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It has been estimated that about 11% of the United Kingdom population at some time has suffered from a migraine attack. These attacks can take various forms and to encompass all these variations migraine is usefully defined as a recurrent headache with two or more of the following five factors: (a) unilateral headache; (b) nausea; (c) visual or other neurological disturbance; (d) family history of migraine; (e) history of bilious attacks, travel sickness, asthma, eczema or hay fever (Thrush, 1978).

Disturbance of cerebral blood vessels seems to be important in the pathogenesis of migraine. Initially, the aura or prodromal phase occurs associated with vasoconstriction of intracerebral arteries leading to cerebral ischaemia and resulting in cerebral malfunction, such as hand numbness or disorders of vision. This is succeeded by vasodilatation of extracerebral arteries causing headache and tenderness (Dukes & Vieth, 1964). It is hardly surprising, therefore, that vasoactive compounds are strongly implicated in provoking a migraine attack, one of the leading contenders being 5-HT*.

About 99% of the total blood 5-HT is contained in the platelets. The platelet itself lacks the enzymes 5-hydroxytryptophan decarboxylase and tryptophan 5-hydroxylase and consequently cannot synthesize 5-HT. However, the enzymes of 5-HT catabolism, namely aldehyde dehydrogenase and monoamine oxidase, are present (Fig. 1). Platelets take up 5-HT actively with the 5-HT uptake being proportional to the platelet ATP content. Now one of the physiological actions of 5-HT is to cause platelet aggregation; 5-HT produces reversible aggregation of platelets and single platelets by ADP and adrenaline. The aggregation promoted by 5-HT is potentiated by ADP, which appears to be the result of a disorder in the ATPase or Na+/K+ gradient across the platelet's plasma membrane (Coppen et al., 1975). Control platelets, which implies either that the platelets from migraine sufferers have diminished 5-HT-retaining capacity or that the platelet 5-HT-uptake receptors bind 5-HT less readily (Hilton & Cumings, 1972). Although Kalendovsky & Austin (1973) found increased platelet aggregation in some migraine sufferers experiencing neurological disturbance during their attacks, platelet aggregation alone is not sufficient to induce migraine, as in diabetes mellitus there is increased platelet aggregation but no increased incidence of migraine. It has been proposed that the reduction in 5-HT by migraineur platelets may be the result of a disorder in the ATPase or Na+/K+ gradient across the platelet's plasma membrane (Coppen et al., 1979). There is evidence that 5-HT uptake is inhibited by ADP, which alters the Na+/K+ gradient; indeed some workers have claimed that the platelets of migraine sufferers have a raised ADP level.

One fundamental observation is that platelet 5-HT content is reduced during a migraine attack. Curran and co-workers were probably amongst the first to observe a fall in plasma 5-HT during the headache period (Curran et al., 1965). Further information has come from the work of Mück-Seeler et al. (1979), who found that the mean platelet concentration of 5-HT in non-migraine subjects was about 0.55 pg/10^9 platelets, which was similar to that of migraine sufferers during a headache-free period, namely 0.58 pg/10^9 platelets, but during a migraine attack a significant 15% decrease in platelet 5-HT occurred. It was also found that when platelets collected during headache-free periods were incubated with platelet-poor plasma taken from another migraine sufferer during an attack, there was a 22% reduction in 5-HT content; conversely, if the plasma was taken during a period of no headache, there was no significant 5-HT release. Further, plasma taken from a migraine sufferer during an attack did not evoke 5-HT release from platelets of non-migraine subjects.

From these findings it has been suggested that there is a platelet abnormality in some migraine sufferers who during a migraine attack a 5-HT-releasing factor is present. In support of these ideas is the finding that platelets from migraine sufferers, when incubated with 5-HT, aggregate more readily than do control platelets, which implies either that the platelets from migraine sufferers have diminished 5-HT-retaining capacity or that the platelet 5-HT-uptake receptors bind 5-HT less readily (Hilton & Cumings, 1972). Although Kalendovsky & Austin (1973) found increased platelet aggregation in some migraine sufferers experiencing neurological disturbance during their attacks, platelet aggregation alone is not sufficient to induce migraine, as in diabetes mellitus there is increased platelet aggregation but no increased incidence of migraine. It has been proposed that the reduction in 5-HT by migraineur platelets may be the result of a disorder in the ATPase or Na+/K+ gradient across the platelet's plasma membrane (Coppen et al., 1979). There is evidence that 5-HT uptake is inhibited by ADP, which alters the Na+/K+ gradient; indeed some workers have claimed that the platelets of migraine sufferers have a raised ADP level.

It has been shown that 5-HT causes arterial constriction, while a relative lowering of the 5-HT level results in arterial dilation (Anthony et al., 1969). The basic model for 5-HT involvement in migraine is that the initial platelet 5-HT release causes a short-lived increase in free plasma 5-HT levels, which results in raised brain 5-HT levels and consequent vasoconstriction of intracerebral arteries, hence initiating the aura phase. This is followed by a fall in plasma 5-HT levels resulting from catabolism and excretion of 5-HT, and the relative lowering of 5-HT, in part, results in extracerebral arterial vasodilatation. The vasodilatation itself may not be wholly responsible for the headache pain (due to stretching of nocireceptors in the vessel walls). Instead, the initial increase in 5-HT levels may evoke a sterile inflammation, resulting in pain and local oedema due to prostaglandin and bradykinin release. Sicuteri (1978) has also proposed 5-HT involvement as a neurotransmitter, for it is known that 5-HT is involved in the anti-nociception system, which causes a physiological analgesia. The lowering of brain 5-HT seen in migraine is thought to interrupt this analgesic system, in accord with the fact that morphine loss of analgesic action in 5-HT-depleted states. The anti-nociception system involves the release of endorphins and enkephalins and it has been shown by Sicuteri that levels of endorphins and  

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* Abbreviations: 5-HT, 5-hydroxytryptamine; 5-HIAA, 5-hydroxyindol-3-ylacetic acid; VMA, 4-hydroxy-3-methoxymandelic acid; MAO, monoamine oxidase; GABA, γ-aminobutyric acid.

**Fig. 1. The pathway of 5-hydroxytryptamine metabolism**

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plasma albumin, making more tryptophan available for conversion into 5-HT and hence restoring the 5-HT level. The actual migraine symptoms with brain 5-HT deficiency as the initial trigger (Kety, 1971). As 5-HT does not readily traverse the blood/brain barrier it has been suggested that 5-HT may also act upon the carotid body via a chemoreceptor and hence influence vascular calibre indirectly (Lance et al., 1967).

The essential amino acid tryptophan is the precursor of 5-HT and it has been shown that free plasma tryptophan was significantly higher on the day of a migraine attack (Salmon et al., 1970). It is thought that the low levels of brain 5-HT associated with migraine, by some unknown feedback mechanism, cause displacement of tryptophan from its binding sites on plasma albumin, making more tryptophan available for conversion into 5-HT and hence restoring the 5-HT level. The excretion of 5-HT and its metabolites have been much studied during migraine attacks. Increased levels of 5-HIAA in the urine during migraine attacks have been reported by Sicuteri et al. (1971) and Curran et al. (1965). However, this has not been found by all workers and what may be a more reliable determinant of 5-HT metabolism during migraine may be the actual amount of 5-HT excreted; such studies seem to be conclusive in showing an increase in 5-HT excretion during the migraine attack. The rate of fall in platelet 5-HT may be more important than the actual concentration in the plasma. Evidence for this is based on experiments using the drug reserpine, which causes 5-HT depletion by mobilizing 5-HT, perhaps by making storage vesicles leaky. Reserpine, which is a 5-HT depletor, may be one of the releasing factors previously mentioned. Tyramine can be converted into 5-HT in brain (Herberg, 1975). The 5-HT lowering in migraine has been shown in experimental animals to give rise to irritability and, indeed, irritability is often seen in the initial stage of a migraine attack. Bright light and stress are both documented triggers of migraine and it is interesting that both are capable of reducing brain 5-HT levels. It could be that migraine sufferers have a reduced threshold to fluctuations in brain amine content at the receptor level. In this connection it is worth considering the proposal that noradrenaline deficiency may be responsible for the actual migraine symptoms with brain 5-HT deficiency as the initial trigger (Kety, 1971).

Having established catecholamine involvement in migraine it is pertinent to consider how catecholamines are actually involved in migraine initiation. First, as implied already, noradrenaline is vasoactive and may exert an effect upon the cerebral vasculature, which we know is of importance in the pathogenesis of migraine. Also, in keeping with the 5-HT model, it is known that noradrenaline is capable of causing platelet aggregation and 5-HT release (Hsu et al., 1979). Catecholamines also have a lipolytic action, mediated by cyclic AMP, with a resulting increase in plasma non-esterified fatty acid levels. As will be seen later some non-esterified fatty acids act as 5-HT releasers. Another vasoactive amine that seems to be important in migraine is tyramine. This substance occurs in the body partly as the result of endogenous synthesis by decarboxylation of tyrosine and partly from the diet. Now it has been known that tyramine-rich foods such as cheese and citrus fruits are migraine triggers. In one study by Hanington et al. (1970) cheese was indicated the presence of a platelet 5-HT release site, which is thus unavailable for 5-HT and hence preventing aggregation (Cummings & Hilton, 1971). Unfortunately methysergide has a number of unpleasant side-effects, notably fibrosis. Anthony et al. (1969) have found that the migraine headache can be alleviated by an intravenous 5-HT infusion of about 5 mg during a migraine attack. It should be emphasized here that the decline in 5-HT level is not a non-specific response resulting simply from the headache pain or stress but is specific to migraine.

The platelet incubation experiments previously mentioned indicated the presence of a platelet 5-HT releasing factor or factors, which appear in the blood during the attack. By plasma filtration through different-pore-size membranes it has been shown that these have molecular weights of less than 50000 (Anthony, 1972).

Catecholamines also appear to be implicated in migraine aetiology. In a manner analogous to that for 5-HIAA there has been controversy as to whether VMA increases in the urine during a migraine attack. The issue is further complicated as VMA excretion reflects both noradrenaline and adrenaline metabolism. Reserpine, which is a known migraine precipitant as well as releasing 5-HT, can also release noradrenaline from its stores, with consequent increase in VMA excretion (Curzon et al., 1969). Also of note is the finding that in a group of migraine sufferers whose migraine attack usually woke them up from their sleep, significantly higher catecholamine blood levels were observed just prior to the attack (Hsu et al., 1976). The work of Adams et al. (1968) has also suggested the involvement of noradrenaline in migraine. Using a paraformaldehyde fluorescence method they showed that the tunica adventitia of temporal arteries, biopsyed from migraine sufferers, had a significantly elevated binding capacity for noradrenaline. Dopamine β-hydroxylase, the final enzyme in the biosynthesis of noradrenaline, was found to have a significantly higher activity in migraine sufferers than in controls (Gotok et al., 1976). This enzyme is well localized in blood vessels and upon sympathetic stimulation it is released by exocytosis in quantities proportional to the amount of noradrenaline released. It has been suggested that the elevation of dopamine β-hydroxylase may be the result of either primary involvement of noradrenaline in the pathogenesis of migraine or a heritable instability of the vascular system in migraine sufferers. Stress, which is frequently implicated in triggering migraine, results in the release of catecholamines; furthermore, clonidine, a drug that may decrease the vasoactive actions of catecholamines upon blood vessels, has been found to be of value in migraine (Zaimis & Hanington, 1969). Biofeedback using electromyogram-assisted muscle relaxation has become well established in anti-migraine therapy, and during therapy significant decreases were found in the levels of plasma catecholamines (adrenaline and noradrenaline) and also of monoamine oxidase activity (Mathew et al., 1980).

Another vasoactive amine that seems to be important in migraine is tyramine. This substance occurs in the body partly as the result of endogenous synthesis by decarboxylation of tyrosine and partly from the diet. Now it has been known that tyramine-rich foods such as cheese and citrus fruits are migraine triggers. In one study by Hanington et al. (1970) cheese was frequently mentioned by subjects as a cause of their attacks and on analysis it is found that cheese can have very high tyramine and stored within the tissue, which has the amine-depleting effects including 5-HT displacement (Sever, 1979). Octo-
pamine, which may also act as a false transmitter substance, has a much longer half-life than tyramine, due to its binding in neuronal storage granules, and can also cause depletion of tissue catecholamines. Tyramine itself is a vasoactive amine and could be directly responsible for the initial vasoconstriction of the blood vessels of migraine aura phase (Fig. 2).

But why is it that tyramine can induce migraine in migraine sufferers but not in control subjects? It has been shown that abnormally small amounts of conjugated tyramine are excreted by tyramine-sensitive migraine sufferers after a tyramine loading dose (Youdim et al., 1971). Hence, there is evidence of defective tyramine metabolism in some migraine sufferers, possibly enabling tyramine of dietary origin to remain more easily in the circulation. About 15% of ingested tyramine is converted into tyramine O-sulphate in normal subjects, but tyramine-sensitive sufferers but not in control subjects. It has been shown that by tyramine-sensitive migraine sufferers after a tyramine loading they excreted abnormally small amounts of conjugated tyramine, although not as low as in normal subjects. Although not as low as dietary-sensitive migraine sufferers (Mullen et al., 1976).

On a similar theme phenylethylamine has also been implicated in migraine. Like tyramine, it is able to release stored 5-HT and catecholamines and has a direct vasopressor action upon cerebral vasculature. Chocolate, which is one of the most commonly mentioned migraine precipitants, contains about 3 mg of phenylethylamine per 2 oz bar (Sandler et al., 1974). Phenylethylamine readily crosses the blood/brain barrier, where it releases noradrenaline (McCulloch & Harper, 1977). Initially, and in small doses, phenylethylamine causes an increase in cerebral blood flow and also in cerebral O2 consumption, but further increases cause constriction of cerebral blood vessels.

Consideration has already been given to the involvement of platelet aggregation and the migraine attack. Hanington, in her blood-disorder hypothesis (Hanington, 1978), has proposed a primary platelet abnormality and that migraine may be one of the commonest of the blood disorders. In relation to this idea, the level of platelet MAO seems to be important. MAO is one of the principal enzymes involved in the metabolism of monoamines, such as those we have considered already, i.e. 5-HT, tyramine, phenylethylamine and the catecholamines, by the process of oxidative deamination. Sandler (1977) found that during a migraine attack MAO levels in the platelets were significantly decreased compared with those in controls and in migraine-free periods. It is suggested that when the MAO activity falls below a certain level, which will vary from person to person, the levels of vasoactive amines will rise sufficiently to cause a migraine. It is interesting that MAO levels increase with age and yet the frequency and, indeed, the severity of migraine attacks decline. Hanington's blood-disorder hypothesis proposes that it is the combination of low platelet MAO levels during an attack plus the unusual aggregation of platelets that is responsible for provoking a migraine. To give fair representation, however, it must be recorded that Grant has attacked this blood hypothesis, stating that platelet MAO is not found to be low in all migraine sufferers and that the MAO levels may be secondary to food or humoral changes (Grant, 1978).

Overall levels of MAO per se may be too simplistic an explanation, as on electrophoresis multiple forms of MAO are observed. Basically two forms are of importance. MAO-A, which prefers 5-HT as substrate, and MAO-B, which prefers phenylethylamine; both isoenzymes can metabolize tyramine and noradrenaline. Sandler et al. (1974) found a large deficit in platelet MAO-B during an attack and suggested that platelet damage, perhaps as a result of circulating fatty acids, may cause MAO-B and 5-HT release. Sandler has also postulated that the defective inactivation of vasoactive amines could cause local accumulation of amines, perhaps in the lungs, with subsequent release into the systemic circulation and eventually the cerebral circulation. In relation to this is the finding that there is an anomaly in the blood/brain barrier of migraine sufferers, with increased permeability to vasoactive substances (Harper et al., 1977). It is thought that stress, which increases the activity of brain-stem noradrenaline pathways, can actually increase the blood/brain barrier's permeability, perhaps by increasing vascular permeability (Fig. 2).

Another proposal by Sandler is that tyramine and 5-HT may cause the release of prostaglandins from the lungs and that these prostaglandins may also be responsible for the vascular effects seen during the migraine attack (Sandler, 1972). The release of prostaglandins may be simply a secondary phenomenon during the attack. However, intravenous infusion of prostaglandin E1 does evoke headache, possibly in part by its potent vasodilating action on cerebral blood vessels (Carlson et al., 1968).

Alternatively, prostaglandins may be implicated in a sterile inflammation reaction in the blood vessel wall, causing pain and oedema. Prostaglandin F2α, which is a potent vasconstrictor, may be an important mediator in the migraine aura phase (Vardi et al., 1976). There is also evidence of a hereditary hypersensitivity of blood vessels to prostaglandin E in migraine subjects. The prostaglandin precursors, namely the endoperoxides prostaglandin H2 and prostaglandin G2, and also the thromboxanes A2 and B2, are powerful platelet aggregators, causing 5-HT release. The proposal has been made that there may be a defect in prostacyclin metabolism. Prostacyclins have been shown to prevent platelet aggregation, possibly by a cyclic AMP-mediated mechanism.

Some fatty acids have been shown to be platelet 5-HT-releasing factors. Searate, linoleate, linolenate and oleate all have the ability to cause platelet aggregation, with stearate, a long-chain saturated fatty acid, being more potent than the unsaturated acids (Inouye et al., 1970). It seems that the fatty acids bind to the platelet membrane, altering its properties. Fatty acids can also activate clotting factors involved in blood coagulation, which may also be important for platelet aggregation (Hoak et al., 1967). There is an association with type IV hyperlipoproteinemia and migraine. Type IV hyperlipoproteinemia is a disorder in which there is raised triacylglycerol in the blood, with increased plasma viscosity and platelet aggregation. Clofibrate, a drug capable of reducing triacylglycerol and cholesterol levels, has been found to be of significant benefit in reducing the migraine incidence in these subjects (Leviton & Camenga, 1969). Endogenous heparin levels are decreased in some migraine sufferers. These subjects have been shown to have fewer basophilic leucocytes, which release reduced amounts of heparin. Furthermore, this group of migraine sufferers excrete lower levels of heparin in the form of uroheparin in their urine than do non-migraine sufferers (Thonnard-Neumann, 1969). This is of relevance as endogenous
Carbohydrate metabolism has long been of interest in migraine. Initially it was found that maintenance of a high blood glucose by frequent carbohydrate meals could reduce the incidence of migraine (Gray & Burtness, 1935). Indeed, missing a meal, prolonged sleep and exercise are all events known to cause hypoglycaemia and are all recognized migraine precipitants. Blau & Cumings (1966) showed that migraine can be induced by fasting in some subjects but that the lowest blood sugar levels for this group were not significantly different from those of controls. After glucagon administration it was observed that some migraine sufferers had a diminished glucose increase, which suggested reduced glucose release from glycogen in the liver (De Silva et al., 1974). A further insight into the involvement of carbohydrate metabolism and migraine came from the important work of Hockaday et al. (1972), who studied the effects of intravenous glucose administration. Interestingly, it was found that some migraine subjects actually started an attack. It was also shown that the rate of decrease of blood glucose was significantly less in some migraine sufferers than in controls and that there was an increase in ketone bodies in fasting. Furthermore, a reduction in output of somatotropin occurred. Thus both glucose administration and fasting are capable of triggering a migraine attack in some migraine sufferers. These workers have proposed that the hypoglycaemic unresponsiveness and the insulin resistance may be a consequence of reduced somatotropin output and chronic sympathetic hyperactivity. There is probably also an aberration in the central mechanisms involved in the response to calorie reduction, which may also provoke a migraine attack via a neurogenic process.

The incidence of migraine in males and females is about the same until puberty, when it is observed that the incidence for females then becomes about twice that of males. Moreover, about 60% of women migraine sufferers find that their migraine attack is related to their menstrual cycle, commonly occurring at the premenstrual phase (Klee, 1968). Levels of MAO are related to the menstrual cycle with a peak at the time of ovulation and a trough about 11 days later (Southgate et al., 1968). There is evidence that progesterone raises MAO levels, perhaps explaining the 10-fold increase in MAO of the endometrium of the uterus during the luteal phase. Hence low MAO levels occur premenstrually, the time of increased migraine prevalence. Now MAO is an important enzyme in the inactivation of vasoactive amines, compounds that we have already seen to be of relevance in the initiation of migraine. Premenstrual water retention may also be important. The water retention is evidenced by oliguria (diminished urine output) and increase in body weight at the onset of the migraine attack; in fact, some patients obtain migraine relief when treated with diuretic drugs to reduce the water retention. The actual mechanism of water retention is obscure. However, it is known that progesterone competes for aldosterone at receptor sites (Laidlow et al., 1962) and as the progesterone level declines during the premenstrual phase this may cause the water retention. How the water retention triggers the migraine is also unclear, although it has been shown that prolactin can evoke vasomotor changes during electrolyte and water retention (Nattero et al., 1979). These workers also observed a significant decrease in plasma aldosterone level at the onset of the premenstrual attack. As aldosterone is known to be a Na+ ion- and water-retaining hormone, a paradox is evident, and it has been suggested that prolactin may also cause water retention. Prolactin is also thought to stimulate prostaglandin synthesis and prolactin secretion itself is increased during stress. Aldosterone, urinary excretion of progesterone and oestradiol are all factors that may cause hypoglycaemia and are all recognized migraine precipitants. These factors may also provoke a migraine attack via a neurogenic process.

Changes in histamine levels have been observed over a migraine period (Anthony & Lance, 1971), blood levels being 0.35 μmol/litre before the headache, 0.39 μmol/litre during the headache and 0.43 μmol/litre after the headache. Histamine receptors have been found in the superficial arterial vessels of the head and may be partly responsible for the vasodilatation component of the migraine headache. Certainly histamine injected into the
superficial arteries results in headache; however, it is more likely that the histamine release is secondary to the headache pain. The histaminergic hypothesis is consistent with the fact that mast cells degranulate on the side of the migraine headache.

The elevated histamine levels during migraine may explain the high GABA and lactate levels in the cerebrospinal fluid of migraine sufferers owing to increased tissue permeability (Welch et al., 1975). GABA, an inhibitory transmitter, is not normally found in the cerebrospinal fluid and an alternative explanation may be that its release results from brain ischaemia during the migraine attack. In relation to this, Pollock & French (1975) have suggested the aetiological importance of glutamate in migraine. Glutamate, which is a precursor of GABA, has also been found to be elevated in the blood and cerebrospinal fluid of migraine sufferers. Glutamate occurs in higher concentrations in brain than in any other tissue and is thought to act as an excitatory neurotransmitter, which may be the reason for changes in brain electrical activity during a migraine. Glutamate and some of its metabolites can be neurotoxic. This is well documented in the Chinese Restaurant Syndrome induced by high concentrations of the food additive monosodium L-glutamate, causing a burning sensation in the face along with headache (Schaumberg et al., 1969). Further, there is an association between people heterozygous for ornithine transcarbamoylase deficiency and migraine, ornithine transcarbamoylase being the urea-cycle enzyme that catalyses the formation of citrulline from ornithine and carbamoyl phosphate. In this study by Russell (1973) high fasting levels of blood ammonia were observed in some migraine sufferers. It has been proposed that the initial vasoconstriction of the aura phase in migraine may be a homeostatic response to minimize the elevated ammonia from entering neuronal cells in the brain. The deficiency in ornithine transcarbamoylase and also possibly in carbamoyl phosphate synthetase may explain the high glutamate levels of migraine. It has been suggested that citrulline administration, which would by-pass the enzyme block and consequently lower glutamate levels, may be of benefit in this group of migraine sufferers.

Another alternative explanation of the dilating phase of migraine cerebral vessels during the migraine attack is the release of adenosine and adenosine compounds as a result of the initial vasoconstriction and resulting ischaemia (Harder & Edvinsson, 1979). ATP, ADP and adenosine are all potent vasodilator substances and may thus be important in the migraine headache phase. The release of adenosine compounds may also explain the finding that during a migraine attack there is an increase in cyclic AMP levels in the cerebrospinal fluid (Welch et al., 1976). However, it must be said that there is conflict as to whether it is extra- or intra-cerebral vessel dilatation that plays a part in the headache; this is of importance as it is believed that adenosine compounds can only dilate intracerebral vessels. There is further confusion, as it has been suggested that there are two separate groups of migraine sufferers, namely those that vasodilate during the headache phase and those that vasoconstrict.

We have discussed the possible involvement of food in migraine, such as cheese, containing tyramine, and chocolate, containing theobromine. It has also been proposed that food allergy may be important in some migraine sufferers. This is based on the fact that some sufferers have high titres of immunoglobulin E antibodies specific for some common foods (Munro et al., 1980). But quite how a migraine can be provoked is unclear, although mast-cell degranulation and release of vasoactive amines may be important. Studies by Lord & Duckworth (1977) have revealed that migraine sufferers have a higher mean immunoglobulin level than control subjects. An interesting finding by these workers was that different clinical groups of migraine sufferers had different patterns of immunoglobulin levels. In classical migraine with preceding aura signs, levels of immunoglobulin A were raised; in common migraine, i.e. headache but no aura signs, both immunoglobulin A and immunoglobulin G levels were raised; and finally migraine sufferers who experienced aura signs after the headache had raised immunoglobulin A, immunoglobulin G and immunoglobulin M levels. These studies also showed a pathological complement activation, as about 3h prior to the onset of headache the presence of complement factor 3 (C3) break down products were found in the blood, suggesting that the complement activation is not secondary to the migraine headache. The formation of C3a and C5a products of the classical complement pathway can cause mast-cell and basophil degranulation and hence may explain the histamine involvement in migraine; moreover, immune complexes seen in this type III-immune complex-mediated response can cause platelet 5-HT release. Lord & Duckworth (1977) also showed reduced levels of C1 complement factor in the early headache period. This factor is thought to inhibit kallikrein and coagulation factor XI, so the lowered C1 levels may explain the increased thrombotic tendency of some migraine sufferers and also the presence of kinins in migraine (Fig. 4). However, not all workers have found lowered C1 levels or evidence of reduced complement levels and abnormal immunoglobulin patterns (Sovak et al., 1980). Either way, blood kinin levels do increase during a migraine attack (Sjaastad, 1970). It is believed that the increase in kinins alone is not responsible for the actual headache even though bradykinin injection into the cerebral vasculature causes headache, by direct chemical stimulation, on the same side of the head as the injection, an effect potentiated by the presence of 5-HT. It is suggested that the headache may be the result of a combination of vasodilatation, bradykinin, histamine, 5-HT and the prostaglandins; in other words the combination of a vasculature change plus sterile inflammation. Chapman et al. (1960) isolated what they termed neurokinin from the tissues around dilated extracranial blood vessels during neuronal excitation and the levels found closely correlated with the headache severity. More recently Moskowitz et al. (1979) have proposed that substance P and possibly other vasoactive substances are released from the terminals of the trigeminal nerve (5th cranial nerve) during a migraine attack. Substance P, which co-exists with 5-HT in the trigeminal nerve terminals, is an extremely potent vasodilating peptide and may be important in the headache phase of migraine. The release of substance P, by either the left or right trigeminal nerve, may also explain the unilateral headache often experienced in migraine (Fig. 5).

In summary, we have seen that a wide variety of biochemical phenomena are associated with the migraine attack. Furthermore, the migraine attack itself can take various forms and can
be initiated by a range of factors. It is hardly surprising, therefore, that it is difficult to construct a coherent story to encompass this diversity. Although there are areas of opacity and controversy, there can be no doubt that many people suffer greatly from their migraine attacks, a grim reminder of how mischievous molecules can give you a terrible headache.


Kaledovsky, Z. & Austin, J. M. (1973) *Headache* 16, 293–312


Klee, A. (1968) *Clinical Study of Migraine*, Munksgaard, Copenhagen

Kudrow, L. (1976) *Headache* 16, 66–69


Fig. 5. Summary of the various factors important in the migraine process.
Sicuteri, F. (1978) Headache 17, 253–257