyte loss resulting from the method of surgical treatment undertaken.

As most of the electrolyte analyses were undertaken by the writer himself in addition to his normal surgical duties, the number of patients investigated and the number of investigations performed had to be reduced below the desired minimum. For this reason, when one fact had been established, the investigation had to be slightly altered to incorporate new features as they presented without necessarily repeating the old. It was hoped that a large series of inter-related facts about a few patients, accurately ascertained, would be of more

value than a few readings collected from a large number of patients.

Details of Method.

Blood was withdrawn at the same time each morning from the patients, and always after a twelve-hour fast. Dry, autoclaved syringes were always used except in the instance of Case 1. 20 ml. blood was taken off on a day before the operation, and on several occasions following the operation. An attempt was made to vary the intervals as much as possible, and even to withdraw blood on the day of operation. All specimens on the operation day were always collected before the operation. 12 ml. of the blood, without added anti-coagulant, was centrifuged as soon as it had clotted to prevent haemolysis. The serum was withdrawn for sodium and potassium estimations by biochemical methods. The remaining blood was put into tubes with dried heparin, and used for eosinophil counts, and for haematocrit and haemoglobin readings. So far as was possible, these were performed almost immediately. On alternate days, blood was again withdrawn, 5 ml. put into oxalated tubes under paraffin oil for plasma chloride estimations, and the remainder, on occasions,

into tubes containing sodium fluoride for blood-sugar determinations.

On the same day as the serum sodium and potassium estimations were performed, a complete 24-hour urine specimen was collected, and the 17-ketosteroid content measured. On alternate days, a complete 24-hour urine specimen was again collected, thoroughly mixed, and a sample used for sodium, potassium and chloride estimations. An accurate fluid intake and output record was kept of almost all the patients before and after operation and extended for some time beyond the completion of the tests.

Some patients were weighed before and after operation on the same scales, and at about the same time each day. In a few cases, blood-pressure recordings were obtained in the morning and after at least one hour's bed rest.

In some patients, the plasma volume or the extracellular fluid space volume was estimated by the writer before and after operation.

In a few cases, towards the end of the investigations described, blood was withdrawn into two heparin tubes. The heparin was specially prepared to be free from electrolytes. One specimen was centrifuged

immediately and the supernatant plasma drawn off.

By estimation of the plasma sodium and potassium in these specimens and by whole blood electrolyte estimations in the other specimens, the respective cellular and plasma electrolyte content could be calculated after reference to a haematocrit reading. The electrolyte estimations in these cases were performed by means of a flame photometer.

In those instances where a large number of estimations were being performed on one patient, the investigation was confined to male subjects.

The details of the laboratory methods used are described in Appendix II.

Tables of Results.

In the text, the results appropriate to the section have been placed opposite the typescript. A complete table of results for each patient examined in detail is supplied in Appendix I along with a brief summary of the case. In each table, the day of operation is indicated by zero, the days before operation prefixed by a "minus" sign, and the days after operation by a "plus" sign.

Because the electrolyte changes detected were not of great magnitude, the results are tabulated in milligrammes per 100 millilitres of blood rather than in milli-equivalents per litre.

PART I

TABLE 1. Urinary Chloride Concentration in Grams NaCl/Litre Urine.

Patient No.	-2	-1	0	1	2	3	4	5	6	7
1	5.75					1.87				
2			8.38		3.67		5.69			9.92
3		6.60		4.97			0.61		0.83	
4		4.83				1.05			1.89	
5		7.25		2.75		4.26		9.31		
6			7.03			3.46		5.87		9.21
7		6.41		4.13		1.04		4.68		
8		12.99			3.23		5.70			
9		11.02		4.43		9.78				

TABLE 2. Absolute Urinary Chloride as Grams NaCl per diem.

Patient No.	-2	-1	0	1	2	3	4	5	6	7
1		4.69				1.94				
2			8.68		8.47		7.32			17.49
3		4.44		2.37		0.55			1.27	
4		6.81				1.08			3.27	
5		6.53		4.16				20.85		
6			2.17			2.69		4.23		8.97
7		6.41		2.44		1.01		4.71		
8		19.4			5.14		12.77			
9		13.0		6.08		13.59				

CHAPTER 1.

URINARY CHLORIDE EXCRETION BEFORE AND AFTER OPERATION.

In Tables 1 and 2 opposite are shown the estimated concentration and total excretion of chloride in the urine before and after operation in nine cases studied. It will be seen that, following operation, there is a considerable reduction in the total amount, and in the concentration, of chloride excreted. Until the time of operation the patients appeared to be in adequate chloride balance as judged by the concentration in urinary chloride. Even on the very day of operation, the concentration in urinary chlorides in Cases 2 and 6 was adequate, and did not indicate chloride depletion. The chloride excretion in the urine tended to return towards normal before the seventh day, when a compensatory increase in chloride excretion begins to become evident.

The preoperative urinary chloride estimations in Cases 2 and 6 were performed on the day of operation. The

concentration of chloride, as already remarked, was within normal limits. No urine was passed by these two patients on that day following the operation. As a result the volumes of urine were considerably less than their usual daily excretion - Case 2, 812 mls.; Case 6, 308 mls. (See Appendix I for full details of all urinary volumes). This fact accounts for the relatively low total excretion of chloride before operation in these cases, and for the slighter changes to be seen during the post-operative period. In general, however, these two cases correspond with the others, and the same reduction, and gradual rise in urinary chloride excretion is demonstrated.

The changes shown are all the more remarkable when it is observed that Cases 1, 3 and 4 received pre-operative saline and Cases 1 and 3 blood, and that Case 1 received intravenous or oral saline on the 2nd to 5th post-operative days (See Appendix I). This sudden diminution in chloride suggested to the writer an analogy with the well-known fall in chloride excretion following the onset of lobar pneumonia. It is believed by him that the same factors may be operative in both cases.

The tables here shown include only those patients upon whom many other biochemical estimations were performed,

and relate only to the subjects of the present series of experiments. This reduced chloride excretion in the urine following operation had been noted by the writer on many occasions before this, and indeed led to the present investigation. While this was in progress, Wilkinson et al. (1949) demonstrated similar results following operation in a careful study of postoperative metabolic changes. Marriott (1951) also mentions a diminution in urinary chloride excretion following operation. A diminution in urinary chloride excretion has recently been observed by Higgins and his associates (1951) following severe head injury. Following burns (Crassweller et al. 1950) a reduced urinary chloride output is also common, but, unlike the previous conditions mentioned, the body fluid changes are so great that the mechanism may well be different. The reduced renal blood flow and consequent diminution in glomerular filtration after burns are not features of the other conditions described.

These changes in urinary chloride will be related to plasma chloride changes (Chapter 2), and to serum and urinary sodium changes (Chapters 3 and 4). When the whole picture of postoperative changes has been built up, the factors influencing these changes will be considered in the summary at the end of Part I.

TABLE 3. Plasma Chloride as mgms. NaCl/100 ml. Blood.

Patient No.	-3	-2	-1	0	1	2	3	4	5	6
1			535			519				544
8	597					556		556		
9	592					543		560		
20		580				560				
21		560				560				
22		550				530				
23			600		540					
24			570		560					
25			580			560				
26			580			480				

CHAPTER 2

PLASMA CHLORIDE LEVELS BEFORE AND AFTER OPERATION

Table 3 shows the concentration of chloride in the plasma, measured as sodium chloride, in 10 cases. The plasma chloride concentration was determined in only two of the patients whose chloride excretion has been studied in the previous chapter. The remaining patients are collected from a later part of the series.

No change is observed in the postoperative plasma chloride in Case 21, and the reduction in Case 24 is within the experimental error of the method employed. The changes in Cases 1, 8, 9, 20, 22, 23, 25 and 26 are, however, significant. In all these cases there is a reduction in the postoperative chloride concentration in the plasma. This reduced plasma concentration appears to occur at the same time as the reduced excretion of chloride in the urine. Whether this chloride reduction in the plasma and urine is due to chloride loss from the

body will be discussed along with similar changes in sodium metabolism in Chapter 4.

The changes are not in themselves great, but if they are a reflection of the chloride reduction throughout the whole extracellular fluid compartment of the body, the chloride loss, if indeed it is a loss, is appreciable. As Case 1 was developing a postoperative complication which, after the sixth day must have interfered with electrolyte balance (See Appendix I), the later changes in his plasma chloride concentration are not of interest. It is worthy of note, however, that this patient received both blood and saline at the time of operation and thereafter. In spite of this, a small decrease in plasma chloride concentration is detectable.

Fullerton et al. (1932) have stated in another context that the kidney normally excretes chloride in abundance as long as the plasma chloride concentration is greater than 520 milligrams per 100 ml. blood. Smith (1951) indicates that it is very difficult to determine the critical plasma level below which chloride is not excreted in the urine. As he points out, this average critical level may be considerably reduced when potassium is excreted, even in the presence of a sodium deficiency.

As indicated in Chapter 5 of this work, potassium is indeed excreted in excess in the urine after operation. It is therefore correct to expect that chloride might be excreted in the urine below the critical level in this series. From a study of Tables 1 and 3 it will be noticed that this is not so in the post-operative period, and that a reduction in urinary chloride excretion occurs when the plasma chloride levels are considerably higher than 520 mgms. per 100 ml. blood. This indicates that the reduction in chloride excretion in the urine is greater than the proportionate fall in plasma chloride concentration.

According to Smith (1951), the greater part of the sodium and chloride of the glomerular filtrate is absorbed in the proximal kidney tubules. The final regulation of sodium and chloride excretion is exerted at the distal tubules, depending on the osmotically active state of the body fluids, but also on the activity of the hormonal elements of the adrenal cortex and the neuro-hypophysis. For example, the adrenal steroids promote increased tubular re-absorption of chloride and sodium.

The reduction in plasma chloride in Case 26 is the greatest yet noted by the writer. This particular patient did lose more blood at operation than the others, but postoperative vomiting was not marked.

The evidence of other workers upon the blood chloride concentration following operation and associated conditions is conflicting. The changes following massive blood loss, shock, abnormal vomiting and similar conditions, are not, of course, under consideration here.

Christy (1927) observed a decrease in plasma chloride after exercise. Whether this was due in part to chloride loss by sweat, and to upset in acid-base balance cannot be determined. However, Sinclair-Smith et al. (1949) demonstrated that this reduced chloride excretion after exercise was not associated with an increase in blood lactic acid. Annersten and Norinder (1946) quote Lambret and Driessens as having observed a decrease in the plasma chloride concentration after surgical operations. In their own paper, they observed similar changes, but did not consider them statistically significant. Wilson and Stewart (1939) observed a fall in the plasma chloride, but a rise in the whole blood chloride following burns. Wilkinson et al. (1951) also noted a slight decrease in the plasma chloride and a decrease in the blood chloride after operation. They calculated that the concentrations in the plasma and the erythrocytes remained fairly constant, and that the changes in whole blood chloride were due to the changes in relative proportions of the cells and plasma.

In their cases, and in those of Annersten and Norinder, however, major surgical procedures were undertaken with replacement transfusion. It is possible that the slight changes to be detected would be masked by replacement therapy.

To dissociate changes in plasma chloride from alterations in acid-base balance is difficult. As has been mentioned, however, after exercise, the decrease in plasma chloride is not associated with any marked upset in the acid-base balance. Wilkinson et al. (1951) have shown that, after operation, the carbon dioxide combining-power of the plasma does not vary beyond the normal limits.

It is rather surprising that an increase in plasma chloride is not detected associated with the apparent chloride retention. Higgins et al. (1951) have recently observed hyperchloraemia associated with reduced urinary chloride excretion following severe head injury. They point out that such an occurrence has been recorded in disturbances in acid-base balance in the following conditions, massive gastro-intestinal haemorrhage, cerebral damage and sulphathiazole poisoning. They were unable to determine in their patients whether this disorder of metabolism was due to cerebral damage or to cortical steroid activity.

Following uncomplicated operation, however, the writer is not aware that any increase in plasma chloride has been regularly observed associated with decreased urinary chloride excretion. This statement does, however, exclude those cases commonly seen in surgical practice suffering from a relatively greater water than salt deficiency, where the increased plasma chloride is a reflection of dehydration, and the diminished salt excretion, of reduced renal plasma flow.

To recapitulate some points about chloride metabolism; where the plasma chloride is reduced below about 520 mgms. per 100 ml. blood, the kidney will markedly reduce the excretion of that ion. It would appear, however, that following operation, some factor increases renal reabsorption of chloride even when the plasma chloride is not below the critical level, when the renal blood flow is adequate, and when the volume of urine excreted is also within normal limits. As has been mentioned, the cortical hormones of the adrenal cortex possess this property of inducing renal reabsorption of chloride, sodium and water. Thorn et al. (1938) have demonstrated this effect of deoxycorticosterone. In a comparison of the effects of deoxycorticosterone and 17-hydroxy-11-dehydrocorticosterone,

Ingle and Thorn (1941) noted that both sodium and chloride were retained in the body by the former, but that the effect of the latter on electrolyte metabolism was very much less marked. Selye and Dosne (1941) noted this retention of chloride following injections of deoxycorticosterone acetate in animals, and a reduction in plasma chloride, if this had previously been normal. If the plasma chloride had been reduced before the injections, then there was an initial rise to normal after injection. However, a prolonged series of injections always led to a reduction of the blood chlorides even after adrenalectomy. Selye (1950) has recently shown that both plasma and urinary chlorides are observed to increase during the "counter-shock" and resistance phase of the General Adaptation Syndrome after a fall during the earlier phase.

TABLE 4. Urinary Sodium Concentration as Grams Na/Litre Urine.

Patient No.	-1	0	1	2	3	4	5	6	7
4	14.96				3.92			1.06	
5	3.86		1.94		2.41				
6		3.02			2.71		2.80		4.48
7	4.54				2.45		2.69		
8	2.23			1.07		1.89			
9	3.79		2.39		2.99				

TABLE 5. Absolute Urinary Excretion as Grams Na per Diem.

Patient No.	-1	0	1	2	3	4	5	6	7
4	21.09				4.01			1.83	
5	3.47		2.93		3.84				
6		0.93			2.11		2.01		4.36
7	4.54				2.38		2.69		
8	3.34			1.7		4.1			
9	4.51		3.27		4.15				

CHAPTER 3

THE EXCRETION OF SODIUM BEFORE AND AFTER OPERATION

Tables 4 and 5 show the results of the estimation of urinary sodium concentration and total sodium excreted before and after operation. It will be noted that there is a considerable reduction in the excretion of sodium following operation, and this in patients with no preoperative sodium deficiency. Indeed, in the following chapter, Table 6, the serum sodium concentrations of these patients are shown to be within normal limits before operation. Urinary sodium estimations were not performed on patients 1, 2 and 3. As with urinary chlorides already discussed, Case 6 shows the evidence of estimating the ion on the day of operation. As before, the urine volume was 308 mls. The urinary sodium concentration again fell after operation, but the total sodium excreted was greater, because of the small preoperative urine

volume. None the less, there is evidence of a reduction in concentration of sodium in the urine after operation, followed by a gradual rise, approaching the normal range about the seventh day.

The excretion of sodium as such has not been widely studied following operation in patients in whom there is no reason to suspect a pre-existent sodium deficiency. It appears from the results shown here that there is a definite decrease both in concentration and in total amount of sodium excreted in the urine following operation. Normal sodium excretion appears to commence about the seventh day.

Wilkinson et al. (1949), in balance experiments, were able to demonstrate a similar retention of sodium in the first postoperative week. These changes, as in the present study, paralleled the diminished output of urinary chloride. Marriott (1951) also draws attention to a postoperative sodium retention. He suggests this is due to an attempt on the part of the kidney to maintain the diminished plasma volume. Howard and Carey (1949) remark a postoperative retention of sodium and chloride in amounts greater than theoretical requirements would suggest. Darrow and Pratt (1950) discuss a similar retention of

sodium after operation, after injury, and during heart failure. Any relationship that these apparently dissimilar conditions may bear will be considered at a later stage.

TABLE 6. Serum Sodium as Milligrams Sodium per 100 ml. Blood.

Patient No.	-4	-3	-2	-1	0	1	2	3	4	5	6	7	8	30
1				305	4.5G		0.5G / 320	2.25G	1.1G / 306	1.1G	292			316
2				336					316.5		340			
3				318.7	9 G		310.1			302.1			327	
4	325.8				4.5G			312			319		335	
5			334.6				323.8		332.5		336.2			
6				335			314		328		334.6			
7				340.5		332		320		330				
8		331					328.7		340					
9		326.7					342.2		327.2					

CHAPTER 4

SERUM SODIUM LEVELS BEFORE AND AFTER OPERATION

Table 6 shows the results of the investigations into the serum sodium concentrations before and after operation. In the table, the calculated intake of sodium by intravenous route, and by oral intake over and above the diet, is shown in red above the line as grams NaCl per day. The results demonstrate that there is a clearly detectable fall in the serum sodium concentration following operation, even in those cases receiving intravenous sodium chloride or blood. The early postoperative findings in Case 1 are an exception to this, but even in this case, the serum sodium falls at a later stage. The early post-operative rise is, in part, due to blood transfusion. Case 9 proves to be an exception, the observed values of serum sodium following operation appear to increase.

This different reaction of Case 9 will be noted again at a later stage in some other respects. The fall in serum sodium in the first eight cases appears to parallel the fall in concentration in the plasma chlorides already noted, and occurs at the same time as the diminished excretion of sodium and chloride in the urine.

This fall in serum sodium concentration might be due to:-

1) a considerable loss to the body of sodium, or
2) a dilution phenomenon, or
3) a loss of sodium (and water) into the tissue fluids, or
4) an apparent loss of sodium into the tissue cells, or any combination of these.

Loss of Body Sodium.

The considerations affecting loss of body sodium are equally applicable to loss of body chloride.

It has been shown in the previous chapter that there is no undue loss of sodium in the urine in the post-operative phase. Indeed, there is a considerable diminution in the excretion of sodium, as if in an effort to conserve this ion. It might be suggested that the loss of base could be accounted for by postoperative vomiting.

This is not so, for none of these patients vomited more than an ounce or two of fluid, and some none at all. Only Case 3 could be considered as having any postoperative sickness. The calculated sodium loss by vomiting is shown in the appropriate record of results for each patient in Appendix I. Some base might undoubtedly be lost by sweating, but could not have been to the degree shown. As Darrow and Pratt (1950) point out, the electrolyte content of 'invisible' perspiration is very low.

For a day before operation, there is usually some degree of sodium and chloride deprivation, but not in Cases 1, 3 and 4, who received intravenous blood or saline. However, the diminished sodium intake associated with diminished output in the urine could not be the cause of the changes observed. According to the studies of Howard et al. (1946) on convalescence, an increased loss of sodium and chloride in the urine is noted in the first three days of starvation, or in graduated decreased diet, but no change in the blood sodium. Duncan et al. (1948) have also shown an increased sodium and chloride excretion in the urine during short periods of starvation when minerals only are supplied in the diet. Diminished intake for the short period of 3-4 days does not therefore account for the electrolyte changes.

If the fall in the serum sodium is an accurate index of the diminution in the total extracellular fluid sodium (and at this stage there is no reason to doubt it) then the amount of blood lost at operation to account for the total apparent sodium loss would need to have been nearly one litre. If the plasma chloride changes are a reflection of the chloride changes throughout the total body water, then the loss of blood in Cases 8 and 9 would have been greater than one litre for a near normal body water of 36 litres. Furthermore, the factor of blood loss would only be effective on the day of operation, and one would not expect to find a continued fall in the serum sodium and chloride after this time, as evidenced by Cases 1, 3, 4 and 7. A blood loss and tissue fluid loss of nearly a litre is unthinkable in a simple operation like inguinal herniorrhaphy.

From all this evidence it is clear that there is no known loss of sodium or chloride from the body of such a magnitude as to account for the changes described following operation.

Dilution Phenomenon.

The reduced concentration of sodium in the serum and chloride in the plasma may be the result of a water

retention and a dilution of the tissue fluids. The evidence for water retention is considered in Chapters 6 and 7. At this stage it can be said that, if such a dilution effect were to occur, then an increase in the total extracellular body water, or even total body water, would result. In Chapter 6 evidence is presented that no such increase in total extracellular body water can be detected following operation. Evidence of a slight increase in total body water is also presented, but not in a proportion greater than the apparent retention of sodium. Indeed the sodium retention may bring about the water retention, and there is therefore no evidence of a dilution of the body fluids.

Loss of Sodium, Chloride and Water into the Tissue Fluids.

If sodium and chloride were to be lost from the circulation into the tissue fluids, then there would be a considerable transudation of water with the electrolytes, or sodium in the circulation would need to be replaced by the other body base, potassium, and chloride by bicarbonate. In Chapter 5, page 46, it is clearly shown that no such evidence of any regular postoperative accumulation of potassium in the serum in sufficient quantity can be detected.

In Chapter 6, page 58, it will be demonstrated that there is no measurable increase in the total extracellular fluid volume following operation. It is true that, in the same chapter, evidence is adduced of some increase in the extravascular extracellular fluid compartment, accompanied by some evidence of reduction in the circulating blood volume and by haemoconcentration. If, therefore, there be a transudation of water from the vascular bed to the extravascular spaces, the sodium and chloride would no doubt pass with it. Wilkinson et al. (1951) suggest from similar evidence that such a transudate of plasma takes place into the damaged tissues due to increased capillary permeability, and that increased amounts of circulatory water and electrolyte collect in the damaged tissue spaces. However, Tammann et al. (1933) have shown that, though there is an increased water content in a gaping wound, the sodium and chloride content is decreased and the potassium and calcium increased as compared with blood serum. Further, Fox (1944) has shown that, in the treatment of shock following burns and trauma, effective electrolyte replacement therapy requires a volume of sodium-containing fluid in excess of the loss at the site of injury. In experimental studies on shock (Fox and Baer, 1947), it has

been shown that changes also occur away from the site of injury, and that these changes are essentially cellular. This will be discussed later, but this evidence, so far as it may be applicable to unshocked postoperative patients, tends to indicate that a simple transudation of plasma at the site of injury is not the whole cause of the reduced concentration of circulating electrolyte. Wilkinson et al. (1949) cite the work of Fox and Baer to prove that there is a local accumulation of sodium and chloride at the site of injury. However, this is a cellular accumulation, and the injury they produced was that of total interruption in the circulation to the part to produce shock. Such long-continued anoxia of a part for two hours must produce factors which are not operative at a wound site, nor is the accumulation of sodium in the cell evidence of a transudation of this ion from the vascular compartment.

"Loss" of Sodium into the Tissue Cells.

It was believed by the writer that a part of the apparently lost sodium might have passed into the tissue cells. The discussion of changes in cell permeability following operation is reserved for the next chapter, but

TABLE 7. Plasma and Cell Sodium as mgm. Na per 100 ml. Blood.

Patient No.	- 1		0		+ 1		+ 4	
	Plasma Na.	Cell Na.	Plasma Na.	Cell Na.	Plasma Na.	Cell Na.	Plasma Na.	Cell Na.
14	342	89			322	99		
15	327	74			317	93		
16			327	83			336	45
17			331	61.5			340	20.5
18	330	33			327	40.4		
19	336	46.5			333.5	46		

TABLE 8. Whole Blood Sodium as mgm. per 100 ml.Blood.

Patient No.	Before	After
14	431	421
15	401	410
18	363	367.4
19	382.5	379.5
16	410	381
17	392.5	360.5

Table 7 (opposite) demonstrates the results of a short study of the erythrocyte and plasma sodium content before and after operation. It will be observed that quite large changes in erythrocyte sodium content result from the stimulus of operation, and that these changes are associated with changes in the plasma sodium.

In patients 14, 15 and 18, where the estimations were made on blood withdrawn on the day before and the day after operation, a rise in cell sodium content is associated with a corresponding fall in the plasma sodium concentration. How close this association is can be seen from Table 8, where the total blood sodium concentrations per 100 ml. blood are shown. It will be observed from this table that the whole blood sodium in these cases before and after operation does not vary by more than 2.5 per cent. This applies also to patient 19, but no appreciable alterations are observed in the relative plasma and cell sodium contents.

In patients 16 and 17, where the postoperative measurements were not performed until the fourth day, a considerable decrease in cell sodium is noted, accompanied by an increase in plasma sodium (Table 7). As can be seen from Table 8 the whole blood sodium in these cases was not so unchanged as in the others, the total reduction

being about 7.5 per cent. These figures, of course, as with the others throughout this work, are not subjected to statistical analysis, as the number of cases investigated is much too small.

The close correspondence in the whole blood sodium before and after operation in cases 14, 15, 18 and 19 does indicate, however, that the increase in cell sodium in these patients is obtained at the expense of the plasma sodium, suggesting an intake of sodium by the cell from the plasma. At the fourth day after operation, the loss of cell sodium is not so accurately reflected in the gain in plasma sodium.

The writer has not been able to trace any extensive studies of changes in erythrocyte sodium after operation. As has been mentioned earlier, Wilson and Stewart (1939) observed an increase in cell sodium after burns, but the factor of decreased plasma volume is very much more marked in such cases. In Table 37, in Appendix I, the haematocrit readings for the patients of the present series before and after operation are shown. No regular haemoconcentration is detected. It would appear therefore, from the present study, that the decrease in plasma sodium in the early stages after operation is associated with a

corresponding increase in erythrocyte sodium content. At a later stage, as the plasma sodium concentration returns to or above the preoperative level, the erythrocyte sodium content is reduced. Whether such changes occur in the fixed tissue cells cannot be determined in this study. It was felt that muscle biopsy before and after operation could not be justified to the patients.

A summary of the work included in this chapter demonstrates that the retention of sodium in the body after operation is associated with an anomalous decrease in the serum or plasma sodium concentration. It has been shown that sodium is not lost to any appreciable extent, and a later chapter indicates that, if water is retained in the body after operation, there is no reason to suspect that it is held in greater amounts than the corresponding sodium retention to produce an isotonic solution. The hypothesis of Wilkinson and his associates (1951) that the retained fluid and sodium collects in the damaged tissues has not been proved, whereas evidence from the present study indicates that the retained sodium is, in part, held within the body cells. This cellular increase of sodium accounts for the anomalous fall in the plasma or serum sodium concentration after operation.

TABLE 9. Urinary Potassium Concentration as grams K/Litre Urine.

Patient No.	- 2	- 1	0	1	2	3	4
8		0.92			0.65		0.78
9		1.4		1.42		1.15	
10	1.28			3.4		3.37	
11	1.39			2.32		3.03	
12	1.55			1.92		2.25	
13	1.45			1.5		1.97	

TABLE 10. Absolute Urinary Potassium Excretion as grams K per diem.

Patient No.	- 2	- 1	0	1	2	3	4
8		1.38			1.03		1.71
9		1.67		1.94		1.60	
10	2.17			4.08		5.39	
11	2.75			3.71		4.15	
12	3.4			3.41		2.34	
13	2.94			2.4		1.82	

CHAPTER 5

POTASSIUM LOSS AFTER OPERATION

Tables 9 and 10 demonstrate that the concentration of potassium salts in the urine is maintained or increased (Cases 9, 10, 11, 12 and 13) following operation; the total excretion of potassium not being increased markedly except in three cases (10, 11 and 12). This effect occurs on the first postoperative day, and is maintained until at least the third day.

The increased potassium excretion is all the more remarkable when it is recalled that the intake of potassium is very much reduced during this period of maximal excretion. The usual routine dietary arrangement with these patients was to continue normal feeding until the afternoon of the day before operation, from which time only a little food and drink of low or negligible potassium content would be consumed. No food was taken on the day of operation, nor on the first postoperative day.

Milk and milk-foods with only a relatively low potassium content - 160 mgm. per 100 ml. (McCance and Widdowson, 1946) - would be given during the second postoperative day, and gradually the diet assumed normal content and proportions during the next two days. There was thus a minimal intake of potassium salts during the period of maximal potassium excretion. None of these patients received blood transfusion or saline infusion at operation or thereafter. Clearly these patients, with a diminished intake of potassium, and an increased excretion of this electrolyte, must have been in a state of 'negative' potassium balance. It would have been ideal to have performed repeated potassium balance experiments. Attempts were made, but the scheme proved impossible for a single worker with other commitments. To have used the food tables of McCance and Widdowson (1946) would have been of little value, considering the negligible potassium intake, and the liability to error of the tables in any particular case (Wilkinson et al. 1950).

It should be noted further that the potassium excretion was not particularly related to the severity of the operation, but seemed to be an individual variation.

TABLE 11. Serum Potassium as mgms. Potassium per 100 ml. Blood.

Patient No.	-4	-3	-2	-1	0	1	2	3	4	5	6	7	8	30
1							19.6		21.3		22.2			19.7
2			21						24					
3				22.7			22.8						22.1	
4	22							18.9			19.7			
5			22.2				20.7		21		22.5			
6				20.7			22.7		22		25.8			
7				20		22.5		20.7		23.7				
8		20.9					21.8		21.1					
9		19.7					23.8		22					

During the period under consideration, Table 11 shows that the concentration of potassium ions in the serum of some of these patients (Cases 8 and 9) showed some variation. It was not possible to estimate the urinary potassium in every case upon which estimations of serum potassium had been performed. However, as the increased potassium excretion proved to be such a constant finding, and as the serum potassium levels proved to be so variable, it was presumed that such variable levels of serum potassium could be expected in every case. In general, it seemed that the serum potassium concentration was elevated at some point in the postoperative period (Cases 1, 2, 6, 7, 8 & 9). Again it is assumed that the serum level in Case 1 on the thirtieth postoperative day was similar to the preoperative concentration not determined because of some haemolysis in the serum. According to Annersten and Norinder (1946), Lucerna et al. (1940) have observed a raised value of serum potassium and a reduction in serum sodium following operation.

Potassium, like urea, is normally reabsorbed partially through the renal tubule epithelium (Leaf and Camera, 1949). When, however, potassium is present in excess the kidneys can excrete more potassium than can be

accounted for in the glomerular filtrate (Darrow and Pratt, 1950), i.e. accumulation of excess potassium in the serum is prevented by its rapid excretion in the urine.

In the cases shown here, because of the reduced potassium intake during the operation and postoperative period, the excess potassium excreted must be derived from an endogenous source. The slightly raised serum potassium level suggests that, once derived from this source, a small excess may collect in the plasma for a short time prior to its excretion. The writer does not believe that any greater significance can be attached to the variable levels of circulating potassium here demonstrated, provided kidney function be normal. It is believed that evidence of a real accumulation of potassium in the serum can be demonstrated in the presence of renal insufficiency (Part IV, Chapter 15). Grahame (1951) also shows a tendency to a rising serum potassium in 19 of 24 patients within 24 hours of operation. However, these patients had undergone major surgical operations, and had been receiving considerable amounts of intravenous saline. This, in itself, is enough to induce potassium loss in the urine (Darrow and Pratt, 1950; Stewart and Rourke, 1942; Gamble, 1942).

The Source of the Lost Potassium.

As potassium is primarily the base of tissue cells, it would seem that the excess potassium must be derived from this source. It has been shown that cells - for example, erythrocytes and muscle cells - are not so impermeable to transfer of cations as used to be thought, and that they do allow the passage of potassium and sodium across the cell membrane under certain circumstances. Maizels (1949) has shown that, in blood stored at 37° C., an active expulsion of sodium from the cell takes place, accompanied by an uptake of potassium; energy for the process being supplied by glycolysis. Mullins et al. (1941) have shown the rapid penetration of the erythrocyte by radio-active potassium, and to a lesser extent by sodium, in three hours. During anaerobic metabolism, in the absence of glucose, the potassium concentration of the serum (Danowski, 1941) or the brain tissue fluid (Dixon, 1949) has been shown to rise, due to a loss of potassium from the cells of the respective tissue. Ferrebee et al. (1941) have shown clearly that, in dogs, symptoms of cellular depletion of potassium may arise following the administration of deoxycorticosterone acetate. They produced muscular weakness and paralysis, associated with

a partial replacement of intracellular potassium of skeletal muscle by sodium. It has also been shown that, in animals fed on a low potassium and high sodium diet, a partial replacement of deficient cellular potassium can be induced by increase in cell sodium (Heppel, 1939; Miller and Darrow, 1940b). This has also been noted under certain circumstances in alkalosis (Gamble et al. 1945; Darrow, 1945). Elkinton et al. (1948) summarise these cation exchanges in their experiments and the factors involved as under:-

1) Potassium will leave a cell in significant amounts only if it can be excreted.

2) Transfers of large amounts of potassium into the cells have been observed only when exogenous potassium is available.

3) Sodium, unlike potassium, can enter the serum from cells even though renal function is greatly impaired or ceases.

4) In contrast to potassium, large increases in cellular sodium are not dependent on exogenous supply.

It is interesting to observe that these experimental findings were similar to those found in the clinical researches in this paper under different conditions.

Fenn and Cobb (1936) found that after 30 minutes indirect stimulation of the muscles in anaesthetised rats,

potassium was lost from the muscle cells and replaced by sodium. They found also an increase in the intracellular space due to the passage of water and sodium chloride. It is to be noted that, after two hours rest, these changes were reversible, indicating that no permanent damage had been done to the cell.

The conditions under which these cation exchanges were studied are mentioned in the various works. Whether such changes occur following operation or trauma has now to be considered.

Cuthbertson et al. (1939) have shown that, in rats, following fracture of the femur by open operation, there was a well-marked loss of nitrogen, phosphorus and potassium in the urine. The fact that Cuthbertson (1941) has shown that potassium is lost from the body during the negative nitrogen balance phase after injury would suggest that the body excretes the accumulated potassium, derived during the destruction of tissue cells and their protein, in this catabolic phase. Cuthbertson himself, however, pointed out that the potassium loss was far greater than could be accounted for by local tissue injury, and he showed that potassium is lost to a greater corresponding extent than nitrogen. He believed, therefore, that the nitrogen

and the potassium could not arise from a parallel loss of the body cells. Wilkinson et al. (1950) have also shown that the potassium loss after operation in their ten cases was considerably greater than the proportionate nitrogen loss, if they were both to be derived from the destruction of tissue cells. Further, they showed that the excretion of excess potassium in the urine ceases some days before the end of the nitrogen catabolic phase. Blixenkrone-Møller (1949) has shown that the onset of the increased phase of potassium excretion occurs within six hours of the operation and continues for at least 24 hours. Wilkinson et al. (1950) demonstrate that this phase precedes the phase of increased nitrogen catabolism. In the writer's own experience, he was able to detect increased excretion of potassium in the urine at the end of 20 hours after operation in Cases 10 and 11.

It is therefore probable that the potassium excreted in excess after operation is derived from tissue cells independently of the destruction of tissue protein, that the loss in the first three days is relatively greater than the nitrogen loss, and that it commences earlier after operation and ceases before the increased nitrogen catabolism terminates. As Cuthbertson (1942), Wilkinson et al. (1949;

1950) and Blixenkrone-Møller (1949) have shown, both these phases of excess potassium and nitrogen loss after injury or operation are followed by phases of relative potassium and nitrogen retention. Though, therefore, the potassium and nitrogen are derived at different times and in different proportional amounts from the tissue cells, there is no evidence to show that the causal factor in either case is different.

Undoubtedly some of the excess potassium might be derived from cell destruction during the operation, but the excretion seems excessive if derived from this source alone. As has already been stated - Cuthbertson et al. (1939) - the potassium loss was far greater than could be accounted for by local changes. Starvation, or reduced food intake by itself, causes an increased excretion of potassium in the urine. Howard et al. (1946) have shown that the loss of potassium during starvation is directly proportional to the loss of nitrogen and phosphorus, and that all three are lost in the same proportion as they exist in muscle protoplasm. In fact, they point out that, having established this fact, any large deviation from the pattern, if found in injured patients, must be presumed to be a direct result of injury. This is exactly the point

TABLE 12. Plasma and Cell Potassium as mgm. K per 100 ml. Blood.

Patient No.	- 1		0		+ 1		+ 4	
	Plasma K	Cell K	Plasma K	Cell K	Plasma K	Cell K	Plasma K	Cell K
14	19.4	405			20.4	405		
15	18.2	367			16.3	371		
16			16.0	385			14.5	407
17			16.3	385			14.4	391
18	17.6	389			19.0	386		
19	19.2	383			18.0	380		

that the writer wishes to make.

Changes in Cell Potassium.

If the potassium be derived from tissue cells, and if it be replaced by sodium, then it might be possible to detect such changes in erythrocytes after operation. As has been demonstrated in Chapter 4, such changes in erythrocyte sodium content have been detected. Table 12 (opposite) shows the plasma and erythrocyte concentration of potassium before and after operation in the same six patients whose cellular sodium content was also determined. It was hoped that this study might show direct evidence of the loss of cell potassium which has already been discussed. It will be observed, however, that no regular change has been detected in erythrocyte potassium content in the post-operative period. The writer has not been able to discover any similar studies of potassium metabolism after operation.

The fact that no appreciable change in erythrocyte potassium content has been detected does not invalidate the assumption that the potassium excreted after operation is derived from cell potassium. If there is no exogenous potassium supply, the potassium excreted can only be derived from the body's store. The largest amount of potassium

in the body is contained within the muscle cells. It had been hoped to perform some muscle analysis before and after operation, but as has been stated in the previous chapter, this could not be justified to these patients.

The whole blood sodium and potassium studies in this series may be summarised now. In the early stages after operation, an increase in cellular sodium takes place, this sodium being derived from the plasma sodium. By the fourth day after operation, the plasma sodium has returned to the preoperative level, and the cell sodium content is considerably reduced. No corresponding changes have been observed in cellular potassium.

It is indeed curious that the normal cell to tissue equilibrium should remain established at any time. As Maizels (1949) has indicated, this accumulation of potassium in the animal cell against the concentration gradient has long been a cause for speculation. The failure of any physical diffusion theory to explain the cellular cation content led Dean (1941) to accept an active interchange of electrolyte, and to suggest a 'pump' mechanism to rid the cell of sodium. Maizels does not believe that an active excretion of sodium requires an active uptake of potassium by the cell, and in the absence

of such an active uptake, he believes that potassium passes into the cell passively, and secondarily to the active output of sodium.

It would seem, therefore, that, following operation or trauma, the relative permeability of the cell membrane is altered, potassium is liberated, and any tendency to a rising potassium level in the plasma prevented by the rapid excretion of potassium in the urine. Either to replace this loss, sodium appears to enter the cell from the surrounding plasma, or else, if Maizel's view is correct, the 'pumping' mechanism breaks down, sodium is not sufficiently expelled from the cell, and perhaps to maintain the correct osmotic tension, potassium leaks out into the plasma.

CHAPTER 6

THE CHANGES IN THE BODY FLUIDS FOLLOWING OPERATION

Since changes were detected in the excretion of electrolytes following operation in the earlier observations, it was decided in the present series to study some of the essential changes which might accompany them in the water metabolism of the body. At the outset, the weight, blood pressure, haemoglobin and haematocrit, urine volume and fluid intake of some of the patients were measured at the same time as the alterations in electrolyte equilibrium. To elucidate certain features, a few measurements of circulatory plasma volume, extracellular fluid space volume, and plasma proteins were performed.

The Plasma Volume.

Following the haemorrhage of an operation, there is a tendency to a reduction in the total circulating blood

TABLE 13.

Patient No.		-3	-2	-1	0	1	2	3	4	5	6	7	8
2	Haemat. Hb.			42 97				41 97	41 92		40 89		
3	Haemat. Hb.			49 118			48 100			47 100		47 112	
5	Haemat. Hb.		47 97				46 100		45 95		44 98		
6	Haemat. Hb.			46 98			43 96		40 95		40 94		
7	Haemat. Hb.			35 74					32 68				
1	Haemat. Hb.			38 84			44 98		40 86		37 80		
4	Haemat. Hb.		45 89					47 92			41 89		41 94
8	Haemat. Hb.	43 98					48 100		46 106				
9	Haemat. Hb.	49 102					50 112		51 100				

volume. This is corrected to some degree by the passage of tissue fluids into the circulation. This tissue fluid contains water and electrolytes in similar concentration to that present in the plasma, but is, of course, deficient in the plasma proteins (Gamble, 1942). In this way, a theoretical dilution of the blood - a hydraemia - takes place, while the total circulating volume of fluid remains very nearly the same as before operation. This change can be detected by means of serial haematocrit and haemoglobin estimations. Cases 2, 3, 5, 6 and 7 show such a reduction in haematocrit and haemoglobin levels following operation, without returning to preoperative levels by the seventh day (Table 13). Only Case 3 of this group received intravenous infusions, and must therefore be considered in more detail. On the day of operation he received 560 ml. blood and the same volume of 6 per cent. dextrose in normal saline. The pint of blood would no doubt stay in the circulation, thus reducing the hydraemic tendency, whereas the normal saline, though retained in the body for at least 24 hours, would leave the circulation at an early hour after infusion. The loss of $1\frac{1}{2}$ litres of fluid by gastric suction during the first four post-operative days, would, if anything, also tend to reduce the haemodilution. The

fact that this did occur is therefore emphatic evidence of blood loss in this patient.

Four cases, on the other hand, Cases 1, 4, 8 & 9, showed slight evidence of haemoconcentration, as measured by an increase in haematocrit readings and in haemoglobin concentration. Only Case 1 received 560 ml. of blood at operation. Case 4 received 560 ml. normal saline and 1,400 ml. 6 per cent. dextrose. It is unlikely that the glucose, electrolyte and water would remain in the circulation until the third postoperative day, when the first estimations in that period were made. This haemoconcentration in these four cases is presumptive evidence of a reduction in plasma volume.

Wilkinson et al. (1951), in a study of ten cases undergoing major surgical operation, have shown evidence of a reduction in plasma volume, the decrease averaging about 16 per cent. of the calculated preoperation volume. This estimation was made by direct measurement of the plasma volume by the dye T 1824. In their series there is also evidence of a haemoconcentration as detected by an increase in the haematocrit after operation. The cases in their study were all undergoing major surgery and all received blood transfusion. They consider this further evidence that the haemoconcentration is significant, and believe

TABLE 14. Plasma Volume in ml.

Patient No.	Initial	Postoperative	Change
6	3850	4010	+160
12	3210	2980	-230

that this is evidence that there is a diminution in plasma volume alone, over and above the blood loss of operation. There is, however, no evidence available to show whether the blood loss in these patients in their series was completely replaced or not.

In the present series, there is undoubted evidence that a haemodilution may occur following operation without any parenteral fluid therapy. It is difficult to believe that this haemodilution could occur in the presence of a diminishing total plasma volume. To elucidate this point further, it was determined to measure changes in the plasma volume by the dye method. Unfortunately, this was undertaken in only two patients (Table 14). They do demonstrate, however, that the changes in plasma volume are not so constant as Wilkinson and his associates suggest. The method of plasma volume measurement employed was that using T 1824 described by Gregersen and Stewart (1939). That the dye method does not supply an accurate measure of the true plasma volume has been indicated by Gregersen (1944), but as only relative changes were being considered, the method may be accepted. The technical difficulties of performing the dye injection accurately, however, are a very real objection to any accurate dye-dilution method of plasma

volume measurement. Lack of available apparatus prevented the use of more accurate radio-active ion methods of plasma volume determination. Table 14 indicates that, of the two patients, one showed evidence of an increased plasma volume with haemodilution (Case 6), and one (Case 12) of a decreased plasma volume. Neither of these patients received blood transfusion or electrolyte and water infusion.

From a consideration of all these results, the only conclusions which can be reached are:-

1) With any appreciable degree of haemorrhage, where no fluid replacement therapy has been undertaken, the blood loss after operation is replaced by extracellular fluid. This is too well known to need any emphasis.

2) In some cases there is evidence of haemoconcentration following operation. If Wilkinson and his associates are correct, this is a measure of the reduction in plasma volume which they were able to detect. It is possible that, where no fluid replacement therapy is undertaken, the slight tendency to a reduction in plasma volume is masked by the haemodilution which follows simple haemorrhage.

TABLE 15. Plasma Proteins as Grams per 100 ml. Blood.

Patient No.	-2		-1		0		+1		+2		+3	
	Alb.	Glob.	Alb.	Glob.	Alb.	Glob.	Alb.	Glob.	Alb.	Glob.	Alb.	Glob.
27	3.9	3.2							4.7	1.5		
28					4.5	2.1			4.8	2.3		
29			5.0	2.3			4.8	2.3				
30					4.6	2.4					4.6	2.2
31			5.0	2.7					4.2	2.0		

The Plasma Proteins.

Table 15 (opposite) shows the changes to be detected in the plasma albumin and globulin after operation. From this table it can be seen that no regular change was detected either in the absolute amounts of these proteins or in their relative proportion following operation.

Wilkinson and his associates (1951), in 10 cases, noted a decrease in plasma albumin in eight cases, and an increase in plasma globulin in seven after operation. In these cases they had detected a decrease in plasma volume, as has been noted already, and they concluded that the fall in plasma albumin following operation was further evidence of the transudation from the circulation of fluid and the smaller albumin molecule into the damaged tissues. It will be recollected that their cases received blood transfusion to replace blood loss at operation.

The present small series did not receive any fluid replacement at operation. Although the plasma volume was not estimated in this particular group, the results show that no conclusive change in the particular plasma proteins was detected, although, in four out of the five cases there was a reduction in the total quantity of plasma protein. This would be consistent with the haemo-

dilution after haemorrhage which has already received comment. On the other hand, in Wilkinson's series receiving replacement transfusion, only half the cases showed evidence of a decrease in total plasma protein per unit volume of plasma, the other half showing an increase.

The writer believes, therefore, that there is insufficient evidence to suggest an alteration in the relative proportions of the plasma proteins after operation, and that, if no fluid or blood replacement therapy is undertaken, a slight reduction in the total plasma protein concentration can be expected after the haemorrhage of operation. In these stated circumstances, the view that the plasma volume is reduced after operation in association with a transudation of albumin from the vessels, cannot be accepted.

The Extracellular Body Fluid.

As measured by the "thiocyanate space", this volume of water includes the blood plasma. Lands et al. (1940) have shown that, in fact, sodium thiocyanate is distributed through a volume of fluid greater than that contained in the extracellular compartment alone. Since, however, only relative changes in the fluid are of interest

TABLE 16. Extracellular Fluid Space volume in Ml.

Patient No.	Initial	Postoperative	Change
12	16500	16100	-400
13	14800	14550	-250

in this study, the method may be presumed to be relatively accurate in this respect. The method used was that of Gregersen and Stewart (1939), using sodium thiocyanate to determine the 'available' fluid volume. In their similar study, Wilkinson et al. (1951) were unable to detect any constant change in the extracellular fluids after operation in 10 cases. Reference to Table 16 shows that, in the two cases studied here, only a slight decrease was found in the thiocyanate space volume. Considering the inaccuracy of the method, these decreases are not significant.

No conclusions can be drawn from the very few estimations of plasma volume and thiocyanate space recorded in this series. Considered in addition to the results of other observers, however, they tend to demonstrate that, if any changes in extracellular body water do occur following an uncomplicated operation, they are too slight to be regularly detected by the crude methods commonly applied to these studies. Wilkinson and his associates believe from their more extensive work that the diminution in plasma volume detected by them, in association with little change in the total extracellular fluid compartment, indicates that an increase in the extravascular extracellular compartment has occurred, associated with, and possibly due

TABLE 17. Blood Pressure in mms. Mercury.

Patient No.	-2	-1	0	+1	+2	+3	+4	+5
3		140/80		145/80	155/80			
4	135/90	140/90	135/60	140/65				
6	150/85			145/80		145/90	145/85	145/80
8	130/80		108/72	130/70		130/80		
9		120/70		120/50	120/70		120/60	

to, a transudation of plasma from the vessels into the tissue spaces at the site of injury.

Table 17 shows the serial blood pressure estimations performed on some of the patients in this series. These estimations were performed only in those cases in whom postoperative shock of any degree could be definitely excluded. The observations were always made after at least one hour's bed rest, and in the fasting state. The results indicate that no constant change in blood pressure, either systolic or diastolic, could be detected in the postoperative period after the day of operation itself.

The pressure in the circulating blood system is the summation of the factors of the force of the cardiac contraction, the peripheral resistance, and the recoil of the vessel walls (Lovatt Evans, 1936). Within fairly wide limits, the volume of circulating blood does not affect blood pressure changes; adequate peripheral resistance being maintained by the variation in calibre of the vessels. Unless, therefore, some other hypertensive or hypotensive factor be at work, small changes in circulating volume are not likely to be detected by changes in blood pressure.

The Cellular Fluid.

The total body water can be measured by means of 'heavy' water (Smith, 1951). By subtracting the total extracellular body water, an accurate measure of the cellular water compartment can be obtained. This method was not open to the writer. Since no appreciable change can be detected in the extracellular fluid volume, it was believed that changes in body weight following operation might be a direct measure of changes in body water, and therefore of the cellular water content. Allowance would need to be made for loss of body weight during starvation. Wright (1940) states that, in starvation, after a part of the liver glycogen is consumed for energy purposes, the remaining energy requirements are supplied by the destruction of body fat and body protein. The urinary nitrogen excretion can be used as a means of determining the protein consumption, the remaining calories being supplied by fat combustion. He cites a starving man, in the fifth day of fasting as excreting 11.4 grams. of nitrogen in the urine, representing the breakdown of about 71.5 grams. of tissue protein. This would yield roughly 300 calories for energy requirements, the remaining 1,700 calories being supplied by fat. This would represent about 190 grams. fat.

The daily weight loss for the average male during starvation and without water depletion might therefore be about 261 grams. or 9 ounces. If, as has been remarked in Chapter 5, many observers have shown that the nitrogen loss after operation is greater than during starvation, a greater daily weight loss might be expected in the first few days after operation.

Table 18 shows the weight in pounds of patients before and after operation who could reasonably be expected to get out of bed in the early postoperative period. All these patients were weighed on the same machine on each occasion after a twelve-hour fast, except patient No. 24. This man was weighed on both occasions one hour after a similar meal. For all these patients, the day of operation and the subsequent day were complete fasts. On the second postoperative day only small amounts of carbohydrate and protein were consumed, and on the third postoperative and last preoperative days, the diets were deficient in total calory requirements. Cases 8, 9 and 21 demonstrate a loss of weight which corresponds almost exactly to the loss calculated from consumption of body tissues. Cases 2, 20 and 24 underwent a gain in weight during the postoperative phase, and the weight of one patient (Case 5) remained constant.

TABLE 18. Weight in Pounds.

Patient No.	-3	-2	-1	+1	+2	+3	+4	+5	+6	+7
2			151.37	151.75		152.5	152.5	152.5		152
5			132			132				
8	166.5	166.75	166.33			164.33	164.33	163.75		
9	131	131.63	132.25			130.75	130.7		130.13	
20		144.25			145.5					
21		112 -			110.5					
24			138.25						142.37	

The results in these four cases are surprising in view of the expected weight loss. These weight gains must therefore be significant as the measurements were performed with reasonable accuracy, and the patients were undoubtedly starved. Any weight gain over and above calculated losses must therefore be a measure of water retention within the body.

If the fact that no increase in total extracellular fluid volume was detected in this and other series, then any weight increase must be caused by retention of water in the body cells. If there is an increase in extracellular body fluid which has not been detected in this paper, then the weight increase, when it occurs, is partly a measure of this increased extracellular fluid volume. In either case, the weight increase indicates an expansion of the total body water.

The Urine.

Changes in electrolyte content of the urine have already been considered in previous chapters, and changes in 17-ketosteroid concentration in the urine will be considered later. In this chapter, only urine volume studies are presented. In Appendix I the fluid intake and urine output of the nine patients whose electrolyte metabolism has been studied is shown in detail. Table 19 is a composite

TABLE 19.

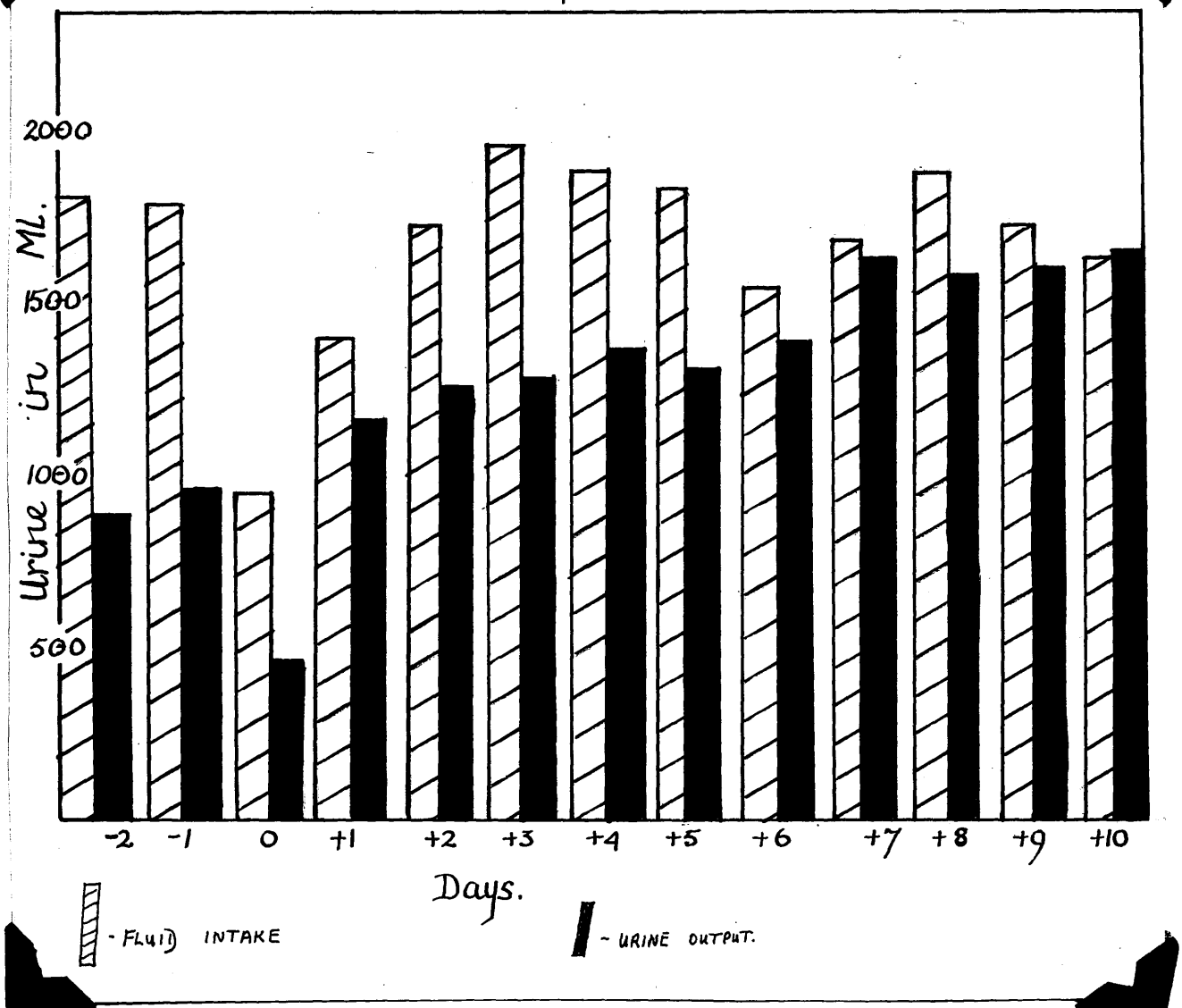

2000
1500
1000
500
Urine in ML.
-2
-1
0
+1
+2
+3
+4
+5
+6
+7
+8
+9
+10
Days.
- FLUID INTAKE
- URINE OUTPUT.

diagram of the average daily fluid intake and urine output before and after operation for the nine patients. Except for the day of operation and the first postoperative day, the average urinary output of these patients appears to be remarkably constant. The fluid intake in the early postoperative period is remarkably little greater than the urine output. As the postoperative period extends, this difference between fluid intake and urine output becomes even less. It appears almost as though the fluid intake requirements decrease, or that there is a relative but not absolute diuresis at the end of the first week. These patients were free to drink as much water or other fluid as they wished - provided that it was measured - and the only stimulus to drinking was their own thirst. No attempts were made to force fluid upon them. In this way it was hoped that the electrolyte-water ratio in the body fluids would exert their own unaided effect. It appears from the table that the patients' thirst was not greatly increased by the operation, and that it diminished as the urine excretion increased. Since it has been shown that sodium and chloride are retained within the body after operation, a sufficient excess of water would also be retained, reducing both the body's salt and water requirements. Any excess water drunk during

this period would therefore be excreted in the urine, accounting for a urine excretion very nearly equal to a water intake, i.e. a relative diuresis. Because the water and salt retained in the body were beyond normal requirements, the increase in urine occasioned by their subsequent excretion did not require an appropriate consumption of an equal volume of water and salt.

Conclusions.

The increase in total body water, associated with a relative water diuresis at the end of the first week after operation, seems to indicate that water is retained in measurable amounts after operation at the same time as the retention of sodium and chloride. Since it has been shown that there is no real reduction in body electrolyte after operation, this feature of retained sodium, chloride and water is not due to a relative deficiency or excess of any one of these factors. It would appear that some factor is exerting its influence to retain these electrolytes and water in the body. Since, also, the renal plasma flow and the glomerular filtration rate are not likely to be influencing this result, it would appear that there is increased renal tubular reabsorption of them. Wilkinson et al. (1951) have suggested that the cause is due rather

to the accumulation of water and electrolyte in the damaged tissues. Such a condition would make no difference to the relative ionic concentration of these substances throughout the plasma and extracellular body fluids. Smith (1951) has pointed out that it used to be believed that the kidney took no notice of indefinite expansion in the extracellular fluid spaces provided that the ionic concentration remained normal. He indicates, however, that recent work has demonstrated that this is not so, and that factors over and above changes in ionic concentration cause the kidney to prevent an indefinite accumulation of isotonic fluids in the tissue spaces. If this be so, then it would appear that a very active influence must increase renal tubular reabsorption of water and electrolyte after operation. Such an influence is exerted by the cortical steroids of the adrenal gland.

CHAPTER 7

SUMMARY OF THE ELECTROLYTE AND BODY WATER CHANGES

In the preceding chapters, some essential changes in the electrolyte and body water pattern have been demonstrated following operation. They are summarised here to crystallise the findings before proceeding to a proof of their origin.

(1). Immediately following operation, there is a considerable reduction in the excretion of sodium and chloride in the urine even in patients without a previously established hypochloraemia or hyponatraemia.

(2). This may be associated with a fall in the serum sodium and plasma chloride, although there is no evidence of undue loss of these ions. This is not an invariable phenomenon, but seems to be evident in many cases where there is no undue disturbance of body electrolyte content by massive haemorrhage or large-scale replacement infusion.

(3). There is some evidence of an increase in the concentration of cellular sodium, and little or no reduction in the whole blood chloride. From this evidence it may be deduced that the apparent decrease in the body fluid sodium and chloride is due, in part, to their transudation into the cells.

(4). Concurrently with all these changes, there is a considerable increase in the urinary potassium excretion, and a slight tendency to a rise in the serum potassium concentration. It is presumed that the source of the potassium is the body cells. Attempts to prove this have not been successful. This phase occurs at a time when the potassium intake is reduced, and is probably distinct from the phase of increased nitrogen metabolism already known to follow operation or injury.

(5). While these electrolyte changes are occurring, there is possibly some evidence of a reduction in plasma volume, no alteration in total extracellular fluid volume, but some adduced evidence of increased extravascular body water. This is based partly on the evidence of a relative reduction in the plasma albumin. As has been indicated, this may be caused by factors other than a seepage of the relatively smaller albumin molecule through the capillary wall at the site of injury. It would appear that the

body weight is frequently increased after operation, indicating a retention of water in the body. Whether this water is held in the extracellular spaces or in the cells is not clear.

(6). After a consideration of all the factors concerned, it appears that these changes in electrolyte and water balance are due to the operation. Since the operations performed are various in magnitude and extent, it would appear that no specific factor inherent in any particular operation can be isolated as the causal circumstance of the changes. The writer believes that no alternative factor remains for consideration apart from the essential trauma or 'stress' entailed in any surgical operation.

(7). From the work of other observers it would appear that the phase of increased retention of sodium, chloride and water after operation, with increased excretion of potassium and nitrogen, is followed by a phase of increased excretion of sodium, chloride and water, and a compensatory retention of potassium and nitrogen. It is worthy of note that the termination of the period of increased nitrogen output appears to occur about the seventh to tenth day, but that the phase of increased potassium excretion terminates some time before this.

(8). It has been suggested that these changes may be due to an accumulation of fluid and electrolyte in the damaged tissues. Evidence against this explanation has been presented.

(9). It has been indicated briefly that an alternative explanation is possible.

PART III

CHAPTER 8

THE SIGNIFICANCE OF THE ELECTROLYTE CHANGES

A vast amount of observation, both clinical and experimental, has been made in the past on the various electrolyte and body water changes following operation. The interest of that work has lain in the various deficiencies of electrolyte, water, and plasma protein which arise following abnormal loss either by shock, by the processes of operation, or as a result of some complicating factor of the disease or operation. This work is not considered in the present investigation because the maintainance of the circulatory economy, the prevention of cellular and extracellular dehydration, the treatment of shock, the maintainance of the intravascular osmotic pressure by plasma proteins, and the prevention of tissue anoxia are all established on a sound basis. The appreciation of the results of the loss of base, water, acid radicles, and plasma protein has led to the formulation of adequate methods of replacement therapy.

The changes described so far in this work have been shown to arise in patients with no pre-existing electrolyte or water deficiency, and are demonstrably different from those encountered in simple starvation. They are, admittedly, of no great magnitude, but may well have serious effects. They seem to be constant, and within the limits of the experiment, appear to be associated with operation. They have not been suspected until recently, have not received proper attention once discovered, and are without adequate explanation, except by analogy only. That they appear to be due to a fundamental alteration in cell metabolism has not been fully appreciated before. The authors to whom reference has been made in the text have each, in some way, drawn attention to one or more of the features described, and have differentiated the changes from the well-recognised deficiency features alluded to above.

It was believed that these changes encountered in the present study were due to the effects of adrenocortical hormone, more especially deoxycorticosterone. Why this should be so will be demonstrated after the effects of the adrenal steroid hormones have been examined in detail. Evidence adduced from electrolyte changes alone, however, is not, in the writer's opinion, sufficient. The control of

electrolyte balance, and the concentration of electrolytes in the tissue fluids is subject to so many factors, unknown and known, such as deficiency, excessive loss, maintainance of acid-base balance, circulatory efficiency, both general and local, and the maintainance of osmotic equilibrium, that such changes prove insufficient evidence of a single effector. The electrolyte changes must therefore be amplified by other evidence of the effective mechanism. Wilkinson et al. (1949) suggested that adrenocortical activity might be the cause of some of the changes in electrolyte pattern which they had demonstrated. In a later paper, however, (1950) they suggested that the results were in accordance with altered capillary permeability at the site of operation trauma. They suggested that the sodium and chloride changes could be ascribed to the accumulation of these substances in damaged tissue as shown by Fox and Baer (1947). They suggested also that the reduction in plasma albumin was due to a similar transference of albumin to the extracellular compartment. To counteract the altered osmotic balance, potassium is envisaged as passing out from the cells to the tissue spaces and is then excreted in the urine. It would seem that, if the body attempted to restore osmotic equilibrium between cells and fluids, a retention of this potassium in the fluids would soon maintain the

osmotic balance, and prevent continued loss of electrolyte. Further, the accumulation of electrolyte as described by Fox and Baer is referable only to anoxic tissue. Wilkinson and his co-workers made no observations on the alterations in cell base content, and failed to follow up their suggestion that increased potassium excretion might be due to adrenocortical activity. Gamble (1942) indicates that potassium loss in dehydration, such as severe diarrhoea in infants, may be taken as an estimation of the loss of cell water on the premise of preservation of the normal potassium and water relationship. The potassium loss after operation as described in this study appears to commence almost immediately after operation, and in patients in whom a relative retention of water and of sodium has been demonstrated. Since dehydration has not, therefore, been produced in these patients, changes in cell base after the operations described here cannot be due to this dehydration effect.

This work has shown clearly that such alterations in cell base substance must also be considered as a cause of the altered electrolyte pattern in the plasma and tissue fluids, and that they are accompanied by widespread changes which cannot be entirely due to the accumulation of electrolytes, albumin, and fluid locally in the damaged tissues. For

these reasons, attempts were made to show further evidence of increased cortical adrenal activity after operation. Before considering these results, the effects of adrenal cortical function itself must be reviewed.

CHAPTER 9

ADRENAL CORTICAL FUNCTION

History.

Following the publication in 1855 by Thomas Addison of his observations on the effect of diseases of the suprarenal glands, some light was cast on their function, and interest aroused in these small organs which could have such extensive control of health and life itself. Brown-Séquard, in 1856, showed that excision of both adrenals in many species of animals rapidly led to death. From these observations it was realised that the adrenal glands were essential to life. It was not until the work of Houssay and Lewis (1923), however, that it became quite clear that it was the adrenal cortex which was the life-preserving factor. Following upon the concept of chemical hormones in other branches of physiological research, many attempts were made to isolate the active principle of the cortex. In 1927, Stewart and Rogoff showed that an aqueous

extract of the cortex prolonged the life of adrenalectomized dogs. An extract such as this was called 'cortin' by Hartman. Swingle and Pfiffner (1930) extracted, by means of lipid solvents, a much more powerful cortical extract which could prolong the life of adrenalectomized animals indefinitely. From that time, the modern work on the hormones of the adrenal cortex may be dated. In 1936, the first crystalline principle, cortisone, was isolated by Kendall, and in 1937, corticosterone by Reichstein. At the present time no less than 28 different crystalline steroids have been isolated, seven of these being active in maintaining the adrenalectomozed animal in health (Young, 1951). Other workers do not consider that progesterone should be included among those steroids essential to life. The amorphous fraction remaining after the extraction of the crystalline steroids maintains this ability to preserve life to a high degree, as well as many of the properties of those steroids often referred to as the mineralosteroids. The total effect of the adrenal cortical hormone or hormones is probably greater than the sum of the effects of the cortical steroids and the amorphous fraction.

The Cortical Steroids and their Function.

Such a vast literature has grown up in recent years on aspects of this subject that only the most important features which affect this work can be considered here. The steroids generally considered essential to life are corticosterone, 17-hydroxycorticosterone, 11-dehydrocorticosterone, 17-hydroxy-11-dehydrocorticosterone, 11-deoxycorticosterone and 17-hydroxy-11-deoxycorticosterone (Best and Taylor, 1950). Besides these compounds with actions specific of the adrenal cortex, steroids with androgenic and with oestrogenic activity are secreted, in part at least, by the adrenal cortex. The androgen substances, without the side-chain at the 17-carbon atom, and therefore the double-bonded C = O linkage (the so-called 17-ketosteroids), are considered in the female to be solely derived from the adrenal cortex, and in the male, partly from this source, and partly from testicular tissue.

Although it is customary to divide the crystalline steroids into certain groups in relation to function, it has become clear that adrenal cortical function is not represented by any one of the groups alone, nor are the steroids in one group totally devoid of the functions of those in another group. For example, Long et al. (1940) and Lewis

et al. (1940) showed that 11-deoxycorticosterone had a slight effect on carbohydrate metabolism. Wells (1940) noted that 17-hydroxy-11-dehydrocorticosterone (cortisone) was less effective than 11-deoxycorticosterone in maintaining life. Ingle and Thorn (1941) demonstrated that, in rats, cortisone, though it did not produce sodium or chloride retention, did cause potassium loss in the urine, similar to the effect of 11-deoxycorticosterone. Further, it is now known that both 17-hydroxycorticosterone and cortisone can correct the electrolyte loss in the adrenalectomized animal (Ingle, 1950).

With this evidence in mind, the usual group classification will be followed here for convenience and simplicity, viz:-

1) Steroids mainly affecting carbohydrate metabolism.
2) Steroids mainly concerned in electrolyte balance.
3) The adrenal sex hormones- androgens and oestrogens.

Steroids Mainly Affecting Carbohydrate Metabolism.

These steroids have an oxygen atom at the 11-carbon position, e.g. cortisone and 11-dehydrocorticosterone. In general, these steroids affect carbohydrate metabolism by opposing the action of insulin. They tend to elevate the fasting blood-sugar in animals and man, increase the rate of

gluconeogenesis, increase deposition of liver glycogen in varying degree, and in some species, reduce the renal threshold for glucose. The effects of these steroids on metabolism is more widespread than this, as they increase protein catabolism and the excretion of urinary nitrogen, and also increase utilisation of fat, as well as rather less marked effects on electrolyte excretion and balance. It has been shown also that it is this group of steroids that tend to produce an eosinopenia, a lymphopenia, and cause involution of lymphatic tissue in certain species of animals. Such other effects as increase in uropepsin excretion in Addison's disease, diminution in hyaluronidase activity, inhibition of fibroplasia, increased electro-encephalographic activity, and a host of other features have been demonstrated in recent years (Best and Taylor, 1950; Carlisle, 1950). The peculiar and beneficial effect of cortisone, as one of this group of compounds, on rheumatoid arthritis as demonstrated by Hench and his co-workers (1949) has marked the commencement of an epoch in medicine. Such various conditions as acute rheumatoid arthritis, disseminated lupus erythematosus, dermatomyositis, and status asthmaticus, have all shown a dramatic response to therapy with these substances or with ACTH (Elkinton et al. 1949).

The "Mineralosteroids".

Substances such as 11-deoxycorticosterone exert their effect mainly on electrolyte balance. The striking features resulting from the administration of 11-deoxycorticosterone to adrenalectomized animals (Ingle and Thorn, 1941) are:-

1) Gain in body weight - by retention of water.

2) Decrease in excretion of sodium and chloride in the urine.

3) Increased urinary potassium excretion.

4) Maintenance of life.

Ferrebee and his co-workers (1941) have shown that continuous administration of 11-deoxycorticosterone to normal dogs may lead to muscular paralysis. They have shown that the attacks of paralysis are due to partial replacement of muscle potassium by sodium, and that the paralysis could be prevented by the administration of potassium chloride. Unlike the 11-oxysteroids, this group have little effect in increasing muscle work and liver glycogen (Young, 1951), nor do they increase urinary nitrogen excretion or cause glycosuria (Ingle and Thorn, 1941). The effects of deoxycorticosterone on electrolyte metabolism are so strikingly similar to the electrolyte changes described in Part I of this investigation that it is tempting so to ascribe them.

Analogy by itself is not enough. More direct proof of cortical function is required.

Androgens and Oestrogens.

A part of the androgen secretion in the male and all in the female is derived from the adrenal cortex, and conversely all in the male and a part in the female of the normal oestrogen secretion is derived from the adrenal cortex. The effects of these substances when being secreted in excess are noted only as heterosexual changes; these substances being responsible for the secondary sexual characteristics. In women, various manifestations of virilism may be observed following increased androgen secretion including hirsutism, amenorrhoea, hypertrophy of the clitoris, acne, baldness, masculinisation of the voice, and often increased excretion of urinary 17-ketosteroid compounds (Walters, 1952). Increased oestrogen production may lead in men to impotence and gynaecomastia, and in women to excessive vaginal bleeding and sexual precocity.

The effects of these compounds are so closely related to the functions of the sex glands themselves that it may be difficult to dissociate the function of the adrenal cortex in these respects from the appropriate sex organ. For this reason, adrenal cortical function can rarely be

estimated from a study of sexual changes except in cases of gross hyper- or hypo-function associated with tumour, hyperplasia, or destruction of the glands by disease. The excretion of the presumed end-products of these substances, the 17-ketosteroids and urinary oestrogens and pregnandiol may be taken as some measure of their formation by the adrenal cortex provided testicular and ovarian abnormalities and pregnancy can be excluded (Walters, 1952).

The regulation of the secretion of the cortical steroids is clearly under the control of the nervous system. Harris (1948) believes that a stimulus from the higher centres affects the hypothalamic region which in turn leads to the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary lobe. ACTH, carried in the blood to the adrenal cortex, stimulates the production and secretion of the various steroids. Vogt (1943, 1944) has shown that the adrenal cortex, under stimulation, can deliver very large amounts of hormones into the blood. Conn and his fellow-workers (1950) believe that blood cholesterol may be a source for the synthesis of cortical hormones after the cortex has been depleted of its cholesterol store during prolonged ACTH stimulation. In this way, the natural production of the adrenal hormone or hormones appears to be

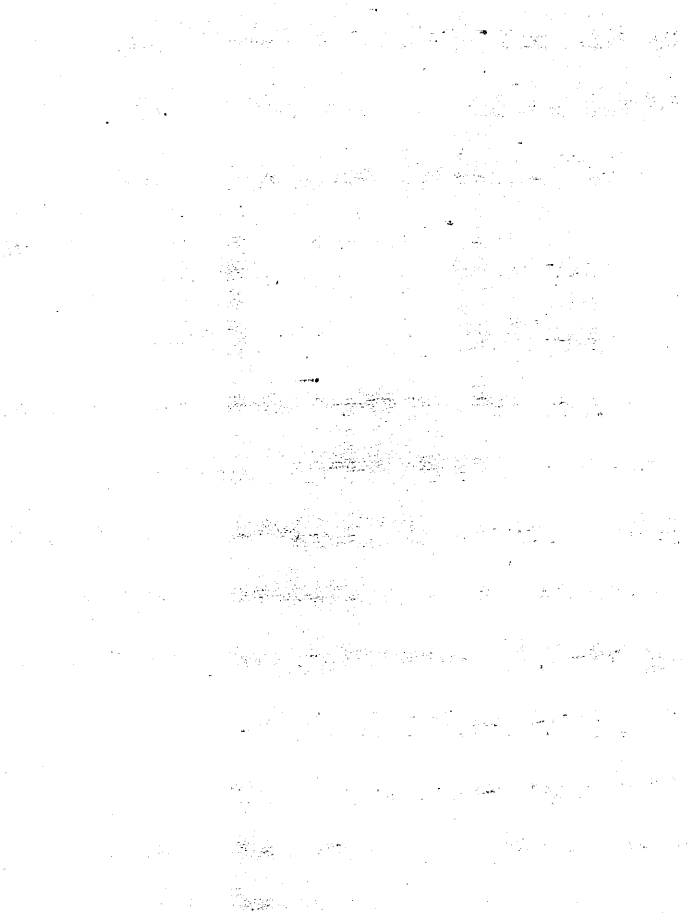
TABLE 20

Effects of ACTH	Effects of Operation
Na & Cl_2 retention	+
Increased K excretion	+
Retention of water	+
Depletion of cell K	+
Increase in cell Na	+
Impairment of CHO tolerance	+
Negative nitrogen balance	+
Diminution in eosins	+
Lymphopenia	Not estimated
Reduced plasma cholesterol	+
Increased urinary corticosteroids	Not estimated
Increased urinary 17-ketosteroids	+
No increase in oestrogens and pregnandiol	Not estimated

under the control of the anterior pituitary gland, and perhaps the closest approximation to the natural production and effects of adrenal cortical hormone in its varying forms, can best be studied experimentally by injecting ACTH. Table 20 opposite has summarised the results of some investigators in a large number of cases after injecting ACTH in man in therapeutic doses (Forsham et al. 1948; Mason et al. 1948; Elkinton et al. 1949). The effects referable to the three different groups of adrenal corticoids have been separated in the table as far as possible by the present writer in a purely artificial way.

The electrolyte changes demonstrated in Part I of this work bear a close similarity to the effects of the mineralosteroids detailed in this chapter. For convenience, the results are compared in Table 20. Because of this similarity, confirmatory evidence of the secretion of other groups of corticoids was sought under the same conditions and at the same time, in the patients considered in Part I. As an expression of 11-oxysteroid activity, circulating eosinophil counts and fasting blood-sugar estimations were performed. As an expression of androgenic activity, 17-ketosteroid excretion was measured. The relative values of these particular tests are considered in each section,

but they were chosen not necessarily as the best indicators of cortical function, but because they were the only suitable tests performed routinely in the particular hospital in which the investigation was carried out.



CHAPTER 10

URINARY 17-KETOSTEROID EXCRETION

The average values in health for the excretion of 17-ketosteroids in adults each 24 hours was found by Kenigsberg and his colleagues (1949) to be:-

Males	13-16 years	- 9.4 mgm.
	17-34 "	- 18.0 mgm.
	35-49 "	- 15.0 mgm.
	50-75 "	- 9.0 mgm.
Females	all adult ages	- 9.3 mgms.

Landan et al. (1948) showed that starvation by itself decreases the total 17-ketosteroid excretion. The whole 17-ketosteroid excretion in women, and a part in men, is derived from cortical androgens (Forbes et al. 1947). The remainder in men, about 4-6 mgms. per day, is derived from testicular tissue. Fraser et al. (1941) and Pincus (1947) consider that the excretion of the ketosteroids is, to some extent, a direct index of adrenal hormone secretion. Others do not accept it as a measure of adrenal cortical

function. For example, Long (1947) has shown that the 11-oxysteroid content of the urine may be rising while the 17-ketosteroid content is falling during stress. Hanlon et al. (1950) also consider that 17-ketosteroids are not such a good index of adrenocortical activity as are corticosteroids. This being accepted, it is noteworthy that the ketosteroid excretion in the urine does frequently parallel that of the corticosteroids under a variety of circumstances. Hanlon et al. themselves observed that both 17-ketosteroids and corticosteroids were reduced in the urine in leukaemic patients. All the writers mentioned below consider that increased 17-ketosteroid excretion is some evidence of adrenocortical activity. It was early noticed (Fraser et al. 1941) that there was a diminished excretion of 17-ketosteroids in the urine following trauma and surgical procedures. However, the same workers (Forbes et al. 1947), demonstrated later that they had missed an early rise in 17-ketosteroid excretion in the first 24 hours after operation. Following this, ketosteroid excretion fell to its lowest point about the 4-5th day, and by the tenth day regained normal levels. Control patients showed that starvation alone did not cause this rise and then fall in excretion. A sharp rise in the excretion of 17-ketosteroids followed by a fall to below normal levels in 30 patients suffering from haemorrhage,

fracture, burns, infection, and operation was also shown by Stevenson and others (1944). A similarly elevated 17-ketosteroid excretion was noted by Freeman et al. (1944). after severe muscular fatigue. Talbot and his workers (1945) showed evidence of increased urinary excretion of 11-oxysteroid-like substances in active Cushing's syndrome, in adrenal cortical virilism, after burns, and in post-operative patients. Cope and his colleagues (1951) have recently observed increased excretion of 11-oxysteroids in acute medical conditions such as diabetic ketosis, congestive cardiac failure, bronchopneumonia, pneumococcal meningitis, coronary infarction, and status asthmaticus. Forsham et al. (1948) have demonstrated an increase of both 17-ketosteroids and 11-oxysteroids in the urine after ACTH therapy. This has been confirmed during the study of a large series of cases on such therapy (Sprague et al. 1950). Following the administration of ACTH, Sayers et al. (1949) noted that the peak rate of 17-ketosteroid excretion appears to occur rather later than that of the neutral reducing steroids. They found the maximum excretion rate following injection to occur about the sixth hour, and excretion to be diminished markedly at the end of twelve hours after a single injection.

TABLE 21. 17-Ketosteroids in mgms. per Diem.

Patient No.	-3	-2	-1	0	+1	+2	+3	+4	+5	+6	+7
1			2.63			4.05		3.74		1.85	
2			11.12		5.65		5.99			6.78	
3			10.5			17.48			9.94		5.63
4		9.05				14.90		7.00	6.23		
5		8.4				10.55		10.01		12.70	
6			7.75			17.65		16.60		9.25	
7		8.62				12.97		6.77		7.40	
8		9.78					12.2		7.8		
9	24.9					14.4		23.0			

From the evidence of this extensive work detailed above, it appears that 17-ketosteroid excretion may be considered as a direct measure of some adrenocortical function. Though by no means the best evidence available, that it has been used as a measure of adrenocortical response to the trauma of disease or injury, has also been made clear.

The measurement of 17-ketosteroid excretion as evidence of adrenocortical activity was used in the present study only as an adjuvant to the other evidence obtained. This was done advisedly because of the doubts cast by some workers on its value as the only determinant of cortical function. For the reason stated in the "Methods", the 17-ketosteroids, though less valuable as an index of such function in males, was determined only in males because they alone were included in the present series. Ketosteroid excretion determined in two normal women before and after operation showed a rising excretion in the first 24-hour postoperative period, but are not included in the series, because no other estimations were performed upon these patients.

Table 21 shows the excretion rate of 17-ketosteroids per day in the present series. In all but two cases, there is a considerable rise in 17-ketosteroid excretion, following operation. It should be observed that the rapid subsequent

fall, as noted by Forbes et al. (1947), is not so marked in this study, but there is evidence of low excretion on the 4th-6th days in Cases 1, 3, 4, 7 and 8. Cases 2 & 9 do not show the rapid rise in ketosteroid excretion. In Case 2, a fall is noted, followed by a continuous low excretion. Case 9, excreting ketosteroid at a level at the very upper limit of normal, shows a marked fall after operation followed by just as rapid a rise again. So far as could be ascertained, this patient had no disease condition to account for his rather high rate of excretion of ketosteroids. This rate must be considered as normal for him.

From the evidence of these results it can be claimed that seven of the nine patients excreted increased quantities of 17-ketosteroids in the early postoperative phase, that this is evidence of increased androgenic activity, and that the adrenal cortex might well have played a part in this increased activity. Of the two patients who failed to show this response, one (Case 9) has already been shown to respond in a fashion different from the others in some respects.

CHAPTER 11

EVIDENCE OF INCREASED 11-OXYSTEROID FUNCTION

The Eosinophils.

Cortisone has the ability to reduce the number of eosinophils in the circulating blood in man (Carlisle, 1950). In a study of the results of treatment with ACTH, Forsham et al. (1948) were able to demonstrate a reduction in the circulating eosinophils. A reduction in circulating eosinophils has been demonstrated also in some species of animals following cortisone injection. Cope et al. (1951) point out that it is specifically cortisone and 17-hydroxy-corticosterone which exert this influence in the adrenal-ectomized animal. ACTH apparently exerts its influence by the liberation of these steroids. Unfortunately, other factors may interfere with the production of an eosinopenia by cortical steroids. Godlowski (1951) has demonstrated that heparin in large doses may produce an eosinophilia in spite of injected cortisone or ACTH.

The reliability of an eosinopenia as the only evidence of adrenal steroid function therefore remains in question.

It is generally believed that Lams (1907) first noticed the disappearance of eosinophils from the circulation in severe illness, and their return during convalescence. Schreiner and Pucsko (1925) noted that the disappearance of eosinophils from the blood following burns was a grave prognostic sign. They noticed also that figures rose to normal levels again during later stages of recovery.

Roche and his co-workers (1950) state that the fall in the eosinophil counts after the injection of 25 mgm. ACTH is an index of function of the adrenal cortex to excrete the 11-oxy and 17-oxysteroids. They noticed that, in the presence of normal adrenal cortical activity, there is an almost complete disappearance of the circulating eosinophils during the first 24-48 hours after a major operation. There is usually a sharp rise toward normal again during the 2nd-4th day. The only case in their series which did not respond by eosinopenia after operation proved to have bilateral adrenal disease, death ensuing in the postoperative period. Crassweller and his colleagues (1950) have also noticed a reduction of circulating eosinophils in severe burns in children. In diabetic acidosis (McArthur et al. 1949), a fall in the eosinophils has been noted

along with increased urinary corticosteroid excretion. Electrically induced convulsions as a method of treatment of psychotic patients has also been shown to cause an eosinopenia (Altshule, 1949). Renold et al. (1951) have demonstrated evidence of a great reduction in circulating eosinophils following very severe exercise and nervous strain.

The "dry" method of counting leucocytes has been found much too inaccurate in the estimation of eosinophil response, and consequently all modern work tends to be done with cells in an aqueous suspension. Dunger's method, or some modification of it, where acetone or other solution is used to disrupt the erythrocytes, may also lyse the leucocytes (Randolph, 1944). For this reason, Randolph's method, or some modification, is now used where estimation of adrenocortical function is being carried out. The enumeration of eosinophils by this method is considered both accurate and easy. Before commencing the present investigation, the writer made an extensive series of eosinophil counts before and after operation to familiarise himself with the method. It was, in his opinion, neither reliable nor easy. The records which are shown in this section of the work were performed, accordingly, by competent pathologists.

The so-called normal level of eosinophil cells in the blood has been reckoned in the past as varying between the limits 0-400 per cu.mm. Recent knowledge has helped to show that, though the individuals were "normal" in the sense of having no evident disease, various factors are at work which vary the eosinophil count from hour to hour in the individual's life. Rud (1947), who has done extensive work on the study of eosinophils in health and disease, has shown that wide variations take place in a single person during the course of a day. His studies indicate that the eosinophil count tends to mount during the day to a maximum in the evening, and then to decline again. This is not accepted by some (Smart, 1950). Rud also believes that digestion does not influence the eosinophil levels as was generally accepted. He considers that counts from 40 to 228 per cu.mm. in the same person should be considered as within a normal range in a day, and a reduction of less than 66 per cent. within this range is not significant. From this work it becomes fairly evident that only very large changes in the eosinophil count can be of any value as evidence of adrenocortical activity. Swanson et al. (1952) also stress the wide variation in the eosinophil count in health. They show that meals do not interfere with the counts, but that the counts should be performed at the same

TABLE 22. Eosinophil Counts per Cu.mm.

Patient No.	-3	-2	-1	0	1	2	3	4	5	6	7	8
1			82			62		87		45		
2			156				75	180		116		
3			34			10			55		260	
4		216					74			344		76
5		350				169		156		231		
6			40			50		160		25		
7			86					64				
8	221					254		456				
9	54					294		425				

time each day. They demonstrate that there is a greater range in variation of normal counts in one individual during the forenoon than the afternoon, and suggest the latter part of the day is most suitable if reduction in counts has to be determined. The writer, from his own experience, has little faith in the accuracy of eosinophil counting.

Table 22 (opposite) shows the results of eosinophil counts on the patients of this series, and the influence of operation. Six patients show a reduction in the first postoperative count, but only Cases 3, 4 and 5 show anything like a two-thirds reduction. The postoperative rise after an initial fall as observed by Roche is present in Cases 2, 3, 4, 5 and 6. It will be recollected that all these counts were performed on patients who had had a 12-hour fast, and at about the same time in the morning. It is interesting to observe that the pre- and postoperative results in Case 9 lie almost outside Rud's "normal" range for the individual in one day. Once again, Case 9 shows a response which differs from the majority.

Carbohydrate Metabolism and the Adrenal Cortex.

The knowledge of the metabolism of glucose by the body has expanded greatly in recent years. The question

of the ultimate utilisation of glucose by its conversion to glucose-6-phosphate, to carbon dioxide and water, or to fatty acid cannot be considered here. Certain endocrine factors which influence the control of blood sugar only can be examined briefly. Not all blood sugar stabilising factors are endocrine. The intestinal mucosa has the ability to absorb carbohydrate at varying rates, and the liver and skeletal muscle are extremely important factors in the maintenance of the blood sugar level.

Long, in his Banting Memorial Lecture (1951), has pointed out that the central nervous system depends entirely on glucose for its metabolism and function. The maintenance of an adequate minimal blood sugar level is therefore vital for the continued survival of the individual. This adequate minimal blood sugar level depends on the adrenal cortex and on its stimulation by the anterior pituitary. Hypoglycaemia promotes a rapid release of adrenaline, which produces an immediate release of glucose from liver and muscle glycogen. While this immediate response is taking place, ACTH secretion is increased by the adrenaline, resulting in the release of cortical hormone and the steroids affecting carbohydrate metabolism. In this way a slow and sustained gluconeogenesis takes place, maintaining a raised blood-sugar level.

TABLE 23. Blood Sugar as Milligrams Glucose per 100 ml. Blood.

Patient No.	-3	-2	-1	0	1	2	3	4	5	6	7	8
1			70			97		80		75		
2			70			73		72		59		
3			86			150			79		60	
4		70					67			68		67
5		64				57		67		65		
6			73			84		88		82		
7			58				83				77	

Elaborate studies upon carbohydrate metabolism could not be made, but the fasting blood-sugar was determined in seven of the nine patients (Table 23). It was not expected that such a simple and crude measure would detect any changes in carbohydrate metabolism. However, as the results show, a quite surprising rise in the blood-sugar was observed in four cases, and no change in three. No glycosuria was detected in any of these patients at any time during the investigation. Patients 1, 3 and 4 received intravenous 6 per cent. glucose on the day of operation to the extent of 560 ml., 280 ml., and 1,680 ml. respectively. As the small infusions received by patients 1 and 3 ceased more than 12 hours before the withdrawal of blood, it is hard to believe that 30 and 15 grams. glucose could have any effect on the result in otherwise fasting patients. The much larger infusions received by patient 4 ceased a whole day before the first postoperative blood sugar estimation. It will be observed that Case 6, who showed no evidence of increased adrenal cortical function as estimated by reduction in the eosinophil count shows a definite increase in blood-sugar. Conversely, Cases 2, 4 and 5, who showed little evidence of altered carbohydrate metabolism, showed increased adrenal cortical function as evidenced by reduced eosinophil levels following operation.

It is believed that these results indicate some evidence of a hyperglycaemic factor at work a day or more after operation. It was hoped that it might be possible to perform insulin-tolerance tests as a further study of altered carbohydrate metabolism. However, if did not prove possible to undertake these studies.

Annersten (1949), in measuring the postoperative rise in blood-adrenaline concentration, has observed an immediate postoperative rise in blood sugar at the same time. In an earlier paper (Annersten and Norinder, 1946) a raised blood sugar was also observed on the first and second postoperative days, following major surgery. Lambret and Driessens (1937) and Habelmann (1941) quoted by Annersten and Norinder have all observed this early postpperative rise in blood sugar. In view of the observations of Annersten (1949) and of Cannon (1929) this early hyperglycaemia is undoubtedly due to the liberation of excess adrenaline. The hyperglycaemia of the first and second postoperative day, as observed by Annersten and Norinder in a very large series of cases, has received no comment by them. In his paper in 1949, however, Annersten has shown that the concentration of blood adrenaline is falling in the first and second postoperative days and that, therefore, the

direct influence of adrenaline must be diminishing. If this be the case, it seems highly probable that the hyperglycaemia noted by these workers at this time, and observed again in the present series may well be due to increased corticosteroid function. Menkin in 1943 showed that trauma, as induced by turpentine in dogs, caused an evanescent rise in blood sugar concentration. In depancreatised dogs, on the other hand, the rise in blood sugar proved to be sustained for a greater period of time. Menkin believed this to be evidence of the new production of sugar at the site of injury, but it rather appears as if the gluconeogenesis was a generalised effect, which, in the normal dogs was soon counter-balanced by increased insulin liberation, but in the depancreatised dogs, persisted as a hyperglycaemia.

TABLE 24. Patient 34

	Preop.	Operative	+ 1	+ 5	+ 11
Blood Pressure	130/85	130/85		120/65	110/65
Serum Na.	339		322	311	341
Serum K.	16.3		23.7	22.8	24.8
Plasma Cl_2	548		481		512
Urine Cl_2	9 G.		1 G.	1 G.	5 G.
17-ketos.	9 mgms. /diem				
Corticosteroids	0.9 mgm. /diem				
Cholesterol	125		90		125
Total Serum Proteins	7.75		5.65		6.95

CHAPTER 12

A CASE OF ADRENAL CORTICAL ADENOMA

The findings in a case of adrenal cortical adenoma are included here because it was thought that they might prove instructive. In fact, however, they are difficult to interpret, and their value is doubtful.

Adequate details of the case are presented in Appendix I, Case 34. Briefly, this patient, an active muscular girl of 14, had developed hirsutes and acne. The radiographic appearances of her skeleton were typical of a girl five years older. A tumour of the right adrenal cortex was diagnosed and confirmed by perirenal air insufflation. A tumour as large as an orange was resected through the chest.

The results of interest in this study are tabulated in Table 24 (opposite). A preoperative study of carbohydrate metabolism demonstrated normal glucose and insulin tolerance tests. Before operation, the eosinophil response to ACTH by the method of Roche and his associates

demonstrated a 50 per cent. reduction at the fourth hour. This is the minimal decrease accepted by Roche as evidence of adrenocortical activity. Such evidence would suggest that the carbohydrate-active steroids were not being secreted in excess. However, the urinary corticosteroid excretion before operation was undoubtedly increased. The preoperative 17-ketosteroid excretion was within normal limits, but, as Pincus (1943) has indicated, this is not always increased in cortical tumour. The preoperative blood pressure was undoubtedly elevated for a girl of her age, and did decrease following the resection of the adenoma. From all this evidence it would appear that the main increase in adrenocortical function was due to the masculinising effect, but there was also some evidence of increased cortical function in other respects.

A study of the pre- and postoperative electrolyte concentrations demonstrates the previously noted fall in serum sodium and plasma chloride and a rise in serum potassium. The diminution in urinary chloride is also observed. The total serum protein and the serum cholesterol concentration fell in the first postoperative day and rose again toward normal by the 11th postoperative day.

In respect of electrolyte disturbance, this patient therefore reacted in a way similar to the other patients in

this study. The operation was undoubtedly more severe, and postoperative blood and saline infusion was carried out on a scale not observed in the other patients. It had been hoped that this patient might help to elucidate the electrolyte changes which are a part of this present work. If these changes are indeed due to, rather than associated with, enhanced adrenocortical activity, then this patient surely shows similar evidence of this activity. With reference to parathyroid activity, it is not unusual to encounter diminished secretion and hypofunction after removal of one active parathyroid adenoma. To what extent this parathyroid tetany is due to an atrophy of the remaining glands is not known. If the case of simple adrenocortical adenoma be analogous, its removal should precipitate an acute cortical insufficiency. No evidence of clinical adrenocortical insufficiency was observed in this case, and no special measures were undertaken to prevent its occurrence. Walters (1952) has recently pointed out that very active measures are usually required to prevent cortical insufficiency following the resection of a unilateral cortical tumour.

How far it is correct to assume that, because no such clinical evidence of insufficiency was detected, the

function of the remaining adrenal cortex was at least adequate, is difficult to decide. Unfortunately, the opportunity to have postoperative urinary 17-ketosteroid and corticosteroid excretions measured, was missed. The writer believes, however, that it is extremely significant that the serum cholesterol concentration was considerably reduced on the first postoperative day. If the work of Conn and his associates (1950), previously alluded to, is correct, then the circulating cholesterol is a source of supply for the synthesis of cortical hormones when the cortex has been depleted of its own cholesterol store. This could only happen in the presence of an extremely active adrenal cortex. The suggestion and findings of Conn receive support from the fact that there is a distinct reduction in plasma free cholesterol after the injection of ACTH (Mason et al. 1948). It is therefore suggested in this case that the contralateral adrenal cortex was not inactive. Where a cortical neoplasm is suspected, bilateral cortical hyperplasia is sometimes found to account for the symptoms. The writer believes that, though a true adenoma appears to have been present in this case, the opposite adrenal cortex may have been hypertrophied and active. This is supported by the fact that cortical insufficiency did not occur after operation, that the serum cholesterol

was reduced, and that electrolyte changes were observed similar to those already noted in this work and associated with increased cortical activity.

PART III

CHAPTER 13

CONCLUSIONS

A review of the results of this investigation indicates that electrolyte and body water changes have been observed in the patients studied, and these in general, are associated with increased 17-ketosteroid excretion, reduction in the eosinophil count, and some alteration in the balance of carbohydrate metabolism. There is no evidence that these alterations are due to any other factor but the procedures of operation. Starvation by itself does not produce the changes discovered. Bed-rest, by itself, does not alter the preoperative findings. The operations were diverse and of varying magnitude, but neither of these features influenced the result. Only the incident of operation, with its attendant circumstances, can be cited as the stimulus precipitating the changes.

As has been shown in Part II of this study, the action of the cortical steroids, more especially the

11-deoxysteroids and the amorphous fraction, can be summed up as causing a retention of sodium, chloride and water in the body, associated with a gain in body weight and an increased excretion of potassium in the urine. It has also been shown that prolonged DOCA administration reduces the plasma concentrations of sodium and of chloride, as well as reducing their excretion in the urine (Selye, 1950). It will be recollected that, in Part I, similar changes of retention of sodium, chloride and water have been detected in the body following operation, associated with a rather less well-marked reduction in the plasma chloride and sodium. Increased potassium excretion in the urine was demonstrated as occurring at the same time as the other electrolyte changes. It was also suggested that the water was retained not in the circulation, but either in the extracellular spaces or in the tissue cells.

The features of altered electrolyte and water balances are consistent with the changes induced by those adrenal cortical steroids influencing mineral metabolism. Some of the changes may be due to the accumulation of water and electrolytes within the injured tissues, but evidence has been presented of altered cell-membrane permeability in uninjured tissue, and of the excretion of potassium in excess, which cannot be accounted for in this way. Some

of these electrolyte and body water changes have been demonstrated following operation and injury by other writers. They have not been proved to be due to adrenocortical activity.

The features of reduced eosinophil counts and altered carbohydrate metabolism, along with the phase of nitrogen catabolism demonstrated by previous workers following injury, burns, and operation, are consistent only with the secretion of the 11-oxy and 17- oxysteroids of the adrenal cortex. This has been noted by earlier investigators.

The increased excretion of 17-ketosteroids in the urine is consistent with the increased formation of androgens by the adrenal cortex. This, considered with the evidence of increased corticosteroid excretion observed by others, may also be evidence of active adrenocortical function in general.

It is believed by the writer that increased activity of the adrenal cortex following operation has been clearly demonstrated for the three great groups of adrenal steroids. In the light of the evidence of other writers, and as a result of the hypothesis of Hans Selye, it seems established that a variety of injuries and "stresses" may cause such results in the presence of functioning

TABLE 25.

Case 9	Initial	Postoperative
Urin. Chlor.	Concen. - High Total - High	→ Falling → Falling
Plasma Chlor.	Normal	→ Falling
Urin. Na.	Concen. - Normal Total - Normal	→ Slight fall → Slight fall
Serum Na.	Low	→ Rising
Urin. K.	Concen. - High Total - High	→ Slight rise → Slight fall
Serum K.	Low	→ Rising
17-ketos.	Very High	→ Fall, then rise
Eosins	Low	→ Rising to high level

adrenal cortical tissue. It has been known for a long time that nervous "stress", i.e. fear, worry, apprehension, may cause an increased liberation of adrenaline from the adrenal cortex (Cannon, 1929). This, in turn, stimulates an increase in ACTH formation, which increases adrenocortical hormone liberation (Harris, 1948). The writer believes that some such mechanism is responsible for the apparently anomalous behaviour of Case 9 throughout the investigation.

A Consideration of Patient 9.

A summary of all the results previously recorded for this patient is shown opposite (Table 25). In view particularly of the high preoperative 17-ketosteroid excretion, the low eosinophil count, and the high urinary potassium excretion, it appears as if a considerable preoperative adrenocortical activity is evident. On the chart opposite, it is rather as if the stimulus to function had been shifted to the left, preceding the preoperative findings, and that the preoperative results have corresponded to the first postoperative results in the other patients. This would also account for the rise in the postoperative serum sodium in spite of a relatively large sodium excretion. As no exogenous sodium had been supplied at this time, this

might be a revelation of the sodium 'hidden' in the cells at an earlier stage.

This patient, a young man of 21, an active healthy individual, though not an unduly nervous person, did appear to be apprehensive of his approaching operation. He had been waiting some time for admission to hospital, but this was a factor common to almost all the patients. It is fully appreciated that there is no real evidence to support this rationalisation. No other explanation of the apparently increased preoperative adrenocortical function can be offered, in view of this man's behaviour at variance with the other cases in the series.

CHAPTER 14

THE SIGNIFICANCE OF THE CONCLUSIONS

If the findings demonstrated in this work are accepted, a number of significant deductions may be derived from the conclusions. Provided adrenal cortical function be normal, the response of an individual to stress factors entails an apparent upset in electrolyte metabolism. The features of this which have been encountered by the writer are considered below.

1). Urinary Sodium and Chloride in Postoperative Electrolyte Management.

Following an injury or an operation there is a retention of sodium, chloride and water in the body over and above calculated requirements. For this reason, estimation of the postoperative urinary chloride levels as a means of controlling saline therapy in the first week after operation is valueless, as Wilkinson et al. (1949) suggested, and as Marriot (1951) has recently admitted.

The writer has not used this method by itself for controlling electrolyte therapy during the past three years. An inference from the present work is that, if preoperative stress be great enough, the retention of sodium and of chloride may be present before operation. This may lead to fallacious readings and dangerous results if preoperative saline therapy has been controlled by urinary chloride excretion. The writer has seen evidence of this in his experience. Further, it is believed that the all too common postoperative saline overload, with resulting pulmonary oedema frequently arises from therapy based on the concentrations of urinary chloride during this period. The writer has seen this occur frequently elsewhere and has noted that, though the excretion of chloride in the urine is reduced right up to the onset of pulmonary oedema, the very next urine passed frequently has a high chloride content. By paying attention to these facts and to others detailed below, he has not observed a single case of postoperative pulmonary oedema due to salt and water overload during his supervision of electrolyte and water balance in the past three years.

2). Serum Sodium and Plasma Chloride in Postoperative Electrolyte Management.

The reduction in the postoperative serum sodium and plasma chloride, though not so marked as the diminished urinary chloride, may also lead to salt and water overload if these results are used to control postoperative therapy. As has been demonstrated, the sodium ions are not really lost to the body, but are 'hidden' in the cells, from which they are slowly released. Some such similar mechanism appears to exist controlling chloride ions. The writer invariably considers a daily plasma chloride reading as necessary as a urinary chloride reading, but aims at maintaining the plasma chloride level no higher than 550 mgm. per cent. in the presence of adequate hydration. It is safe to allow a higher plasma chloride value if there is a pure water deficiency present. He now believes that a whole blood chloride estimation is a safer index of body chloride content for the reasons evident in the present work. The ideal control is, of course, a serum and whole blood sodium index as obtained by flame-photometry. The real problem of the "water-binding" capacity of sodium can then be clearly estimated.

What has been said about preoperative stress in paragraph 1 above is probably also valid as regards pre-

operative sodium and chloride estimations of the plasma in the presence of stress.

3). Postoperative Potassium Depletion.

The importance of potassium in the serum and extracellular fluids has been well recognised ever since the work of Ringer (1883). In recent years, great interest has been focussed on the loss of potassium in various acute medical and surgical conditions. These must be considered briefly in view of the results of the present investigation.

In 1944, Brown et al., described low levels of serum potassium in chronic nephritis, associated with muscular weakness and paralysis. In 1946, Holler drew attention to a similar low potassium level during the treatment of diabetic coma. It is, however, largely due to the work of Darrow and his associates that clinical potassium deficiency has become widely recognised (Govan and Darrow, 1946; Darrow, 1948; Darrow et al. 1949; Darrow and Pratt, 1950). As shown by these and other workers, potassium can be lost to the body in gastro-intestinal disorders such as diarrhoea (in children), sprue, intestinal fistulae, prolonged vomiting, and on certain types of diet, such as the Borst diet (Kolff, 1950). Tarail and Elkinton (1949) have demonstrated that potassium,

when administered to patients with gastro-intestinal disorders and potassium deficiency, is retained in significant amounts. Such retention, they believe, indicates cellular potassium depletion, and is frequently, but not always associated with a low potassium concentration in the serum. They observed further that the kidney in both normal and potassium depleted patients, under conditions of maximal need to conserve the ion, has a limited minimal excretion of potassium, below which minimal level it does not fall. This continued potassium excretion, even in the presence of cellular potassium deficiency, they believe to be an important factor in producing further depletion.

The Recognition of Potassium Deficiency.

Our means of recognising potassium depletion in routine clinical practice are by biochemical estimation of the serum potassium, or by direct clinical evidence. The relationship of the serum potassium concentration to cellular potassium content in any given condition appears to be affected by a variety of factors. Folk et al. (1948) have shown that, under normal conditions, the serum potassium concentration accurately reflects the extracellular fluid potassium content. Talbott (1941) has shown that normal serum concentrations of potassium may be present

when there is evidence of cellular potassium depletion. Danowski et al. (1949) have found, on the other hand, that a hypopotassaemia may coexist with an apparently normal cellular potassium content. Tarail and Elkinton (1949) have also shown that the serum potassium level is not necessarily an index of cellular potassium deficiency, the latter being encountered in the presence of a normal serum level. The influence of the kidney on potassium excretion will be considered in Part IV of this work, but it becomes obvious at this stage that the increased renal excretion of potassium due to adrenocortical activity following operation can greatly augment the factors tending to cause potassium depletion. The writer believes that some of the apparently anomalous findings in the relationship of cellular to serum potassium may be explained in the following way. In the presence of prolonged potassium depletion, the ratio of cellular to extracellular potassium becomes relatively constant again, and the serum potassium content may be taken as a relatively accurate index of cellular potassium content. In the early stages of depletion, and where there is increased adrenocortical activity, cellular potassium depletion may be present while the serum concentration is near-normal due to the lag in excretion of the

endogenous potassium by the kidney in the first three days. In the writer's opinion, two important features emerge from this:-

A). If adrenocortical function is normal, there is evidence of a high potassium excretion in the urine in the postoperative period. This will magnify any other source of potassium loss which may coexist, and may precipitate overt potassium depletion symptoms.

B). In the early postoperative period, it is dangerous to control potassium therapy by serum potassium readings. Cellular potassium depletion may not be suspected because of the normal or even raised serum potassium concentration.

This being so, the clinical features of potassium depletion must be examined briefly. Darrow and Pratt (1950) summarise the symptoms and signs of potassium depletion, though not with a view to demonstrating cellular insufficiency in the presence of normal serum concentration. Their list includes:-

1. Weakness and hypotonia of skeletal muscle - in the later stages, paralysis.
2. Dyspnoea with gasping respirations.
3. Cyanosis, mainly respiratory in origin, due to muscle weakness.
4. Abdominal distension, due to atony of smooth muscle.
5. Nausea and vomiting.

TABLE 26. Case 32

	1st.Op.	2nd.Op.	+1	+2	+3	+4	+5
Plasma Chloride	500		610	560	560	560	550
Urine Chloride	680			10			
Serum K							15.4

All results shown as mgms. per 100 ml. blood or urin

6. Cardiac enlargement with, frequently, a praecordial systolic bruit.

7. Increased pulse-pressure.

8. Elevated venous pressure and signs of cardiac failure.

9. Electrocardiographic changes.

This list, apart from the electrocardiographic changes, included many signs which occur as a result of several postoperative complications. Considering electrolyte deficiencies only, sodium depletion with reduced circulatory blood volume leading to deficient glomerular filtration and a rising non-protein nitrogen in the blood, may provide most of these signs. Table 26 (opposite) shows in summary the biochemical features of just such a case. The fact that a low serum potassium was demonstrated during the later stages of the course of his condition does not prove that the signs were due to potassium deficiency. The fact that they subsided on increased saline therapy indicates that it was not so.

Case Report (in brief) - fuller details in Appendix I - Case 32.

This patient had a partial gastrectomy performed for duodenal ulcer. On the eighth day after operation, a duodenal fistula developed, and a second operation was undertaken to drain the peritoneum on that day. The

fistula was not closed. As can be seen from the table, the urinary chloride excretion was markedly diminished following this second operation, although the plasma chloride concentration was high. There was, however, a relative water deficiency, as evidenced by dehydration and reduced circulatory volume. Adequate parenteral hydration reduced the plasma chloride to 550-560 mgm. per 100 ml. blood while saline infusion replaced the daily loss of chloride. The urinary chloride excretion continued to be low. The plasma chloride concentration was kept near normal at 550-560 mgms. per 100 ml. blood during the next few days by replacing the chloride lost via the fistula. It was fully realised that the sodium loss, as sodium bicarbonate, from the fistula would be considerably greater than the chloride loss, due to the higher sodium than chloride content of the intestinal secretion. However, to avoid pulmonary oedema, no increase in the saline was allowed. During the next five days there was noticeable muscular weakness, intestinal ileus, abdominal distension, dyspnoea and cyanosis, although there was no evidence of pulmonary collapse or cardiac failure. On the fifth day, the serum potassium concentration was 15.4 mgms. per 100 ml. blood. Because of the lack of laboratory facilities at this hospital, no potassium therapy was commenced, but the saline infusion was increased and the

symptoms subsided within 24 hours. Clearly the sodium deficiency was the cause of the physical signs.

Electrocardiographic Changes and Potassium Depletion.

According to Darrow and Pratt, the undernoted features develop in the electrocardiographic recordings as potassium deficiency becomes progressively worse. It is to be noted that they relate these findings to observable decrements in the serum potassium:-

a). The first feature usually noticed is a slight prolongation of the Q-T interval,

then b). Decreased height and inversion of the T wave,

c). Rounded and prolonged T,

d). Depression of the S-T segment,

e). Possibly an inversion of the P wave.

The writer has experience of a case of post-operative duodenal fistula following subtotal gastrectomy where certain of these features became manifest in the presence of a normal serum potassium level. The duodenal fistula had persisted for some days and the patient, an elderly man, was seriously ill. He showed evidence of a central cardiac failure following upon a peripheral vascular insufficiency. The serum potassium concentration was within normal limits. Electrocardiographic recordings (the three standard limb leads) were interpreted by those

more qualified than the writer as showing evidence of recent coronary occlusion. There was, however, depression of the S-T segment which the writer, in view of the lack of history and physical signs of cardiac infarction, interpreted as due to a cellular potassium deficiency. When oral feeding was commenced shortly after this, the patient made a rapid recovery. No evidence of permanent cardiac damage was detected later in his convalescence. Unfortunately, the records of this patient are not available to the writer for presentation here. It is difficult, however, to believe that an elderly patient could make such a satisfactory recovery and show adequate exercise tolerance following a major surgical operation, the very serious complication of duodenal fistula with all its train of deficiencies, in addition to a recent coronary thrombosis. The writer, therefore, considers it possible that cellular potassium depletion may be detected by the electrocardiographic changes when the serum potassium may still be within the normal range.

From the evidence presented on both serum potassium estimations and on the basis of clinical features, it becomes evident that potassium deficiency presents many difficulties in its detection in the early postoperative phase. This

work has indicated that such a deficiency must be expected if oral feeding is not commenced by the third postoperative day. The simplest measure, in the writer's experience, is to presume that potassium depletion has commenced following the "stress" factor even though it may not be detectable by ordinary serum biochemical estimations. If feeding is not commenced by the third day, and if kidney function be normal, potassium should be given by parenteral administration. Darrow (1948) believes that, in the presence of marked potassium deficiency, 3.5 milli-equivalents per kilogram body weight can be administered safely in a period exceeding 4-8 hours. His "K-lactate solution" is excellent for the purpose, but in the early stages of potassium deficiency, the writer believes that much weaker solutions should be employed. Davidsen and Kjerulf-Jensen (1951) describe solutions containing 2 grams of potassium per litre. They recommend for adults a dosage of not more than 0.5 litre per hour, and not more than 3-4 litres per day. When potassium deficiency is not marked, much smaller dosage is recommended.

4). Cellular Physiology.

The results of the present work indicate that certain changes in cellular content of electrolyte take

place as a result of the response of the body to stress factors. These cellular changes are not reflected in the extracellular environment, and do not appear to be forced upon the cell by changes in the tissue fluids. The ultimate nature of the cellular response cannot even be guessed at this stage. Only a few crude cation changes have been demonstrated, and what the significance of these changes in cellular economy can be, has not been determined. Whether the changes are due to essential alterations in cell function imposed from without, or whether due to alterations in cell-membrane permeability, or whether due to a defensive mechanism within the cell cannot be determined in the light of the meagre information presented here. It seems clear, however, that such changes have been detected in association with increased adrenocortical function. The significant feature is that the electrolyte changes do not appear to be determined by alterations in the state of the extracellular electrolyte environment. This is not in accord with recognised physiological teaching. It is customary to read into the response of an organism to changes in its environment a modification which prevents it being damaged or injured by these changes.

As Young (1951) has recently pointed out, the dictum of Claude Bernard that the constancy of the internal

environment of the body is of the greatest importance in the maintenance of function has dominated medical thought for nearly a hundred years. Homer Smith (1951) quotes Haldane as saying that it is the most important concept of physiology. Young, however, in the light of recent knowledge of adrenal steroid function does admit that these substances do enable the cell to withstand abnormality in the internal environment. He points out that possibly the organism which can tolerate greater changes in its environment without diminution in function is, in fact, a better adapted organism than one in which a close control of the internal environment is required to maintain function. He suggests that the protection of heart muscle by cortisone during rheumatic fever may be an example of the process of control of the conditions within the cell in the presence of serious alteration in the environment.

The writer of the present work believes that some such explanation may account for the changes which have been demonstrated in this investigation. They are, in fact, the converse of those discussed by Young, in that cellular electrolyte changes appear to take place without any pre-existant change in the environment. Both suggestions indicate that the cell may be protected without slavishly

modifying itself to changes in the tissue fluids. Such a concept must entail an extension of the Bernardian dictum to embrace changes in cell metabolism which we do not yet understand.

PART IV

INTRODUCTION

In the preceding parts of this thesis, changes in the body, and their significance, have been considered following a variety of factors. In this section, a variety of other conditions will be considered in which it is believed evidence of similar changes has been encountered, but where the proof of the mechanism has not been obtained. It is emphasised, to save repetition, that the underlying factors uniting the conditions discussed here have not always been proved. This Part, while lying mainly outside the writer's experimental work, does support the general contention of the paper, that the stress of disease evokes an adrenocortical response.

CHAPTER 15

RENAL INSUFFICIENCY AND THE ADRENAL CORTEX

It seems to have been Marshal and Davis (1916) who demonstrated the direct effects of the adrenal cortex upon kidney function. They showed that, in adrenalectomised cats, urea and creatinine excretion was diminished following the injection of these substances. They emphasised that this occurred when the animals still remained in good health and that their blood pressure was still within normal limits. Loeb et al. (1933) demonstrated that, in the adrenalectomised dog, the fall in plasma sodium was due to the loss of this substance by the kidney. Harrison and Darrow (1939) considered that the disturbance of renal function following adrenalectomy in the dog was of a specific type, and due to the failure of the renal tubules to maintain the necessary concentration gradient between urine and plasma of certain ions. The disturbance in

tubular function was evidenced by the failure to reabsorb sodium adequately from the glomerular filtrate even when the plasma sodium was low, and conversely, by a failure to excrete potassium and phosphate in high concentration when there was an undue accumulation of these substances in the blood. As a result of the loss of body sodium and chloride, the secondary effect of diminished glomerular filtration contributed to further interference with renal function. Corey and his associates (1939) considered, from experimental observations on the rat, that the posterior pituitary exerted a direct action on water and salt excretion by the kidney, and that the action of the adrenal cortex on salt excretion was only indirect. Smith (1951), however, agrees that the sequence of events in acute adrenal insufficiency is due, in a considerable degree, to reduction of the body fluids as a result of the failure of the renal tubules to reabsorb sodium.

In the presence of normal renal function, Swisher et al. (1950) have shown that the effect of ACTH on tubular reabsorption of sodium in man seems to be a function of the glomerular filtration rate; the greater this, the greater the tubular absorption of sodium. ACTH also affects directly the tubular reabsorption of potassium. Durlacher

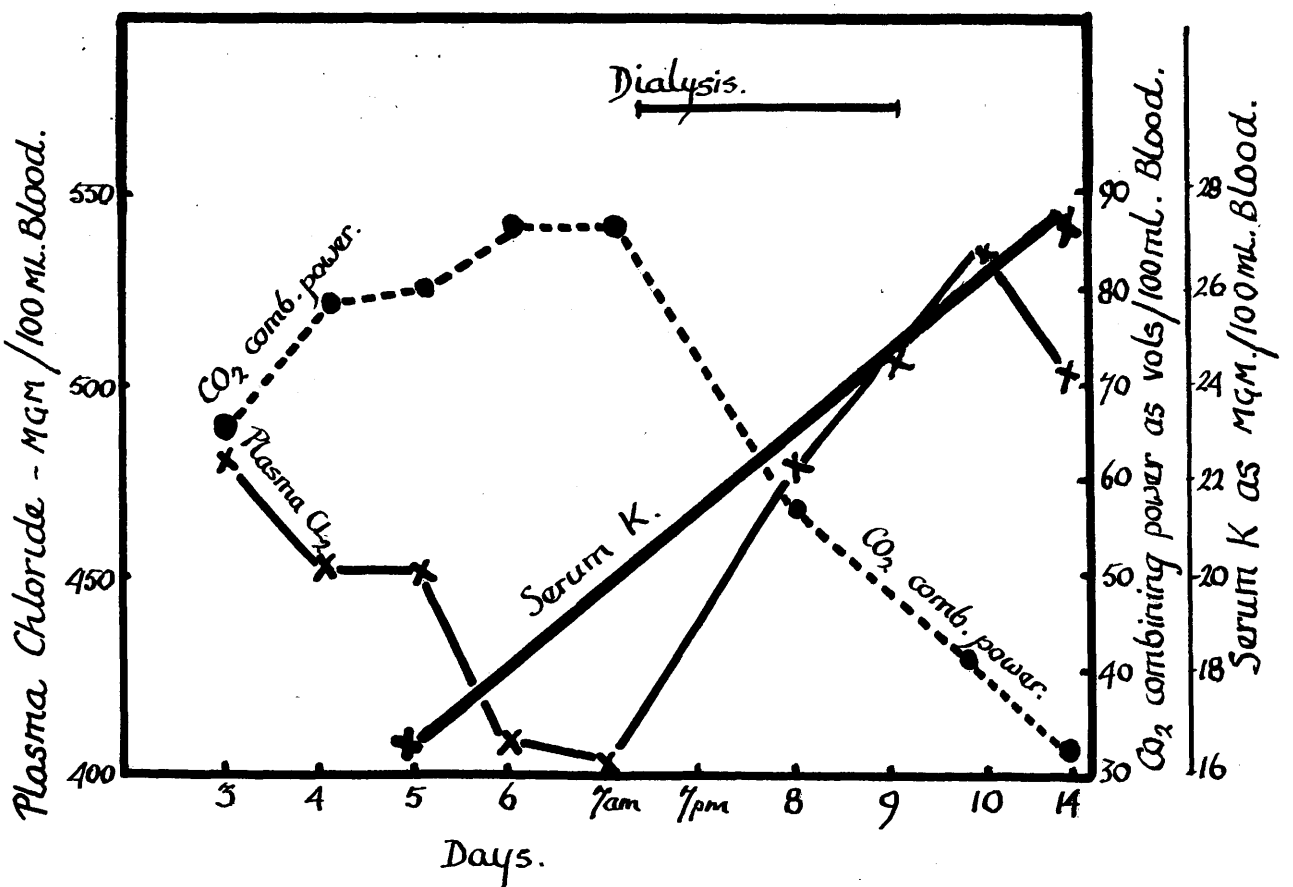
et al. (1942) demonstrated that diets low in potassium caused hypertrophy of the kidney, and that similar results obtained following injections of deoxycorticosterone acetate. The kidney enlargement in both conditions was due to dilatation, hypertrophy and hyperplasia of the loops of Henle and the collecting tubules. They believed that the tubular hypertrophy in these two conditions was connected with an attempt by the renal tubules to reabsorb potassium from the glomerular filtrate.

In view of all this evidence of the close association of the kidney and the adrenal cortex in the control of electrolyte balance, it is interesting to consider what might occur when adrenal cortical function should exert its influence in the presence of acute renal failure. As shown in the earlier chapters, potassium would tend to be mobilised from the tissue cells and be replaced by sodium. The excess potassium, unable to be excreted by the kidneys would accumulate in the plasma and tissue fluids. As the concentration of potassium rose, that ion might finally exert toxic effects on the body and accelerate death.

This rise in extracellular potassium in acute renal insufficiency has been observed many times. Durlacher and Darrow (1942) quote Voit (1868) and Herringham (1900) as showing that this accumulation of extracellular potassium

explains a part of the toxic effects of renal failure. Addis and Lew (1939) confirm this, and Hoff, Smith and Winkler (1941) showed clearly that the toxic effects in acute renal insufficiency were accompanied by electrocardiographic changes which followed exactly the same sequence as poisoning by injected potassium. They correlated each type of electrocardiographic change with the serum potassium level in each case and found them to be similar. Crismon et al. (1943) showed that the lethal effect in cats, during renal failure, was the elevation of the extracellular potassium and not changes in the cellular potassium. Miller and Darrow (1940a) also demonstrated that the toxic effects of injected potassium were directly related to elevations in the concentration of serum potassium and only indirectly to muscle potassium. All this evidence of the toxicity of increased extracellular potassium is of great interest when it is noted that Elkinton et al. (1949) showed that the increased plasma potassium concentration in renal insufficiency is derived from cellular potassium, and not from intake or other sources. Durlacher and Darrow showed that depletion of the body potassium definitely increased the duration of survival of animals after nephrectomy. They found that a low potassium diet or the use of deoxycorticosterone acetate before nephrectomy greatly increased

Table 27.



The Serum Potassium is shown in red.

the survival time of rats.

The work of Elkinton and his associates clearly dispels older views as to the source of the increasing potassium in the serum. In renal failure following mis-matched transfusion it had been suggested that the increased extracellular potassium was derived from the lysis of the transfused cells. Once the source of the hyperpotassaemia has been determined, it only remains to decide the mechanism of its derivation. In this respect, a case submitted for publication by the author in the medical press recently is of interest. The features considered here were not emphasised in the published paper.

Case 33.

This woman, aged 42, while awaiting an operation, received an incompatible blood transfusion. This resulted in severe oliguria which lasted for 13 days before diuresis commenced. The chart opposite (Table 27) shows a graph of some of the biochemical estimations in this case. She was treated in the early stages with saline and glucose infusions, and with sodium bicarbonate by mouth and 1/6 molar sodium lactate intravenously to correct acidosis. As a result of this, an alkalosis was induced, accompanied by a continued fall in the plasma chloride level. This

curious fall in the plasma chloride could not be accounted for by vomiting or other source of chloride loss. Unfortunately, serum sodium estimations were not performed, but it must be assumed that the level was relatively greater than the chloride concentration because of the fact that the carbon dioxide combining-power of the plasma continued to rise. That the serum sodium concentration must, however, have been low is evidenced by the fact that, following peritoneal dialysis with Ringer's solution, a massive absorption of water took place, accompanied by the rise in plasma chloride as shown in the chart, and a fall in the carbon dioxide combining-power of the plasma. Because of the oedema induced, the dialysis had to be stopped on the tenth day. Diuresis commenced on the thirteenth day, when 1.92 grams. of potassium was excreted. In spite of this, the serum potassium concentration on the next day was 27.7 mgm. per 100 ml. blood, the serum sodium being 305 mgm. per 100 ml. blood. The minute quantities of potassium in Ringer's solution could not have increased the serum potassium concentration, and indeed, transudation of potassium would be much more likely to take place from the body into the dialysing medium. The falling plasma chloride in the first six days of the anuria in spite of high intake, and the massive absorption of water after

dialysis was commenced, indicate a falling concentration of sodium in the serum during the early stages. The net result of this, a falling serum sodium and chloride and a rising serum potassium, is very similar to the electrolyte changes associated with injury demonstrated in this work. Muirhead and Hill (1948) report in great detail similar features in renal insufficiency, with a rising serum potassium and a falling serum sodium and plasma chloride. Mudge and Vislocky (1949) have shown from biopsy specimens of human striated muscle in chronic renal acidosis without glomerular insufficiency that a significant depletion of intracellular potassium does occur, associated with a rise in intracellular sodium. The interest of their findings is that these changes occur in the presence of systemic acidosis, indicating, as they point out, that the alteration in intracellular electrolyte pattern may not be specifically related to changes in the acid-base equilibrium.

It is suggested that, following the profound disturbance which results from an incompatible transfusion, continued or increased adrenocortical activity takes place. Whether this aids in the continual existence of the organism is not known, but that it results in a toxic accumulation of potassium seems to be clear. By analogy, the same effect may be produced in all those other forms of acute

renal insufficiency such as the crush syndrome, blackwater fever, and burns, which were attributed by Maegraith et al. (1945) to renal anoxia.

CHAPTER 16

CARDIAC FAILURE AND STRESS

If any of our ideas of cortical adrenal response to stress factors be correct, cardiac failure must certainly provide a stress source in which the mechanism might become evident. Such evidence would, in turn, depend upon the degree of cardiac failure. Failure of advanced degree may well be attended with tissue anoxia, and diminished adrenocortical function might well result. Further, advanced failure, with diminished renal circulation, and resulting diminished glomerular filtration in turn seriously interferes with the estimation of cortical function. The retention of sodium and water in this condition cannot therefore be considered as any more than a reflection of diminished renal plasma flow.

It is interesting to note, however, that Parrish (1949) found evidence of a considerable increase, as compared with normal, in the urinary excretion of adrenal corticoids

in four of ten patients suffering from congestive heart failure. It was suggested that this might be a result, and not necessarily the cause of the symptoms experienced in heart failure. Alexander and his associates (1950) found that the sodium, potassium, water and chloride content of heart muscle was identical with normal in uncomplicated left ventricular hypertrophy. In the hypertrophied digitalised heart, there was a reduction in potassium content, while in the digitalised decompensated heart, there was an even greater reduction in potassium concentration. Wedd (1939) has produced similar evidence that overdosage of digitalis causes an intracellular deficiency of potassium in heart muscle, and Sampson et al. (1943) have demonstrated that the premature systoles in such a toxicity may be dispelled by the administration of potassium salts.

This meagre evidence might be compounded to suggest that, in some stages of heart failure, there is evidence of increased adrenal cortical function. This increased function may lead to cardiac intracellular potassium depletion which seems to be similar to the effect of digitalis in full doses. It is tempting to speculate as to whether the decreased cellular potassium content due to cortical activity can produce the decreased conductivity, and therefore slowing of the rate with increased filling and emptying of the cardiac

chambers so typical of the digitalis effect. That the cardiac glucosides of the digitalis group contain sterols such as digitoxigenin with the characteristic cyclopentenophenanthrene ring system in common with the sterols of the adrenal cortex is well known (Wright, 1940). How far such an analogy may be pressed is difficult to know.

CHAPTER 17

SHOCK AND THE ADRENAL CORTEX

The relationship of cortical function to many forms of trauma has already been considered. The place of the adrenal cortex in the body's response to injury so great as to produce shock has proved to be an extremely difficult problem. The evidence, both clinical and experimental, has been conflicting, and it is discussed here because the writer believes that much of the work that has been done on this subject has been unsatisfactory because the true physiology of cortical function has not been appreciated. The traumatic shock considered here is not, of course, the same as the "shock" of Selye's alarm reaction.

It would appear that much of the difficulty of this problem depends on how the shock is produced, and on exactly what is expected of the adrenal cortex, if it plays any part at all, in the protection of the organism from

either the shock-inducing mechanism or the results of the shock. The difficulties can be seen from the references described below. Heuer and Andrus (1934) observed that adrenal cortical extract combined with plasma transfusion prevented the shock which follows the injection of the contents of a closed intestinal loop. Wohl, Burns and Pfeiffer (1937) noted that injections of cortical extract combined with saline infusions had a beneficial effect in cases of high intestinal obstruction. Fine et al. (1940) discovered that deoxycorticosterone acetate (DOCA) prevented the plasma volume decrease after intestinal obstruction, but did not prevent the onset of fatal shock. Wilson and Stewart (1939), on the other hand, found that DOCA rapidly corrected all the blood abnormalities following burn shock, and accelerated recovery. In 1942, Koster and Kasman selected two groups of patients who would be likely to develop shock after major surgical procedures. One group were treated by saline infusions, and the other by saline and DOCA. They found no evidence that DOCA prevented shock or, once developed, influenced it favourably. Fine et al. (1942) concluded that, in the dog, DOCA was not effective in the therapy of shock due to massive haemorrhage. Cortin alone was not an effective agent either, but if

combined with parenteral fluids, did appear to have an ability to restore the animal to health much more quickly than parenteral fluid alone. The writer considers this a very significant experiment.

Helfrich et al. (1942) gave cortical extract to dogs before inducing shock by intestinal manipulation and noted that it greatly retarded the fall in blood-pressure. This, also, is a significant paper. Similar results were noted by Weil et al. (1940) in rabbits, but DOCA was not effective. Selye and his co-workers (1940) observed similar results after intestinal manipulation in rats, the protective effect of cortical extract being noted, but they found that DOCA was actually harmful. It should be observed that these experiments are not associated with attempts on the part of the experimenter to induce shock by fluid loss. The shocked state in these cases precedes the fluid loss. This has not received attention by the workers concerned, but appears to be a significant feature.

Swingle and his associates (1941) noted that adrenalectomized dogs, maintained in normal condition by doses of cortical extract, are much more susceptible than normal dogs to trauma. Injury to muscle masses, intravenous injection of massive doses of adrenalin, or intra-

peritoneal injection of glucose invariably induced circulatory collapse and shock, whereas no such effect was produced on animals with intact adrenal glands. They observed that circulatory failure did not develop in the adrenalectomized dogs which had received large priming doses of cortical extract before the shock induction. In this respect it is interesting to observe that in the case of intestinal manipulation shock, DOCA did not give protection to the adrenalectomized dogs, but corticosterone did (i.e. 11-oxycorticosterone). In this connection, they induced a delayed potassium depletion syndrome with DOCA in the shocked animals. In 1943, Swingle and his associates produced a careful paper, where the shock inducing mechanism was studied. They induced shock in dogs by a tourniquet applied to the hind limb for five hours, by muscle trauma, and by venous occlusion of the leg. In none of these standard forms of shock did DOCA or cortical extract have any effect in preventing shock, nor in delaying the fatal outcome.

This last paper is most significant, as all these forms of shock production depend upon the reduction in the circulating blood volume, either by tissue anoxia or trauma leading to increased capillary permeability. Swingle and

his associates also draw attention to this fact. It is very difficult to see how cortical extracts can be expected to prevent or overcome this type of shock, where there is an initial reduction in blood volume. The widespread tissue anoxia, leading to further increased capillary permeability away from the injured site cannot be prevented by cortical extracts under such circumstances. Swingle states that the decreased resistance of the adrenalectomized animal to circulatory stress is due to the loss of the adrenal hormones active in carbohydrate metabolism, and he believes it to be a manifestation of a breakdown in the normal intermediary carbohydrate metabolism in the tissues. This defect is reflected in the reduced capacity of the arteriolar smooth muscle to maintain prolonged tonic contractions. He states that, so far as is known, there is no evidence that a derangement of carbohydrate metabolism is concerned in the shocked intact animals whose adrenal glands are presumed to be functioning.

From a review of the work briefly described here it does appear that the adrenal corticoids cannot protect an animal from the type of shock which is induced by large reductions in circulating blood volume. There is evidence, however, that when the circulating volume is restored to

normal after the induction of shock, certain cortical extracts accelerate recovery from the shocked state itself. There is also evidence that cortical extracts have a protective value against those forms of shock produced by means other than diminution in the circulating blood volume. It appears that it is the steroids active in carbohydrate metabolism which exert this effect, and not the "life-preserving" mineralosteroids. To pursue this subject in greater detail would create too great an increase in the scope of this work. The writer is, at present, engaged in the elucidation of some of these points, but they cannot be included in the present study. There is, however, some evidence in the material presented which demonstrates an adrenocortical activity in the response to shock.

CHAPTER 18

FAMILIAL PERIODIC PARALYSIS

After an exhaustive study of this curious condition, Talbott (1941) was unable to detect any upset in metabolism except a reduced serum potassium concentration during the paralytic phase. The relationship of free potassium ions to muscular contraction cannot receive a full consideration here. It has been shown in earlier chapters of this work that a diminution in extracellular potassium from whatever cause may lead to the onset of muscular weakness and paralysis. Brown and Feldberg (1936) have shown that the injection of potassium chloride causes a liberation of acetyl choline at ganglionic synapses. Feldberg and Guimarais (1936) suggested that a discharge of acetyl choline may be effected by the potassium ions liberated during the passage of nerve impulse.

Danowski and his colleagues (1948) have shown that, in familial periodic paralysis, at the onset of the paralysis,

potassium moves into the cell, reducing the extracellular potassium concentration. They did not know whether there was an initial total potassium deficit in the body or not. Talbott, however, has shown in his paper that paralysis in this condition can occur with normal serum potassium concentrations. The place of extracellular potassium in muscle paralysis is further complicated by the findings of Danowski and other workers (1949) that, in diabetic acidosis, a pronounced hypopotassaemia can occur without paralysis ensuing. In a study of muscular exercise and potassium metabolism in rats, Miller and Darrow (1941) have obtained some interesting results. Within wide limits, the amount of potassium in the muscle cell does not limit the animal's capacity for exercise. Abnormally low serum potassium levels are not, in themselves, sufficient to produce paralysis. Following exercise, there is an increase in potassium in the serum, but if DOCA is injected into the exercised animals, the serum concentration of potassium falls.

In spite of all this conflicting evidence as to whether reduced serum potassium is or is not sufficient to cause muscular paralysis, the general attitude is to consider that it does, and that the attacks in familial periodic

paralysis are precipitated by a fall in the extracellular potassium concentration. Talbott has said that it is possible that many persons are susceptible to periodic paralysis of this kind under certain circumstances. If the assumption is correct, he believes that periodic paralysis may be interpreted as an abnormal physiological response in the same way as hyperventilation tetany and heat-cramps are abnormal physiological responses. This is significant in view of the observations of Gass and others (1948) that attacks of paralysis in this condition were quite frequently precipitated by stresses during military training of recruits.

The writer has not, unfortunately, encountered a case of this disease, but would suggest that, if the reduction in serum potassium before the onset of the paralysis be due to increased urinary excretion of the ion, then the mechanism of the condition becomes clear. In an unduly susceptible individual, the application of a stress factor may cause an increased adrenocortical activity and increased potassium excretion. When the short phase of increased potassium excretion, lasting only 3 or 4 days, has come to an end, the body retains its cellular potassium at the expense of the extracellular fluid potassium as has been demonstrated earlier. This stage might then be accompanied by paralysis

and account for the apparent transfer of potassium - the ingested potassium - from the fluids into the partially depleted cells.

CHAPTER 19

EVIDENCE OF ADRENOCORTICAL ACTIVITY IN SOME OTHER DISEASE PROCESSES

Throughout the preceding text, the evidence of adrenocortical function in various disease processes has been mentioned. In this chapter a brief description of some accurate studies on several other disease processes is appended, where similar evidence has been suggested, or may be interpreted.

Semmen (1940) observed that the administration of DOCA to patients suffering from severe toxic forms of diphtheria, scarlet fever, and dysentery had no influence on the increased blood potassium or on the decreased blood sodium or chloride, nor on the clinical course of the disease. If, in fact, the altered electrolyte pattern were due to adrenocortical activity, it is not surprising that DOCA produced no effect on electrolyte pattern or on the course of the disease. It is, of course appreciated

that the decreased blood sodium and chloride might well be due to loss by vomiting, intestinal secretions and excessive sweating rather than to the type of mechanism discussed in this work.

In 1943, Sarason studied the adrenal glands of 110 patients suffering from various systemic diseases. He observed cortical enlargement with lipoid depletion in inflammatory diseases, cachexia, pemphigus, and in protracted vomiting. This appears to be gross microscopic evidence of increased adrenocortical function in these patients preceding death.

Jacobs (1943) observed that, in a controlled series of children suffering from pertussis, a definite improvement followed the injection of pertussis antigen. He obtained a similar response with typhoid vaccine, and concluded that the improvement was the result of a non-specific effect. In a group of 15 children, he injected adrenal cortical extract, and found that, compared with the controls, the same reduction in severity and in duration of the whooping-cough resulted. The improvement with non-specific protein therapy is in accord with Selye's suggestion of a second stressor falling on the counter-shock phase of the first stressor.

Prunty (1949), in a study of acute porphyria, observed a phase of decreased plasma sodium and chloride concentration. This was associated with diminution in the circulating eosinophils, increased uric acid excretion, and an increase in the neutral reducing steroids in the urine. He believed this to be evidence of increased adrenal cortical activity during the acute stage of the disease. He stated that there was evidence to show that cortical hypertrophy had been noted by some observers in this condition.

SUMMARY OF THE WHOLE WORK.

Within the strict limits of the clinical experiment described, evidence has been presented of increased activity of the adrenal cortex following injury. Rather less convincing evidence has been presented of a similar increased adrenocortical activity following a variety of injuries and disease processes. As the various stimuli appear to have evoked a similar response, they have been termed stress factors. Important electrolyte changes in the body have been studied and these changes, perhaps for the first time, have been proved rather than ascribed to be due to the adrenocortical response.

No evidence has been obtained in this study of diminished cortical steroid production following stress. In consequence, the features of such a reduced activity have not been discussed.

Although such an increased adrenocortical activity following stress has been demonstrated, what the real nature of the activity entails has not been determined. Whether

the response is even protective to the organism can be no more than conjectured. What relationship the altered cell metabolism bears to the hypothetical protection afforded lies beyond our present knowledge.

It would be naïve to imagine that an organ essential to life has not some important part to play in the body economy following injury. To assume that such a reaction is necessarily for the good of the body as a whole is to appeal to the teleological argument. Such an assumption, though usually implied in medical investigations, must be proved in every aspect. The writer believes that there is some evidence indicating that the protection afforded, if any, may be to the cells of particular tissues; the whole organism benefitting from the continued function of its parts, but suffering from the measures that the tissues take to protect themselves.

An investigation such as the present one cannot elucidate what ultimate function the adrenocortical response serves in the body economy, but simply when and to what extent the response occurs, how it may be recognised, and what gross changes in metabolism result. How far these requirements have been fulfilled remains to be determined.

APPENDIX I

DESCRIPTION OF THE PATIENTS

A very brief description of the patients is detailed below. Any postoperative complications are mentioned. Only details not presented in other sections of this work receive consideration here.

Case 1. J.B. Male - 68 years. Duodenal ulcer, no stenosis. No recent vomiting before admission but loss of appetite and of weight. Well hydrated before operation.

Day of Operation: Operation - sub-total gastrectomy. Anaesthetic - general. Postoperative gastric aspiration on day of operation - 10 ml. Intravenous fluid therapy - 560 ml. blood (i.e. about 280 ml. fluid) and 560 ml. 6 per cent. dextrose.

1st postoperative day: No vomiting, no gastric aspiration, and no intravenous infusion.

2nd - 6th postoperative days: As 1st postoperative day. On 6th postoperative day, both the serum and urine were slightly bile-stained. Following this the patient developed a duodenal fistula. This healed satisfactorily before the 30th postoperative day, when the final blood specimens were examined.
Discharged in good health.

Case 2. J.S. Male - 30 years. Uncomplicated hydrocele. Preoperative condition - a general physical examination did not reveal any other disease.
Operation: Excision of hydrocele sac. Anaesthetic - general. No intravenous infusion. No post-operative vomiting. A thrombophlebitis in the superficial veins of the right leg observed on the fourth postoperative day. Recovery.

Case 3. I.T. Male - 41 years. Duodenal ulcer, no stenosis. No severe vomiting before admission to hospital. General condition - satisfactory.
Day of Operation: Operation - sub-total gastrectomy. Anaesthetic - general. Intravenous fluid therapy - Blood - 560 ml. (i.e. 280 ml. fluid) and 560 ml. normal saline in 6 per cent dextrose. No post-operative vomiting.
1st postoperative day: No vomiting. Gastric aspiration - a little altered blood. No intravenous infusion.
2nd postoperative day: Gastric aspiration - 297 ml. blood-stained fluid. No intravenous infusion. Water by mouth, but no saline.
3rd postoperative day: Gastric aspiration - 988 ml. fluid. Water by mouth.
4th postoperative day: Gastric aspiration - 343 ml. Fluid. Water by mouth.
5th postoperative day: Gastric aspiration discontinued. Water by mouth and fluid diet.
After this time his convalescence continued uneventfully.

Case 4. M.I. Male - 42 years. Peptic ulcer. No pre-operative dehydration.
Day of Operation: Operation - abdominal vagotomy and gastro-jejunostomy. General inhalation anaesthetic.
Intravenous fluid replacement therapy - 560 ml. normal saline and 1,400 ml. 6 per cent. dextrose. Gastric suction - 60 ml.

1st postoperative day: Gastric aspiration - 46 ml.
Water by mouth only.
2nd postoperative day: Gastric aspiration - discontinued.
Convalescence uneventful.

Case 5. J.I. Male - 18 years. Right inguinal hernia.
A fit young man.
Operation: Inguinal herniorrhaphy. General inhalation anaesthesia.
No appreciable postoperative vomiting.
No intravenous fluid replacement therapy.
An uneventful convalescence.

Case 6. W.T. Male - 68 years. Right inguinal hermia.
preoperative condition satisfactory.
Operation: Inguinal herniorrhaphy. General anaesthetic.
No appreciable postoperative vomiting. No intravenous fluid therapy.
An uneventful convalescence.

Case 7. J.C. Male - 61 years. Bilateral inguinal herniae.
Evidence of anaemia before operation.
Operation: Repair of inguinal herniae. Anaesthetic - general.
No appreciable postoperative vomiting.
A postoperative lower lobe collapse developed in the right lung.
Recovery ensued.

Case 8. J.M. Male - 41 years. Left inguinal hernia.
In good health.
Operation: Repair of hernia. Anaesthetic - general.
Postoperative vomiting - almost nil.
An uneventful convalescence.

Case 9. J.McD. Male - 21 years. Right inguinal hernia.
In good health.
Operation: Repair of inguinal hernia. General anaesthetic.
No postoperative vomiting.
Uneventful recovery.

Case 10. Male. Inguinal hernia. In good health.
Operation: Repair of inguinal hernia. General anaesthetic.
Uneventful recovery.

Case 11. Male. Inguinal hernia. In good health.
Operation: Repair of inguinal hernia. General anaesthetic.
Uneventful recovery.

Case 12. Male. Inguinal hernia. In good health.
Operation: Repair of inguinal hernia. General anaesthetic.
Uncomplicated recovery.

Case 13. Male. Inguinal hernia. In good health.
Operation: Repair of inguinal hernia. General anaesthetic.
Uncomplicated recovery.

Case 14. I.H. Female - 40 years. Umbilical sinus discharging for some years.
At time of operation, sinus almost dry.
Operation: Excision of umbilicus and sinus. General anaesthetic.
The sinus did not communicate with the bowel.
Vomiting after operation - minimal.
Uncomplicated recovery.

Case 15. E.C. Female - 38 years. Haemorrhoids.
Operation: Haemorrhoidectomy. General anaesthetic.
Some vomiting following operation.
Uneventful convalescence.

Case 16. E.C. Female - 35 years. Varicose veins.
In good health.
Operation: High ligation - long saphenous vein. General anaesthetic.
Minimal postoperative vomiting.
Uneventful convalescence.

Case 17. M.O. Female - 39 years. Right inguinal hernia.
In good health.
Operation: Repair of hernia. General anaesthetic.
Little postoperative vomiting.
Uneventful convalescence.

Case 18. R.S. Male - 48 years. Left inguinal hernia.
In good health.
Operation: Inguinal herniorrhaphy. General anaesthetic.
Little postoperative vomiting.
Uneventful convalescence.

Case 19. A.J. Male - 44 years. Right femoral hernia.
Good health.
Operation: Repair of femoral hernia. General anaesthetic.
No postoperative vomiting.
Satisfactory recovery.

Case 20. Male. Bilateral varicose veins.
Satisfactory preoperative condition.
Operation: High ligation of both long saphenous veins.
General anaesthetic.
No postoperative vomiting.
Recovery.

Case 21. H.M. Male. Haemorrhoids. In good health.
Operation: Haemorrhoidectomy. General anaesthetic.
Some postoperative vomiting.
Recovery.

Case 22. C.L. Male. - 51 years. Left inguinal hernia.
In good health.
Operation: Inguinal herniorrhaphy. General anaesthetic.
A little postoperative vomiting.
Satisfactory convalescence.

Case 23. J.D. Male - 56 years. Right inguinal hernia. Fit.
Operation: Repair of inguinal hernia. General anaesthetic.
No postoperative vomiting.
Uneventful convalescence.

Case 24. W.J. Male - 51 years. Epididymal cyst.
In good health.
Operation: Resection of right epididymal cyst.
Little postoperative vomiting.
Uneventful recovery.

Case 25. M.E. Female - 60 years. Incisional hernia.
Good health.
Operation: Repair of incisional hernia. General anaesthetic.
No postoperative vomiting.
Uneventful convalescence.

Case 26. E.Y. Female - 52 years. Haemorrhoids. In good health.
Operation: Haemorrhoidectomy. General anaesthetic.
Some haemorrhage at operation.
A little postoperative sickness.
Uneventful convalescence.

Case 27. D.S. Male - 27 years. Haemorrhoids. In good health.
Operation: Haemorrhoidectomy. General anaesthetic.
Uncomplicated convalescence.

Case 28. A.H. Male - 32 years. Left inguinal hernia.
Operation: Repair of inguinal hernia. General anaesthetic.
Uncomplicated recovery.

Case 29. G.N. Male - 29 years. Bilateral varicose veins.
Operation: Ligation of long saphenous veins. General anaesthetic.
Recovery.

Case 30. H.A. Male - 32 years. Epididymal cyst.
Operation: Resection of epididymal cyst. General anaesthetic.
Recovery.

Case 31. A.C. Female - 50 years. Left inguinal hernia.
Operation: Repair of inguinal hernia. General anaesthetic. Uncomplicated recovery.

Case 32. W.A. Male - 52 years. Duodenal ulcer. No stenosis. No recent history of copious vomit. Some preoperative chloride deficiency (Plasma chlorides - 500 mgms. per 100 ml. blood.) Total serum protein - 5 Grams per 100 ml. blood. Haemoglobin - 86 per cent. (Haldane).

1st Operation: Subtotal gastrectomy. General anaesthesia. Intravenous saline during the operation.

Well until -

7th postoperative day: Abdominal distension, bilious vomit, paralytic ileus.

8th postoperative day: Duodenal stump leak. Free fluid in peritoneal cavity.

2nd Operation: Drainage of peritoneal cavity without closure of necrotic duodenal stump.

Following both operations, considerable fluid was withdrawn by continuous gastric suction. Intravenous infusion of saline and dextrose appeared to maintain adequate chloride and water balance as judged by the urinary output, and the plasma chloride concentration.

560 ml. blood was given by infusion on the 2nd day after the second operation to maintain adequate plasma osmotic tension and to prevent anaemia.

The details of the biochemical findings are supplied in the text.

Paralytic ileus, abdominal distension, cyanosis and weakness persisted to the 7th day after the second operation in spite of adequate hydration and chloride balance. Duodenal drainage stopped by the 8th day after the second operation, and the patient was able to take food by mouth. The symptoms and signs described above rapidly subsided and the patient made a satisfactory recovery.

Case 33. H.G. Female - 42 years. Severe ologuria following incompatible blood transfusion. Treated at first by intravenous saline and dextrose and by alkali. Carbohydrate diet only. Peritoneal dialysis commenced on the afternoon of the 7th day and stopped after 43 hours continuous dialysis. Severe oedema and water overload had developed. Pulmonary oedema and cardiac failure evident on the tenth day. All fluids and electrolytes stopped. Very slow recovery, but diuresis commenced on the 13th day.

The chart of this patient shows the changes in the concentration of plasma chloride, plasma carbon dioxide-combining capacity, and serum potassium, and the effect of peritoneal dialysis.

Case 34. E.C. Female - 14 years. Complaining of acne commencing 2 years before and of hirsutes commencing a year before admission. Menarche - 13 years.

A well-developed girl, apparent age 19-20 years. Marked muscular development. Hair developed to umbilicus, on calves, thighs and arms.

An outstanding athlete, but of a gentle disposition.

Breasts normal for 14 years. Clitoris enlarged.

X-ray pituitary fossa - not enlarged. Bone development of skeleton, comparable with that of female age 20 years.

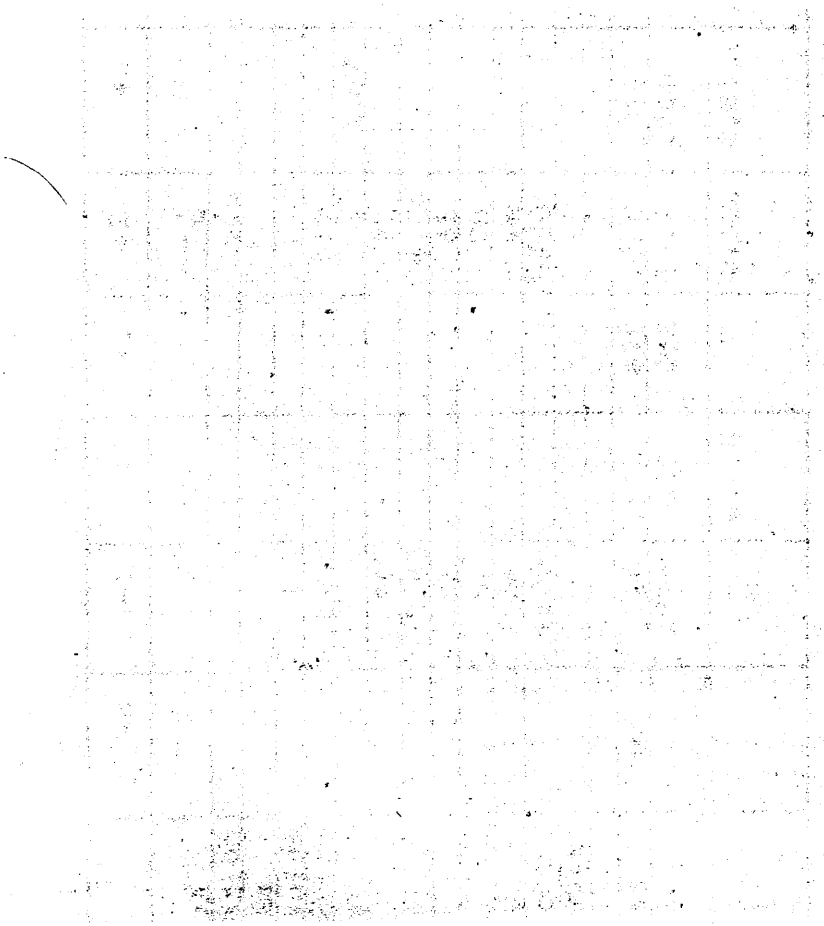
Glucose and Insulin Tolerance Tests - normal response.

Operation: Suprarenal tumour removed through a chest incision. A small piece of normal cortical tissue left in situ. General anaesthesia - no untoward reactions.

Pathology Report: "Paraffin sections show a completely simple cortical adenoma of the suprarenal. In many places the vessels are dilated to give a cavernous angioma."

Details of biochemical estimations supplied in the text.

The patient made a rapid and uncomplicated recovery after operation. Apart from a saline and blood infusion on the day of operation, no effort was made to supply extra water or saline.



Case 1. SUMMARY OF RESULTS Table 28

	-2	-1	0	+1	+2	+3	+4	+5	+6	+7	+30
Serum sodium		305			320		306		292		316
Serum potassium					19.6		21.3		22.2		19.7
Urine sodium											
Urine potassium											
Plasma chloride		535			519				544		
Urine chloride	5.75					1.87					
Blood sugar		70			97		80		75		
Urin.17-ketos.		2.63			4.05		3.74		1.85		
Eosins		82			62		87		45		
Haemoglobin		84			98		86		80		
Haematocrit		38			44		40		37		
Leucocyte count		4100			8900		8200		6400		
Blood pressure											
Weight											
Urine volume	820	700	nil	616	980	1036	1140	1564	840	1062	726
Fluid intake	Not measured	1876	1400	686	1596	2740	1820	2212	1820	1428	2098
NaCl intake (as NaCl)			4.5 G.		0.5G.	2.25G.	1.1G.	1.1G			

Case 2. SUMMARY OF RESULTS Table 29

	-2	-1	0	+1	+2	+3	+4	+5	+6	+7	+8	+9
Serum sodium		336					316.5		340			
Serum potassium	21						24					
Urine sodium												
Urine potassium												
Plasma chloride												
Urine chloride			8.38		3.67		5.69			9.92		
Blood sugar		70			73		72		59			
Urin.17-ketos.		11.12		5.63		5.99			6.78			
Eosins		156				75	180		116			
Haemoglobin		97				97	92		89			
Haematocrit		42				41	41		40			
Leucocyte count		7800				7500	5800		8700			
Blood pressure												
Weight		151.37		151.75		152.5	152.5			152	152	152
Urine volume		870	812	1785	2308	1560	1286	950	1020	1764	1726	1974
Fluid intake		2006	1120	2912	2492	2212	2380	1876	1736	1624	2184	1984
NaCl intake												

Case 3. SUMMARY OF RESULTS Table 30

	-1	0	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10
Serum sodium	318.7			310.1			302.1			327		
Serum potassium	22.7			22.8						22.1		
Urine sodium												
Urine potassium												
Plasma chloride												
Urine chloride	6.60		4.97			0.61		0.83				
Blood sugar	86			150			79		60			
Urin.17-ketos.	10.5			17.48			9.94		5.63			
Eosins	34			10			55		260			
Haemoglobin	118			100			100		112			
Haematocrit	49			48			47		47			
Leucocyte count	4300			12500			5500		5200			
Blood pressure	140/80		145/80	155/80								
Weight												
Urine volume	672	708	476	1060	810	905	560	1536	610	938	672	1152
Fluid intake	2128	1724	720	674	1232	1568	1428	1724	1706	1988	2156	1736
NaCl intake		9G.										
Chloride loss (as NaCl)				2.5G	5G	3.5G						

Case 4. SUMMARY OF RESULTS Table 31

	-4	-3	-2	-1	0	+1	+2	+3	+4	+5	+6	+7	+8	+9
Serum sodium	325.8							312			319		335	
Serum potassium	22							18.9			19.7			
Urine sodium				14.96				3.92			1.06			
Urine potassium														
Plasma chloride														
Urine chloride				4.83				1.05			1.89			
Blood sugar			70					67			68		67	
Urin.17-ketos.			9.05				14.90		7.00	6.23				
Eosins			216					74			344		76	
Haemoglobin			89					92			89		94	
Haematocrit			45					47			41		41	
Leucocyte count			7200					9900			8600		7600	
Blood pressure			135/90	140/90	135/60	140/65								
Weight		194												
Urine volume		624	1035	1410	368	1060	1330	1025	1660	1275	1729	1512	1652	1576
Fluid intake		1140	2180	1120	2100	1078	2240	2716	2224	2014	1988	2023	1904	1764
NaCl intake					4.5G									

Case 5. SUMMARY OF RESULTS Table 32

	-2	-1	0	+1	+2	+3	+4	+5	+6	+7	+8
Serum sodium	334.6				323.8		332.4		336.2		
Serum potassium	22.2				20.7		21		22.5		
Urine sodium		3.86		1.94		2.41					
Urine potassium											
Plasma chloride											
Urine chloride		7.25		2.75		4.26		9.31			
Blood sugar	64				57		67		65		
Urin.17-ketos.	8.4				10.55		10.01		12.70		
Eosins	350				169		156		231		
Haemoglobin	97				100		95		98		
Haematocrit	47				46		45		44		
Leucocyte count	5700										
Blood pressure											
Weight		132				132					
Urine volume	1736	900	504	1512	1560	1596	1590	2240	2250	2842	2352
Fluid intake	1820	3100	460	1600	1808	1820	1456	2128	1488	1988	1918

Case 6. SUMMARY OF RESULTS Table 33

	-2	-1	0	+1	+2	+3	+4	+5	+6	+7	+8
Serum sodium		335			314		328		334.6		
Serum potassium		20.7			22.7		22		25.8		
Urine sodium			3.02			2.71		2.80		4.48	
Urine potassium			1.62								
Plasma chloride											
Urine chloride			7.03			3.46		5.87		9.21	
Blood sugar		73			84		88		82		
Urin-17-ketos.		7.75			17.65		16.60		9.25		
Eosins		40			50		160		25		
Haemoglobin		98			96		95		94		
Haematocrit		46			43		40		40		
Leucocyte count		7900			11800		6800		5200		
Blood pressure	150/85			145/80		145/90	145/85	145/80			
Weight		136¼									
Urine volume		630	308	1166	1020	780	980	720	660	974	1378
Fluid intake		1468	280	1460	2240	1428	1820	2506	1260	2324	2252

Case 7. SUMMARY OF RESULTS Table 34

	-2	-1	0	+1	+2	+3	+4	+5	+6	+7	+8
Serum sodium		340.5		332		320		330			
Serum potassium		20		22.5		20.7		23.7			
Urine sodium		4.54				2.45		2.69			
Urine potassium											
Plasma chloride											
Urine chloride		6.41		4.13		1.04		4.68			
Blood sugar		58					83			77	
Urin.17-ketos.	8.62				12.97		6.77		7.40		
Eosins		86					64				
Haemoglobin		74					68				
Haematocrit		35					32				
Leucocyte count		8100					7700				
Blood pressure											
Weight											
Urine volume	1040	1005	336	592	495	972	805	1006	1120	1064	1288
Fluid intake	1344	Not measured	476	1316	1316	1596	1870	1672	1672	1120	1400

Case 8. SUMMARY OF RESULTS Table 35

	-3	-2	-1	0	+1	+2	+3	+4	+5	+6	+7	+8
Serum sodium	331					328.7		340				
Serum potassium	20.9					21.8		21.1				
Urine sodium			2.23			1.07		1.89				
Urine potassium			0.92			0.65		0.78				
Plasma chloride	597					556		556				
Urine chloride			12.99			3.23		5.70				
Blood sugar												
Urin.17-ketos.		9.78					12.2		7.8			
Eosins	221					254		456				
Haemoglobin	98					100		106				
Haematocrit	43					48		46				
Leucocyte count	7300											
Blood pressure		130/80		108/72	130/70		130/80					
Weight	166.5	166.75	166.33				164.33	164.33	163.75			
Urine volume	3100	3380	1500	Not known	2013	1591	2360	2240	1620	1919	2556	2290
Fluid intake	-	2464	1456	476	1904	1796	2296	1580	1456	1260	1344	1820
Blood urea	18											

Case 9. SUMMARY OF RESULTS Table 36

	-3	-2	-1	0	+1	+2	+3	+4	+5	+6	+7	+8
Serum sodium	326.7					342.2		327.2				
Serum potassium	19.7					23.8		22				
Urine sodium			3.79		2.39		2.99					
Urine potassium			1.4		1.42		1.15					
Plasma chloride	592					543		560				
Urine chloride			11.02		4.43		9.78					
Blood sugar												
Urin.17-ketos.	24.9					14.4		23.0				
Eosins	54					294		425				
Haemoglobin	102					112		100				
Haematocrit	49					50		51				
Leucocyte count	9200											
Blood pressure			120/70		120/50	120/70		120/60				
Weight	131	131.63	132.25				130.75	130.7		130.13		
Urine volume	962	448	1198	772	1372	1000	1390	1680	1804	1368	1928	1232
Fluid intake	756	1260	1288	616	1204	1640	1568	1652	1428	1280	1204	1548
Blood urea	25											

TABLE 37

Patient No.	Before Operation					After Operation				
	Haematocrit	Serum K	Cell K	Serum Na	Cell Na	Haematocrit	Serum K	Cell K	Serum Na	Cell Na
14	42.6	19.4	405	342	89	40.3	20.4	405	322	79
15	43.1	18.2	367	327	74	44.7	16.3	371	317	93
16	40.3	16.0	385	327	83	41.4	14.5	407	336	45
17	41.2	16.3	385	331	61.5	40.5	14.4	391	340	20.5
18	49.1	17.6	389	330	33	48.5	19.0	386	327	40.4
19	45.6	19.2	383	336	46.5	50.2	18.0	380	333.5	46.0

APPENDIX II

LABORATORY METHODS

The laboratory methods used throughout this work are mentioned below, but a detailed description is not included.

All the electrolyte estimations and controls were performed in duplicate except plasma chlorides.

1). Serum sodium. Estimated by the zinc uranyl acetate method of McCance and Shipp (1931). The resulting solution was estimated in a Stekker absorptiometer. Urinary sodium estimations completed in the same way, after first treating the urine with mercuric chloride and calcium hydroxide.

2). Serum potassium. Estimated by the sodium cobalti-nitrite method of Jacobs & Hoffman (1931). Result again estimated by photometric methods. Urinary potassium completed in the same way after first ashing in an electric furnace and then extracting with N/10HCl.

3). The plasma and cell base estimations in patients 14 - 19 were performed in an internal standard flame photometer.

4). Plasma chloride. Estimated in the protein-free filtrate by precipitation with excess silver nitrate, the excess being determined by back titration with potassium thiocyanate, using iron-alum as the indicator. The method is described by Harrison (1947).

5). Urinary 17-ketosteroids. Estimated by the "rapid" method of Robbie and Gibson (1943), where the urine is hydrolysed, extracted with carbon tetrachloride and then treated with meta-dinitrobenzene. The estimation was completed by photometric methods.

6). Blood sugar. Estimated by the method of Folin and Wu as described by Harrison (1947).

7). Eosinophil counts. Performed in the manner described by Randolph (1944).

8). Leucocyte counts. Performed in the usual way.

9). Haematocrit readings. Obtained in the usual way, after centrifuging in haematocrit tubes. Haemoglobin estimated by the Haldane method.

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