Psychological Medicine, 1976, **6**, 359–369

Possible association of schizophrenia with a disturbance in prostaglandin metabolism: a physiological hypothesis

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SYNOPSIS Schizophrenia may be associated with increased prostaglandin synthesis in certain parts of the brain. This hypothesis is based on the following findings: (1) Catalepsy, which is the nearest equivalent in animals to human catatonia, develops in cats when prostaglandin E_1 is injected into the cerebral ventricles and when during endotoxin or lipid A fever the prostaglandin E_2 level in cisternal c.s.f. rises to high levels; however, when fever and prostaglandin level are brought down by non-steroid anti-pyretics which inhibit prostaglandin synthesis, catalepsy disappears as well. (2) Febrile episodes are a genuine syndrome of schizophrenia.

The late Lord Brian once told me that many clinicians take the view that the dreaming state resembles schizophrenia, and that schizophrenia can be looked upon as dreaming in the waking state. Since dreaming is an alteration in our state of consciousness, we should expect the pathological disturbance or dysfunction of schizophrenia to be seated in those regions of the brain which we associate with consciousness.

The cerebral cortices are not the seat of consciousness. On the contrary, as often pointed out by Jefferson (1938, 1944, 1958), there is abundant neurological evidence, if observers were only prepared to look for it, that impairment or loss of consciousness is associated with damage in the upper brain stem and in the diencephalon. The evidence has been summarized elsewhere (Feldberg, 1959). In the two maps of Fig. 1, the stippled parts indicate the areas, damage of which leads to depression of consciousness, to hypersomnia or to coma. In the lower (later) map, the area extends more anteriorly. This extension is based on observations in patients, in whom unconciousness occurred from bleeding aneurysms of the anterior cerebral and the anterior communicating arteries. In schizophrenia no definite pathological changes have been found in these regions or elsewhere in the brain. The psychosis, however, may well result from a biochemical disturbance or a biochemical lesion in these regions. In recent years, various attempts have been made to explain schizophrenia as being a biochemical disturbance in the brain.

Whenever a pharmacologically potent substance is found to be a natural constituent of brain tissue, the possibility exists that a disturbance in its metabolism results in mental disease. There is no convincing evidence that a disturbance in the metabolism of acetylcholine, 5-HT or noradrenaline is associated with schizophrenia but there are impressive clinical observations suggesting that this psychosis may be associated with excessive dopamine activity. The latest pharmacologically potent substances detected in the brain are the prostaglandins (Horton & Main, 1967; Pappius *et al.* 1974). They are present also in the upper brain stem and diencephalon, and so is the enzyme system for their synthesis.

Could it then be that schizophrenia is related to a disturbance in the prostaglandin metabolism of the brain or, more precisely, of the upper brain stem and diencephalon? At present, no definite answer can be given to this question, but there are at least two findings, both made in cats, which point in this direction. First, the finding of Horton (1964) and of Holmes & Horton (1968)

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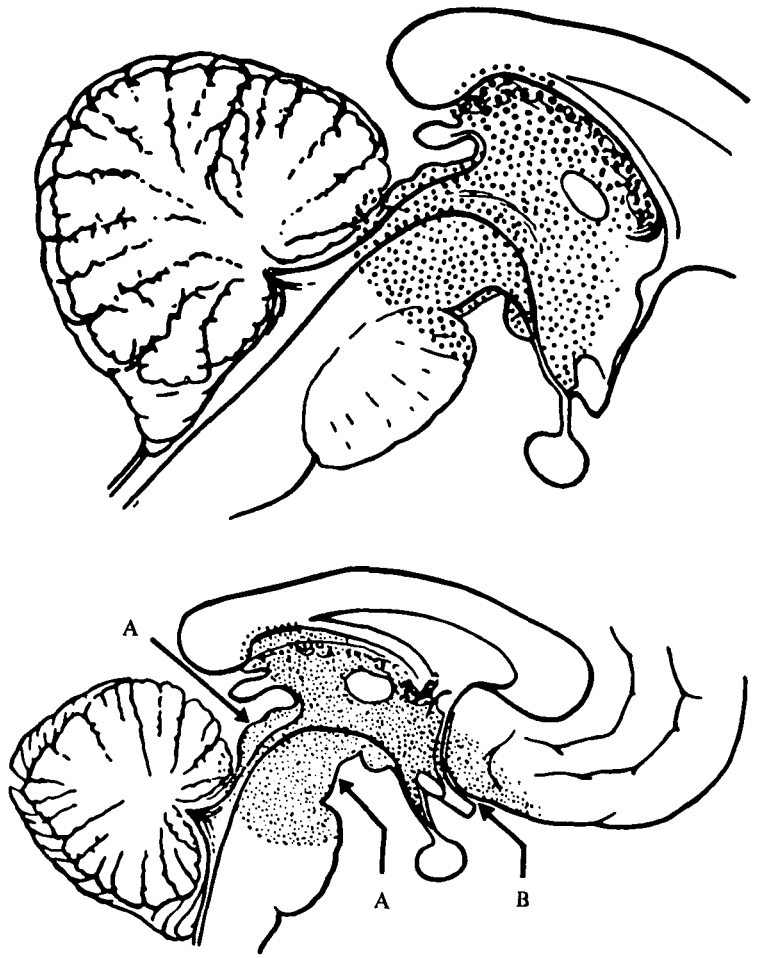

FIG. 1. Diagrams of midsagittal sections of human brain. The stippled areas are those most related to preservation of conscious states. A, B, critical points in relation to consciousness. Upper diagram from Jefferson & Johnson (1950); lower diagram from Jefferson (1958).

that on injection into the cerebral ventricles, small doses of prostaglandin E_1 (PGE_1) produce a stuporous state in which the cat does not react to events in its environment, while larger doses induce frank catalepsy. Secondly, there is the association of stupor and catalepsy with a high PGE content of cisternal cerebrospinal fluid (c.s.f.) observed during fever produced by endotoxins or their toxic constituent, lipid A.

Some of our general ideas about the role of prostaglandins fit the idea that the pathological or biochemical disturbance in schizophrenia consists in increased synthesis and release of prostaglandins in certain parts of the brain. For instance, 'mammalian cells seem to disgorge prostaglandins at the slightest provocation'. This was pointed out by Piper & Vane (1971). We have, further, the views of Collier (1971, 1974) that prostaglandins often play a role in pathological reactions or defence responses. In the same way as the release of histamine in the human skin with the ensuing triple response represents the first defence mechanism to an injury not harmful enough to set in motion the whole range of inflammatory responses, so increased synthesis and release of prostaglandins may be the first response of the brain, or of certain parts of it, to the slightest disturbance or to the mildest injury. The simple 'disturbance' of injecting a small volume of physiological salt solution into the cerebral ventricles of cats is often sufficient to produce this effect leading to

the appearance, for several hours, of prostaglandin in the cerebrospinal fluid (Dey *et al.* 1974).

CATALEPSY

Catalepsy in animals is the nearest equivalent to catatonia in humans, and is produced experimentally either by drugs or by lesions in certain parts of the brain. Electrical stimulation, however, does not induce the condition. Therefore, when catalepsy develops in response to a drug it seems justified to conclude that the drug acts not by exciting specific nerve cells, but by impairing their function, paralysing them, causing synaptic block or, to express it in a more general way, by producing a pharmacological lesion.

The pharmacological lesion should be at the same site or sites where actual lesions, for instance electrolytic lesions, produce catalepsy, and these lesions, in turn, should lie within the areas illustrated in Fig. 1 as being associated with consciousness. And so they do (for references, see Feldberg & Sherwood, 1955).

In his book on 'Experimental Catatonia', de Jong (1945) lists a number of drugs which produce catalepsy. The one most frequently associated with this condition is bulbocapnine, the name pointing to the site of action. Bulbocapnine produces stupor and catalepsy in cats on injection into the cerebral ventricles in a dose of 0·5 mg/kg as compared to between 20 and 30 mg/kg on intramuscular injection (Feldberg & Sherwood, 1955). Another drug found to induce catalepsy when injected in small doses into the cerebral ventricles of cats is the inhibitor of cholinesterase, diisopropylfluorophosphate (DFP). To interpret the catalepsy produced by DFP as a pharmacological lesion, we have to assume that the persistence of undestroyed acetylcholine acts not by exciting, but by paralysing nerve cells, analogous to the action of DFP at the neuromuscular junction. Here DFP quickly converts the excitatory action of acetylcholine into a paralysing one (Brown *et al.* 1948). We cannot, therefore, conclude from the catalepsy produced by DFP that catatonia, when it occurs in schizophrenia without DFP, is an acetylcholine effect. The most we can say is that it is probably due to an impairment of function in nerve cells which are normally impinged upon by cholinergic neurones. There are also effects produced in man by DFP which are of interest in relation to schizophrenia and which may have to be interpreted along similar lines. For instance, in patients with myasthenia gravis who were given daily injections of DFP the treatment had to be discontinued because of nightmares, confusion and hallucinations (Grob *et al.* 1947), and DFP given to schizophrenics caused activation of the psychosis (Rowntree *et al.* 1950). Excessive dreaming, nightmares and confusion have also been reported on exposure to, or on oral application of, other organophosphorus compounds that are cholinesterase inhibitors (Grob, 1956; Holmes & Gaon, 1956; Grob & Harvey, 1958). If these effects of DFP result from a paralytic action of the persistence of undestroyed acetylcholine, then an antagonist of acetylcholine should produce similar symptoms. And so it does. Atropine poisoning is associated with hallucinations and has mistakenly been diagnosed as an acute schizophrenic episode; patients have been committed to psychiatric institutions for observation and diagnosis (quoted from Goodman & Gilman, 1965).

There may even be an association between the catalepsy produced by DFP and that produced by prostaglandin. Thus, on a smooth muscle preparation, the isolated guinea-pig ileum, the response to PGE_1 was shown to be somewhat potentiated by DFP (Harry, 1968).

Morphine is yet another drug known to produce catalepsy. In rats, catalepsy is generally regarded to be the most prominent early effect. In rabbits, it develops not only when the morphine is injected into the cerebral ventricle, in doses between 25 and 100 μg, but also when injected into the cisterna magna in a dose of 100 μg. On cisternal injection, the morphine does not enter the cerebral ventricles; the structures affected must therefore be reached from the subarachnoid space and they must be superficially situated structures. The same structures will also be reached when the morphine or other drugs are injected into the cerebral ventricles because they quickly enter the subarachnoid space through the lateral recesses, i.e. through the foramina of Luschka. So the structures affected are probably the same with both routes of administration.

What then are these structures? Most probably they are located in the most ventral parts of the mesencephalon and in the region of transition between mesencephalon and diencephalon because small electrolytic lesions in these

regions at the base of the brain stem were found by Ingram *et al.* (1936) to produce catalepsy in cats. These regions would be reached from the cisterna interpeduncularis as the morphine spreads in the subarachnoid space rostrally along the ventral surface of the brain stem. Some of these regions are also reached from the third ventricle, so that on injection into the cerebral ventricle they may be reached both from the inner and outer surface of the brain (Banerjee *et al.* 1968).

The following is a description of the stupor produced in a cat by an injection of bulbocapnine into the cerebral ventricles (Feldberg & Sherwood 1955).

'The cat no longer reacted to events in the room, nor did it come forward when approached. A hand could be waved close to its face, eliciting nothing beyond a blinking of the eyes. It was also difficult to obtain the cat's attention by noises, but when stimulated by stroking, or inducing it to move, the cat betrayed its awareness by lashing its tail and changing its facial expression and, in several instances, by uttering hoarse cries which continued for some time after the stimulus ceased.'

Another cat made no withdrawal movement when smoke was blown into its face, but when touched it responded with howling and crying.

During the condition of catalepsy, the cat can be put in abnormal positions or postures and may retain them for some time. When one of its forepaws is abducted or placed across its back, it makes no attempt to remove it; put in an erect posture with its forepaws placed over the upper rung of an inverted stool, or when placed over the rungs, or across two stools, the cat retains these positions for many seconds and even minutes. Nevertheless, its movements are not impaired because when pushed from behind, it jumps in a well coordinated manner.

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 erect posture with its forepaws placed over the upper rung of an inverted stool' – a common procedure adopted for testing catalepsy – and this posture is maintained. We can sympathize with the attitude of the psychiatrist, but how can we find out if a cat has hallucinations or paranoid ideas? Stupor and catalepsy may still act as a guide if produced by a substance which, like prostaglandin, occurs naturally in the brain, and if these features develop during a pathological condition in which the substance appears in abnormal amounts in the c.s.f.

AN ASSOCIATION OF CATALEPSY WITH HIGH PROSTAGLANDIN CONTENT OF c.s.f. DURING FEVER

This association was more a chance observation made during experiments in which direct evidence was sought for the theory that prostaglandins are the final mediator of the fever produced by bacterial endotoxins, or perhaps of the fever of all infectious diseases. Here a few introductory remarks and explanations of the terms endotoxins, lipid A and endogenous pyrogen may be helpful.

Endotoxins are the toxic principle produced by Gram-negative bacteria. They are lipopolysaccharides firmly bound to the outer membrane of the bacterial cell wall. When the bacteria undergo disintegration, or lysis, the lipopolysaccharides are released into the surrounding medium. Their chemistry has been worked out mainly by Westphal, Lüderitz and their coworkers (see Westphal, 1975). The lipopolysaccharides stick out as long chains from the bacterial wall and each chain consists of three regions. Region III, the one nearest to the bacterial wall and directly attached to it, is lipid A; Region I sticks out furthest away from the cell wall and is called the O-specific chain; in between connecting III with I, lies Region II, called the basal core. For our purpose it is sufficient to know that the antigenic property of an endotoxin resides in its O-specific chains, whereas the toxicity including the pyrogenic property resides in the lipid A moiety of the macro-molecular complex. Further, the chemical composition of lipid A which has a molecular mass of about 2000, varies little if at all, for different endotoxins. With lipid A fever we therefore imitate the fever of all endotoxins.

A small dose of an endotoxin or of lipid A injected intravenously into rabbits or cats produces fever after a latency of varying duration. The fever results from an effect on the pre-optic anterior hypothalamic region, the part of the brain which controls body temperature. However, endotoxins and lipid A do not act.

directly on the pre-optic anterior hypothalamic region. They act solely on leucocytes and on cells of the reticulo-endothelial system to produce and release from them a fever-producing substance, 'endogenous pyrogen', which in turn acts on this part of the brain. The term 'endogenous pyrogen' is used to distinguish it from 'bacterial pyrogen' which is synonymous with endotoxin or bacterial endotoxin. The first, and for a time the only, known source of endogenous pyrogen was the leucocyte, and the pyrogen derived from these cells was often referred to, and still is, as leucocyte pyrogen.

According to the latest opinion endogenous pyrogens, whether produced by endotoxins, lipid A or by viruses, produce fever because they have the property of stimulating prostaglandin synthesis in the pre-optic anterior hypothalamic region. The synthesized prostaglandin is an E prostaglandin which in cats appears to be PGE_2. This theory was suggested by two findings. First, that PGE_1 and PGE_2 injected into the cerebral ventricles of cats and rabbits produce fever through an action on the anterior hypothalamus (Milton & Wendlandt, 1970, 1971; Feldberg & Saxena, 1971) and secondly, that antipyretics of the aspirin type, the so-called non-steroid antipyretics, inhibit prostaglandin synthesis (Vane, 1971).

If pyrogens were to stimulate synthesis, and consequently the release, of prostaglandins, this might lead to increased prostaglandin levels in the 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 evidence for this idea, c.s.f. was collected from unanaesthetized cats and tested for prostaglandin activity on the rat stomach fundic preparation. In the first experiments of this kind the c.s.f. was collected from the cannulated third cerebral ventricle, and had thus been in close contact with the anterior hypothalamus. But the same result was obtained when the c.s.f. was collected from the cisterna magna. During endotoxin or lipid A fever, the PGE_2 content of the c.s.f. rose, but it was brought down with the fever by intraperitoneal injections of aspirin, indomethacin or paracetamol (Feldberg & Gupta, 1973; Dey *et al.* 1974, 1975). Similar results have since been obtained in rabbits and also with endogenous pyrogen as well as with a virus, that of Newcastle disease (Phillip-Dormston & Siegert, 1974; Cranston *et al.* 1975; Harvey & Milton, 1975).

It would be strange if pyrogens were to stimulate prostaglandin synthesis only in the pre-optic anterior hypothalamic region, although to produce fever the synthesized prostaglandin has to act on it. More probably pyrogens stimulate the synthetase in all parts of the central nervous system in which the enzyme occurs, and perhaps in peripheral tissues as well. Therefore, the prostaglandin detected in the cisternal c.s.f. during pyrogen fever may, to a small extent only, be derived from the pre-optic anterior hypothalamic area; most of it may be synthetized in other regions of the brain, and particularly of the brain stem bordering the subarachnoid space and then released into the c.s.f. It is thus not surprising that there is no strict correlation between the degree of fever and the rise of PGE in the c.s.f. This has led to questioning of the validity of the prostaglandin theory of pyrogen fever (Cranston *et al.* 1975).

The idea that pyrogens stimulate brain synthetase in all parts of the brain in which this enzyme occurs, poses the intriguing question of whether some of the symptoms of high fever like malaise, stupor and perhaps even delirium are really the result of the high temperature. Instead, they may be effects produced by prostaglandins acting on parts of the brain other than the anterior hypothalamus. Marathon runners develop extremely high temperatures during running on account of the tremendous heat production; the temperature regulating mechanism may even break down; yet they show no signs of malaise, stupor or delirium (personal communication by Dr R. H. Fox).

In our experiments on cats it was found that during the fever produced by endotoxins or lipid A, the cats often became stuporous and cataleptic and that there was an association of the catalepsy with the PGE_2 content of c.s.f. Whenever catalepsy developed, the PGE_2 values were high. Fig. 2 illustrates an experiment in which fever was produced by an intravenous injection of 1·5 μg/kg of lipid A. The vertical columns indicate the times when samples of c.s.f. were collected and the figures above them refer to the PGE_2 content in ng/ml. During the long lasting fever the cat became very stuporous and showed definite signs of catalepsy when tested before and after collectingt he fifth sample.

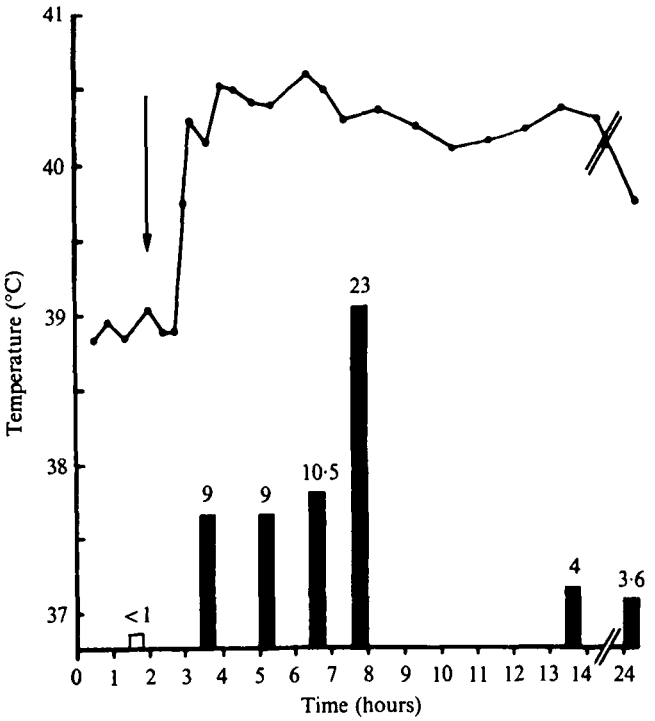

FIG. 2. Record of rectal temperature from an unanaesthetized cat. The columns indicate the times when samples of cisternal c.s.f. were collected and their height and the figures above refer to PGE_2 content in ng/ml c.s.f. At the arrow, intravenous injection of 1·5 μg/kg of lipid A. (From Dey *et al.* 1975.)

We were therefore not surprised to find a high PGE_2 value for the fifth sample. Stupor and catalepsy disappear when the high PGE_2 content of the c.s.f. and the fever are brought down by an intraperitoneal injection of paracetamol or indomethacin.

FEBRILE EPISODES IN SCHIZOPHRENIA[1]

The idea that schizophrenia may be associated with increased synthesis and release in certain parts of the brain, does not imply that there must also be an association with fever. Fever would be present only if the increased synthesis and release were to take place within the anterior hypothalamus, or very near to it. Yet, surprisingly, fever is a genuine sign, though not a frequent one, occurring in some schizophrenics.

There are a number of publications on body temperature in schizophrenia which do not deal with the problem of whether temperature rises during an activation of the psychosis. They deal simply with body temperature in chronic schizophrenic patients, with diurnal variations and with the response to changes in the environmental temperature. Temperature appears to be a little subnormal in chronic schizophrenic patients, the diurnal variations appear to be atypical and there are some differences in the response to cold but not to heat, suggesting some disturbance in temperature regulation of chronic schizophrenic patients (Cameron, 1934; Freeman, 1939; Buck *et al.* 1950).

On the other hand, in the thirties, several publications on febrile episodes as a symptom of schizophrenia appeared, mainly by Gjessing in Oslo and by Scheid in Munich. The point stressed in these publications was that, during a schizophrenic illness, febrile episodes may develop which are not due to infectious diseases, focal infections or to any other source known to the clinician to cause fever; nor are they brought about by emotion. They are symptoms or bodily manifestations of the schizophrenic disease.

Scheid wrote a monograph in 1937, and gave

[1] My thanks are due to Professor Michael Shepherd of the Institute of Psychiatry for having drawn my attention to the relevant literature.

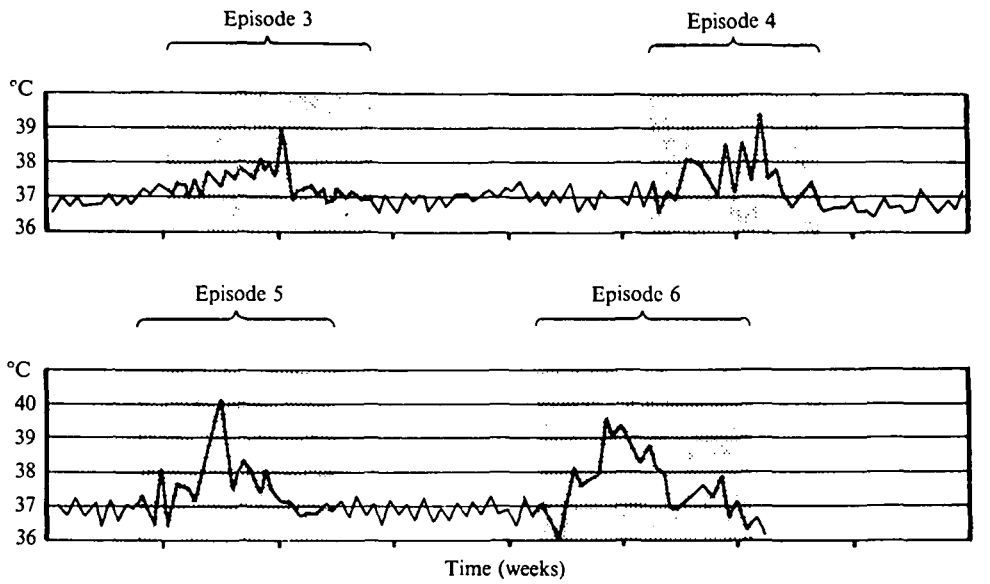

FIG. 3. Febrile episodes in a schizophrenic patient. All other parameters apart from temperature have been omitted. (From Scheid, 1938.)

a lecture in 1938, with the title 'Febrile episodes in schizophrenia'. He observed genuine febrile episodes in 57 out of 1000 schizophrenic patients examined over a period of five years. The incidence may well have been greater, because whenever there was the slightest suspicion of the fever having arisen from another disease, the case was omitted. Of the 57 patients with genuine febrile episodes, 47 were apparently fully examined. Scheid distinguished between three groups of febrile episodes, although transitional forms made a clear distinction not always possible.

(1) Febrile episodes coinciding with activation of the psychosis (21 patients).

(2) Febrile cyanotic episodes which are more often than not lethal (22 patients).

(3) Febrile stuporous episodes which can also be lethal (4 patients).

(1) FEBRILE EPISODES COINCIDING WITH ACTIVATION OF THE PSYCHOSIS

Taking routine daily records of rectal temperature in his patients, Scheid was struck by the facts that in some of his patients an activation of the psychosis ('Schübe' in German) coincided with the development of fever and that as the psychotic symptoms subsided, the rectal temperature returned to normal. The duration of the febrile schizophrenic episodes varied between a few days and weeks. The case history of one of his patients, a 19-year-old male schizophrenic, may serve as an illustration. In this patient there occurred regularly, every few weeks, an activation of the psychosis which was associated with a rise in rectal temperature up to 40 °C. During these febrile episodes, the patient became paranoid and hallucinatory, whereas in the intervals he gave the picture of a bland hebephrenic. The temperature curve of Fig. 3 was obtained from this patient. The periods in which he became paranoid and hallucinatory are indicated by the darkened areas which, as Scheid points out, clearly coincide with the periods of elevated temperature.

In some patients the psychotic manifestations during activation of the psychosis were not so much hallucinatory as stuporous and catatonic. In other patients, again, an activation of the psychosis developed with high fever, but whereas the fever subsided within a few days, the psychotic symptoms persisted for a few weeks. During this time, however, temperature appeared to be labile; it was sometimes found to be elevated for a day. Scheid apparently never gave antipyretics to his patients during the febrile episodes.

Other bodily changes observed during the

febrile episodes were increased pulse rate, mild leucocytosis, and changes in the red cell count and haemoglobin content, suggesting both increased destruction and formation of red cells, and increased urobilinogen excretion in the urine. These changes occurred also during the cyanotic and stuporous febrile episodes.

When rectal temperature became elevated but did not reach fever level during an activation of the psychosis, Scheid speaks of subfebrile schizophrenic episodes. They occur relatively frequently. Scheid estimates that in his admission ward, every fourth or fifth admission occurred during a subfebrile schizophrenic episode.

(2) FEBRILE CYANOTIC EPISODES

They are characterized by the following 'Triad of symptoms': fever, tachycardia and cyanosis without dyspnoea. Temperature rises, the pulse becomes rapid and small, and the lips, tip of the nose, heads and feet become cyanotic, but there is no dyspnoea. Some of the cyanotic episodes are lethal; some patients recover and in some they occur periodically at long intervals during the psychosis. The lethal cases may be identical with the so-called lethal catatonia of Stauder. All cases have in common that after various psychotic prodromes of depressive, paranoid or asthenic nature, or in the course of a prolonged illness, these bodily signs develop more or less violently together with a more or less sudden exacerbation of the psychosis – for instance, a sudden change to a paranoid-fearful condition, with hyperkinesis, confusion and some impairment of consciousness. A critical condition is produced which often ends in death. If recovery occurred, the febrile cyanotic episodes lasted between a few days and a few weeks

In some patients, rectal temperature rose to just over 38 °C, in others the hyperthermias became so extreme that the temperature could no longer be measured with the normal thermometer. Usually the temperature rose as the active phase developed, remained high for some time and then returned to normal as the syndrome subsided. In some patients temperature suddenly dropped to normal and a critical condition developed: the patient became nearly unconscious and the pulse could scarcely be felt. Sometimes the temperature rose before the psychotic symptoms developed, but more often fever and psychotic symptoms developed together. The cyanosis without dyspnoea developed together with the fever. Tachycardia could reach extreme values, but during the day pulse rate changed from hour to hour. Sometimes the tachycardia preceded the appearance of fever and of the psychotic symptoms. The pulse was weak and feeble. When the arterial blood pressure was recorded the systolic–diastolic difference was found to be small; but blood pressure remained normal until just before death.

(3) FEBRILE STUPOROUS EPISODES

These are patients in whom the psychosis suddenly turns into a stuporous condition with fever or subfebrile temperatures. This condition may develop within a few hours, or more slowly. It may take days, weeks, or months before such an episode fully subsides. Or it may end in death. During the episode the patient may show an abnormal secretion of the sebaceous glands. The mask-like face looks as if it is covered with cream or ointment (*Salbengesicht*). Sometimes it was possible to scrape the sebum from the skin. This abnormal secretion developed with, but subsided a little earlier than, the stupor and fever.

Scheid points out that it has been known for a long time that temperature can rise during an activation of the psychosis. In the older German textbooks of Kraepelin, Reichardt, Bumke and others this has been described as 'catatonic fever'; but in later textbooks, i.e. those nearer to 1937, this was no longer mentioned.

It was actually Gjessing, and not Scheid, who, in 1932, rediscovered the association between fever and an exacerbation of the psychosis. Between 1932 and 1954, Gjessing published eight papers on the symptomatology of catatonia. Some points made in his first publication deserve special mention. He stated that exogenous fever can be the cause of an exacerbation of the catatonic stupor and that in his experience whenever the source of the fever was found and removed (e.g. enlarged infiltrated tonsils or bad teeth) and the temperature returned to normal, the stupor disappeared and did not return, at least for years. Gjessing's contention was that the irregular periods of fever he recorded, whether they were exogenous in origin or not, were associated with an exacerbation or onset of the stupor. He thought that most of the catatonic patients had

some kind of chronic inflammation, and in 67 % of them he recorded periods of irregular fever up to 38 or 38·5 °C. But he himself doubted that a chronic inflammation was the root of the fever in all cases. As he said, 'it is beyond doubt' that in some of them the fever was caused by the same functional disturbance as that underlying the onset of the stupor. He suspected that in many of his catatonic patients a chronic inflammation, if it existed at all, had nothing to do with the fever and exacerbation of the psychosis, a suspicion later shared by Scheid. Both may have erred by being over cautious.

In Gjessing's later papers the close association between elevated temperature and activation of the psychosis was again stressed and strikingly illustrated, but nothing new was added to the solution of the problem. He recorded numerous parameters, apart from temperature, and his main interest lay not in the febrile episodes, but in changes of the nitrogen metabolism.

An early publication on fever in schizophrenia which appeared prior to the publications of Scheid in 1935, is that by Kroll from Greifswald. In the spring of that year, he had observed five cases of schizophrenia with an acute onset of lethal fever which could not be attributed to any cause. The fever differed from that of infectious diseases in that the skin temperature did not rise and the skin remained cool, whereas during the fever of infectious diseases the skin becomes hot.

There are a number of publications on lethal catatonia which appeared after Scheid's monograph and in some of these publications the condition was associated with high fever. They are brought together in a review by Peele & Loeken (1973) in which the authors suggest that the so-called 'phenothiazine death' described in schizophrenic patients receiving phenothiazine treatment may, in fact, be lethal catatonia and not the effect of the drug.

Failure to appreciate that elevated temperature is a syndrome of schizophrenia may have led to the assumption sometimes made that there is an association between tuberculosis and schizophrenia. I recently heard of a patient who developed very high fever during an acute schizophrenic phase. The patient had become more and more stuporous and seemed to have shown catatonic features. First a bacterial origin was suspected, then a virus infection, and when that, too, proved to be wrong, tuberculosis. But again no evidence for it could be found. In the meantime the patient was treated with antibiotics. Neither the psychiatrist nor the clinician seemed to have been aware that high temperature is a sign of schizophrenia. If it should be shown that in such cases the high fever is due to increased prostaglandin synthesis near the anterior hypothalamus, the treatment of choice would be large doses of antipyretics which inhibit prostaglandin synthesis.

DRUGS THAT INHIBIT PROSTAGLANDIN SYNTHESIS

The idea that schizophrenia may be associated with increased prostaglandin synthesis in certain parts of the brain raises the question of whether neuroleptic drugs are inhibitors of the prostaglandin synthetase in brain. This question cannot be answered today. The only two investigations so far carried out on the effect of psychotropic drugs, including some neuroleptic compounds on prostaglandin synthetase, were on the enzyme system of peripheral tissue, on homogenate of guinea-pig lung (Lee, 1973) and on the microsomal fraction of seminal vesicles (Krupp & Wesp, 1975). We know, however, that drugs may affect the synthetase of the brain quite differently. For instance, paracetamol, which is relatively ineffective on the synthetase of peripheral tissue is a potent inhibitor of brain synthetase as was shown by Willis *et al.* (1972) and by Flower & Vane (1972, 1974).

On the synthetase of peripheral tissue chlorpromazine was about as active as aspirin but promazine was less active. As a neuroleptic, chlorpromazine is also more effective than promazine. But otherwise there was no correlation with the effectiveness in schizophrenia. The potent neuroleptic, haloperidol, did not inhibit the synthetase activity. Other psychotropic drugs had an inhibitory effect. Desipramine and imipramine were less, but doxepin was more, active than chlorpromazine. Monoamine oxidase inhibitors which are known to aggravate the psychosis (see Price & Hopkinson, 1968) were found also to inhibit the prostaglandin synthetase in homogenate of guinea-pig-lung. On this enzyme system pargyline was about as active as chlorpromazine, tranylcypromine was more potent and about as active as indomethacin, and phenelzine was more active still.

Since the psychotropic drugs tested may show entirely different activities on the synthetase system of brain the relative activities obtained have little meaning for our problem, but they at least show that some neuroleptics are inhibitors of the synthetase. Even a comparison of their inhibitory action on brain synthetase need not reveal a direct correlation with their potencies as neuroleptics. The conditions are so different. Their effects in schizophrenic patients occur after a latency period of some days. To test them on the synthetase system they are added for a short time to a brain homogenate.

Perhaps the best way to test the theory that schizophrenia is associated with a disturbance in prostaglandin metabolism resulting in increased prostaglandin synthesis would be to find out if an antipyretic with a strong inhibitory action on the synthetase of brain has a beneficial effect in schizophrenic patients. The antipyretic of choice would be paracetamol because of its selective action on the synthetase in brain. Another potent although not a selective inhibitor of brain synthetase would be indomethacin. A clinical trial with these antipyretics would be justified.[1]

The point to be stressed is that the effects of antipyretics should be tested not only in patients with febrile or subfebrile episodes but during any activation of the psychosis, whether it is associated with a rise in body temperature or not. A rise in temperature would only indicate that the biochemical disturbance which we assume to be increased prostaglandin synthesis is within the pre-optic anterior hypothalamic area, or very near to it. Naturally, there would appear to be a particularly strong indication in those fortunately rare instances in which high fever develops suddenly during the psychosis, to try large and frequent doses of paracetamol and/or indomethacin, instead of experimenting with antibiotics.

The relatively frequent occurrence of fever with signs of stupor and catatonia may be explained by the fact that anatomically the sites at the base of the upper brain stem and diencephalon from which these symptoms can be produced are not far away from the pre-optic region. For the other symptoms of schizophrenia the same biochemical lesion is assumed, but the sites may be situated some distance away from the liquor space, though in the same parts of the brain.

Antipyretics cannot be expected to provide a cure. At most they would have a relatively short-lasting effect and should therefore be given several times a day. But if they should bring about an improvement, though not a permanent one, this might change the direction of our research concerning the treatment of this mental disease.

The idea of schizophrenia being associated with increased prostaglandin synthesis in certain parts of the brain need not be contrary to the theory of over-activity in dopaminergic neurones as a basis of the psychosis. The activity in peripheral adrenergic neurones is known to be associated with release of prostaglandin, as shown, for instance, by Davis *et al.* (1968) on stimulation of the splenic nerves in dogs. The released prostaglandin then inhibits further release of noradrenaline by a presynaptic action. It is not yet known whether prostaglandin release occurs also with activity in central dopaminergic neurones, and if so, whether a similar feed-back mechanism applies. Finally, it may be pointed out that there are at least two features of schizophrenia, namely fever and catatonic stupor, which are not readily explained by over-activity in dopaminergic neurones.

[1] Such a study is currently being organized under the auspices of the Medical Research Council.

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