Energy metabolism after injury

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Trauma to a part of the body such as that which occurs in fractures and burns leads to a multitude of changes in the rest of the body and most organs are affected. These changes may be divided into haemodynamic, neuro-endocrine, and metabolic. Of the many metabolic changes which occur, those which come under the heading of energy metabolism are probably the most important, since bodily function depends on energy transformations. Two stages can be discerned in these responses to injury. The first, the 'ebb' period of Cuthbertson (1942), is common to both fatal and non-fatal injuries; the second depends on the outcome. If the patient or animal recovers, the 'ebb' period is followed by Cuthbertson's 'flow' period. If the injury is fatal, the character of the 'ebb' phase alters and death is preceded by a period which has been called necrobiosis (Stoner, 1961). To interpret the changes in injured patients and animals correctly, it is essential to be clear about the differences between these stages. The object of this paper is to discuss the changes in energy metabolism during these stages and also, as far as possible, the underlying alterations in the normal control mechanisms. Although clinical parallels will be drawn when possible, the description of the changes is based mainly on the results of animal experiments, since small mammals, such as the rat, with their small thermal capacity, reflect changes in heat production and loss much more rapidly than larger ones like man.

When a rat is injured at an environmental temperature below the thermoneutral range (29-32°C) its deep body (core) temperature falls. The rate of fall is related to the severity of the injury. If the injury is fatal, the core temperature will continue to drop until death when it may be only a few degrees above the ambient temperature. After a non-fatal injury the core temperature does not usually fall below 32-33°C. After a

variable interval, it will recover and 36 to 48 hours after the injury may be above the usual level even in the absence of infection. When faced with changes in core temperature the first step is to decide whether they are due to changes in the rate of heat production or in the rate of heat loss. In this case the question has been decided by direct gradient-layer calorimetry. In the 'ebb' phase and in necrobiosis heat production is decreased while in the 'flow' period it is increased (Cairnie, Campbell, Pullar, and Cuthbertson, 1957; Stoner and Pullar, 1963; Miksche and Caldwell, 1968). The changes in oxygen consumption run parallel with those in heat production. The matter therefore resolves itself into the study of the effect of injury on heat production.

Heat is produced in the body during the oxidation of substrates in the tricarboxylic acid cycle. All tissues can produce heat, but the most important sites of heat production are the muscles, liver, kidneys, and brain. In certain circumstances, as in the newborn, a specialized tissue, brown adipose tissue, is used to apply heat to specific parts of the body. From the physiological point of view it is useful to divide heat production into shivering and non-shivering thermogenesis. The amount of heat produced is regulated according to the needs of the body, the most important stimuli coming from changes in the environment. In a thermoneutral environment (30°C) O₂ consumption is minimal and the heat produced by this basal metabolism is sufficient to maintain the 7°C gradient between the body core and the exterior. The lower limit of the thermoneutral range is called the 'critical temperature' and as the environmental temperature is lowered below this, O₂ consumption increases linearly and more heat is produced by both shivering and non-shivering thermogenesis. The latter mechanism is probably involved first. The main centre for the control of these events is in the hypothalamus which is kept

Fig. 1 Diagram of the hypothalamic connexions concerned in thermoregulation.

informed of external and internal conditions by superficial and deep thermoreceptors (Fig. 1). This information is integrated along with that from many other parts of the brain by a complex system of neurones from which impulses pass out to control the rates of heat production and loss. The precise nervous pathways used are not completely known. The sympathetic nervous system, including the adrenal medulla, plays a large part in the control of non-shivering thermogenesis. An increase in the sympathetic outflow will mobilize the stores of fat and carbohydrate and stimulate brown fat activity. However, an increase in heat production can probably not be achieved simply by increasing the availability of substrate as phosphate acceptor (adenosine diphosphate) must be made available if the tricarboxylic acid cycle is to turn more quickly. The ways in which these mitochondrial reactions are controlled is still a matter for debate. Space does not permit a detailed account of either the nervous or biochemical mechanisms involved in thermoregulation. However, enough has probably been said to show that there are many places in this system where injury could interfere. An important question to be decided for each stage of the response is whether the injury is primarily affecting the peripheral sites of heat production or the central nervous control mechanisms.

Acute 'Ebb' Phase

While the mechanism of the fall in heat production during this initial phase cannot be fully explained, certain possibilities can be eliminated and others suggested.

Since heat production depends on oxidation, the simplest way of decreasing heat production in an organ is to reduce its O_2 supply. Failure of O_2 transport is naturally the first possibility

to consider in traumatic shock. However, contrary to expectation, after many injuries in the rat the O_2 supply to the main organs appears to be adequate during this early stage. After a fatal period of hind-limb ischaemia in the fed rat, for instance, the arterial blood pressure remains between 70 and 80 mm Hg for many hours before finally falling precipitously shortly before death (Koletsky and Klein, 1956). This level is above the threshold for the auto-regulation of blood flow in most of the organs in which it occurs so that the perfusion of the brain, liver, kidneys, and myocardium is better maintained than might be supposed (Johnson, 1954; Stoner, 1954 and 1958a). There is also biochemical evidence of adequate tissue perfusion during this phase. An indication of the redox state of the body can be obtained by measuring the lactate/pyruvate and β -hydroxybutyrate/acetoacetate ratios of the blood and tissues. The changes in these ratios during this stage are no greater than during a 24-hour period of fasting in a normal rat (Barton, 1970; Threlfall, 1970). The large increases in these ratios characteristic of tissue hypoxia do not occur until later when death seems certain. Another explanation must therefore be sought for the initial depression of heat production after injury.

There are some further possibilities which can probably also be discarded. For instance, liver mitochondria isolated from rats injured by limb ischaemia, even if they were on the point of death, behaved normally *in vitro* without added co-factors (Aldridge and Stoner, 1960) so that it is unlikely that the changes are due to severe structural damage to them. The fall in heat production cannot be attributed to lack of substrate. The increased sympathetic outflow which follows any injury mobilizes the stores of both carbohydrate and fat. At this early stage there is hyperglycaemia (Stoner, 1958b) and frequently an increase in the non-esterified fatty acid concentration in the plasma (Stoner, 1962). The latter depends on the preservation of an adequate blood flow through the fat depots and this is often reduced after injury (Stoner and Matthews, 1967; Kovách, Rosell, Sándor, Koltag, Kovách, and Tomka, 1970).

A possible lead to the site of the 'lesion' came when the O_2 consumption of rats placed at different environmental temperatures after a standard injury was measured (Stoner, 1969a). In the 'ebb' phase only the thermoregulatory part of the total O_2 consumption was altered by the injury (Fig. 2). In the thermoneutral zone, where there is no thermoregulatory O_2 consumption, O_2 consumption was not altered by trauma unless the injury proved fatal; even then it was maintained at the normal rate until just before death. The critical temperature was lowered by trauma. Within this extended thermoneutral range the O_2 consumption of the injured rats fell to the basal rate of the controls and remained there, only declining further in the terminal stages. At

ambient temperatures below the new critical temperature O_2 consumption was inhibited but the direct correlation with the environmental temperature was retained. The slope of the regression line was the same as in the controls and its separation from the controls depended on the severity of the injury.

The systematic nature of this effect suggests that it is due to an alteration in the thermoregulatory control mechanism. The insulation of the body may show some increase after trauma but this would not explain the findings since the regression lines would not be parallel in this case (Barnett and Mount, 1967). The picture shown in Fig. 2 is not what one would expect if the changes were due to non-specific interference with heat production through failure of O_2 transport or release of toxic inhibitors from the damaged tissue. The release of the latter would be at least as great in a 30°C environment as at lower temperatures and cardiovascular function fails more rapidly at these higher environmental temperatures when the survival time is shortened (Stoner, 1958a and 1963). Thus, with a certain amount of hesitation, one comes to the view that injury alters the thermoregulatory capacity of the hypothalamus and further evidence of this is coming to hand (unpublished results).

The normal rat shivers when its core temperature falls as well as when it is exposed to a low ambient temperature. After injury the core temperature falls without evoking shivering although exposure to cold (3°C) still causes shivering.

In addition to cholinergic neurones, the part of the hypothalamus concerned with thermoregulation also contains neurones which use either noradrenaline or 5-hydroxytryptamine as transmitters (Bligh, 1966). Burns and limb

ischaemia did not affect the concentration of 5-hydroxytryptamine in the hypothalamus but decreased that of noradrenaline. This change in the noradrenaline concentration was found very soon after the injury; in limb ischaemia it occurred while the tourniquets were in place, before the core temperature fell. The decrease in the concentration was about the same after both fatal and non-fatal injuries, and in the latter restoration of the normal level took up to 72 hours. The significance of these changes will become clearer when we have information on the effect of trauma on the turnover of noradrenaline and 5-hydroxytryptamine in the hypothalamus.

The injured rat at 20°C behaves from a thermoregulatory point of view as if its environment were much warmer than it really is. Why should an injury, such as muscle damage or burning, in which the most important common factor seems to be loss of circulating fluid into the damaged area, lead the rat to make this apparent mistake? One can only speculate on the answer to this question (Stoner, 1970) but in this discussion of the changes in heat production during the 'ebb' phase these effects of trauma on the function of the hypothalamus have been emphasized, because it is beginning to look as if they are the primary ones. The alterations in heat production which follow are, of course, accompanied by biochemical changes at the periphery in heat-producing organs such as the liver and kidneys. These peripheral changes have been studied in some detail.

As pointed out above, an early consequence of trauma is mobilization of stored carbohydrate (glycogen) and fat (triglyceride) with resulting hyperglycaemia and an increase in the plasma concentration of non-esterified fatty acids. In both cases this is due to an increased sympathetic and adrenal medullary outflow. This is probably not related to the thermoregulatory changes described above, but is the reflex response to a noxious stimulus which was first studied by Cannon (1929). In the rat this hyperglycaemia indicates the limits of the 'ebb' phase (Stoner, 1958b).

The rate of removal of glucose from the circulation is most accurately measured with ^{14}C -glucose (Ashby, Heath, and Stoner, 1965), and 1.5 hours after a fatal four-hour period of bilateral hind-limb ischaemia in the rat it was only slightly less than in the controls (1.07 v. 1.17 mg/min/100 g body weight). Similar experiments with ^{14}C -palmitate showed that the removal of non-esterified fatty acids was unaffected by injury (Heath and Stoner, 1968) so that their uptake would be related to their concentration in the plasma as in normal animals.

The most striking metabolic changes were found when the oxidation of the products of glucose and fatty acid breakdown were examined in rats in a 20°C environment using ^{14}C -labelled

Fig. 2 The relation between the rate of O_2 consumption and environmental temperature in fed rats 100-150 min after a four-hour period of bilateral hind-limb ischaemia (●) and in their controls (○). The points give the mean values and the vertical lines show the SE when they exceed the size of the symbols. (Reproduced from Stoner (1969a) by kind permission of the Editor, British Journal of Experimental Pathology.)

substrates (Ashby *et al*, 1965; Heath and Stoner, 1968; Heath and Threlfall, 1968). When ^{14}C -pyruvate is given intravenously it is oxidized mostly in the liver and kidneys. During the early stage after the injury pyruvate oxidation by these tissues is reduced. At the same time there is a very similar decrease in the production of $^{14}\text{CO}_2$ from 1- ^{14}C -palmitate. In the normal rat palmitate, given intravenously as an albumin complex, is oxidized by many tissues. The decrease in its oxidation after injury occurs mainly in those organs which have small bicarbonate pools such as the liver and kidneys. The difference between the injured and the controls can be large. In rats 1.5 to three hours after a four-hour period of bilateral hind-limb ischaemia, the oxidation of pyruvate and palmitate to CO_2 is 50-70% less than in the controls. This difference is greater than would be expected from the fall in body temperature or from the fall in the O_2 consumption of the whole body. The conclusion from a detailed mathematical analysis of these results was that at this early stage after injury there is slowing of the citrate synthase reaction in which oxaloacetate and acetyl-CoA combine to form citrate (Heath and Threlfall, 1968). This conclusion can be supported with a good deal of evidence (Koltun and Gray, 1957; Heath and Threlfall, 1968; Stoner, 1969b; Threlfall, 1970).

These experiments were done in a 20°C environment and if they reflect the impairment of thermoregulation after injury described above, they might be interpreted as a failure by the injured rat to increase mitochondrial oxidation as the ambient temperature falls below the critical temperature (30°C). If this is correct, the metabolic picture in these injured rats should resemble that of normal rats in a thermoneutral environment and the difference between the control and injured rats should be minimal in such an environment. Experiments to examine these predictions are not yet complete because of technical difficulties. Such information as is available suggests that the difference between injured and controls in the conversion of the label of ^{14}C -pyruvate to ^{14}C -glucose is less in a 30°C environment.

Much more work will be necessary before the biochemical changes in heat production after injury can be explained. The complete explanation probably awaits the full description of the regulation of heat production by mitochondria in normal animals and this is still not available.

When the normal homeostatic balance is disturbed, as by injury, the animal is usually pictured as striving to regain its normal position. This may be true for the cardiovascular system, but in the case of energy metabolism the changes might be better described as the transition from the normal 'steady state' to another more-or-less 'steady state' characterized by decreased heat production, the level of heat production being determined by the severity of the injury. The situation is well illustrated by the changes in O_2

consumption shortly after a severe, but not fatal, scald in the rat (Stoner, 1968). After this injury O_2 consumption quickly falls to a new level which is maintained reasonably constant for up to eight hours before recovery occurs. Earlier in this paper these changes in O_2 consumption and heat production were attributed to an apparent mistake on the part of the rat. Is this really the case? By injecting catecholamines and by other means, such as cold acclimatization, it is possible to increase heat production in the injured rat through effects on the peripheral mechanisms (Haist, 1960; Stoner, 1965 and 1968; Stoner and Little, 1969a and b) but this always has an adverse effect on survival. The optimum temperature for the survival of the injured rat or mouse is about 20°C (Tabor and Rosenthal, 1947; Green and Stoner, 1950; Haist, 1960), ie, a temperature which allows a fall in heat production to occur. One is therefore left with the question, first discussed by John Hunter (1794), Are these early changes in energy metabolism after injury part of a defence reaction?

Because of the small thermal capacity of the rat these changes in heat production are quickly reflected in its body temperature. The thermal capacity of man is much greater so that large temperature changes during the 'ebb' phase would not be expected. However, the metabolic changes in man and the rat are very similar and small falls in temperature have been reported in man (Wiggers, 1950). Every effort should be made to assess the thermoregulatory ability of injured man. Knowledge of this would be useful in choosing the optimum environmental temperature for operating theatres, intensive care wards, etc.

Terminal Phase of Necrobiosis

The mechanism of the decreased heat production of this phase is more completely understood than that of the other stages. The basic cause is failure of the O_2 supply to the tissues. After non-fatal injuries the steady state of the 'ebb' phase can be maintained for long periods, more than 24 hours. When the size of the injury is increased and the fluid loss is greater there is a limit to the length of time the animal can, by autoregulation of the circulation and other means, maintain that steady state. Although the factors which determine the change from the early steady state to this downward spiral to death are poorly understood, the metabolic consequences of the change-over are very clear.

The total O_2 consumption now falls below the basal rate. The arterial pO_2 remains in the normal range until very near the end. The O_2 supply to the tissues is progressively reduced as a result of the low blood volume, fall in cardiac output, vasoconstriction, pooling of blood in tissues, increased viscosity of the blood when the haematocrit value is raised, intravascular coagulation,

and the occlusion of vessels by emboli of various sorts. The plasma non-esterified fatty acid concentrations may be relatively low in this stage through interference with their removal from the fat depots by the blood stream. With cellular hypoxia glucose phosphorylation is increased (Morgan, Randle, and Regen, 1959) so that the blood glucose concentration falls and at death it may be very low (Stoner, 1958b). Through lack of oxygen, the glucose taken into the cells is only partially metabolized and lactate begins to accumulate in the tissues and blood. As this stage progresses, the lactate/pyruvate ratio in the tissues and blood rises to very high values (Threlfall, 1970) as does the β -hydroxybutyrate/acetoacetate ratio (Barton, 1970). There is thus a fall in the redox potential of both the cytosol and the mitochondria. These changes, coupled with reduced renal function, lead to a 'fixed acid' acidosis with a fall in the arterial $p\text{CO}_2$ and gradual consumption of the buffering capacity of the body. In these circumstances decreased heat production is hardly surprising.

The changes of this stage are common to man and animals. They figure prominently in current literature on both clinical and experimental shock and often there is little mention of the earlier changes. There are a number of reasons for this. There is a natural preoccupation with the very severe injuries which present the greatest clinical problems, and, the severer the injury, the shorter the first phase. The first phase also is shortened when resistance to injury is lowered. For instance, in rats adrenalectomy increased the mortality rate after four-hour bilateral hind-limb ischaemia from 85 to 100% and reduced the survival time from just over 13 hours to under two hours. This difference is almost entirely at the expense of the first stage. As soon as the tourniquets were removed from the adrenalectomized animals, signs of the terminal stage began to appear. A similar acceleration of events is seen if the rat is fasted for 24 hours before the injury.

Other reasons are to be found in the models used for the experimental study of injury and from the amount of work done on so-called 'irreversible' shock which could be another name for this stage. This is justified if we are to discover ways of reversing this process and so save the lives of those patients who present themselves to the surgeons in this state. Nevertheless, the concentration of effort on the Wiggers' haemorrhagic shock model in the anaesthetized dog has obscured matters. This model is specifically designed to reproduce this terminal stage, for Wiggers (1950) states that 'The only reliable evidence that shock exists in animals is the production of a state so severe that it cannot be reversed by substantial infusions of blood'. When the effects of haemorrhage have been compared with those of other forms of injury, it has been obvious that after severe haemorrhage,

tissue hypoxia is the dominant factor (Engel, Winton, and Long, 1943; Russell, Long, and Engel, 1943; Engel, Harrison, and Long, 1943; Tabor and Rosenthal, 1947). Haemorrhage is, of course, an important form of injury in man (Grant and Reeve, 1951) but even so few injured patients exhibit the precipitous fall in arterial pressure and maintained severe hypotension (50 mm Hg for 90 min followed by 30 mm Hg for 45 min) which are essential features of Wiggers' model. More work is required on unanaesthetized animals subjected to more gradual and less severe haemorrhage (Kim, Desai, and Shoemaker, 1969) in order to assess the changes in energy metabolism before the onset of the terminal tissue hypoxia.

'Flow' Period

After a non-fatal injury the 'ebb' phase may persist for many hours (Stoner, 1958a and 1968). After a severe but not fatal scald, for instance, it may be more than 72 hours before the rat is able to produce adequate amounts of heat on exposure to cold (3°C) although it can maintain a normal body temperature in a 20°C environment. Little is known about the precise factors in the injury which determine the duration of the 'ebb' phase or about the way in which the body recovers from it. It is, however, well known that after injuries of more than minor severity the body does not immediately return to its normal metabolic state; it first passes through the 'flow' phase (Cuthbertson, 1942).

The existence of this phase of increased metabolic rate had been surmised in the last century (Malcolm, 1893). It had become generally known under the name 'traumatic fever', ie, a raised temperature after severe injury without infection, but the syndrome was first defined by Cuthbertson (1929) forty years ago and most of our knowledge of it is due to his work. For a more detailed discussion of it than will be attempted here the reader is referred to his reviews (Cuthbertson, 1957, 1959 and 1964; Cuthbertson and Tilstone, 1968). This response seems to occur throughout the animal kingdom, in invertebrates as well as in vertebrates (Needham, 1955 and 1958). Of the three phases distinguished in the response to injury it has the longest duration. Whereas the duration of the other two phases is measured in hours, the 'flow' phase may last for days or even weeks. As already pointed out, the rise in body temperature which first attracted attention to this phase is due to an increase in heat production and this is its hallmark (Cairnie *et al*, 1957). Thus, by the third day after a non-fatal injury the metabolism of the body has altered, over a period of perhaps 48 hours, from the steady state of the 'ebb' phase to a new steady state characterized by accelerated heat production from which it eventually returns to normal.

What fuel is used to provide the extra heat? In the 'flow' phase there is increased urinary excretion of nitrogen (mainly as urea), inorganic sulphate, phosphate, potassium, and creatine. Negative nitrogen balance is one of the best known features of this phase and can be very large. The maximum daily loss of nitrogen in man may exceed 23 g/day and more than 1 kg of protein may be broken down during this phase. The excess nitrogen is derived from the catabolism of muscle protein and the oxidation of the non-nitrogenous residues is thought to account for the extra heat (Cuthbertson, 1964). This may differentiate the increased heat production of the 'flow' phase from that due to exposure to cold, for although nitrogen excretion increases on exposure to cold (Beaton, 1963), there is then a general increase in metabolism and fat is the preferred fuel. Although the changes in the 'flow' period appear to reflect alterations in protein metabolism, detailed studies of carbohydrate and fat metabolism during this period, using labelled substrates, are required. The results of such studies are now beginning to appear (see Kinney, 1970, on pages 65-72).

Although several features of the metabolism of this stage can be described many questions arise and the deeper ones remain unanswered. Why should muscle protein be catabolized during recovery from an injury? What is the mechanism of this response? What is its object, if, indeed it has one?

It might be thought that the amino-acids liberated by the breakdown of the protein were required for repair processes and that large amounts of protein had to be broken down to provide sufficient amounts of the rarer but essential ones while the remainder were oxidized. In this scheme the increased heat production of the 'flow' phase would simply be a byproduct of this search for amino acids. There is, however, no real evidence for this. The size of the 'flow' phase response is not as strictly related to the size of the injury as that of the 'ebb' phase. While a small negative nitrogen balance can be alleviated by a very high protein diet, if the injury is at all severe, the extra protein is broken down and the nitrogen excreted.

Although it is difficult to alter the response by dietary changes after the injury, it is markedly influenced by the diet before the injury. The size of the response is related to the amount of protein in the diet before the injury and it is not observed if the animals have been kept on a protein-free diet before being injured (Munro and Cuthbertson, 1943; Munro and Chalmers, 1945; Cairnie *et al*, 1957). This implies that the protein broken down in this response is first drawn from the labile protein stores held in muscle (Fleck and Munro, 1963; Munro, 1964). Work of this type has shown that these changes associated with the 'flow' period are not essential for recovery since the rate of healing does not depend on the size

of the response. This important conclusion has been confirmed by more recent work on the effect of environmental changes on the response which will be discussed later.

Since trauma increases adrenal cortical secretion and since the injection of adrenal cortical hormones raises the level of nitrogen excretion, it was natural to see if the adrenal cortex was causally concerned in the changes of the 'flow' period (Campbell, Sharp, Boyne, and Cuthbertson, 1954). Although the response is prevented by adrenalectomy, cortical hormones are not its main mediators. Their role is permissive. Provided a certain amount of cortical hormone is present in the tissues, the full reaction will occur without any increase in cortical hormone secretion being required. This has been shown in man as well as animals (eg, Jepson, Jordon, Levell, and Wilson, 1957).

Although the emphasis during this stage is on the catabolism of protein, the synthesis of certain plasma proteins by the liver is increased as discussed by Davies (1970). Not all plasma proteins are equally affected. Albumin turnover only seems to be increased when there is actual loss of albumin from the body as in burns. The synthesis of some other proteins which are not normally present in the plasma or present only in very small amounts is stimulated. The proteins involved in this reaction are known collectively as the 'acute phase reactants' and include fibrinogen, haptoglobulin, C-reactive protein, the α -glycoprotein of Darcy, caeruloplasmin, and serum-mucoid. Our knowledge of this effect of injury, although still incomplete, has increased greatly in recent years (Neuhaus, Balegno, and Chandler, 1966; Chandler and Neuhaus, 1968; Koj, 1968, 1970; Gordon and Koj, 1968; Van Gool and Ladiges, 1969). The synthesis of acute phase reactants requires the presence of a permissive level of adrenal cortical hormone. The increase in protein synthesis in the liver occurs in response to the formation there of messenger RNA. Some of these factors are involved in the increase in the activity of the microsomal drug metabolizing enzymes of the liver after injury (Rupe, Bousquet, and Miya, 1963; Driever, Bousquet, and Miya, 1966) and in the increase in the synthesis of cholesterol (De Matteis, 1968 and 1969). Further work on these reactions should be profitable and perhaps lead to the explanation of many of the phenomena of the flow period.

Recent work on burns has exposed an additional feature of the 'flow' period, namely, its sensitivity to changes in environmental temperature. A burn increases the permeability of the skin to water even when the skin does not blister and expose a raw area. Even the hard eschar is permeable to water (Lieberman and Lansch, 1956; Wilson and Moncrief, 1965). As a result the evaporative loss of water from the body is increased after burns, and, although this may be small in the 'ebb' phase, it is large, often very

large, in the 'flow' phase (Roe, Kinney, and Blair, 1964; Caldwell, Hammel, and Dolan, 1966; Miksche and Caldwell, 1968; Stoner, 1968). The latent heat for the evaporation of this water must be provided by the body so that during the 'flow' phase after a burn a large amount of extra heat must be produced. There is no doubt that this demand is in part responsible for the increased metabolic rate of the post-burn 'flow' period. Measures which decreased the evaporative loss from the surface of the burn lowered the metabolic rate (Moyer, 1962; Roe *et al.*, 1964), and Harrison, Moncrieff, Duckett, and Mason (1964) claimed that there was a direct relationship between the water loss and the increased heat production after burns. In consequence, a view began to develop that the excess heat production of the 'flow' period was determined by changes in the evaporative loss of water. The fact that the increased metabolism of the flow period after burns could be eliminated by raising the environmental temperature to 30-32°C so as to spare heat normally spent in maintaining the temperature gradient between the body and its surroundings for the evaporation of water was taken as further support for this. This effect of raising the ambient temperature to the thermoneutral zone is now well established in the case of burns (Caldwell, Osterholm, Sower, and Moyer, 1959; Caldwell, 1962; Caldwell *et al.*, 1966; Barr, Birke, Liljedahl, and Plantin, 1968; Davies, Liljedahl, and Birke, 1969). However, it has now been shown that a thermoneutral ambient temperature also inhibits the 'flow' period response to fracture of a bone which does not increase the evaporative water loss from the body (Campbell and Cuthbertson, 1967; Cuthbertson, Smith, and Tilstone, 1968). Changes in food intake which occur when the environmental temperature is altered can make such experiments difficult to interpret but the effect appears to be a real one. One must differentiate then between the true 'flow' response

to an injury and the additional increase in metabolic rate which occurs if the evaporative water loss is also increased as in burns. Both effects are inhibited by raising the ambient temperature to the thermoneutral zone, but for different reasons.

At present the influence of environmental temperature on the true 'flow' period response cannot be explained. It would be useful to know the relationship between O₂ consumption and environmental temperature during this phase. Whatever the shape of this curve, it seems unlikely that central thermoregulatory mechanisms in the hypothalamus are causally concerned in the production of the raised heat production of the 'flow' period if the response in invertebrates is really the same as in mammals.

Much further work will be needed before the changes of this period can be explained. It seems most likely that the increased heat production results from changes in the peripheral mechanisms which are susceptible to a number of influences and in which, it has been suggested, the thyroid may be involved (Miksche and Caldwell, 1967).

Conclusions

The changes in energy metabolism following trauma can be divided into three distinct phases (Fig. 3). All injuries are followed by an 'ebb' phase of variable intensity and duration in which heat production is depressed not through lack of substrate or oxygen, but possibly through changes in the central thermoregulatory mechanisms. If the injury is fatal, this phase passes into a further one of necrobiosis in which heat production is depressed even further from progressive failure of O₂ transport. If the injury is not fatal, the 'ebb' phase changes to the 'flow' phase in which heat production is increased through changes at the peripheral sites of thermogenesis. It is important to distinguish between these three phases if one is not to be confused by the multiplicity of metabolic changes which follow injury.

Fig. 3 Diagram to show the changes in the rate of heat production during the different stages of the response to injury in the rat.

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