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Body temperature and fever: changes in our views during the last decade

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In the past, research on body temperature too often nearly became a branch of physics. A model from physics, the thermostat, was taken to explain the thermoregulatory functions of the anterior hypothalamus. A change occurred when simple methods became available for injecting drugs into the cerebral ventricles of unanaesthetized animals, and when intraventricular injections of noradrenaline and 5-hydroxytryptamine were found to affect temperature. These monoamines appear to exert a tonic influence on temperature by being released from monoaminergic neurons ending in the hypothalamus. But they are not the mediators of endotoxin fever. Nor are they essential for maintaining normal temperature. The mediators of endotoxin fever are E prostaglandins. They raise temperature when injected intraventricularly, appear during endotoxin and lipid A fever in cerebrospinal fluid, but disappear from it when fever is brought down by antipyretics which inhibit prostaglandin synthesis. Many bodily functions, other than temperature, are kept constant. It is the ‘milieu intérieur’ of Claude Bernard that is kept constant. A factor which apparently governs the ‘milieu intérieur’ in the hypothalamus is the calcium ion concentration, since lack of calcium in the hypothalamus raises (and excess lowers) temperature.

When we talk about body temperature, the two expressions most frequently used are ‘normal temperature’ and ‘fever’, and it is about these two conditions I am going to talk. But first I want to state a few simple facts.

Temperature varies in different parts of the body, but when we talk of body temperature, we mean the core temperature, that is, the temperature inside the body, in the viscera and in the brain. We obtain a fair indication of this temperature by taking oral or rectal temperature.

Second, in a healthy person, and the same applies to other warm blooded or homioothermic animals, body temperature is kept relatively constant throughout life. For this to happen, heat production and heat loss must balance. The most effective mechanism for increasing heat production is shivering. Heat loss occurs to a great extent through the skin, and is easily reduced or increased by constricting or dilating its vessels, i.e. by increasing or inhibiting sympathetic vasomotor
tone. This mechanism is particularly effective in the tail of the rat and in the ears of the rabbit, because the skin in these parts contains numerous arterio-venous anastomoses and heat loss is greatly affected by opening up or closing down these anastomoses. So the tail of the rat and the ears of the rabbit play a major role in temperature regulation. Two other effective mechanisms for increasing heat loss are sweating and panting. Sweating occurs in man and horses, and panting is used in some species at the slightest heat provocation, for instance, in dogs. Another mechanism for increasing heat loss through fluid evaporation is used in small furred animals, like mice, rats and guinea-pigs. They spread saliva on their fur which then evaporates. From these few instances, it should be clear that the mechanisms involved in temperature regulation may, and do, vary greatly in different species.

Now the third and last fact. In order to keep temperature constant, there must be a central regulating mechanism, and the part of the brain in which this regulation takes place is the hypothalamus, particularly the anterior hypothalamus with its pre-optic region.

What has been said so far is common textbook knowledge, but what now follows is a more personal account.

How did it happen that I began working on body temperature? One day, over ten years ago, I made a silly mistake. I poked a thermometer into the rectum of a cat, and from this mistake I have never recovered. I became so interested in body temperature that I am still working on it. I became interested in three problems: in what goes on in the hypothalamus to produce changes in temperature, and in what goes on in the hypothalamus to prevent changes in temperature. This is not the same problem, which becomes clear when we express it differently, and say what goes on in the hypothalamus to keep temperature constant. And finally, what goes on in the hypothalamus to bring about the fever of infectious diseases. To find answers to these problems we investigated the role of the monoamines, of prostaglandins and of ions in temperature regulation.

Ten years ago, research on body temperature revolved mainly around the idea that the thermoregulatory centre in the anterior hypothalamus acts like a thermostat with a fixed set-point which ensures constancy of body temperature, and that the set-point is raised in fever. There is nothing wrong with this idea. Temperature has to be 'sensed' in order to be regulated, and there is good evidence, particularly that provided by Hellon (1967) that some neurons in the hypothalamus have a special thermosensitivity. But temperature is only one of the many bodily functions that are kept constant: blood pressure, heart rate, blood glucose, in fact the concentration of all ions in the blood and in the cells of the body are kept constant. It is the milieu intérieur, as Claude Bernard called it, which is kept constant. Body temperature is but one manifestation of this general principle. In the past, research on temperature too often nearly became a branch of physics. We thought we could take a model from physics, the thermostat, and with this model explain thermoregulation. But models, useful though they may be for
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making clear, by analogy, a physiological function, rarely explain the biological processes in living tissue underlying a physiological function. By looking at the hypothalamus the way a physicist looks at a thermostat, we neglected to find out what biochemical processes occur in the anterior hypothalamus to produce either a fall or a rise in temperature, or to keep temperature constant. And we neglected to study the pharmacological sensitivity of this part of the brain.

A change in the direction of our research was brought about when simple methods became available for injecting drugs into the cerebral ventricles of unanaesthetized animals, and when it was realized that with these methods the drugs would reach the anterior hypothalamus, could act on it and thereby affect body temperature. The first breakthrough in this direction occurred when it was found that the monoamines adrenaline, noradrenaline and 5-hydroxytryptamine (5-HT), known to be natural constituents of the hypothalamus, produced changes in temperature on their intraventricular injection.

Since then, the intraventricular route has been widely used for studying drug effects on temperature. By this route the drugs act from the liquor space. The next step was to find out if substances would also be released into the liquor space in response to changes in body temperature. Both methods require some knowledge of the anatomy of the liquor space, particularly of the communication between the cerebral ventricles and the fluid space surrounding the brain, the subarachnoid space. This communication takes place through three openings, all of which lie in the walls of the fourth ventricle, two at the lateral recesses and the third at its caudal end. This third one, however, the foramen Magendie, exists in primates only, not in dogs, cats, rabbits or rats. People working with these species are often not aware of this fact. It is important to know that if one withdraws cerebrospinal fluid (c.s.f.) from the cisterna magna in cats and rabbits, the ventricular fluid has a relatively long way to go before it reaches the cisterna, because it enters the subarachnoid space near the ventral surface of the brain stem.

For injection of drugs into the cerebral ventricles, a Collison cannula is implanted chronically either into a lateral or into the third ventricle. The two cannulations are illustrated diagrammatically in figure 1a and b. Figure 1a shows a frontal section of the cat’s brain with a Collison cannula screwed into the skull. The tip of the cannula lies in the lateral ventricle and its outer end is closed by a rubber diaphragm (given in black) through which the injections are made. Figure 1b shows a mid-sagittal section of the cat’s brain with the Collison cannula implanted in such a way that its tip lies in front of the massa intermedia (M.I.).

Once a temperature effect is obtained with a drug injected into the cerebral ventricles the next step is to find out if the action is on the anterior hypothalamus. For this purpose a Collison cannula with a finer shaft is implanted into the wall of the third ventricle so that the tip lies in the region of the anterior hypothalamus. The drug is then infused through the cannula in a minute volume.
Figure 1. Diagrams of cannulation for injecting drugs into a lateral ventricle (a) or into the third ventricle (b) and for collecting c.s.f. from the cisterna magna (c) in cats. (a) From a film by Feldberg & Sherwood (1953); (b) from Feldberg & Gupta (1973); (c) from Feldberg, Gupta, Milton & Wendlandt (1973).

The monoamines

Injected into a lateral ventricle of unanaesthetized cats, adrenaline and noradrenaline produce a fall and 5-HT a rise in temperature. The upper record of figure 2 shows the hypothermic effect of 50 μg of adrenaline (A) and of 50 μg of noradrenaline (N). Adrenaline is about twice as potent as noradrenaline. The lower record which is from another cat shows the long-lasting biphasic rise in temperature produced by an intraventricular injection of 200 μg of 5-HT. The 5-HT is injected as creatinine sulphate which itself is ineffective, as shown at C. Doubts have arisen whether the late rise following the 5-HT injection is actually due to 5-HT itself. It may be an unspecific response to intraventricular injections which will be discussed later on in this lecture. When the monoamines were introduced by microinfusions directly into the anterior hypothalamus, temperatures responses similar to those shown in figure 2 were obtained, but with much smaller doses. Microinfusions of the monoamines into the posterior hypothalamus, however, were ineffective (Feldberg & Myers 1965).
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How simple the problem would have been if all animals responded to the monoamines in the same way as cats. But they don't!

Table 1 summarizes the temperature effects obtained in different species with the monoamines injected into the cerebral ventricles or directly into the anterior hypothalamus. Dogs, monkeys, fowl and pigeons, responded like cats. The opposite effects were obtained in rabbits and sheep, a rise with the catecholamines and a fall with 5-HT, but the fall was usually small and not consistently obtained, as indicated by the dotted arrow. Again, other effects were obtained in goats and oxen and again in rats and mice.

![Graph](image)

**Figure 2.** Records of rectal temperature from two unanaesthetized cats. At the arrows, injections into the left lateral cerebral ventricle of 0.1 ml 0.9% NaCl solution (S); 50 µg adrenaline (50A); 50 µg noradrenaline (50N); 100 µg creatinine sulphate (C), and 200 µg 5-HT (200 5-HT). (From Feldberg & Myers 1964.)

If these pharmacological effects of the monoamines mimic their central transmitter function in temperature regulation, it would follow that in some species these functions are mediated by the catecholamines and 5-HT, and in others mainly by the catecholamines, and again in others by 5-HT alone, and further, that the same monoamine may be used in one species as a central transmitter for raising, in another for lowering temperature. Such great variability of transmitter functions has not been observed elsewhere. But as pointed out at the beginning of
this lecture, the mechanisms for temperature regulation also vary in different species.

The situation is even more complicated because in some species the temperature response to intraventricular noradrenaline changes with the ambient temperature. For instance, rabbits and sheep, when kept in a very cold environment, no longer respond with a rise in body temperature to intraventricular injections of noradrenaline. Instead temperature falls as shown by Bligh & Cottle (1969). This reversal is due to the fact that in these animals, noradrenaline has two effects which have the opposite result on body temperature. It constricts the skin vessels which raises body temperature, and it inhibits shivering which lowers temperature. At room temperature, or in a hot environment, the animals do not shiver and the skin vessels are not constricted. The intraventricular noradrenaline constricts them and temperature rises. In a cold environment the skin vessels are already constricted by the animals shiver, and the noradrenaline inhibits this shivering; body temperature therefore falls.

| Table 1 |
|---------------------|---------------------|---------------------|---------------------|---------------------|
|                    | catecholamine       |                     |                     |                     |
|                    | 1 cat               | 2 dog               | 3 monkey           | 4 fowl and pigeon   |
|                    |                     |                     |                     |                     |
| 5-HT               |                     |                     |                     |                     |
| 6 Ruckebush, Grivel & Laplace (1965, 1966) |
| 7 Findlay & Robertshaw (1967) |
| 8 Andersson, Jobin & Olsson (1966) |
| 9 Feldberg & Lotti (1967) |
| 10 Brittain & Handley (1967) |

In other species no reversal is produced; the only effect is an attenuation or accentuation of the noradrenaline response. Hellon & I (unpublished experiments) found that the normal fall produced in cats by intraventricular noradrenaline was greatly attenuated, but not reversed, at a high ambient temperature (about 30 °C). The attenuation is readily explained. At a high ambient temperature, for instance, in a cat lying in the sun, the same changes – dilatation of the skin vessels and reduction in muscle tone are brought about which would otherwise be produced by noradrenaline when given at a neutral or low ambient temperature.

In order to explain the noradrenaline reversal in rabbits and sheep, Bligh & Cottle proposed a model of interneuronal connections which is shown in the middle diagram of figure 3; the bottom diagram gives a later modification. These two diagrams apply to rabbits and sheep. The top diagram, by Myers & Yaksh
applies to monkeys. It, too, has undergone modification in the meantime. With these models or diagrams we summarize the facts known at the time; sometimes they allow us to predict results of experiments. They are popular with students who nowadays have to learn more than they can digest, and they do no harm as

Myers & Yaksh (1969)

Bligh & Cottle (1969)

Maskrey & Bligh (1971)

![Diagram](http://rspb.royalsocietypublishing.org/)

**Figure 3.** Three proposed models of interneural connections to explain temperature regulation in the hypothalamus.

long as it is realized that they are merely models, which do not tell us what is actually going on in the brain. Instead of discussing them in detail, I give you my personal view about them. It has been said that teleology is a lady without whom no biologist can live, yet he feels ashamed to show himself with her in public.†

† Attributed to the late physiologist of Vienna, Ernst Wilhelm von Brücke (1819–92).
These models, too, are ladies without whom many of our colleagues working on temperature regulation are apparently unable to live. But there is this difference. They do not need to feel ashamed to show themselves with them in public because we all know the ladies will be different ones in a few years’ time!

Our present view about the role of the monoamines in temperature regulation is mainly based on the results obtained with a number of drugs which either deplete the monoamines in the hypothalamus or block their action. Reserpine and phenoxybenzamine are two representative drugs of this kind. Their choice has been determined solely by the fact that I had worked with them. To understand their temperature effects it has to be remembered that at a medium ambient temperature, noradrenaline raises body temperature in the rabbit, but lowers it in the cat.

*Reserpine* depletes the monoamine stores in the tissues and when injected into the cerebral ventricles, it releases noradrenaline from the hypothalamus and its noradrenaline stores become depleted, as was shown by Cooper, Cranston & Honour (1967).

Now what temperature effects are to be expected from an intraventricular injection of reserpine, if its effects were mediated through noradrenaline? The release of noradrenaline should raise temperature in rabbits and lower it in cats, but after noradrenaline depletion reserpine should no longer produce these effects, and, as shown in figure 4, this is what happened. The injections of reserpine were made at 24 h intervals but in the figure the effects of the first and third injection only are shown. In the rabbit, the first injection produced a long-lasting large rise, whereas the third injection no longer raised temperature. The sensitivity of

![Figure 4](http://rspb.royalsocietypublishing.org/Downloaded from http://rspb.royalsocietypublishing.org/ on June 27, 2017)
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the anterior hypothalamus to noradrenaline, however, was not abolished. As shown in figure 4, it produced its usual hyperthermic response on intraventricular injection. In the cat, the first injection of reserpine produced a fall in temperature followed by a rise; but the third injection no longer produced a fall but after a latency of about 2 h temperature gradually rose. This late rise may not be an effect of reserpine, but may be an unspecific response to intraventricular injections, referred to earlier and to be discussed later on.

Phenoxybenzamine, also called dibenamine, is an α-adrenoceptor blocking agent and thus blocks the action of noradrenaline. Assuming there is a continuous release of noradrenaline from the nerve endings of adrenergic neurons innervating the cells of the anterior hypothalamus, it should exert a tonic influence on temperature, and suddenly blocking this effect by an α-adrenoceptor blocking agent should lower temperature in the rabbit and raise it in the cat. And these were the temperature effects produced by phenoxybenzamine injected intraventricularly.

Figure 5 illustrates its effect in the rabbit. The upper records show the temperature lowering effect of 50 μg in two rabbits. The other records show what happened when the hypothalamus was depleted of its noradrenaline stores by reserpine. As there is then no adrenaline left for continuous release, there would be no tonic influence on temperature. Therefore, phenoxybenzamine would no longer lower temperature, and this is shown in the records b obtained 1 day and 2 days respectively after the noradrenaline depletion. As the noradrenaline stores became gradually replenished the hypothermic response to intraventricular phenoxybenzamine returned. On the fourth day, this had not happened in rabbit 2, but some return had occurred on the fifth day in rabbit 1 (records c). Full recovery, suggesting full replenishment of the noradrenaline stores, took seven days in rabbit 2, and longer in rabbit 1, because in this rabbit this had not happened on the ninth day; but on the fifteenth day, the hypothermic response had fully returned (records d and e).

There is not much direct evidence for the release of monoamines during activation of adrenergic or tryptaminergic neurons ending on the anterior hypothalamus when the animals are exposed to a cold or hot environment. The best and perhaps the only convincing evidence so far obtained is that of Beleslin & Myers (1970) on 5-HT release in the monkey. With Gaddum's push-pull cannula, they collected fluid which had bathed the region of the anterior hypothalamus for a short time. This fluid contained minute amounts of 5-HT, but when collected whilst the monkey was packed in ice so that it started to shiver, the 5-HT activity in the fluid increased many times.

Instead of giving more details, I shall summarize my views about the role of the monoamines in temperature regulation.

The role of the monoamines in temperature regulation

It was natural at the time when the temperature effects of the monoamines in cats were discovered to think that the constancy of temperature was brought
about by an equilibrium in the release of catecholamines and 5-HT, and that the fever in response to pyrogen, i.e. the fever of many infectious diseases, might result from a disturbance of this balance. This view proved to be wrong when it was found that the monoamines affect temperature differently in different species, and when the effects of depletion of the monoamines in the hypothalamus were examined.

![Figure 5](http://rspb.royalsocietypublishing.org/)

**Figure 5.** Records of rectal temperature from two anaesthetized rabbits. The interrupted vertical lines indicate intraventricular injections of 50 µg phenoxybenzamine. Between records *a* and *b*, intraventricular injections of reserpine phosphate (0.75 mg) at 24 h intervals. The days refer to days after last reserpine injection. (From Feldberg & Saxena 1971a.)

According to our present view, the monoamines are continuously released from adrenergic and tryptaminergic neurons ending on the anterior hypothalamus, and thereby exert a tonic influence on temperature. But they are not essential for maintaining a constant temperature, nor are they the mediators of the fever response to pyrogens. When we deplete the hypothalamus of its monoamines, constancy of temperature is maintained and pyrogens still produce fever. But in
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this condition, the animals do not stand up as well as normal animals to thermal stress, i.e. to a very hot or very cold environmental temperature. Similarly, the fever response to pyrogen is either accentuated or attenuated according to whether the hypothalamus has lost its hyperthermic or hypothermic monoamine (Teddy 1971). So a certain deficiency is produced. The situation resembles that of the sympathetic nervous system. As Cannon showed over 40 years ago, animals survive complete sympathectomy, and such animals show no signs of deficiency under normal conditions, but under conditions of stress, they do.

Acetylcholine

Cholinergic neurons and interneurons are so numerous in the central nervous system that there can scarcely be any central pathway without involvement of some of them. To me, the fundamental difference between the role of monoamines and acetylcholine in temperature regulation is that adrenergic and tryptaminergic neurons converge on the anterior hypothalamus, whereas cholinergic neurons do not!

Involvement of cholinergic mechanisms in temperature regulation was first suggested by Burn & Dutta (1948) when they found that atropine lowered temperature in mice. Since then the temperature effects of cholinomimetic substances when injected into the cerebral ventricles or into the anterior hypothalamus, have been widely studied. Most of the authors obtained hypothermia in the rabbit, goat, rat and echidna (Meeter & Wolthuis 1968; Lomax, Foster & Kirkpatrick 1969; Bligh, Cottle & Maskrey 1971; Meeter 1971; Lang, Baird & Hales 1974) and hyperthermia in the cat, sheep, monkey and pigeon (Myers & Yaksh 1969; Bligh, Cottle & Maskrey 1971; Chawla, Johri, Saxena & Singhal 1975). The effects apparently do not result from an action on the anterior hypothalamus. In monkeys, Myers & Yaksh obtained, with microinjections of acetylcholine and carbachol, hyperthermic responses from many sites throughout the hypothalamus, and the most intense responses were obtained from the posterior hypothalamus. This suggests that cholinergic interneurons, involved in temperature regulation, are widely distributed in the hypothalamus and concentrated near the posterior hypothalamus. Their activation in cats exposed to a cold environment was shown recently by Ford, Hellon & Luff (1973). They injected a small dose of physostigmine into the cerebral ventricles, to inhibit the destruction of released acetylcholine. Such injections have scarcely any effects on temperature in cats kept at room temperature, but after exposure to a cold environment the injections brought on such intensification of shivering that body temperature rose about 1 °C. Since the physostigmine was injected into the cerebral ventricles, the cholinergic neurons activated in this condition, lie most probably in the ventricular walls near the lumen. So much about acetylcholine.
Prostaglandins, pyrogen fever and antipyretics

A mediator for the fever response to pyrogen should raise temperature in all species in which pyrogen produces fever. On this count alone, the monoamines would fail. On the other hand, the prostaglandins of the E series would qualify. When injected in minute amounts into the cerebral ventricles, they produce fever

![Graph](a)

![Graph](b)

Figure 6. Records of rectal temperature from two unanaesthetized cats. The arrows at a indicate injection into the third ventricle of PGE₁ in the doses indicated. The ↑↑ in b indicates 4 h infusion into a lateral ventricle of PGE₁ for the first 20 min at a rate of 40 and then at 20 ng/min. (Upper records from Milton & Wendlandt (1971); lower record from Feldberg & Saxena (1971 b).)

in nearly all species so far examined (echidna being an exception (Lang et al. 1974)). Like the monoamines, they are natural constituents of the hypothalamus. They were introduced into the field of thermoregulation by Milton & Wendlandt (1970) when they found that these prostaglandins produced fever on intraventricular injection into unanaesthetized cats.
The evidence that they are the mediator of the fever response to endotoxins, which is another word for bacterial pyrogens, is threefold:

*first*, their ability to produce hyperthermia in so many species and the finding that it resulted from an action on the anterior hypothalamus;

*second*, the appearance of prostaglandin E activity in the c.s.f. during endotoxin fever; and

*third*, the disappearance of this activity in the c.s.f. when the fever was brought down by antipyretics which inhibit prostaglandin synthesis.

Figure 6 illustrates the hyperthermic effect of prostaglandin E₁ (PGE₁) in unanaesthetized cats. The upper part shows the graded responses to increasing doses of PGE₁ injected into the third ventricle, and the lower part the effect of a continuous infusion of PGE₁ into a lateral ventricle. Temperature rises steeply at the onset of the infusion; fever is maintained throughout the infusion, but temperature goes down when the infusion stops. The PGE₁ has thus the ideal properties of a mediator for endotoxin fever: a rapid onset of fever, the ability to maintain high temperature and rapid recovery.

Two further findings are illustrated in figure 7. The PGE₁ fever results from an action on the anterior hypothalamus and occurs also in rabbits and rats. On the left are shown hyperthermic responses to microinfusions of PGE₁ into the anterior hypothalamus. In contrast, temperature did not rise when PGE₁ was infused into the posterior hypothalamus. Similar results were obtained more recently in rabbits (Stitt 1973). On the right are shown hyperthermic responses to PGE₁ injected into the lateral ventricle of the rabbit and rat. PGE₂ acted like PGE₁. Hyperthermic responses with these prostaglandins were obtained also in monkeys (Lipton & Fossler 1973; Waller & Myers 1973; Crawshaw & Stitt, 1975), sheep (Bligh & Milton 1973; Hales, Bennett, Baird & Fawcett 1973) and birds (Nistico & Marley 1973; Artunkal & Marley 1974).

Milton & Wendlandt (1971) made another important observation, namely that antipyretics which bring down pyrogen fever did not affect prostaglandin fever. They therefore concluded that antipyretics interfere not with the action of prostaglandins, but with their release. However, it is not the release which is inhibited by antipyretics, it is the synthesis, as was discovered by Vane (1971), although synthesis and release are usually closely linked with each other.

If pyrogens were to increase synthesis and consequently the release of prostaglandins, this might lead to increased prostaglandin levels in c.s.f., and antipyretics which inhibit prostaglandin synthesis should not only bring down the fever, but also the prostaglandin level in the c.s.f. To obtain direct evidence for this idea, we collected c.s.f. from unanaesthetized cats and tested it for prostaglandin-like activity on the rat stomach fundic preparation, rendered insensitive to 5-HT. The activity was then expressed in nanograms PGE₁ per millilitre of c.s.f.

These experiments were actually begun before the inhibition of prostaglandin synthesis by aspirin-like substances was discovered. What started us on these experiments were the findings *(a)* that in minute doses, the prostaglandins of the
E series produced fever in nearly all species so far examined, and would therefore be ideal mediators of the fever response to pyrogen and (b) that prostaglandin-like activity and prostaglandins had been detected in the effluent from perfused cerebral ventricles (Feldberg & Myers 1966; Holmes 1970).

**Figure 7.** Records of rectal temperature from unanaesthetized cats, rabbits and rat. The top two cat records are from the same cat. The arrows indicate on the left injections of 0.1 ml artificial c.s.f. and of 2–100 ng PGE₁ into the anterior hypothalamus, and on the right of 0.1–2.5 μg PGE₁ into a lateral ventricle. (From Feldberg & Saxena 1971 b, c.)

In our first experiments the injection of the endotoxin and the collection of c.s.f. was made through a cannula implanted into the third ventricle in such a way that the tip of the cannula lay rostral and ventral to the massa intermedia as shown in figure 1b. As the tip of the cannula lay in close proximity to the anterior
hypothalamus, the c.s.f. collected, or at least some, must have been in close contact with it. For the collection, the cap of the cannula was unscrewed and a hollow needle with a polythene tube attached to it was inserted into its shaft. If the free end of the tube was kept a little below the head, clear c.s.f. flowed out.

![Graph showing temperature change over time](http://rspb.royalsocietypublishing.org/)

**Figure 8.** Record of rectal temperature from an unanaesthetized cat. The arrows indicate injections of 75 mg endotoxin of *Shigella dysenteriae* (*Shig.*) into the third ventricle and of 50 mg/kg paracetamol (para.) intraperitoneally. The black bars indicate periods of collection of ventricular c.s.f. The bottom part shows contraction produced by 0.1 ml of these samples of c.s.f. on the rat fundic preparation compared with those produced by 0.5–4 ng of PGE₁. (From Feldberg & Gupta 1973.)

An experiment is illustrated in figure 8 in which fever was produced by an injection into the third ventricle of 75 ng of endotoxin of *Shigella dysenteriae* and
brought down for a few hours by an intraperitoneal injection of paracetamol. Four samples of c.s.f. were collected from the third ventricle and tested for prostaglandin activity on the rat fundic preparation of Vane (1957) rendered insensitive to 5-HT.

**Figure 9.** Records of rectal temperature from two unanaesthetized cats. The positions of the columns indicate the times when samples of cisternal c.s.f. were collected; the height of the columns and the figures above refer to PGE₁-like activity in ng/ml c.s.f. The first arrow indicates in both records intravenous injection of 250 μg endotoxin of *Shigella dysenteriae* and the second arrow in the bottom record to an intraperitoneal injection of 2 mg/kg indomethacin. (From Feldberg et al. 1973.)

The effects of 0.1 ml of c.s.f. and of 0.5–4 ng of PGE₁ on the fundic preparation are shown in the lower part of the figure. If the activity is expressed in nanograms PGE₁ per millilitre of c.s.f., it corresponded to about 7 ng in sample I, collected before the endotoxin injection; to about 30 ng in sample II, collected during the endotoxin
fever; to about 5 ng in sample III, collected when the fever was brought down by paracetamol, and to about 20 ng in sample IV, collected the next day when the fever had returned.

We need not have been so anxious about the origin of the c.s.f. because the same results were obtained with c.s.f. collected from the cisterna magna and not only when the endotoxin was injected into the cerebral ventricles, but also when it was injected into the cisterna magna, or intravenously. For collecting cisternal c.s.f. a method of cannulation was used which made it possible to obtain samples of c.s.f. every few hours, and on different days, without the cat apparently taking any notice. For this purpose, a Collison cannula was fixed, in an aseptic operation, to the back of the skull with dental cement, so that its tip lay just above the atlanto-occipital membrane. The position of the cannula in situ is shown diagrammatically in figure 1c. For the collection of c.s.f., a hollow needle with a polythene tube attached to it was slowly lowered through the shaft until it touched the membrane, when a slight resistance was felt. By pushing the needle sharply 1–1.5 mm deeper, the membrane was pierced and clear c.s.f. flowed out. On the right of figure 1c the cannula is shown by itself with the hollow needle inserted and fixed by a screw. In between the collections, the tube was stoppered by a pin. This was the method used in all our experiments in which we collected cisternal c.s.f. to determine its prostaglandin activity.

Figures 9 and 10 illustrate the appearance of prostaglandin activity in cisternal c.s.f. during fever produced by endotoxin of *Shigella dysenteriae* injected either intravenously or into the cisterna magna, and further, the ability of the antipyretics indomethacin and aspirin to bring down the fever as well as the prostaglandin activity in the c.s.f. The times when the samples of c.s.f. were collected are indicated by the vertical columns and the figures on top of them refer to nanograms PGE$_1$ per millilitre of c.s.f.

The next problem was to find out the nature of the prostaglandin in the c.s.f., whether it is actually PGE$_1$. Then to find out if the property of stimulating synthesis and release of prostaglandin is common to other endotoxins. If so, it should be a property also of lipid A. Finally, there was the problem of the origin of the prostaglandin in the c.s.f. Did it originate solely from the anterior hypothalamus, or also from other parts of the brain?

*Nature of the prostaglandin*

Not only PGE$_1$ but also PGE$_2$, PGF$_{1a}$, and PGF$_{2a}$ contract the rat fundic preparation (Cocchi & Wolfe 1966). The activity could therefore have been due to any of the four prostaglandins or to a combination of them. The F prostaglandins were excluded by thin layer chromatography. But we should have assayed the activity not against PGE$_1$ but against PGE$_2$ because when Dr Heather Davis in Professor Horton's Department in Edinburgh applied the method of radio-immunoassay to some samples of c.s.f. we had sent her, she found that the activity was due solely or mainly to PGE$_2$. Since PGE$_2$ is about twice as potent as PGE$_1$. 

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on the fundic preparation, the only correction required to obtain the activity in terms of PGE$_2$ is to reduce by half the PGE$_1$ values. But from then the activity in the c.s.f. was assayed against PGE$_2$.

![Graph showing rectal temperature changes](image)

**Figure 10.** Records of rectal temperature from two unanaesthetized cats. The position of the columns indicate the times when samples of cisternal c.s.f. were collected; the height of the columns and the figures above refer to PGE$_1$-like activity in ng/ml c.s.f. In the top record the first and second arrows indicate injections of 150 ng endotoxin of *Shigella dysenteriae* into the cisterna magna, and the third arrow indicates an intraperitoneal injection of 25 mg/kg aspirin. In the bottom record the first arrow indicates an intravenous injection of 250 µg endotoxin of *Shigella dysenteriae* and the second arrow an intraperitoneal injection of 25 mg/kg aspirin. (From Feldberg et al. 1973.)

**Lipid A fever**

Endotoxins are the toxic lipopolysaccharide constituent of the walls of gram negative bacteria. Figure 11 gives a schematic structural diagram of the lipopolysaccharides. The O-specific chains of region I carry the immunological specificities
of the respective O-antigen. Our interest lies in region III, in lipid A, because the pyrogenic property of an endotoxin resides almost entirely in the lipid A moiety of the macromolecular complex (Galanos et al. 1972; Lüderitz et al. 1973). The chemical composition of lipid A, which has a molecular mass of about 2000 may well be the same for different endotoxins, or it varies only a little. Therefore, if lipid A were to act like the endotoxin of *Shigella dysenteriae* and produce fever with increased PGE₂ activity in the c.s.f. it would follow that the property of stimulating synthesis and release of prostaglandin is common to many if not to all endotoxins. Lipid A was found to behave like the endotoxin of *Shigella.*

![Diagram of lipopolysaccharides](http://rspb.royalsocietypublishing.org/)

**Figure 11.** Schematic structural diagram of lipopolysaccharides. (From Lüderitz, Westphal, Staub & Nikaido 1971.)

We were fortunate to receive from Dr C. H. Galanos in Professor O. Westphal’s Institute of Immunology in Freiburg, samples of purified soluble lipid A prepared by him from a mutant strain of *Salmonella.* The appearance of, or an increase in the PGE₂ content of cisternal c.s.f. during lipid A fever produced in four experiments with injections of the lipid A into a lateral cerebral ventricle, and in two experiments with the injections made intravenously, are shown in figures 12 and 13. The sensitivity to lipid A varied greatly in different experiments. This is evident from figure 12 which also shows that the antipyretics aspirin, paracetamol and indomethacin bring down both the fever and the PGE₂ content in the c.s.f. Of the three, indomethacin was the most, and aspirin the least potent.

It is unlikely that endotoxin or lipid A, at least when injected intravenously, stimulate prostaglandin synthesis directly. According to our present view (Atkins 1960) an endogenous pyrogen is an essential intermediate in endotoxin fever and the same would therefore apply to lipid A fever. Stimulation of synthesis and release of prostaglandin would therefore be the property of the endogenous pyrogen which is derived from circulating leucocytes (leucocyte pyrogen) and from the cells of the reticulo-endothelial system. The fever produced by endogenous pyrogen should therefore also be associated with the appearance of prostaglandin activity in the c.s.f., and this was recently shown for the fever produced by leucocyte pyrogen in the rabbit (Phillip-Dormston & Siegert 1974; Cranston, Hellon & Mitchell 1975).

When endotoxin and lipid A are injected into the cerebral ventricles the endogenous pyrogen could be derived from leucocytes invading the ventricular walls or from the microglia which is thought to be related to the reticulo-endothelial system, but in this situation there is also the possibility that the endotoxin and
lipid A stimulate prostaglandin synthesis directly (Dey, Feldberg, Gupta & Wendlandt 1975).

The results obtained with lipid A and leucocyte pyrogen bear out what had been supposed, that the final mediator of probably all endotoxins is a prostaglandin which in cats appears to be PGE₃, and that endotoxin fever is probably always brought about by the action of a prostaglandin on the anterior hypothalamus. In fact the fever of all infectious diseases may well be a prostaglandin fever, particularly since Phillip-Dormston & Siegert detected prostaglandin activity also in the c.s.f. when the fever had been produced by a virus.

![Graphs showing rectal temperature records from four unanaesthetized cats.](http://rspb.royalsocietypublishing.org/download)

**Figure 12.** Records of rectal temperature from four unanaesthetized cats. The position of the columns indicate the times when samples of cisternal c.s.f. were collected; the height of the columns and the figures above refer to PGE₂ in ng/ml c.s.f. The first arrow in a, b and d, and the first two arrows in c, indicate injections of lipid A (LA) into a lateral ventricle in the doses indicated. The subsequent arrows indicate intraperitoneal injections of 25 mg/kg aspirin in a, 50 mg/kg paracetamol in c, and 2 mg/kg indomethacin in d. (From Dey, Feldberg, Gupta & Wendlandt 1975.)

**The origin of the PGE₂ in the cisternal c.s.f.**

The PGE₂ detected in the c.s.f. is probably to a small extent only derived from the pre-optic-anterior hypothalamic region. Most of it would appear to be released from other parts of the brain, mainly from the surface of the brain stem. This
would imply that the property of pyrogens to stimulate synthesis and release of prostaglandin is not confined to the anterior hypothalamus, but occurs in other parts of the brain as well, although to produce fever the prostaglandin has to act on the anterior hypothalamus. Further, the synthesis may have to be stronger and more widespread for the PGE$_2$ to be released into the cisternal c.s.f. in sufficient amounts to be detected with the methods of assay used, than for producing fever. This would explain why no close correlation was found between the degree of fever

Figure 13. Records of rectal temperature from two unanaesthetized cats. The position of the columns indicate the times when samples of cisternal c.s.f. were collected; the height of the columns and the figures above refer to PGE$_2$ content in ng/ml c.s.f. The arrows indicate intravenous injections of 4 mg/kg (top record) and 1.5 µg/kg (bottom record) of lipid A. (From Dey et al. 1975.)
and the PGE$_2$ content of the c.s.f. particularly when endotoxin and lipid A were injected intravenously, and why in some of our experiments no prostaglandin activity was detected in the c.s.f. during these fevers. It would also explain why Cranston et al. (1975) found a dissociation between prostaglandin activity and fever when aspirin was given during fever produced by leucocyte pyrogen in rabbits. The prostaglandin activity disappeared from the c.s.f. but the fever was not brought down. In their experiments the suppression of prostaglandin synthesis by aspirin may have been sufficient for the prostaglandin activity to disappear from the c.s.f. but not sufficient for its local pyrogenic action on the anterior hypothalamus to be abolished.

The idea that stimulation of prostaglandin synthesis by pyrogens in the brain is rather widespread and not confined to the anterior hypothalamus, poses the intriguing question of whether some of the symptoms of high fever, like malaise, are the result of high temperature. Instead, they may be effects produced by prostaglandin on parts of the e.n.s. other than the hypothalamus.

In this connection, it is interesting to note that high temperature when produced by severe muscular exercise, that is, when independent of prostaglandin synthesis in the brain, is not associated with malaise. For instance, the temperature of marathon runners can reach extremely high values during running as the result of the tremendous heat production, and the temperature regulating mechanisms may actually break down. But these athletes show no sign of malaise, stupor or delirium when they develop the high temperature (personal communication by Dr R. H. Fox).

In cats, the fever produced by endotoxin and lipid A was often associated with a stuporous state during which the cat did not react to events in its environment, and the same condition is produced when PGE$_1$ is injected into the cerebral ventricles. In larger doses, PGE$_1$ may produce real catatonic stupor, or catalepsy (Horton 1964; Holmes & Horton 1968a). This condition sometimes developed also during endotoxin and lipid A fever. When this happened, the PGE$_2$ activity in the c.s.f. was usually high; in fact, the development of catalepsy often foretold a high PGE$_2$ content of the e.s.f. For instance, in the experiment illustrated in the lower part of figure 13, we expected the fifth sample to have a high PGE$_2$ content, because the cat became very stuporous during the long-lasting fever and showed definite signs of catalepsy when tested for it after collection of the fourth and fifth sample of c.s.f. When placed in an upright posture by putting its paws across the rungs of an inverted stool, it retained this position without struggling, but when it sagged down after a while and moved away, its movements were not impaired.

A DETOUR INTO PSYCHIATRY

Let me digress for a moment and dwell on the association of stupor and catalepsy, or catatonia, with high prostaglandin activity in the e.s.f. The reason is that stupor and catatonia are characteristic features of certain forms of schizophrenia.
Could it be that schizophrenia is due to a disturbance of the prostaglandin metabolism in the brain, or, to be more precise, in the diencephalon?

The late Lord Brain once pointed out to me that we are all schizophrenic when we dream and that schizophrenia can be looked upon as dreaming in the waking state. Dreaming is an alteration in our state of consciousness, and all evidence so far available suggests that the seat of consciousness is in the diencephalon and not in the cerebral cortex (see Feldberg 1959). Since no definite anatomical-pathological changes can be attributed to schizophrenia, the disturbance probably results from a biochemical lesion in the diencephalon.

Now, whenever a pharmacologically potent substance is found to be a natural constituent of brain tissue, the possibility exists that a disturbance in its metabolism is responsible for mental diseases. There is no convincing evidence that a disturbance in the metabolism of acetylcholine, 5-HT or noradrenaline underlies schizophrenia, but there are impressive, though not decisive, clinical observations suggesting that it may be associated with excessive dopamine activity. The latest pharmacologically potent substances detected in the brain are the prostaglandins. They are also present in the diencephalon, and so is the enzyme system for their synthesis (Horton & Main 1967; Holmes & Horton 1968b; Pappius, Rostworoski & Wolfe 1974).

We cannot blame the psychiatrist if he becomes impatient and irritated with the physiologist and pharmacologist who thinks he is imitating schizophrenia whenever he puts a cat or a rabbit, treated with a drug, in an abnormal posture and this posture is maintained, for instance, when he puts the animal in a vertical position, by placing its forepaws across the rungs of an inverted stool – a common procedure adopted for testing catalepsy. We can sympathize with the attitude of the psychiatrist, but how to find out if a cat has hallucinations or paranoid ideas?

Further, in the present experiments, catalepsy or catatonia was produced by a substance naturally occurring in the brain and developed during a pathological condition in which this substance appeared in the c.s.f. Stupor and catalepsy obtained under such conditions may still act as a guide.

But there is the question: is there any association between schizophrenia and fever? Surprisingly, the answer is yes. We would not expect fever to be a constant feature of the disease since it should only occur when the released prostaglandin reaches the anterior hypothalamus. But fever is a genuine syndrome of schizophrenia, even if not a frequent occurrence. My thanks are due to Professor Shepherd from the Maudsley Hospital for having drawn my attention to the relevant literature. The main publications appeared in the thirties, by Gjessing in Oslo, and by Scheid in Munich. Scheid wrote a monograph in 1937, and gave a lecture in 1938, with the title ‘Febrie episodes in schizophrenia’. According to both authors, a periodic exacerbation of the disease is often associated with fever or subfebrile temperatures.

Figure 14 illustrates such febrile and subfebrile episodes in a patient in which they
occurred every few weeks and lasted for over a week. During the episodes the patient became paranoid and hallucinatory; in between, temperature never rose beyond 37.5 °C. Scheid made the interesting statement that every fourth or fifth admission to his hospital occurred during a subfebrile or febrile episode.

There is another, more severe and critical form of fever associated with schizophrenia which was well known to the psychiatrists at the beginning of the century. A sudden onset of very high, often lethal fever, with an exacerbation of the psychosis. Hyperthermia can be so extreme that temperature can no longer be measured with the normal fever thermometer. Psychiatrists not aware that such a fever is a syndrome of the psychosis, go on looking for a bacterial origin, then for a virus infection, and finally for tuberculosis. In the meantime, they treat the patient with antibiotics. But if the fever were due to increased prostaglandin synthesis near the anterior hypothalamus, the treatment of choice would be large doses of antipyretics. The hypothesis that schizophrenia is due to a disturbance in the prostaglandin metabolism of the diencephalon merits a clinical trial with large doses of antipyretics. The antipyretic of choice would be paracetamol because it inhibits more or less specifically the prostaglandin synthetase of brain, as was first shown for mouse and gerbil brain by Willis, Davison, Ramwell & Brocklehurst (1972), and then for rabbit brain by Flower & Vane (1972, 1974).

There is one more supporting fact, the recent finding by Lee (1974) that some of the drugs used therapeutically in schizophrenia, like chlorpromazine and tricyclic antidepressants, are strong inhibitors of prostaglandin synthesis in vitro.
AN UNSPECIFIC FEVER AND SODIUM FEVER

There are two criteria by which we can judge whether a fever is mediated by prostaglandins. Its association with increased prostaglandin activity in the c.s.f., and its prevention or abolition by antipyretics like paracetamol, indomethacin or aspirin, even if the association is not absolute as discussed in the previous pages. A fever mediated by prostaglandins is the unspecific fever seen on intraventricular injections of physiological salt solutions and a fever independent of prostaglandin synthesis is the sodium fever.

An unspecific fever

It has frequently been pointed out that an intraventricular injection of a small amount of 0.9% NaCl solution, or of artificial c.s.f. can produce, after a latency which can be as long as 3.5 h, prolonged fever. This happens also, though less frequently, on injections into the cisterna magna. These fevers, according to the two criteria are mediated by prostaglandin. The upper record of figure 15 shows such a fever in an unanaesthetized cat and its association with the increase in PGE$_2$ activity in the c.s.f. The lower record, which is from another cat, shows that both fever and increased PGE$_2$ activity are brought down by an intraperitoneal injection of paracetamol.

To explain this unspecific fever we assume that the injections produce some disturbance in the ventricular walls or in the surface structures of the brain stem which leads to increased prostaglandin synthesis. It would appear that at least in certain parts of the brain, the response to the slightest disturbance or to the 'mildest injury stimulus' consists of increased synthesis and release of prostaglandins, in the same way as the release of histamine with the ensuing triple response, represents the first defence mechanism of the human skin to stimuli not harmful enough to set in motion the full range of inflammatory reactions. This is in line with the views expressed by Collier (1971, 1974) that prostaglandins are mediators of defensive responses but do not greatly participate in normal physiological functions.

Sodium fever

In 1970, when Myers, Veale & I perfused the cerebral ventricles of an unanaesthetized cat, we one day made a mistake and used 0.9% NaCl solution instead of artificial c.s.f. as perfusion fluid. The result was high fever due to an effect of the sodium ions. Under physiological conditions their effect is checked by the calcium ions. The opposite effect, a fall in temperature, occurs on perfusion of the cerebral ventricles with a salt solution containing an abnormally high calcium content. The fact that the sodium fever is independent of prostaglandin synthesis is illustrated in figure 16.

The two records are from the same cat and were obtained on different days. The two 30 min periods of perfusion from lateral ventricle to cisterna magna
with calcium-free artificial c.s.f. produced on each occasion a sharp rise in temperature. If the rise were due to prostaglandin synthesis, it should not have occurred in the experiment of the lower record because the perfusion was preceded by an intraperitoneal injection of paracetamol, that is, prostaglandin synthesis was inhibited. Further, there was no increased prostaglandin activity in the cisternal effluent collected during, or in the c.s.f. collected shortly after the perfusion. So the sodium fever is independent of prostaglandin synthesis.

![Graph](http://rspb.royalsocietypublishing.org/)

**Figure 15.** Records of rectal temperature from two unanaesthetized cats. The positions of the columns indicate the times when samples of cisternal c.s.f. were collected; the height of the columns and the figures above refer to PGE\(_2\) content in ng/ml c.s.f. The first arrows indicate injection of 0.15 ml (top record) and 0.3 ml (bottom record), of 0.9% NaCl solution, the second arrow in the bottom record indicates intraperitoneal injection of 50 mg/kg paracetamol. (From Dey et al. 1974.)

The sodium fever and the antagonistic effect of calcium ions form the basis of the theory that the constancy of temperature is brought about by a correct equilibrium between sodium and calcium ions in the hypothalamus. But the situation is not as simple as that. Myers, Veale & Yaksh found that these ions do not
act on the anterior, but act on the posterior hypothalamus (Myers & Veale 1970, 1971; Myers, Veale & Yaksh 1971; Myers & Yaksh 1971; Myers 1974). So they removed the set-point from the anterior and placed it in the posterior hypo-

![Graph](image)

**Figure 16.** Records of rectal temperature from an unanaesthetized cat obtained on different days. The interval between the dotted vertical lines indicate in each record 30 min perfusions at a rate of 0.1 ml/min from lateral ventricle to cisterna magna. The vertical columns indicate the times when samples of cisternal c.s.f. or effluent were collected and the height of the columns and the figures on top refer to PGE₂ content in ng/ml samples. At the arrow intraperitoneal injection of 50 mg/kg paracetamol. (From Dey et al. unpublished experiments (top record), and 1974 (bottom record).)

thalamus, and naturally introduced a new model. Their results may perhaps merely mean that cholinergic interneurons in the efferent pathway are particularly sensitive to the ionic changes.
W. Feldberg

I wonder if it is not time to free ourselves from the concept of a set-point. If so, I should like to conclude my lecture by again re-stating my view that the constancy of temperature is but a manifestation of Claude Bernard's general principle of the milieu intérieur, applied to the anterior hypothalamus. Here, as in other cells of the body, the milieu intérieur does not undergo sudden changes under physiological conditions. But there is a neuronal control exerted by adrenergic and tryptaminergic neurons innervating the anterior hypothalamus, and acting through release of noradrenaline and 5-HT. Finally, fever, the defence mechanism against infectious diseases, is brought about by increased synthesis and release of prostanoids in this part of the brain.

References

Artunkal, A. A. & Marley, E. 1974 Hyper- and hypothermic effects of prostaglandin E$_1$ (PGE$_1$) and their potentiation by indomethacin in chicks. J. Physiol., Lond. 242, 141–142 P.
Bligh, J. 1966 Effects on temperature of monoamines injected into the lateral ventricles of sheep. J. Physiol., Lond. 185, 46–47 P.
Bligh, J. & Milton, A. S. 1973 The thermoregulatory effects of prostaglandin E$_1$ when infused into a lateral cerebral ventricle of the Welsh mountain sheep at different ambient temperatures. J. Physiol., Lond. 229, 30–31 P.


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FIGURE 8. Record of rectal temperature from an unanaesthetized cat. The arrows indicate injections of 75 mg endotoxin of *Shigella dysenteriae* (Shig.) into the third ventricle and of 50 mg/kg paracetamol (para.) intraperitoneally. The black bars indicate periods of collection of ventricular c.s.f. The bottom part shows contraction produced by 0.1 ml of these samples of c.s.f. on the rat fundic preparation compared with those produced by 0.5–4 ng of PGE₁. (From Feldberg & Gupta 1973.)