Papers and Originals

Temperature Regulation*

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It is 333 years since Dr. Goulston left £200 to purchase a rent-charge for the maintenance of a lecture to be delivered annually within the College of Physicians. The Goulstonian Trust is therefore only a little younger than the measurement of body temperature in man.

Though Hippocrates distinguished types of fever by placing his hand upon the patient's breast, measurements of temperature were first undertaken by Sanctorius early in the seventeenth century. During the next 200 years measurements were seldom reported, but the general biological importance of the regulation of temperature was recognized before Claude Bernard (1879) used this as a principal example of the regulation of the internal environment of the body. In 1797 James Currie, a Fellow of the Royal College of Physicians of Edinburgh practising in Liverpool, wrote: "If a definition of life were required, it might be most clearly established on that capacity by which the animal preserves its proper heat under the various degrees of temperature in which it lives."

I should like to consider how body temperature is regulated during health, and then to try to explain some of the abnormalities of temperature in disease, in the light of recent observations. There is an enormous literature on this subject, and it is impossible to cover the entire field. I hope I shall be forgiven if I deal mainly with those aspects which have excited my own interest.

Measurement of Temperature

In the normal person temperature varies considerably from one part of the body to another. It is a matter of common observation that the temperature of the skin of the extremities varies with the environment, and in fact this variability is a manifestation of the activity of thermoregulating mechanisms. The temperature of deeper structures in the trunk and head varies much less than that of the extremities; the former are the ones usually measured in clinical practice, and are called, for convenience, central temperatures. Nevertheless, there are temperature differences between different central sites, of which the fairly constant difference between mouth and rectal temperatures may serve as an example. The temperature of any central structure is determined by its own heat production, its insulation from the environment, and the temperature and flow rate of blood perfusing it. It is therefore not surprising that deep structures may vary not only in respect of their absolute temperature levels but also in the rate and magnitude of temperature changes indicated by thermal stresses. This is a point of some importance; if central temperature is being measured with a view to determining the response of a central regulating mechanism, it is important that this temperature should reflect accurately the temperature change to which the regulating mechanism is exposed.

Both in man and in animals there is evidence that central receptors exist in the hypothalamic region. Ideally, therefore, temperature should be measured at this site. It is possible to make such measurements in animals, but for obvious reasons this is not possible in man, and more accessible sites for temperature measurement must be used. For experimental purposes rectal temperature has been the traditional site, because the temperature here is generally higher than in other accessible areas and because it has been thought that this area is better insulated from external temperature changes. However, when heat is introduced into the body, either by the intravascular infusion of warm saline or by the immersion of a limb in warm water, there may be little or no change in rectal temperature, despite a considerable rise of mouth temperature (Fig. 1). Such an introduction of heat obviously stimulates a receptor somewhere, since it brings about thermoregulatory responses, with an increased loss of heat from the skin, so that the temperature is restored to its original level (Gerbrandy, Snell, and Cranston, 1954). This suggests that mouth temperature provides a better index of rapid temperature changes at the central receptors than rectal temperature. There is, however, some evidence that tongue blood-flow may be affected by thermoregulatory reflexes, and it can be argued that the change in mouth temperature is merely a reflection of changes in blood-flow. That this is not so can be shown by measuring the arterial-blood temperature in such experiments (Fig. 1). This shows the changes of temperature in the mouth, rectum, and subclavian artery of a normal subject after heating the opposite arm.

It is clear that mouth temperature reflects changes in arterial temperature better than rectal temperature. Why there is so much damping of the response of rectal temperature is uncertain. This may be due to a relatively low blood-flow in this area, or perhaps to a counter-current heat-exchange system

FIG. 1.—Temperature measured in the mouth, rectum, and subclavian artery in a normal subject during immersion of one forearm in a bath of warm water (shaded areas indicate duration of immersion).

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within the abdomen. Oesophageal temperature (Gerbrandy *et al.*, 1954) and the temperature of the tympanic membrane (Benzinger, 1960) and external auditory meatus (Cooper, Cranston, and Snell, 1964a) respond in the same way as mouth temperature. It must not, however, be concluded that rectal temperature is useless for practical purposes. For slower temperature changes, as in fever, the rectal temperature behaves similarly to oral temperature (Wendt, Snell, Goodale, and Cranston, 1956) and is less liable to be affected by technical errors.

Alterations of Heat Production and Heat Loss

Central temperature is controlled by balancing heat production and heat loss. I shall not consider changes in heat loss brought about by voluntary control of clothing or environment. Heat is produced by metabolic activity, and to the basal rate of heat production is added that due to activity, the metabolism of food, changes of body temperature, and perhaps emotion. For purposes of thermal regulation heat production may be increased rapidly by increased muscular activity, or shivering, in man; this appears to be the only mechanism whereby heat production can be increased rapidly, since Johnson, Smith, and Spalding (1963) were unable to detect any increase in oxygen consumption in patients paralysed by neurological disease or curare when they were exposed to a cold environment for several hours. In hibernating mammals brown adipose tissue provides a considerable increase in metabolism in response to sympathetic-nerve stimulation or noradrenaline (Hull and Segall, 1965). Slower metabolic responses are probably produced by increased thyroxine secretion (Brown-Grant, 1956), which probably depends upon an intact hypothalamic portal system (Knigge and Bierman, 1958). There is also evidence that exposure to cold causes an increased adrenocortical secretion rate, at least transiently (Egdahl and Richards, 1956), but the relevance of this effect to temperature regulation is uncertain.

Heat loss may be increased most powerfully by sweating, which is largely controlled by sympathetic efferents, and also by evaporation of water from the respiratory tract, in panting. It is also changed by altering radiation and convection from the body surface. DuBois (1937) showed that in naked subjects in environments between 22.7 and 30.5° C. heat production and evaporative heat loss changed very little. At temperatures above 30.5° C. evaporation became the main channel of heat loss, and below this radiant heat loss contributed the major share. Radiant heat loss is largely a function of skin blood-flow, so that one may consider the regulation of skin blood-flow as a fine adjustment mechanism for controlling temperature, with shivering and sweating as relatively coarse adjustments. Radiant heat loss is not exactly related to skin blood-flow, since there is evidence (Bazett, Love, Newton, Eisenberg, Day, and Forster, 1948-9) of a counter-current heat-exchange mechanism in the human forearm. In cold environments the temperature of blood in the radial artery falls because heat is transferred from the proximal arteries to the venae comitantes and thus conserved within the body. Since the temperature of arterial blood flowing to the skin is reduced, radiant heat losses will decrease more than skin blood-flow. These are the effector mechanisms whereby heat production and heat loss may be altered. We must now consider how they are brought into play.

Control of Heat Production and Heat Loss

It is now clear that there are two systems which regulate the effector systems, but there is still some doubt about their relative importance.

Skin Receptors

The first is a reflex whose afferents arise from the skin. If an arm whose circulation is occluded by a cuff is immersed in

cold water vasoconstriction takes place in the opposite hand within a few seconds. As a consequence of the decrease in heat loss there may be a rise of mouth temperature. Though this reflex response was first demonstrated plethysmographically by François-Franck in 1876, its effects on mouth temperature were known to Currie three-quarters of a century before. Whether this vasoconstriction is induced by cold, or merely by the unpleasant sensation, is uncertain. Radiant heating of large areas of skin induces reflex vasodilatation in the hand and an initial fall in mouth and rectal temperature (Kerslake and Cooper, 1950). This reflex does not fatigue, and it behaves quantitatively; the increase in hand blood-flow is linearly related to the intensity of radiant heating (Cooper, Ferres, and Mottram, 1956).

Recordings from human cutaneous nerves have shown that there are skin receptors responding to heating and cooling (Hensel, 1961). There is evidence that this reflex pathway extends above the cervical cord, but whether it extends to the hypothalamus is uncertain. The efferent pathway for both reflexes is sympathetic. It is of interest, and, so far as we have been concerned, of considerable usefulness, that this reflex is not elicited by immersing an arm in warm water. If an arm is immersed in this way while its circulation is occluded blood-flow to the opposite hand either falls transiently or is unaffected. However, if a forearm is immersed in warm water with a free circulation vasodilatation appears in the opposite hand after a delay of a few minutes (Pickering, 1932). This response is due to warming of the circulating blood, and is a manifestation of the response of the second principal controlling mechanism, the central regulating mechanism.

Central Regulating Mechanism

There is now very good evidence from animal studies that central receptors exist which are sensitive to very small changes in their temperature. There is general agreement that receptors exist in the hypothalamus which respond to local temperature rises of 0.4° C. or less, giving skin vasodilatation, sweating, or increased respiration (Magoun, Harrison, Brobeck, and Ranson, 1938; Folkow, Ström, and Uvnäs, 1949). Similarly, cooling of the pre-optic area can provoke vasoconstriction and shivering (Hammel, Hardy, and Fusco, 1960). More recently single neurone recordings have been made from the brains of cats and dogs during heating and cooling experiments. Only in the pre-optic region of the hypothalamus were neurones found whose firing rates were affected by local temperature change (Nakayama, Hammel, Hardy, and Eisenman, 1963; Hardy, Hellon, and Sutherland, 1964). There is thus little doubt that one of the functions of this area of the brain is to regulate temperature.

Whether central receptors exist in other tissues is less certain; Downey, Mottram, and Pickering (1964) cooled the blood flowing to different organs of conscious rabbits and measured the resulting increase in the animals' oxygen consumption. They found that cooling the internal carotid blood caused a much greater proportional rise of oxygen consumption than cooling any other vessel. Cooling the abdominal aorta or the external carotid artery, both of which supply skin, gave a smaller rise in oxygen consumption than cooling any of the veins. Though this may mean, as Bligh (1961) has suggested, that there are temperature receptors in the heart, it may only reflect the fact that total heat lost by the animal is smaller when the cooled blood is circulated to skin, and the existence of other central temperature receptors is not proved.

Evidence in Man

In man evidence for the presence of central temperature receptors is provided by the work of Pickering (1932), already mentioned. Snell (1954) was able to change central temperature, with practically no skin stimulation, by infusing warm or

cold saline intravenously into normal subjects. He found that the heat gained or lost by the body was linearly related to the increase or decrease of heat elimination from the opposite arm. Later it was shown that such an infusion of warm saline caused the mouth temperature to rise for a short time and then return to its original level (Gerbrandy *et al.*, 1954). The sensitivity of the central receptors seemed to be of the order of $0.1-0.2^{\circ}\text{C.}$, and there was a linear relation between the rise of mouth temperature, the amount of heat infused into the subject, and the increase in heat lost from one hand. A similar relationship was found when heat was introduced by immersing one arm in a heated waterbath, and this provides a means of testing the sensitivity of the central temperature-regulating system (Cooper, Cranston, and Snell, 1964b). The heat load causes a measurable stimulus (the temperature change), which causes a measurable increase in heat loss. If temperature regulation is impaired the same heat load might be expected to cause a larger or more prolonged rise in temperature, with a smaller increase in heat loss.

There is very little direct evidence of the location of the central temperature receptors in man: on the basis of animal experiments it is likely that they are situated in the hypothalamus; the observations of Guttmann, Silver, and Wyndham (1958) on patients with high spinal-cord lesions does not suggest that any central thermoregulatory system exists in the spinal cord below the cervical level, even some months after spinal transection. Hyperpyrexia after brain-stem lesions suggests that the regulatory system is rostral to this. We have examined this problem by infusing warm saline into one internal carotid artery of patients having arteriograms under local anaesthesia; all these patients agreed to the investigation, which had been fully explained to them. The effect of a relatively small warm infusion is to cause a very marked increase in heat loss from the fingers, and sometimes a consequent fall in mouth temperature. Similar infusion of saline at body temperature produced no response. This is quite unlike the response after infusing other vessels, and is compatible with the location of the central temperature receptors within the distribution of carotid arterial blood-flow.

Roles of Skin and Central Receptor Systems

There has been considerable doubt about the relative roles of the skin and the central receptor systems in the normal control of body temperature. The pendulum has swung from the belief that skin reflexes can account for almost all the known facts (Burton and Edholm, 1955) to the belief that temperature regulation is entirely controlled by the central temperature-regulating mechanism, provided that skin temperature exceeds 33°C. ; and that skin temperatures below 33°C. modify the activity of the central regulating system (Benzinger, 1962). It is clear from numerous experiments that there is an interaction between the skin reflexes and the central regulating system. Thus in man reflex vasodilatation cannot be induced by exposing the trunk to radiant heating if the mouth temperature is below $36.5-36.8^{\circ}\text{C.}$ (Cooper, Johnson, and Spalding, 1964). An animal at rest may have a higher hypothalamic temperature when shivering in a cold environment than when panting in a warm one (Hammel, Jackson, Stolwijk, Hardy, and Strömme, 1963). It is probable that stimuli from skin and central receptors summate: skin receptors are more important when people are exposed to environmental temperature changes, particularly if these are rapid; central receptors compensate for changes in endogenous heat production and prevent over compensation by the skin reflexes.

It has been suggested by several workers, but most explicitly by Hammel *et al.* (1963), that the central thermostat does not regulate temperature at a single fixed level, but that the level at which it is set is affected not only by impulses arising from skin but also by the state of wakefulness, since there is a fall of up to 2°C. in the hypothalamic temperature of monkeys when

they fall asleep. This hypothesis has also been invoked in the past to explain the regulation of body temperature during exercise. In 1938 Nielsen observed that the rise of rectal temperature on exercise was related to the severity of the exercise performed, and independent of the environmental temperature, within quite wide limits. This observation has since been confirmed by several workers, and it has been shown that the same is true of oesophageal temperature (Nielsen and Nielsen, 1965a).

In order to explain this constant relation between work rate and central temperature rise in different environments it was implied that exercise caused a resetting of the central regulating mechanism. This hypothesis was generally accepted for years but was challenged by Benzinger (1962), who found the relation between heat loss and central temperature was almost identical during rest or steady-state exercise. This confirmed that the central regulating system functioned proportionally, as Snell (1954) had shown previously; with more exercise, more heat was produced, giving a greater central temperature rise and thus a greater stimulus to heat loss. More recently Nielsen and Nielsen (1965b) have performed experiments which confirm this view. They compared the effects of heating the body by exercise and by diathermy in different environmental temperatures and found that the similar rates of heating, however produced, caused similar temperature rises in different environments. There is thus no need to postulate that steady-state exercise affects the level at which the central thermostat functions. This is not necessarily true of the beginning of exercise; Beaumont and Bullard (1963) have shown that there is an increase of sweat rate within $1\frac{1}{2}$ seconds of starting work in a warm environment. This cannot be due to an increased central temperature, and presumably depends upon a neural stimulus.

The normal diurnal temperature change of up to 1°C. appears to be largely related to eating and perhaps to activity, since it can be reduced or abolished by fasting (Iampietro, Buskirk, Bass, and Welch, 1957). The mechanism whereby ovulation raises body temperature is still uncertain; pregnenolone, pregnanediol, and other $5-\beta$ steroids cause a rise of body temperature when injected in man, but not in animals (Kappas, Soybel, Fukushima, and Gallagher, 1959). How they act is uncertain, but this effect may be related to body-temperature changes with ovulation. One other factor which can have a considerable effect upon central body temperature is emotion. Renbourn (1960) found that boxers before a championship fight had temperatures as much as 0.5°C. higher than their temperatures before practice bouts; this difference could not be accounted for by differences in exercise, and appears to be due to emotion. Some animals that are subjected to restraint show marked changes in body temperature, presumably for the same reason. The mechanism whereby these temperature changes are brought about remains speculative, but this kind of phenomenon may account for some unexplained fevers when patients first visit hospital.

Noradrenaline and 5-Hydroxytryptamine

As I have said, the hypothalamus is the site of the main, and probably the only, central receptor system. This part of the brain contains a relatively high concentration of noradrenaline and 5-hydroxytryptamine (5HT), and the possibility that these substances might be concerned in temperature regulation was raised by Brodie and Shore (1957) and by von Euler (1961). In the past two years this hypothesis has received some support from the injection of these substances into the cerebral ventricle or hypothalamus of animals. In 1963 Feldberg and Myers reported that 5HT caused a rise and noradrenaline a fall of body temperature when injected into the cat's lateral ventricle. Subsequently, it has been shown that these substances act upon the hypothalamus and that similar responses may be obtained from the dog and the monkey (Feldberg, Hellon, and Myers, 1966). In the rabbit, however, the results are quite the opposite. We have found (Cooper, Cranston, and Honour, 1965) that

noradrenaline usually causes a rise in temperature and 5HT a fall.

The meaning of this species difference is uncertain, but I do not think there is any question of pyrogen contamination or other technical artifact in either set of experiments. In the rabbit the effect is clearly mediated through the nervous system. The hypothalamic injection of noradrenaline causes vasoconstriction in the intact ear but no constriction in the chronically sympathectomized ear. If the effect were due to noradrenaline diffusing into the systemic circulation one would expect a greater vasoconstriction in the chronically sympathectomized ear. The importance of these findings is still uncertain.

The hypothesis that noradrenaline and 5HT might be concerned, perhaps as transmitters, in the regulation of temperature is an attractive one, and it might explain some hitherto inexplicable observations. Lysergic acid diethylamide, a 5HT inhibitor, causes a rise of body temperature in rabbits, cats, and dogs (Horita and Dille, 1954), and it has been suggested that this effect is a central one. Reserpine has been reported to cause hypothermia in rats without reducing oxygen consumption (Hoffman, 1958), but its effects vary considerably from one species to another. It has been suggested that changes in the concentration of brain amines may be responsible for hyperthermia induced by imipramine in animals previously treated with monoamine oxidase inhibitors (Loveless and Maxwell, 1965). It must be stressed that this hypothesis rests at present upon the effects of injection of relatively large amounts of active agents into the brain. Though the observations are compatible with the hypothesis, they may equally well be no more than a pharmacological curiosity.

Disordered Temperature Regulation

An abnormally high or low temperature may result from defects of the thermoregulatory mechanisms or from extreme circumstances where the regulating mechanisms cannot cope with the thermal loads imposed. The last group is probably uncommon. Immersion hypothermia after shipwreck is probably one example. Hyperpyrexia in hot climates may be another, but there is evidence that this is preceded by a sudden cessation of sweating (Ladell, Waterlow, and Hudson, 1944). Why this happens is uncertain: Bannister (1960) found that the injection of pyrogen caused an abrupt fall of sweat rate in subjects in a very hot environment, and the possibility remains that heat hyperpyrexia represents fever in very hot environments.

Accidental hypothermia is being increasingly recognized in this country, where it usually affects old people in cold environments. To a large extent this condition is determined by social factors, and many of these patients have other serious disease, whether causes or consequences of the hypothermia is uncertain. We do not know how this condition develops; it is clearly related to low environmental temperatures. There is some evidence that otherwise healthy old people in cold environments may have low body temperatures (Taylor, 1964) and quite probably their ability to regulate temperature is deficient. Old people exposed to a cold environment show a smaller increase in oxygen consumption, a greater fall of rectal temperature, and a smaller fall in skin temperature than young people (Horvath, Radcliffe, Hutt, and Spurr, 1955). About 10% of geriatric patients have postural hypotension due to impaired function of central or efferent pathways in the central nervous system (Johnson, Smith, Spalding, and Wollner, 1965); a defect of this nature might explain the impairment of thermoregulation in older people. In many instances, however, the use of chlorpromazine, reserpine, or sedatives probably contributes. Apart from this, hypothermia occurs in some patients in association with disease of the central nervous system. Sometimes this is intermittent (Duff, Farrant, Leveaux, and Wray, 1961) and sometimes persistent (Hockaday, Cranston, Cooper, and Mottram, 1962).

Of our three patients with chronic hypothermia none had evidence of endocrine disease. We obtained evidence that two regulated their body temperatures at an abnormally low level. If they were warmed or cooled they vasodilated or vasoconstricted their skin vessels, but the third patient showed no such response, despite the fact that her sympathetic efferent pathways were intact, as judged by the response of skin blood-flow to emotional stimuli and the response of blood-pressure to tilting. This patient appeared to be regulating her temperature only by altering her clothing or environment. In the two patients with temperatures regulated at a low level the injection of pyrogen was followed by vasoconstriction and a rise of body temperature, but no response was obtained from the patient who could not regulate her temperature. This suggests that an intact central regulating system is necessary for fever to develop. Thus it is clear that hypothermia can be caused by more than one functional defect. The same was found by Duff *et al.* (1961) in two patients with intermittent hypothermia. One of these patients appeared to regulate his temperature at a low level, but the other probably did not. Adequate evidence of the nature and extent of the central nervous system lesions has not been obtained from any of these patients, and it has been impossible to relate the functional defects to structural damage.

Hypothermia may occur in myxoedema, though severe hypothermia from this cause is less common than accidental hypothermia. Preliminary observations suggest that the only defect of thermoregulation in these patients is an inability to increase their low metabolic rate on exposure to cold.

Fever

At the other end of the scale fever is by far the commonest abnormality of body temperature. It is a common sign of any inflammatory disease, whether induced by bacteria, hypersensitivity, tissue damage, or neoplasms.

Although von Liebermeister (1875) suggested that body temperature was regulated at a higher level during fever, little information has been available concerning the exactitude of this regulation. Stern (1892) showed that febrile patients sweated or shivered when they were immersed in hot or cold baths, and that the change of rectal temperature at the onset of sweating or shivering was similar to that in normal subjects. Macpherson (1959) made observations upon a volunteer with an acute febrile illness during exercise tests in different environments. He found that exercise caused similar changes in sweat rate and rectal temperature whether or not the subject was febrile.

We have made qualitative investigations of the skin reflex control mechanism and quantitative measurements of the response of the central regulating mechanism during fever. Normal subjects were exposed to radiant heating after the intravenous injection of bacterial pyrogen. The vasodilator response to radiant heating was unaffected at the onset of fever, when skin blood-flow fell, though the response did subsequently decline when the body temperature was rising rapidly; this may have been due to a decreased skin temperature, since the reflex vasodilatation could be restored in one hand by warming it (Bryce-Smith, Coles, Cooper, Cranston, and Goodale, 1959).

The central regulating mechanism was tested by the method already described. A known heat load was introduced into febrile patients by immersing one forearm in a bath of warm water. The resultant rise of oral temperature was measured, and compared with the increased loss from the fingers of the opposite hand. The relation between these variables was examined in eight patients with febrile illnesses and three normal subjects during pyrogen-induced fever. In both groups the relation between the stimulus (central temperature rise) and the response (increased heat loss from the opposite hand) did not differ significantly from that observed in normal afebrile people (Cooper, Cranston, and Snell, 1964b).

An example of the response of one normal subject to the injection of pyrogen is shown in Fig. 2. After the injection of pyrogen there was a decrease in heat loss from the fingers and a rise of nearly 2° C. in mouth, ear, and rectal temperature. After the temperature had stabilized at a higher level very small increments of temperature brought about by immersing one arm in warm water caused normal increases in heat loss from the other hand, with restoration of the mouth temperature to its previous level. It is therefore clear that temperature regulation is just as precise during fever as in the normal state, and these observations are consistent with the hypothesis that fever represents a resetting of the set point of the central thermostat system. We must now consider how this is brought about.

FIG. 2.—Responses of rectal, oral, and ear temperature, and heat loss from the fingers of one hand, after an intravenous injection of endogenous pyrogen. Body-heating was induced by immersing one forearm in a bath of warm water at the times indicated. Responses of mouth temperature and finger-heat loss are shaded (Cooper *et al.*, 1964b. Reproduced by permission of the Editor of *Clinical Science*).

Since the middle of the last century it has been known that the injection of pus could cause a rise of temperature in animals. Early in this century it was shown that certain bacteria were pyrogenic (Hort and Penfold, 1912) and later that this property was due to a constituent of Gram-negative bacteria (Siebert, 1925). Since then a great deal of work has been done on these endotoxins, which have been shown to consist of high-molecular-weight lipopolysaccharides which do not dialyse and are resistant to boiling.

For years it was then assumed that bacterial endotoxin caused the fever of infections, but it was difficult to ascribe many other forms of fever to this cause. Menkin (1945) obtained a pyrogenic material from sterile abscesses which he termed "pyrexin," but it is likely that this material was to some extent contaminated by bacterial endotoxin. Beeson (1948) obtained a fever-producing agent from granulocytes which had properties clearly distinct from those of endotoxin (Bennett and Beeson, 1953). This material has been termed leucocyte or endogenous pyrogen.

Summary of Recent Work on Pyrogen

A great deal of work has been done in this field in the past 15 years, and I shall summarize this very briefly. Granulocytes may be obtained from peripheral blood or from sterile inflammatory exudates. If washed immediately after harvesting, granulocytes from inflammatory exudates contain no pyrogen, but will form pyrogen upon incubation in saline (Fessler, Cooper, Cranston, and Vollum, 1961). This can be inhibited by the addition of potassium to the incubating medium (Berlin and Wood, 1962). Granulocytes from blood do not release leucocyte pyrogen when incubated in saline but do so if in-

cubated in cell-free inflammatory exudate (Kaiser and Wood, 1962). It has therefore been suggested that exposure to inflammatory process may interfere with electrolyte handling by polymorphs, and that in this situation they can liberate leucocyte pyrogen (Berlin and Wood, 1962).

Leucocyte pyrogen can be obtained by incubating granulocytes with endotoxin both in rabbits (Collins and Wood, 1959) and in man (Cranston, Goodale, Snell, and Wendt, 1956). It can also be obtained by incubating normal blood cells with tuberculin in plasma obtained from tuberculin-sensitive animals (Atkins and Heijn, 1965). A pyrogen with the properties of leucocyte pyrogen has been obtained from the circulating blood of animals after the intravenous injection of endotoxin (Atkins and Wood, 1955), in bacterial infections (King and Wood, 1958a), during hypersensitivity reactions to tuberculin (Hall and Atkins, 1959), and in viral infections (Atkins and Huang, 1958). In man endogenous pyrogen has been found in inflammatory effusions (Snell, 1962) but not in the circulating blood of patients with febrile illness (Snell, 1961). This may be a quantitative problem, since it is hardly reasonable to withdraw large amounts of blood from patients with fever.

We thought that the best chance of detecting circulating pyrogen might be to look at patients with rapidly rising body temperatures, and therefore we investigated some patients with malaria. In four such subjects blood was taken while the patient was afebrile and again while his temperature was rising. In the patient whose chart is here shown (Fig. 3) both samples were separated into cells and plasma, and each was infused separately after his malaria had been treated and he was afebrile. In this patient fever was produced by infusion of the cellular fraction of the blood drawn while he was febrile: none of the other fractions caused fever. The fever began within 30 minutes; this is characteristic of the human febrile response to endogenous pyrogen (Snell, Goodale, Wendt, and Cranston, 1957). One other patient developed fever after the infusion of blood withdrawn at the onset of malarial paroxysm: in the other two no pyrogen was detected. There is thus a consider-

FIG. 3.—Pyrogenic effects of blood removed from a patient with malaria. Upper trace is a continuous recording of rectal temperature during a malarial attack. At points (1) and (2) blood was withdrawn and separated into cells and plasma. The lower part of the figure shows the patient's temperature response to reinfusion of these cells and plasmas on later days. Only the cellular fraction, removed during the febrile episode, contained pyrogen.

able and growing body of evidence to suggest that leucocyte pyrogen may be the final common chemical pathway in the production of fever in disease.

Where and How does Pyrogen Act?

There is good evidence that pyrogen does not cause vasoconstriction in the sympathectomized extremity of the rabbit (Douglas, 1954) or man (Perera, 1941). The injection of pyrogen into a patient with a high cord transection caused shivering only above the level of the lesion (Cooper, Johnson, and Spalding, 1964). One patient with no central thermoregulatory capacity did not develop fever after the injection of pyrogen, as previously mentioned. This all suggests a site of action within the brain. In animals King and Wood (1958b) found that infusions of endogenous pyrogen into the carotid artery caused higher fevers than intravenous infusion. With endotoxin the route of infusion made no difference to the response. This finding has recently been confirmed by Allen (1965), and carries the implication that the site of action of pyrogen is within the brain. Several investigators have now injected pyrogenic material direct into the hypothalamus. Grant, Lewis, and Aherne (1955) were unable to produce fever in this way, using endotoxin, though more recently Villablanca and Myers (1965) were able to do so. Cooper (1965) has also been able to produce fever by injections of endogenous pyrogen in very small doses into the anterior hypothalamus. It was also possible to produce fever with endotoxin injected into the same area, but only if relatively large doses were given. It thus seems highly probable that leucocyte acts directly upon the central regulating system. How it does so is uncertain. Feldberg and Myers (1963) have suggested that the effects may be related to the release of noradrenaline and 5HT locally. As I pointed out, there is very little direct evidence for this, but we have obtained one small piece of evidence which might be compatible with this hypothesis.

Ten rabbits were given a standard dose of leucocyte pyrogen and developed a mean temperature rise of 0.6° C. A week later they were treated with a monoamine oxidase inhibitor intravenously and the same dose of leucocyte pyrogen was injected. Two of the animals died with hyperpyrexia, while the mean temperature response of the remainder was not significantly different from the original one. We have not seen hyperpyrexia with these doses of leucocyte pyrogen in over 200 experiments, and it is possible that the hyperpyrexia may be due to an alteration in the balance of amine concentrations caused by the amine oxidase inhibitor, though there are other possible explanations.

We still, however, have no direct evidence that fever is beneficial, except perhaps the fact that it persists in all homoiothermic species. In conclusion, I can do no better than to paraphrase the words of Dr. Eugene DuBois (1948), to whom the study of temperature regulation owes so much: "One is faced with the question of whether or not fever in disease is beneficial. The literature on this subject is extensive and inconclusive. It is difficult to see how proof could be obtained on human subjects. There is always the possibility not yet proved that the defences of the body are increased at high temperature. There is still much to be learned about fever."

Summary

Normal body temperature is controlled by the regulation of heat production and heat loss. Two main regulating systems are recognized, with receptors in the skin and in the hypothalamus, though the interactions between these systems are still imperfectly understood. The efficiency of both systems can be tested. It is possible that noradrenaline and 5-hydroxytryptamine may play a part in the hypothalamic system, perhaps as chemical transmitters, though the evidence for this is equivocal.

The cause of accidental hypothermia remains uncertain, though there is evidence that old people do not respond as effectively as young ones to cold environments. Chronic hypothermia may be due to a complete failure of the control-regulating mechanism, or it may merely represent the active regulation of body temperature at an abnormally low level.

During fever body temperature is regulated as precisely as in health, but at a higher level. This is almost certainly brought about within the hypothalamus by endogenous pyrogen liberated from cells exposed to inflammatory processes. It is still unknown whether a febrile response confers any benefit upon the sick animal.

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Chemotherapy of Hodgkin's Disease with Cyclophosphamide, Vinblastine, and Procarbazine

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Radiotherapy is undoubtedly the best treatment for localized Hodgkin's disease, and there have now been very encouraging reports from several centres (Peters and Middlemiss, 1958; Kaplan, 1962; Easson and Russell, 1963; Cohen *et al.*, 1964; Fayos *et al.*, 1965). However, it is not always possible to use radiotherapy, because the disease may be too disseminated or there may be a recurrence in an area which has already been heavily irradiated. In these circumstances chemotherapy is indicated.

Of all malignant diseases those arising in lymphoreticular tissue respond most consistently and often dramatically to chemotherapy, and this applies particularly to Hodgkin's disease. In the last few years more agents have become available, and it has been our practice at St. Bartholomew's Hospital, when the need for chemotherapy arises, to treat patients initially with some form of nitrogen mustard, usually cyclophosphamide (Endoxana), and to continue this until the disease is no longer responding; vinblastine sulphate (Velbe) is then used until it becomes ineffective, and this is followed by a methylhydrazine derivative, procarbazine hydrochloride (Natulan). We have used the drugs in this way because it is the order in which they became available, but it has been suggested by Todd (1965a) that the order is unrelated to their therapeutic effects.

The purpose of this communication is to review our results, using these three compounds consecutively, and discuss whether better results might be obtained by using them in a different order or concurrently.

Material and Methods

Only patients with classical Hodgkin's disease (Hodgkin's granuloma) have been included; those with paraneoplasia and so-called Hodgkin's sarcoma have been excluded.

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Since radiotherapy is the treatment of choice in localized Hodgkin's disease, many of the patients had received radiotherapy before being given chemotherapy.

Because of the difficulty in assessing the efficacy of any form of treatment in a disease like Hodgkin's disease, with such a variable course, only the *initial* response to each agent will be analysed. Subjective improvement was assessed by the symptoms of malaise, pruritus, and pain when this could definitely be attributed to the disease, and objective improvement by the abolition of fever, a gain in weight in those patients in whom recent weight loss had occurred, and a reduction in the size of the lymph nodes and the spleen. In assessing the overall results, the response to treatment was considered to be "beneficial" only if there was improvement in one of the objective criteria for at least one month. No patient was recorded as benefiting if there was only an improvement in symptoms.

Results

Treatment with Cyclophosphamide

Sixty-two patients with Hodgkin's disease have been treated with cyclophosphamide for a variable period up to three years. Of these, 54 had previously received some other form of treatment—that is, radiotherapy, mustine hydrochloride, chlorambucil, or corticosteroids—and in only eight was cyclophosphamide the first form of treatment used.

Many patients initially received the drug by intravenous injection, 2 g. being given over a period of 10 days. Maintenance treatment was continued by oral administration, starting with 150 mg. daily and reducing this dose or stopping the drug if severe leucopenia or any other side-effect developed.

The overall results are shown in Table I. Cyclophosphamide was beneficial—that is, it produced objective improvement lasting at least one month—in 43 patients (69%), 6 patients (10%) were unaffected, and in 13 patients (21%) the treatment failed. In these 13 treatment failures there was clinical