ENDOCRINE ASPECTS OF THE METABOLIC RESPONSE TO SURGICAL OPERATION

Hunterian Lecture delivered at the Royal College of Surgeons of England
on
7th April 1964
by

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SURGICAL OPERATION OR any other form of physical injury in a previously healthy person initiates a series of metabolic and endocrine processes which are associated with recovery and normal convalescence.

Two hundred years ago John Hunter appreciated that the recovery from injury followed a distinctive pattern when he 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 means of cure " (Hunter, 1861).

It is now almost 100 years since Bauer (1872) demonstrated that the concentration of nitrogen in the urine was increased after a simple haemorrhage. It was shown later (Hawk and Geis, 1904) that a similar increase occurred after injury in which the loss of blood was negligible. Cannon (1929) was the first to recognize the importance of the endocrine system in the response to injury. He introduced the concept of a neuroendocrine response to stress and described an increase in the activity of the sympathetic nervous system and in the output of adrenaline-like substances.

Cuthbertson (1932) observed that body protein was broken down more rapidly than it was formed after injury and nitrogen appeared in excess in the urine. The increased excretion of nitrogen lasted several weeks after severe injuries such as fractures of long bones and only a few days after minor trauma.

Selye (1946) attempted to find a single explanation for the endocrine and metabolic response to stress. He postulated that increased adrenocortical activity initiated and controlled the total body response to stress. Much of the current knowledge of the endocrine and metabolic changes in the postoperative period has come from the detailed balance studies reported by F. D. Moore (1959). The ability accurately to measure the output of many adrenal steroids has added much to the interpretation of the physiology of injury.

In spite of the advances of the past 10 years, our knowledge of many aspects of the patient's own contribution to recovery is still incomplete.

I shall confine myself to some observations on the response of the adrenal, pituitary and thyroid to surgical operations and discuss the role of these responses in the simultaneous metabolic changes.

Several colleagues in the Departments of Biochemistry and Medical Physics at the Queen's University of Belfast and at the Postgraduate Medical School of London have collaborated with me in the work which I shall describe and I should like to record my appreciation of their efforts.

THE METABOLIC RESPONSE

Let us first of all look at what we mean by the metabolic response as a background to our considerations of endocrine activity. The metabolic response can be detected by an examination of the urinary excretion of nitrogen, potassium, sodium and water (Table I).

TABLE I

EFFECT OF OPERATION ON DAILY URINARY OUTPUT

Substance	*Normal output*	*After injury*	*Duration*
Nitrogen	8–12 gm.	Increased 10–20 gm.	4–10 days
Potassium	70–100 mEq.	Increased 100–140 mEq.	1–3 days
Sodium	70–100 mEq.	Decreased 5–20 mEq.	2–5 days
Water	1,500 ml.	Decreased 500 ml.	48 hours

Nitrogen

The urinary excretion of nitrogen is increased for 4–5 days after most abdominal operations, and a man of average build may lose 500 gm. of lean tissue per day after a major abdominal operation. Various factors associated with injury or operation contribute to this loss of nitrogen and complicate an analysis of its cause. The physical inactivity of enforced bed rest can of itself lead to an increased excretion of nitrogen. The food intake after injury is frequently reduced, and starvation plays an important part in the extent of the losses (Abbott *et al.*, 1958). Some of the urinary nitrogen is derived from damaged and autolysed tissue and blood clot around the injured part, but some comes from normal tissues, such as skeletal muscle, in other parts of the body. It is believed by some that this response is homeostatic and that the breakdown of protein represents the mobilization of amino acids for the repair of the wound (Moore, 1959).

Potassium

Urinary potassium levels are raised immediately after injury and the peak excretion occurs after about 12–24 hours, that is at least 24 hours before the nitrogen peak. The increased output lasts for 1–3 days and ceases before that of nitrogen. It is assumed that the nitrogen and potassium released after trauma have a common intracellular origin.

Sodium

There is a decreased urinary excretion of sodium in the urine after injury in previously healthy individuals. This lasts for 2–5 days. Certain

components of the surgical experience such as oedema and haemorrhage are potent stimuli for sodium retention. Any reduction in extracellular fluid volume also leads to increased tubular reabsorption and retention of sodium by the body.

Water

Water is retained by the body after injury. Oliguria persists even when large amounts of water and sodium are given intravenously during the first 24–48 hours after operation.

Many factors such as sex, age and the severity of the trauma modify the extent of the metabolic response.

ADRENAL RESPONSE

We will look now at the endocrine changes which are taking place at the same time as these metabolic adjustments. The adrenal cortex is

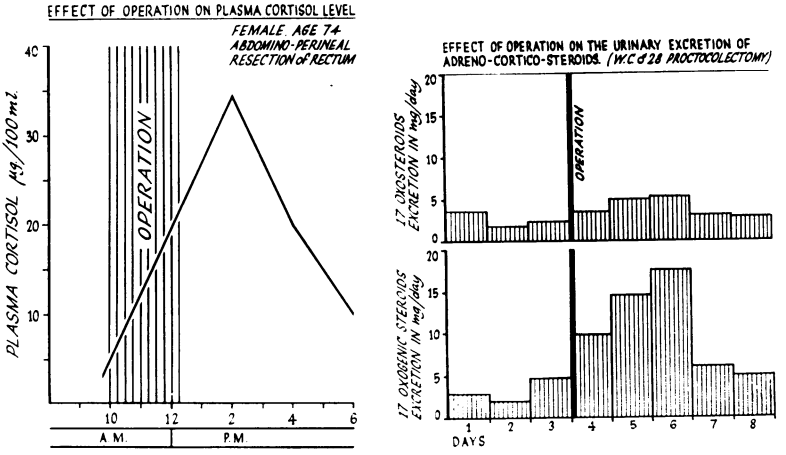

Fig. 1. (*a*) The effect of major operation on the plasma cortisol level. (*b*) The effect of major operation on the urinary excretion of adreno-cortico-steroids.

the most important endocrine organ in this connection and produces three main groups of steroid hormones:

1. The glucocorticoids have important metabolic functions. Cortisol is the main member of this group and its production is increased after injury.

2. The electrocorticoids are secreted in relatively small amounts and because of this their quantitative determination was delayed for some years. Aldosterone is the principal hormone in this group and its production is elevated after operation.

3. The adrenal metabolites of the sex hormones have very little metabolic function and their output barely alters in response to trauma.

Cortisol

The pattern of the adrenocortical response is best demonstrated by studies in individual patients. The level of the plasma cortisol rises quickly during operation and a peak is reached after 5–6 hours. Normal values are resumed within 8–10 hours of the end of most operations (Fig. 1*a*). The rate at which the plasma cortisol level rises and the height of the peak attained depends upon two factors:

1. The increased rate of production of cortisol by the adrenal cortex.

2. The rate of conjugation of cortisol by the liver and the rate of utilization by other tissues.

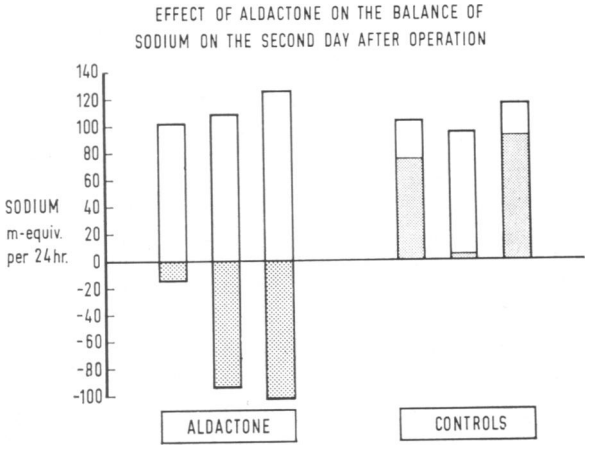

Fig. 2. Effect of an aldosterone antagonist on postoperative sodium balance.

The urinary excretion of adrenocorticosteroids gives a more complete picture of the total adrenal response. The 17-oxogenic steroids which represent cortisol and its metabolites are increased for 3–4 days after major operations. The 17-oxosteroids which are mainly derived from the metabolites of adrenal androgens hardly alter (Fig. 1*b*). The extent and duration of the increased urinary excretion of cortisol metabolites depends upon the severity of the injury. Complications such as secondary haemorrhage or infection lead to prolongation of the increased output. The capacity of the adrenal to secrete at a high rate during very prolonged stress is considerable and exhaustion rarely occurs.

It is now possible to measure the actual rate of production of cortisol by examining adrenal venous blood and measuring the concentration of steroid and rate of blood flow. Production rates about 10 times the resting level have been recorded soon after injury (Hume *et al.*, 1962).

Aldosterone

Raised aldosterone levels were first detected in surgical patients by means of bio-assay techniques. The urine of postoperative patients was found to have sodium-retaining properties when injected into adrenalectomized rats (Llaurado, 1955). Another indirect method of studying aldosterone activity consists of examining the effect of an aldosterone blocking agent (spironolactone) on the postoperative balance of sodium. The daily balance of sodium was measured in six patients after inguinal herniorrhaphy. Three were given spironolactone (400 mg. per day by intramuscular injection) and the remaining three acted as controls. The patients given spironolactone all excreted large amounts of sodium after operation compared to the controls. The striking difference on the second postoperative day is shown in Figure 2. This study suggests that a sodium-retaining hormone is active after operation and that this activity can be abolished by an aldosterone blocking agent.

Direct chemical estimations of urinary aldosterone levels can now be made and an increased output has been recorded after operation (Hume *et al.*, 1962).

THE PERMISSIVE ROLE OF THE ADRENAL CORTEX

The relationship between the adrenocorticoid and the metabolic changes in the postoperative period has been the subject of much speculation. Both responses occur simultaneously and the administration of A.C.T.H. or cortisol to resting subjects produces protein catabolism, an increased excretion of potassium and sodium retention, identical to those recorded after operation. A correlation was also reported between the extent of the postoperative negative balance of nitrogen and the amounts of cortisol and its metabolites found in the urine (Moore *et al.*, 1955). These observations suggested that in the postoperative patient the adrenocortical response was the direct cause of the changes in metabolism. However, there is much evidence against this view. In fact, our present concept is that the role of the adrenal cortex is not so much causative as permissive; that is to say, the presence of cortisol is necessary to permit the changes to occur, but that the adrenal steroids do not initiate the changes.

Evidence of this concept comes from metabolic balance studies on patients undergoing total adrenalectomy who therefore have no adrenal response. It was found that as long as these patients were maintained on constant doses of cortisone before and after operation their metabolic responses were identical to those of patients with functioning adrenals. Patients undergoing complete hypophysectomy also have a normal metabolic response provided they are given constant doses of cortisone (Mason, 1955).

Let us now look at the nitrogen balance after operation in a patient who had undergone total adrenalectomy two years previously (Fig. 3). This lady was maintained on a steady dose of 50 mg. of cortisone per day throughout the period of study. The urinary excretion of nitrogen rose after operation and the patient was in negative balance for at least five days. This response is similar to that recorded in other patients with functioning adrenal tissue undergoing similar operations.

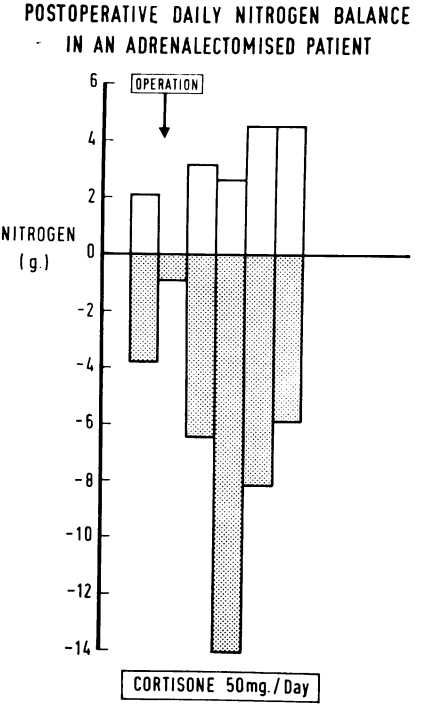

Fig. 3. Nitrogen balance after operation in patient with total adrenalectomy.

However, it should be noted that constant dosage of cortisone does not necessarily mean a constant blood level. The blood level of steroid does rise under these circumstances because of a decreased metabolism of cortisol by the tissues.

Let us now look at two other observations which illustrate the independence of the adrenal and metabolic responses.

Patients with gross malnutrition and wasting who require major operations have no spare protein-containing tissues for catabolism. The urinary excretion of nitrogen is very low after operation and a positive balance of nitrogen is maintained throughout the postoperative period.

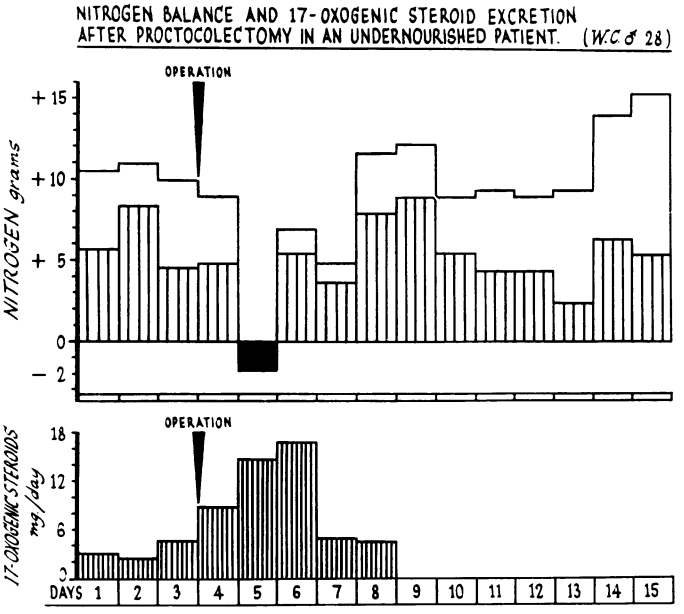

Fig. 4. Nitrogen balance and urinary oxogenic steroid excretion after major operation in a severely undernourished patient.

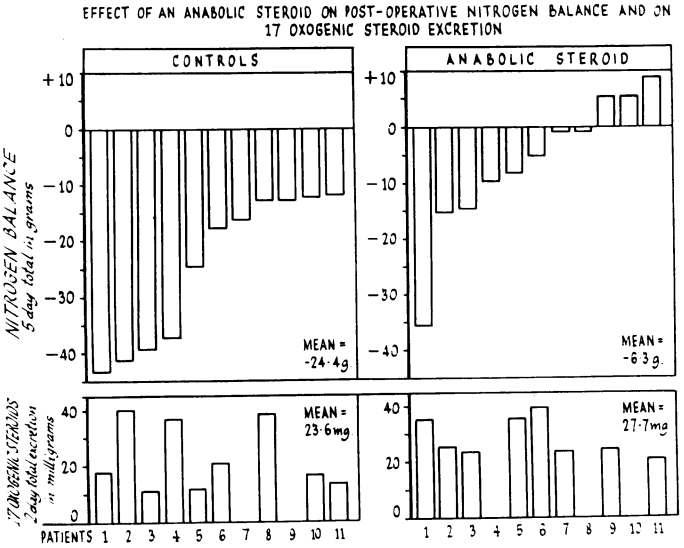

Fig. 5. Effect of an anabolic steroid on postoperative nitrogen balance and 17-oxogenic steroid excretion.

The adrenocortical response to major operations in such situations is brisk and normal in extent (Fig. 4).

Urinary nitrogen levels are a reflection of the general nutrition of the patient rather than an indicator of cortisol liberation. It has been suggested that if debilitated subjects do produce a catabolic response they invariably die.

The independence of the two responses is also demonstrated by a study of the effect of an anabolic steroid on postoperative metabolism. These analogues of testosterone have potent nitrogen-retaining properties in resting subjects, but they have also been shown to suppress some aspects of adrenocortical function. It seemed important to study their effect on the adrenocortical and metabolic response to moderately severe operations and compare the results with control subjects. The total balance of nitrogen for the first five days after operation was calculated and is shown in Figure 5. Negative balance appears below the zero line and positive balance above. All the control subjects were in negative balance and the mean was –26 gm. The patients given an anabolic steroid from the time of operation had a marked reduction in nitrogen excretion and three were actually in positive balance. The mean balance was only –6 gm. The postoperative urinary oxogenic steroid excretion was measured for most of these patients and it was found that while the anabolic steroid reduced the nitrogen loss it had no effect on the adrenocortical response (Johnston and Chenneour, 1963).

It must be emphasized that not only are adrenocortical secretions necessary for a normal metabolic response but also for a satisfactory recovery after severe injury. If adrenal function is impaired and cortisol is unavailable, circulatory homeostasis is threatened in a way which is not fully understood, and death may occur as a result of peripheral circulatory failure.

ADRENAL MEDULLA

Cannon (1914) developed the concept of a neuro-endocrine response to stress and suggested that increased sympathetic and adrenal medullary activity caused the vasoconstriction and tachycardia which often followed injury. Recent studies have shown that the urinary excretion of catecholamines, measured by chemical assay, is increased for many days after severe injury (Pekkarinen, 1960). Other workers using bio-assay methods have found a similar but less prolonged rise after uncomplicated major operations (Halme *et al.*, 1957). Animal studies in which a catheter is inserted in the adrenal vein show that haemorrhage and anaesthesia can stimulate adrenal medullary secretion (Walker *et al.*, 1959).

Heymans (1960) has investigated the way in which the adrenal medulla is activated. Afferent impulses pass from pressure receptors in the carotid

sinus area to the medulla oblongata, and efferent impulses pass from there via the sympathetic outflow tracks to the adrenal medulla.

The relationship of adrenaline production and adrenal cortical activity is important. Adrenaline and noradrenaline are required in the injured for the sensitization of many tissues to the action of cortisol. Both medullary and cortical hormones are required for the maximal vascular response to rapid loss of blood, and in animals adrenaline can stimulate the output of A.C.T.H. from the anterior pituitary. This has not been confirmed with certainty in man.

PITUITARY

Neurohypophysis

A substance with antidiuretic activity has been isolated from the urine of postoperative patients. There is good evidence that this originates in the posterior pituitary. Patients with diabetes insipidus or hypophysectomized patients do not exhibit postoperative oliguria. The stimulus for the release of antidiuretic hormone is a change in the plasma osmolarity which is determined by the concentration of sodium and chloride. Osmoreceptors in the walls of the carotid vessels transmit these stimuli to the neurohypophysis (Verney, 1958).

Anterior pituitary

A.C.T.H. production is increased after injury. The evidence for this comes from bio-assay methods in which the cortisol levels of the adrenal venous effluent are measured in hypophysectomized rats (Cooper and Nelson, 1962). The peak level of plasma A.C.T.H. occurs within a few hours of injury at about the same time as the highest cortisol levels occur.

There is no evidence as yet of any alteration in the postoperative output of thyroid-stimulating hormone or gonadotrophic hormones.

Growth hormone is of some interest in the postoperative period. Recovery from hypophysectomy does not require added growth hormone, so its presence cannot be considered as essential. There is some evidence in man that pituitary growth hormone is rapidly depleted after injury. Experiments in small animals have shown that injections of growth hormone can minimize the weight loss and retardation of growth which follows serious injury. The anabolic activity of potent human growth hormone was investigated in a series of patients after operation who were given between 5 and 10 mg. of hormone by injection immediately after operation. The potency of the hormone was tested by its power to mobilize free fatty acids in resting subjects. Injections of human growth hormone had no effect on the excretion of nitrogen after operation. The role of growth hormone in the anabolic phase of convalescence awaits further study (Johnston and Hadden, 1963).

ACTIVATION OF THE ADRENAL AND METABOLIC RESPONSES

The mechanism by which the adrenal and pituitary activity is stimulated and the metabolic changes initiated has aroused much speculation, and is not completely understood.

Many of the components of the experience of injury can of themselves initiate one or other response. For example the pain, fear and emotional disturbances associated with the preparation for operation can cause a release of excessive adrenaline and aldosterone. Immobilization and starvation are followed often by protein catabolism and increased outputs

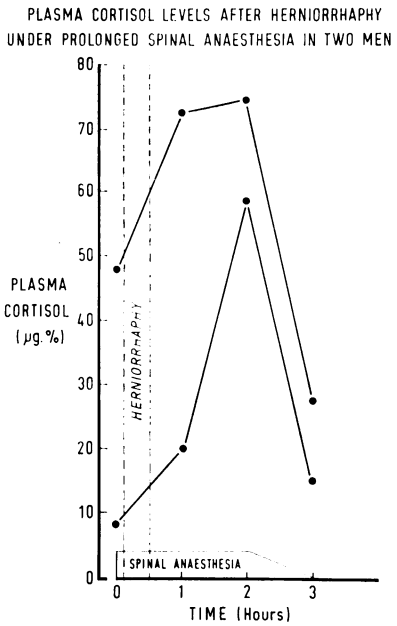

Fig. 6. Plasma cortisol levels during operation under spinal anaesthesia.

of urinary nitrogen. Drugs like morphine and anaesthetic agents such as ether will produce a quick response from the pituitary adrenal axis. Blood loss alone can initiate endocrine as well as metabolic activity.

The main stimuli after injury probably come from afferent nerve endings in the area of the wound. Sensory impulses from the wound pass by way of the posterior columns to the higher centres and on to the hypothalamus. The hypothalamus is connected to the pituitary by nervous tissue as well as a system of fine capillary blood vessels. A corticotrophic-stimulating substance has been isolated from the hypothalamus, which appears to be adrenaline in some animals, but in man its exact nature is uncertain (Ganong, 1963).

The importance of the sensory pathways in the spinal cord can be assessed by studies on the effect of injury or operation in the paralysed areas of patients with spinal cord transection. The adrenocortical response to trauma is delayed in onset and reduced in extent in paraplegic subjects (Hume *et al.*, 1962). The effect of operation after spinal anaesthesia does not follow the same pattern (Osborn *et al.*, 1962) as in paraplegic patients.

The effect of operation on the plasma cortisol levels during prolonged spinal anaesthesia is shown in Figure 6. Inguinal herniorrhaphy in two men resulted in a brisk and normal rise and fall in the level of the plasma cortisol. The pattern of the response was similar to that seen during operation under general anaesthesia. It would appear that other afferent pathways from the frontal lobes, etc., are able to initiate an adrenocortical response in the presence of a spinal block.

The effect of surgical operation and A.C.T.H. stimulation on the output of individual adrenocorticosteroids were compared. If A.C.T.H. is the final common pathway to the adrenal after injury, then the effect of operation and subsequent stimulation with A.C.T.H. should be very similar.

The mean daily output of 17-oxogenic steroids, tetrahydrocortisol, tetrahydrocortisone and allotetrahydrocortisone (cortisol metabolites) was measured before and immediately after operation. The output of each metabolite was found to be increased. The effect of injections of A.C.T.H. on the same metabolites was studied in the same patients after an interval of 3–4 months. The increase after A.C.T.H. stimulation was more marked than that observed after operation.

The mean daily output of 17-oxosteroids and androsterone, aetiocholanolone and dehydroeprandrosterone (metabolites of androgens) were similarly measured. Surgical stress did not produce any increase in the output of these metabolites and in fact the excretion of the latter two was depressed. On the other hand, A.C.T.H. injections did cause an increase in the output of each androgenic metabolite.

It would appear that while A.C.T.H. stimulates all aspects of adrenocortical production surgical stress only stimulates the secretion of cortisol and its metabolites. It is possible that the rate of utilization and conjugation of adrenal androgens is so speeded up after injury that an increased output cannot be detected by measuring urinary levels.

THYROID

Let us now look at the effect of trauma on some aspects of thyroid activity. It has proved exceedingly difficult, in spite of numerous investigations, to demonstrate beyond question that the thyroid responds in any way to the numerous stimuli associated with trauma (Goldenberg *et al.*, 1956). Some of the aspects of altered metabolism which occur after

serious trauma are similar to the metabolic effects of increased levels of circulating thyroid hormone. Such changes are:

1. An increased oxygen consumption and an elevated metabolic rate.
2. An increased heat production and raised body temperature in the absence of infection.
3. The breakdown or catabolism of protein-containing tissues.
4. Elevation of the blood sugar.

Each of these alterations in metabolism can be seen frequently in patients with hyperthyroidism.

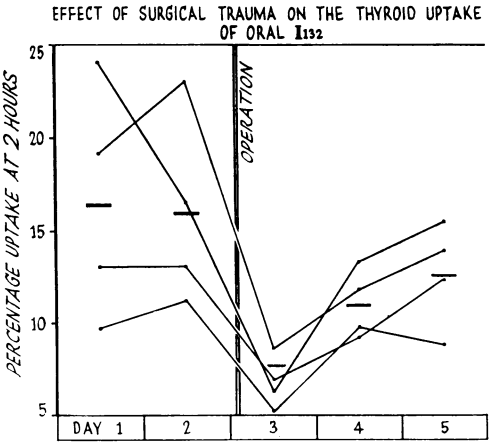

Fig. 7. Effect of operation on the uptake of ^{132}I by the thyroid.

The fact that thyroxine, T4, acts slowly and produces metabolic changes after many hours suggested that it could not in fact initiate the metabolic changes which occur so very quickly after trauma. However, triiodothyronine, T3, produces metabolic activity within a few hours and it is just possible that this hormone may participate in early post-operative metabolism.

In order to detect sudden changes in thyroid activity, three tests of thyroid function were selected which could be repeated at frequent intervals before and after operation.

The thyroid uptake of the isotope ^{132}I was studied first. This isotope has a half-life of only 2.6 hours and after an oral dose less than 1 per cent persists in the thyroid by the next day. In contrast the maximum thyroid uptake of ^{131}I only occurs after 24 hours. The effect of inguinal herniorrhaphy on the daily thyroid uptake of an oral dose of 25 microcuries

^{132}I was studied in four patients (Fig. 7). The percentage uptake at two hours was recorded. Operation took place early on the third day and there was an immediate fall in uptake in each patient on the day of operation with a tendency to return to normal limits on the subsequent two days. The urinary excretion of the isotope was also reduced.

The possibility that this reduced uptake and excretion was due to a postoperative reduction in intestinal absorption was investigated by giving the same dose intravenously. The uptake still fell after operation, although there was not the same tendency to return to normal limits on the next two days. Many explanations claimed investigation; these changes in thyroid function were occurring at a time when the blood levels of A.C.T.H., cortisol, adrenaline and possibly also of thyroid hor-

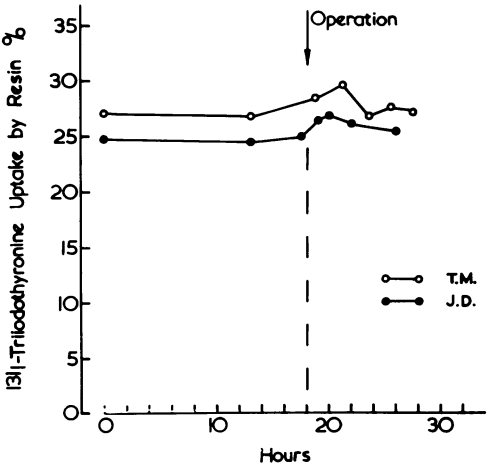

Fig. 8. Effect of herniorrhaphy on the level of circulating thyroid hormone.

mone were increased. There is some evidence that each of these hormones, under certain circumstances, has the property of inhibiting thyroid function. Each component of the endocrine response to operation was investigated separately. An infusion of each hormone was given in an amount approximately equal to the output produced during operation. Healthy men volunteered for this investigation. An infusion of 25 international units of A.C.T.H. produced no change in the daily thyroid uptake of ^{132}I. 100 mg. cortisol was infused in four subjects with again no effect on the uptake of ^{132}I. The slow administration of 100 mg. of adrenaline had no effect on the uptake of the isotope in a further two men. The possibility that the reduction in uptake was due to the inhibition of the pituitary T.S.H. mechanism was studied by giving 80 micrograms of triiodothyronine on the third day of the study in two subjects. This dose is equivalent to the daily output of a healthy thyroid gland and it did not

affect the uptake of iodine on the day of the study. However, the uptake of ^{132}I fell in both patients on the following two days. This suggested that the triiodothyronine did inhibit the production of T.S.H. by the pituitary after at least 24 hours and that this in turn caused a reduced uptake of iodine. This control mechanism can only be altered slowly and is obviously not the reason for the immediate postoperative reduction in uptake. Anaesthesia was similar in all the patients and consisted of an induction with thiopentone and maintenance with nitrous oxide, oxygen and halothane. Three patients who required pelvic examinations under

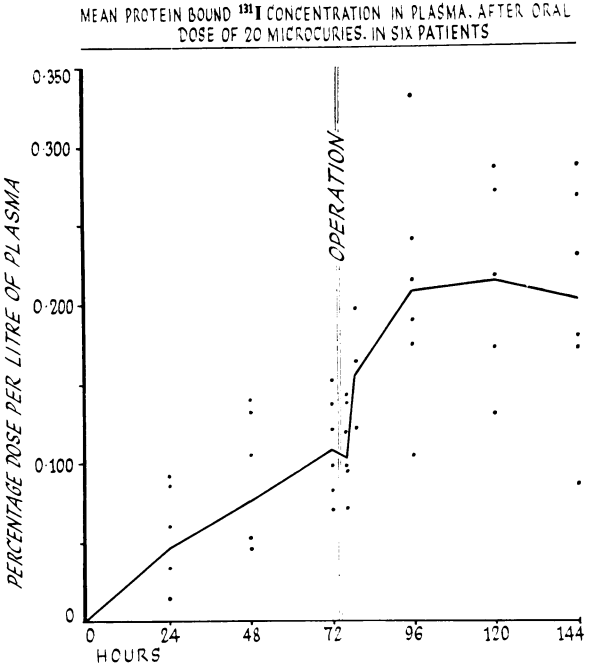

Fig. 9. Changes in concentration of plasma protein bound iodine after operation.

anaesthesia were studied. The anaesthetics were similar in depth and duration to those given for operation and it was found that anaesthesia alone had no effect on the uptake of ^{132}I.

Surgical operation causes an immediate reduction in the uptake of iodine by the thyroid. This is not mediated through other endocrine pathways and is not due to the anaesthetic drugs. It may be due to vasoconstriction and a diminished thyroid blood supply in stress or to a redistribution of iodine throughout the body spaces. The administered iodine may pass more easily to other tissues so that less is available to enter the thyroid.

The output of thyroid hormone was investigated next by measuring the *in vitro* uptake of triiodothyronine ^{131}I by means of a resin sponge placed in samples of plasma collected at short intervals after operation (Goolden and Mallard, 1958).

The amount of labelled triiodothyronine which enters the sponge is proportional to the amount of thyroid hormone already in the plasma and attached to protein. This method shows that there is an immediate rise in the level of thyroid hormone in plasma within an hour of operation. The rise is small and transient and normal levels are resumed within a few hours (Fig. 8).

The level of circulating protein-bound iodine is another method of following the level of circulating thyroid hormone (Fig. 9). The level of radioactive iodine bound to protein rises steadily in the first few days after an oral dose and a plateau is soon established. There is a sharp rise in the protein-bound iodine after operation. This can be detected within six hours and it persists for about 48 hours. These two studies indicate that thyroid hormone is released into the circulation after injury. The amount is small and the period of overactivity is so brief that it is difficult to be sure that these observations can explain the metabolic changes which we have enumerated.

THE PANCREAS

There is as yet no information on plasma insulin levels after injury, but we have some evidence of changes in carbohydrate metabolism which suggests either a reduction in insulin production or an increase in the levels of insulin antagonists after trauma.

Hyperglycaemia, with blood-sugar levels between 400 and 700 mg. per 100 ml., is a frequent finding after severe injury and the idea of " stress diabetes " has been introduced. Single estimations of blood sugar only give limited information. For this reason the capacity of the tissues to utilize added glucose was investigated by means of the intravenous glucose tolerance test. A loading dose of 50 c.c. of 50 per cent glucose was given by a slow intravenous injection over four minutes. The rate of disappearance of glucose from the peripheral venous blood was measured and plotted on a logarithmic scale. It is possible to calculate the rate of utilization of glucose from the slope of this line.

There was a marked reduction in the rate of utilization of glucose immediately after an operation such as herniorrhaphy. This effect was maximal on the first postoperative day (Fig. 10).

The duration of this reduced utilization was investigated by studying patients before and at varying intervals after operation. The absolute values of the co-efficient of utilization were plotted and the means calculated. The maximum fall occurred on the first postoperative day and normal values were almost reached by the third day in this series,

The mechanism of these changes is of interest and almost certainly of endocrine origin. Adrenaline, cortisol, thyroid hormone and growth hormone all have the property of inducing hyperglycaemia either by stimulating glycogenolysis or blocking the utilization of glucose.

It is interesting to note that the change in glucose utilization returns to normal at approximately the same time as the adrenocortical response ends. These changes in glucose metabolism may be another index of the adrenocortical response to injury.

I should like to conclude by discussing some possible relationships between the wound, the endocrine response, and the altered metabolic

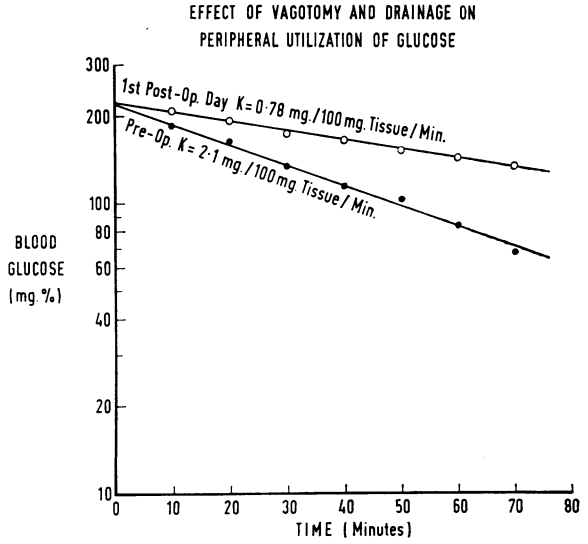

Fig. 10. The reduction in the peripheral utilization of sugar observed after operation.

activity. Recent studies in animals in which the pituitary was completely isolated from the brain showed that a brisk pituitary and adrenal response followed injury in the absence of a neuro-endocrine link. There is evidence that substances such as histamine, serotonin and acetylcholine, which are released in damaged tissues, can directly stimulate the adrenal cortex to produce cortisol and its metabolites. These observations suggest that a substance or " wound hormone " released at the site of injury may participate in the stimulation of the adrenal cortex. It is not known whether or not this wound substance can also initiate metabolic activity provided adrenocortical substances are present to exert their permissive role.

These changes are complex, and the interrelationships between the endocrine and metabolic systems are intricate. If John Hunter had been

alive now I believe he would have summarized our observations by remarking that " the more complicated a machine is the greater dependence each part has upon the other " (Hunter, 1861).

ACKNOWLEDGEMENTS

I am very grateful to Professor R. B. Welbourn for his active help and encouragement, and to Professor H. W. Rodgers for allowing me to study patients under his care.

Dr. R. Chenneour and Mr. D. W. Neill helped with the biochemical studies and Mr. T. K. Bell and Dr. A. W. G. Goolden guided me constantly in the use of radioactive isotopes.

I am grateful to Sisters E. Marks and J. Duff for their detailed care of the metabolic balances in surgical patients, and to Miss M. Pountain for technical assistance.

I wish to thank Mr. G. Smith, Mr. R. Wood, Mr. D. Banks and Mr. C. R. Brecknell for the diagrams.

REFERENCES

ABBOTT, W. E., KRIEGER, H., and LEVEY, S. (1958) *Lancet*, **1**, 704.
BAUER, J. (1872) *Z. Biol.* **8**, 567.
CANNON, W. B. (1929) *Bodily changes in pain, hunger, fear and rage.* New York, Appleton.
CUTHBERTSON, D. P. (1932) *Quart. J. Med.* **1**, 233.
COOPER, C. E., and NELSON, D. H. (1962) *J. Clin. Invest.* **41**, 1599.
GOOLDEN, A. W. G., and MALLARD, J. R. (1958) *Brit. J. Radiol.* **31**, 589.
GOLDENBERG, I. S., LUTWAK, L., ROSENBAUM, P. T., and HAYES, M. A. (1956) *Surg. Gynec. Obstet.* **102**, 129.
GANONG, W. F. (1963) *The Central Nervous System and the synthesis and release of ACTH* in *Advances in Neuroendocrinology*, University of Illinois Press, Urbana.
HAWK, P. B., and GEIS, W. J. (1904) *Amer. J. Physiol.* **11**, 171.
HALME, A., PEKKARINEN, A., and TURONEN, M. (1957) *Acta. Endocrinol.* **24**, Suppl. 32.
HEYMANS, C. (1960) *Perspect. Biol. Med.* **3**, 409.
HUME, D. M., BELL, C. C., and BARTTER, F. (1962) *Surgery*, **52**, 174.
HUNTER, J. (1861) *Essays and Observations on Natural History, anatomy, physiology, psychology and geology*, edited by R. Owen. London, John Van Voorst.
JOHNSTON, I. D. A., and CHENNEOUR, R. (1963) *Brit. J. Surg.* **50**, 924.
————————and HADDEN, D. R. (1963) *Lancet*, **1**, 584.
LLAURADO, J. G. (1955) *Lancet*, **1**, 1295.
MASON, A. S. (1955) *Lancet*, **2**, 632.
MOORE, F. D. (1959) *Metabolic Care of the Surgical Patient.* Philadelphia and London, Saunders.
———————— STEENBURG, R. W., BALL, M. R., WILSON, G. M., and MYRDEN, J. A. (1955) *Ann. Surg.* **141**, 145.
OSBORN, W., SCHOENBERG, H. M., MURPHY, J., ERDMAN, W. J., and YOUNG, D. (1962) *J. Urol. (Baltimore)*, **88**, 1.
PEKKARINEN (1960) *Amer. J. Cardiol.* **5**, 604.
SELYE, H. (1946) *J. clin. Endocrinol.* **6**, 117.
VERNEY, E. N. (1958) *Surg. Gynec. Obstet.* **106**, 441.
WALKER, W. F., SHEREFETTIN, Z., REATTER, F. W., SHOEMAKER, W. C., FRIEND, D., and MOORE, F. D. (1959) *Amer. J. Physiol.* **197**, 773.