natural world from which he has developed, yet his mind is in some way distinct and able to judge that world as though from outside by means of its own conception of value. The world so judged is often found wanting.

A striking part of the discussion is the account of the life history of the malaria parasite and its implications for human life. From the point of view that I may perhaps be allowed to call plasmodio-centric, the story reveals a triumph of adaptation to environment. From the anthropocentric view the triumph is a terrible curse, one of the great disasters. Malaria has destroyed whole civilizations and still brings death and misery to millions. We cannot avoid believing that in this matter the anthropocentric view has a cosmic significance which the plasmodio-centric lacks. We deny that *Plasmodium* has as good a claim to be heard as *Homo*. However, if human moral judgment leads us to condemn some of the happenings of the natural world and approve of others, that is to be taken as a challenge to action, to maintain what is right and alter what is wrong. So far, but no farther, Sir Charles goes beyond his original starting-point of purely natural knowledge, because an honest acceptance of fact compels him to do so. He takes throughout his own line and works things out his own way, but he supports the testimony of a number of thinkers of our time who have deliberately started out from a naturalistic standpoint and found themselves forced to go beyond it by sheer pressure of facts. Alexander, Whitehead, and Laird may be mentioned, and also Woodbridge, in America. Where these thinkers differ most is after they leave the naturalistic view, and there Sir Charles has not committed himself. We must be grateful for what he has given us, expressed with rare felicity. When distinguished men of science, as Gifford Lecturers or otherwise, expound their philosophies they seldom do it so well. Above all, few have the skill in pilotage needed to avoid equally the Scylla of superficiality and the Charybdis of obscurity.

The Synoptic View

In conclusion, perhaps I may turn to Sir Charles's more strictly physiological work, particularly *The Integrative Action of the Nervous System*. Before that book was published there were plenty of facts available but a singular

lack of the right concepts to interpret them. Sir Charles of course marshalled the known facts, adding a good many he had discovered for himself, but above all he provided the concepts which have been used ever since. Pre-Sherringtonian physiology of the central nervous system reminds one of the Oriental tale of the four blind men who examined an elephant. One seized a leg and said the elephant was a kind of tree; another a tusk and proclaimed it a kind of spear; the third the trunk and found it like a snake; the last got hold of the tail and said it was just a rope. Every statement reports a fact, and up to a point does it correctly; but they do not hang together.

The nervous system does contain converging and diverging paths; but how are they interconnected? Its functional unit is the reflex; but how are reflexes interconnected? A reflex does work rather like a penny in the slot machine, but not altogether; what are the differences? Given the Sherringtonian conceptions, anatomical and physiological facts could be seen in a new light—seen all together in a synoptic view and each also better seen in detail. Some of the important points have been well summarized in the foreword added to the new edition of *The Integrative Action*. Any reflex even at the lowest end of the scale operates as part of a system and uses the motor organs of the animal as a whole, though not all at once. It is not a matter of one bundle of receptors, one bundle of paths, and then one bundle of muscles. At the same time, a reflex has a permanent and apparently innate anatomical basis, so that it is an error to confuse reflex action with acquired habit. These more adequate conceptions are not so very easy to grasp; it is much easier to slip into the penny-in-the-slot view and to forget the limitations of reflex action—indeed, it is frequently done.

I mention these points because here, within a definitely restricted scientific sphere, Sir Charles has done the kind of thing the philosopher is always trying to do in a less restricted sphere with rather partial success. In some branches of science it may be possible to do without the synoptic view and see each thing separately; the trees may be more important than the wood. That is hardly possible in physiology, certainly not in the physiology of the nervous system.

METABOLIC DISTURBANCES AFTER INJURY*

BY

J. BEATTIE, M.D., D.Sc.

Bernhard Baron Research Laboratories, Royal College of Surgeons of England

It is remarkable that the existence of a disturbed metabolic state after injury should have remained unrecognized until 1929, when Cuthbertson observed an increase in the urinary nitrogen output following fractures in experimental animals. Later work demonstrated that this phenomenon also appeared in well-nourished human subjects who had sustained injury. The pattern of the metabolic changes in human patients has been worked out in detail (Stevenson *et al.*, 1945). During the first week after injury the urinary nitrogen output rises to a peak and brings about a phase of negative nitrogen balance even on high-calorie and high-protein diets. The output declines until about two to three weeks after injury, when it equals the protein nitrogen input. This phase is called the "katabolic" phase. Following it the input and output remain about equal for a few days or a week, and then the nitrogen output tends to

decline and a phase of positive nitrogen balance begins. This lasts for a variable period, but is usually complete in two to three months after injury. This latter is the "anabolic" phase during which part at least of the nitrogen loss of the "katabolic" phase is repaired. The work of various investigators has shown that at least three factors condition the magnitude of increased nitrogen output in the "katabolic" phase—immobilization in bed, the severity of the injury, and the nutritional state of the individual at the time of injury.

Effect of Confinement to Bed

Keys (1944) observed four normal well-nourished subjects who were put to bed for three to four weeks and allowed out of bed only to evacuate the bowels. At the end of three weeks the nitrogen losses were 51.7, 38.5, 58.6, and 43.5 g.; the body weights, however, showed no appreciable change. In the subject who lost 43.5 g. of

*An abridgment of the Bernhard Baron Lecture given at the Royal College of Surgeons of England on July 4, 1947.

nitrogen the weight fell by only 0.86 kg. at the end of three weeks. With one exception all the nitrogen losses in the third week in bed were in excess of those observed during the first week (Table I).

TABLE I.—*Nitrogen Loss from Confinement to Bed (Calculated from Keys's data)*

Period	Nitrogen Balance per Period			
	Case 1	Case 2	Case 3	Case 4
Control	0	0	0	0
1st week in bed	-18.4	-13.4	-12.0	-12.5
2nd " " "	-9.3	+2.9*	-21.5	-19.5
3rd " " "	-24.0	-28.0	-25.1	-11.5
Total in bed	-51.7	-38.5	-58.6	-43.5
Ten days after getting up ..	+8.6	+5.3	+14.2	+27.4

* Protein input raised from 54 to 200 g. protein for this week.

These findings are of great importance, for they show clearly that a protein intake of 54 g. a day is not sufficient to prevent nitrogen loss in a patient confined to bed on an adequate calorie input. On the other hand Keys noted that in two subjects confined to bed it was possible to bring about a state of positive nitrogen balance on an intake of 110 g. of protein a day. Positive nitrogen balance during the ten days immediately following the three weeks in bed was attained on a protein input of 84 g. a day (13.4 g. of nitrogen). The variations in the speed with which the lost nitrogen was restored were most remarkable, although the diets were identical.

Effect of Injuries of Differing Severity

The following studies indicate how the magnitude of the nitrogen loss varies with different types of injury (Table II).

TABLE II.—*Operations and Injuries (Age of patients, 21-34 years)*

Trauma	Negative Nitrogen Balance		Duration of "Katabolic" Phase (Days)
	G.	G. per Day (average)	
Appendectomy ..	26	2.2	12
..	29	2.4	12
..	37	1.7	17
Burns (lower limbs) ..	201	2.2	39
Burns (hands and arms) ..	216	5.2	47
Fracture of humerus ..	98	4.6	29
Fracture of femur ..	124	3.4	41
Osteotomy ..	32	3.0	14
..	..	2.3	..

The duration of the "katabolic" phase is given. This is measured from the morning of the day of operation in the operation cases and from the morning of the day after injury in the accident cases. All these patients were given diets which contained 2,750 calories and 100 g. of protein (16 g. of nitrogen) daily. On such diets Keys's data would indicate that normal uninjured persons confined to bed would have been in positive nitrogen balance or at least in nitrogenous equilibrium. The losses recorded in these cases of injury or operation may therefore be ascribed to the effects of the injury sustained. The total nitrogen loss and the average daily loss would seem to bear a direct relation to the severity of the injury, being highest in the cases of burns and lowest in the operation cases. Similar results have been reported by Browne and his group.

Effect of Undernourishment Before Injury

Browne *et al.* (1945) drew attention to the apparent absence of a "katabolic" response after operation or injury in persons who at the time of injury were in a poor nutritional state. Howard and Mason (1946) showed that when such people were put to bed they did not go into negative nitrogen balance as Keys's subjects did, and, moreover, when subjected to operation a negative nitrogen balance either did not develop or if one appeared it was of small

magnitude. The following case illustrates the absence of the "katabolic" response in a poorly nourished patient.

A man aged 65 was suffering from an annular carcinoma of the oesophagus. Owing to difficulty in swallowing, food had been restricted for about three months, and for three weeks before admission had been limited to fluids. He had lost about 20 kg. when admitted—normal weight, 64 kg. The late Mr. Tudor Edwards regarded the condition as operable and planned the removal of the section of the oesophagus containing the tumour and anastomosis of the oesophagus to the stomach within the thorax. The necessary freedom was secured by dislocating the major part of the stomach into the left pleural space. The operation was successful and the patient recovered.

Before operation it was estimated that the patient was in nitrogenous equilibrium on a diet containing 1,600 calories and protein equivalent to 5 g. of nitrogen a day. On the day of operation and for the next six days he received by vein solutions of protein hydrolysate and glucose sufficient to provide 1,600 calories and 8.6 g. of nitrogen. Over the seven days the nitrogen balance was:

Input nitrogen ..	60.2 g.	Urinary nitrogen ..	51.8 g.
		Faecal nitrogen ..	6.0 g.
		(10% of input)	57.8 g.

There was thus an apparent but slight positive nitrogen balance equal to 0.34 g. of nitrogen a day. While such a small positive balance is of little significance, it is significant that he did not go into negative nitrogen balance.

Source of the Excess Urinary Nitrogen

Cuthbertson *et al.* (1939) showed that "katabolic" response was absent after injury in experimental animals which had been fed on a protein-free diet until their nitrogen excretion became constant. They suggested that the excessive output of nitrogen which follows injury arises from storage protein and not from essential tissue substances, as when the storage protein was depleted there was no increase in the output of nitrogen after injury. Body protein has been differentiated by Whipple into (a) "fixed" or indispensable cell protein without which cellular life ceases, (b) "dispensable" protein which can be yielded up by the cell as a source of energy during starvation, and (c) "labile" protein which can move out of or into the cell when the concentration of the plasma proteins falls or rises. Presumably Cuthbertson's storage protein can be equated with the sum of "dispensable" and "labile" protein of Whipple.

This protein may be present in the cell cytoplasm either as something apart from the cell protoplasm or as only a part of the cytoplasmic mass. If the cytoplasmic mass were reduced in quantity the cell would yield up not only protein but a quantity of its intracellular fluid. On the other hand it is conceivable that the cytoplasm could yield up protein while conserving its intracellular fluid. Howard and Mason (1946) found in cases of injury that nitrogen loss was not accompanied by a proportionate loss of potassium and phosphorus from the body. Presumably protein was yielded by the cell cytoplasm, but the intracellular fluid, which contains potassium and phosphorus, was conserved. Keys (1944), however, found in patients who were confined to bed but were otherwise normal that there was some potassium loss during the period when a negative nitrogen balance existed. Presumably such persons did lose some intracellular fluid. He noted that the body-weight loss was less than that which might be expected on the basis of the nitrogen loss. Both groups of experiments thus tend to support the idea that the body cells can yield up some of their protein without any proportionate loss of intracellular fluid. The evidence is therefore in favour of some part of the cellular protoplasm being "storage" protein. This, however, must not be taken

to imply that such protein is an inert store. It is difficult to estimate how much protein can be yielded up without causing death of the cell. Lusk (1928) calculated that the average human subject weighing about 68 kg. had a total nitrogen content of 2,000 g. Howard (1943) and Stevenson *et al.* (1945) have reported nitrogen losses of between 250 and 300 g. after fractures and burns. If all this nitrogen came from "storage" protein at least 15% of the body protein is available for the "katabolic" response. It is possible that when this amount of nitrogen is lost some mechanism may come into play to prevent destruction of more protein.

Mechanism of the "Katabolic" Response

Present knowledge of the mechanisms involved in the "katabolic" response is extremely scanty. Some facts have been brought to light which may in the future be found to have some causal relationship to the increased nitrogen output after injury. It has been found in normal persons that a few days after injury the urine contains large quantities of a cortin-like material (corticosteroid). The amount may be from three to five times the normal amount. The peak output is reached by the end of the first week after injury and thereafter tends to decline, reaching the normal level at about the time when nitrogen equilibrium is established (Browne, 1942). There is thus some parallelism between the daily excretion of corticosteroid and that of nitrogen. This material when concentrated has the power of increasing the glycogen content of the liver. This effect is identical with that obtained after the injection of the cortin (corticosteroid) of the adrenal cortex. It is believed that this corticosteroid inhibits the synthesis of amino-acids into protein. Consequently these acids, if not utilized by the body, are deaminated by the liver and in part built into liver glycogen. Their nitrogenous fraction is transformed into urea and excreted. If it be assumed that the increased excretion of corticosteroid after injury represents an increased production of the substance and not a diminished utilization or an increased permeability of the kidney to them, it might be inferred that a causal relationship exists between increased corticosteroid production and increased nitrogen output. Such an inference is however not justified, for many reasons. Injections of pituitary corticotrophic hormone into normal persons induce an increased output of corticosteroid in the urine (Schenker and Stevenson, 1943), an effect which is not accompanied by a parallel rise in nitrogen output. Venning (1944) has reported a case of burns which had a high corticosteroid output until the 28th day after the accident. Nitrogen excretion commenced to decline on the 21st day in spite of an increased protein input which had been given from the 12th day. The nitrogen balance in fact became positive before the level of corticosteroid excretion began to fall. This must mean that the "katabolic" response was waning at least 10 days before the corticosteroid output decreased.

It has been pointed out that in debilitated subjects injury does not lead to an increased output of nitrogen in the urine. The urinary corticosteroid excretion in such cases either is not increased or is reduced below the normal level. This lack of adrenal response to injury suggests that the explanation of Cuthbertson *et al.* (1939) that the lack of response was due only to absence of "storage" protein is not adequate. If such persons were given a large protein input after injury it might be expected that they would katabolize this extra protein as would a normal person who had been injured. The fact that they do not, but instead conserve the increased protein input, suggests that the mechanism for the "katabolic" response is being

inhibited. The following case shows how avidly the organism seizes on the extra protein in the input when injury is sustained in the debilitated state.

A child aged 14 received multiple injuries including fractures of both tibiae and fibulae and severe lacerations to one of the lower limbs. After 10 weeks in hospital the fractures had not united and epithelization of the lacerated area had slowed down considerably. Skin-grafting of this area failed. Observation for a week after the skin-grafting operation showed that the nitrogen input was 39.5 g. and the total nitrogen output 40.2 g. Calorie input averaged 1,520 calories a day. The calorie input was raised to 1,750 daily with a protein nitrogen content of 15 g. a day. Over this week the nitrogen balance was:

Nitrogen input	.. 106.5 g.	Urinary nitrogen	.. 38.5 g.
		Faecal nitrogen	.. 10.7 g.
		(10% input)	.. 10.7 g.
			49.2 g.

Positive nitrogen balance = 57.3 g., or 8.2 g. a day.

At the end of the week there was a noticeable improvement in the clinical condition and an active epithelization of the lacerated area. The denuded area from which the skin-graft had been taken was healing rapidly. The diet was increased to 2,100 calories and 22 g. of nitrogen a day. At the end of this week the nitrogen balance was:

Nitrogen input	.. 160.3 g.	Urinary nitrogen	.. 49.2 g.
		Faecal nitrogen	.. 16.0 g.
		(10% input)	.. 16.0 g.
			65.2 g.

Positive nitrogen balance = 95.1 g., or 13.6 g. a day.

After another week on the same diet the positive nitrogen balance was 81.1 g., or 11.6 g. a day. The total gain in nitrogen was 233.5 g. over a period of three weeks. It was then decided to skin-graft the lacerated area. During the following week, the first day of which was the day of operation, the nitrogen balance was:

Nitrogen input	.. 132.7 g.	Urinary nitrogen	.. 156.2 g.
		Faecal nitrogen	.. 13.3 g.
		(10% input)	.. 13.3 g.
			169.5 g.

Negative nitrogen balance = 36.8 g., or 5.3 g. a day.

Thus after a period of three weeks in a state of positive nitrogen balance a second operation provoked the normal response ("katabolic") which was lacking after the first. The clinical condition during this "katabolic" phase remained good and the skin-graft "took." Healing was rapid, and four weeks after the increased diet had commenced the fractures had united firmly.

The "katabolic" response to injury is thus conditioned not only by the injury itself but by some other unknown mechanism which may or may not involve the adrenal cortex. The fact that a mere increase in the corticosteroid output in the urine in normal uninjured persons produced by pituitary corticotrophic hormones is not associated with increased urinary nitrogen output suggests that increased adrenal activity alone cannot explain the "katabolic" response (Browne, 1943). In the debilitated person who has been injured increase in the protein input is not accompanied by increased nitrogen and corticosteroid outputs, which is precisely the reverse of the reaction of the normal individual. Browne *et al.* (1945), however, have reported two cases in which there had been loss of weight but which responded to increased nitrogen inputs by a typical "katabolic" reaction. Both patients died. It would appear that in them the mechanism which inhibited the "katabolic" reaction in the debilitated state was absent. In one of these cases the corticosteroid excretion was estimated and found to be of the same order as that of previously healthy severely damaged individuals.

In the "anabolic" phase which follows after the "katabolic" reaction the urine contains normal quantities of

the urinary corticosteroids and also of the 17-ketosteroids. The latter substances are derived in part from the adrenal cortex. Kochakian (1946) has shown that a 17-ketosteroid, presumably of adrenal origin, which has the power of conserving nitrogen can be isolated from the urine. This power is possessed by 17-ketosteroids of gonadal origin but is less pronounced in them. The magnitude of the positive nitrogen balance during the "anabolic" phase is not paralleled by the magnitude of the 17-ketosteroid excretion. It is independent of both the corticosteroid and 17-ketosteroid excretion. Testosterone propionate has been used with some success in increasing the positive nitrogen balance, but it has obvious disadvantages. It cannot in any way inhibit the "katabolic" response after injury in normal persons, but can increase the positive nitrogen balance after injury in debilitated individuals. The factors, other than the level of protein input, which influence the magnitude of the positive nitrogen balance in the "anabolic" phase are thus unknown.

Cuthbertson (1943) considered that the increased nitrogen loss after injury might result from the breakdown of protein molecules in an attempt to supply some component amino-acid of the protein molecules which was necessary for the repair process. If such an amino-acid formed, say, 3% of the protein molecule the remaining 97% of the molecule might be metabolized, as it could not be re-synthesized into protein in the absence of an essential part of the molecular structure. The nitrogenous portion (amino-N) of 97% of the protein molecule would be transformed into urea and excreted, leaving the carbon chains to be utilized for energy production or for storage as glycogen. Croft and Peters (1945) thought that in burns the organism might require extra methionine. They reasoned that if this were so then the addition of an adequate quantity of this amino-acid to the diet would satisfy the need and spare protein from being broken down to meet it. Their results suggested that methionine supplements reduced the nitrogen loss after burns. Unfortunately, it has not been found possible to confirm their results in human patients subjected to injury or after burns. This, however, does not imply that Cuthbertson's original hypothesis is untenable. The amino-acid necessary for repair might be one of the other "essential" amino-acids in the protein molecule. Rose, Haines, and Johnson (1942, 1943) have shown that nitrogen equilibrium can be maintained in human subjects when all the input nitrogen is provided by ten "essential" amino-acids. If one of these amino-acids is removed from the daily input a negative nitrogen balance follows. Until it has been shown that supplements of these "essential" amino-acids do not reduce or abolish the negative nitrogen balance after injury or operation Cuthbertson's hypothesis remains as a possible explanation of the reason why a negative balance occurs. It does not, however, offer an explanation of how the body protein is broken down and the "essential" amino-acid rendered available.

The position at present is very unsatisfactory. A hypothesis which suggests that the negative nitrogen balance after injury is due to the demand for some component of the protein molecule, the remainder of the molecule being metabolized, is not proved. On the other hand a possible hormonal mechanism which on being brought into action inhibits protein synthesis and permits the de-amination of amino-acids to take place at an increased rate has not been proved to have a causal relationship to the "katabolic" response to injury. Thus both the "why" and "how" of the "katabolic" response are uncertain. The finding (Cuthbertson, Shaw, and Young, 1941) that injections of crude extracts of the anterior pituitary gland into animals

with experimental fractures prevented the usual weight loss and excessive nitrogen output is difficult to explain. It might have been expected that such injections would lead to increased activity of the adrenal cortex and presumably to an increased output of corticosteroid, with consequent inhibition of protein synthesis. Precisely the reverse occurred.

The same group of workers made the significant observation that skin wounds in experimental animals did not heal as rapidly as normal when crude extracts of anterior pituitary gland were injected. Now that relatively pure corticotrophic hormone from the pituitary gland is available these experiments require to be repeated and some attempt made to assay the urinary output of corticosteroid and 17-ketosteroids.

Vitamin C and Injury

For some years past in most surgical clinics ascorbic acid (vitamin C) supplements of 200–500 mg. have been employed as a routine in the post-operative period and after injuries. Wolbach (1937) defined the function of the vitamin as being concerned with the production and maintenance of intercellular substances. Bourne (1944) showed that the tensile strength of healed wounds was increased when adequate quantities of the vitamin were provided in the diet. The demand for ascorbic acid is, however, much greater than might be expected were it to be used only at the site of injury. All the patients listed in Table II received daily supplements of 500 mg. of ascorbic acid from the day of operation or from the day after accidental injury for periods up to 25 days. During the first five days of administration no trace of ascorbic acid could be detected in the urine. In the second five-day period the operation cases were all excreting between 50 and 100 mg. of the vitamin on the 10th day. The vitamin was not excreted in the cases of accidental injury. During the third five-day period the ascorbic acid output of the operation cases had risen to between 176 and 234 mg. a day on the 15th day. No vitamin was detected in the cases of burns on this day. These cases were given supplements of 500 mg. for a further 10 days. On the 20th day the fracture cases were excreting more than 150 mg., but no ascorbic acid appeared in the cases of burns. These showed traces of the vitamin on the 23rd day, and on the 25th day excreted less than 100 mg.

Long (1947) has pointed out that when the adrenal cortex is thrown into activity by some physiological stress such as injuries or infections the ascorbic acid content of the cortin diminishes. In his article he has noted the work of Lowenstein and his colleagues, who have suggested that ascorbic acid is a necessary component of some of the active corticosteroids existing in the adrenal cortex. It is thus probable that some part of the increased demand for ascorbic acid after injury may come from the adrenal cortex. The relation of ascorbic acid to the "katabolic" response may be even closer than this statement implies. The vitamin in the presence of traces of copper is known to augment the activity of the enzyme arginase (Edlbacher and Leuthardt, 1933). As arginase is concerned with what appears to be the principal urea-producing mechanism in the liver (Krebs and Henseleit, 1932), the importance of this reinforcing action is apparent. Kochakian (1944) has found that after a period of undernourishment rats show a fall in the liver arginase of 52%. It is by no means certain that the local demand for the vitamins at the site of injury, the need for more ascorbic acid in the adrenal cortex, and an increased supply to the liver are sufficient to explain the large over-all requirements of the body for ascorbic acid after injury.

Calcium Metabolism after Injury

It has been pointed out above that mere confinement to bed can produce a negative nitrogen balance. Reifensstein (1942) also showed that under like conditions the urinary calcium output may be doubled and the faecal calcium increased by one-third. In fracture cases the increased urinary calcium excretion reaches much higher levels. It then becomes a potential danger, for if conditions within the urinary apparatus are favourable the calcium may be precipitated as calcium phosphate and give rise to renal calculi. Shorr (1942) has shown that calcium excretion in the urine is balanced accurately in normal persons by the excretion of citrate. If enough of the latter ion is not available precipitation of calcium phosphate may occur. Investigations by Shorr and others have led to three possible methods for preventing calcium phosphate precipitation. The first is to use substances which can act as precursors of urinary citrate. No fully adequate material, however, has yet been found. The second method is to increase the output of urinary citrate by the use of oestrin; but such a method is not always desirable on account of other effects. The third method is to reduce urinary phosphate excretion by increasing faecal phosphate excretion. This Shorr (1943) accomplished by giving aluminium hydroxide by mouth. That substance forms an insoluble precipitate of aluminium phosphate in the bowel and leads to increased passage of phosphate into the bowel lumen. The value of these methods has not yet been fully explored.

Summary

In well-nourished persons subjected to injury the urinary nitrogen output increases to reach a peak by the end of the first week after injury. This high output gradually declines until in less severe injuries it reaches the normal level by the end of two to three weeks. Thereafter the level of output may decline further, but by the end of two to three months it returns to normal. The high nitrogen output may be diminished but not abolished by high-protein diets during the first seven to ten days. Continuation of such diets, however, leads to a positive nitrogen balance during the latter half of the period of high urinary nitrogen output and during the subsequent period. In this way the depletion of body nitrogen is compensated. The magnitude of the nitrogen loss in the urine depends on the nutritional state of the individual and on the severity of the injury. Some of the loss is due to the effects of immobilization in bed, but this part is relatively small. Poorly nourished individuals show either no metabolic response or a diminished one after injury. There is evidence that the severity of the injury conditions the magnitude of the nitrogen loss in the urine. The source of the nitrogen lost in the urine during the period of high output is the body cells. These apparently can yield up protein without affecting their viability.

The mechanisms involved in these metabolic disturbances are unknown. It has been shown that the urine during the period of high nitrogen output contains large quantities of corticosteroid material presumably derived from the adrenal cortex. It is not certain how an increased output of such material is related to the increased urinary nitrogen output.

After injury the body requirement for ascorbic acid (vitamin C) is apparently greater. Some of the increased demand may be due to an increased utilization in the adrenal cortex and the liver and some to the needs of the tissues at the site of injury.

The increase in calcium output in the urine after injury is a potential danger, as insoluble calcium phosphate may be precipitated, leading to the formation of calculi. Various methods of treatment to avoid precipitation have been advocated, but these are still in the experimental stage.

I wish to thank the many surgeons who permitted observations to be made on their patients and the dietitians who co-operated in this work. My thanks are also due to Mrs. P. H. Herbert, Leverhulme Scholar, and to my technical staff—S. P. Steward, L. S. Drewell, and R. D. Chambers—for their assistance in the analytical

work. Dr. J. S. L. Browne has permitted me to quote freely from the reports of his group which have been recorded in the minutes of the Conference on Bone and Wound Healing.

REFERENCES

- Bourne, G. H. (1944). *Lancet*, **1**, 688.
 Browne, J. S. L. (1942). Conference on Bone and Wound Healing, Josiah Macy, Jr., Foundation, **2**, 43.
 — (1943). *Ibid.*, **5**, 19.
 — Hoffman, M. M., Schenker, V., Venning, E. H., and Weil, P. (1945). *Ibid.*, **9**, 15.
 Croft, P. B., and Peters, R. A. (1945). *Lancet*, **1**, 266.
 Cuthbertson, D. P. (1929). *Biochem. J.*, **23**, 1328.
 — (1943). Conference on Wound Healing, Soc. for Exp. Biol.
 — McGirr, J. L., and Robertson, J. S. M. (1939). *Quart. J. exper. Physiol.*, **29**, 13.
 — Shaw, G. B., and Young, F. G. (1941). *J. Endocrinol.*, **2**, 468, 475.
 Edlbacher, S., and Leuthardt, Fr. (1933). *Klin. Wschr.*, **12**, 1843.
 Howard, J. E. (1943). Conference on Bone and Wound Healing, Josiah Macy, Jr., Foundation, **5**, 33.
 — and Mason, R. E. (1946). *Ibid.*, **13**, 143.
 Keys, A. (1944). *Ibid.*, **7**, 90.
 Kochakian, C. D. (1944). *Ibid.*, **8**, 56.
 — (1946). *Vitamins and Hormones*, **4**, 255.
 Krebs, H. A., and Henseleit, K. (1932). *Klin. Wschr.*, **11**, 757, 1137.
 Long, C. N. H. (1947). *Recent Advances in Hormone Research*, **1**, 99.
 Lusk, G. (1928). *The Elements of the Science of Nutrition*, 4th ed. Saunders, Philadelphia, p. 101.
 Reifensstein, E. C. (1942). Conference on Bone and Wound Healing, Josiah Macy, Jr., Foundation, **1**, 37.
 Rose, W. C., Haines, W. J., and Johnson, J. E. (1942). *J. biol. Chem.*, **146**, 683.
 — and Warner, D. T. (1943). *Ibid.*, **148**, 457.
 Schenker, V., and Stevenson, J. A. P. (1943). Conference on Bone and Wound Healing, Josiah Macy, Jr., Foundation, **4**, 91.
 Shorr, E. (1942). Conference on Bone and Wound Healing, Josiah Macy, Jr., Foundation, **2**, 99, 106.
 — (1943). *Ibid.*, **3**, 69.
 Stevenson, J. A. P., Schenker, V., and Browne, J. S. L. (1945). *J. Canad. med. Serv.*, **2**, 345.
 Venning, E. H. (1944). Conference on Bone and Wound Healing, Josiah Macy, Jr., Foundation, **7**, 117.
 Wolbach, S. B. (1937). *Science*, **86**, 569.

SYNCHRONOUS COMBINED TOTAL GASTRECTOMY

BY

J. BASIL HUME, M.S., F.R.C.S.

Surgeon, St. Bartholomew's Hospital and St. Andrew's Hospital,
Dollis Hill

AND

GUY BLACKBURN, M.Chir.

Assistant Surgeon, Guy's Hospital and St. Andrew's Hospital,
Dollis Hill

Since the introduction of transthoracic total gastrectomy in 1938 there has been an appreciable improvement in the results of surgery in carcinoma of the stomach. The work, among others, of Churchill, Sweet, Garlock, and Phemister testifies to this admirably and has altered the whole outlook, but even now the figures leave a good deal to be desired. The five-year cure rate is depressingly low, though it is early to assess it, and the mortality rate far too high. Finney and Rienhoff (1929) quoted a 53.8% mortality in 67 cases, Waugh and Fahlund (1945) 44.2% in 77 cases, and Clagett (1945) 16.6% (five deaths in 30 operable cases of malignant disease of the stomach). These figures illustrate the progressive improvement in surgical treatment of an otherwise fatal disease, and a great many factors are responsible—earlier diagnosis, better pre-operative preparation, an increasing resectability rate, advances in anaesthesia, and the introduction of chemotherapy and antibiotics.

This communication is essentially a preliminary one, recording a new method of approach which we have found useful, and clearly some time must elapse before any instructive figures are available or there are results from which deductions can be drawn.