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A basis for migraine therapy – the autonomic theory reappraised

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Summary

The concept that migraine results from an initial vasoconstriction due to increased release of noradrenaline from the sympathetic nerves to cranial blood vessels has been reappraised in the light of recently acquired knowledge of the mechanisms of action of drugs used in the treatment of migraine, physiological and pharmacological evidence implicating noradrenaline, and the observations by others that several migraine variants may be associated with some degree of sympathetic overactivity. If the theory is correct, it suggests that both prophylaxis and management of the acute condition should be possible by means of selective α-adrenoceptor antagonism. The use of drugs with potentially dangerous vasoconstrictor properties appears to be unnecessary. The suggestion is made that the increased adrenergic activity might result from changes within the hypothalamus.

Introduction

Any plausible theory on the aetiology of migraine should provide a basis for the treatment of this condition. The theory most acceptable will therefore permit or explain:

(1) the symptomatology and the underlying vascular and neurological pathophysiology;

(2) the function of the vasomotor innervation to the vasculature involved;

(3) the mechanism of action of migraine-inducers such as tyramine, phenylethylamine, contraceptive steroids, and other trigger factors;

(4) the basis for the modes of action of apparently dissimilar therapeutic agents and explain why migraine is more likely to respond to treatment instituted in the prodromal phase of the syndrome;

(5) the prediction of drugs likely to be useful in the management of the disease enabling the theory to be challenged in clinical practice.

The more recent theoretical deliberations on the aetiology and management of migraine (Fanchamps, 1974; Heyck, 1970; Sandler, 1972; Sicuteri, 1967; Sicuteri, Anselmi and Fanciullacci, 1974) have failed to satisfy one or other of these criteria, and it appears that as yet no satisfactory unitary hypothesis has been proposed. However, in view of new information on the mechanisms of action of drugs used in migraine therapy, the physiological and pharmacological evidence implicating noradrenaline, and the clinical observations that several migraine variants may be associated with some degree of increased sympathetic drive, it seems timely to reappraise the 'autonomic theory' of the aetiology of migraine to see how well the above five criteria are satisfied.

The 'autonomic theory' requires only that the initial vasoconstrictor element of migraine is due to the transient increased release of noradrenaline from nerve endings to the affected vessels; all other manifestations of the disease follow from this, and all therapeutic and prophylactic drugs will modify the release or prevent the actions (or the consequences of the actions) of the noradrenaline so released. This hypothesis is essentially an extension of that first proposed by Sicuteri (1967).

Symptomatology and pathophysiology

The neurological symptoms that augur the migraine attack have been attributed for many years to the constriction of cranial blood vessels (Dalessio, 1962) and the headache phase has similarly been associated with vasodilatation (Lance, 1973) especially of the extracranial arteries.

Vasoconstriction

The autonomic theory claims that the neurological symptoms of the prodromal phase result from vasoconstriction due to the neurally released noradrenaline acting on vascular α-adrenoceptors. Neurological sequelae would be expected to occur if perfusion were to fall to a level critical for adequate oxygenation. If this noradrenaline constriction is not modified by pharmacological intervention then the vessels will ultimately dilate, possibly assisted by the presence of vasodilator metabolites accumulated during the constrictor phase (Sicuteri, 1967) and also perhaps by a reflex inhibition of the constrictor drive – a form of reactive hyperaemia. It has been established by the krypton method that regional cerebral cortical vasodilatation (functional hyperaemia) occurs in

conscious man in connection with various types of sensory, emotional, and intellectual stimuli (Ingvar and Risberg, 1967). The clearance of radioactive elements has now been applied to the elucidation of haemodynamic changes within the brain during migraine (O'Brien, 1971; Skinhøj, 1973). Using the clearance of ^{133}Xe injected into the internal carotid arteries of patients with migraine, Skinhøj found a marked reduction in cerebral blood flow in all patients during the prodromal phase. In some cases perfusion of the cortex fell to levels known to be critical for adequate oxygenation and these patients had pronounced neurological symptoms. Changes in arterial P_{CO_2} could not account for this flow reduction. In the headache phase significant increase in blood flow occurred together with an intracerebral lactate acidosis. Skinhøj concluded that the intracerebral acidosis, one of the well documented causes of increased cerebral flow, was 'a consequence of hypoxic brain metabolism during the initial phase of the attack'. He also emphasized that the cerebral blood lactate increased in all patients whether suffering from classical, common, or mixed migraine. This lends support to the view that the different manifestations of migraine are merely variants of a single disease which, in turn, is dependent only on the degree of the initial cerebral vasoconstriction during the prodromal phase. The additional important angiographic finding by Skinhøj that the perfusion pressure in the basilar artery system was abnormally increased during the prodromal phase confirmed the findings of Duke and Vieth (1964) and supports the contention of Klee (1968) that some of the 'brain stem' symptoms of migraine are due primarily to a dysfunction of this system.

Evidence has accumulated indicating that visual scotomata and other prodromal symptoms result from ischaemia following intracranial vasoconstriction (Pearce, 1969). Thus Schumacher and Wolff (1941) showed that the inhalation of the vasodilator amyl nitrite in hypotensive doses abolished scotomata in migrainous patients. Inhalation of CO_2 in air also abolished prodromal symptoms. Constriction of the superficial temporal artery and accompanying scotomata were observed by Tunis and Wolff (1953) to be prolonged by ergotamine therapy; and the intravenous infusion of noradrenaline induced scotomata in one patient.

Vasodilatation

There is little doubt that the headache of migraine coincides with some degree of intra- and extracranial vasodilatation (Lance, 1973) on the same side. But it seems unnecessary to postulate that one is the cause of the other. Both may be the contemporaneous sequelae of the constrictor phase, and the pain need not necessarily result from the actions of the same products of ischaemia (e.g. lactate, kinin, prostaglandin, 5-hydroxytryptamine (5HT), histamine, heparin, choline) as the vasodilatation. In most attacks the pain undoubtedly stems from the vicinity of large subsurface cranial arteries upon which distension or displacement leads to a prolonged aching sensation. That dilatation of these vessels *per se* cannot be solely responsible for the pain associated with migraine is consistent with the finding in migraine patients that scalp vessel dilatation, by immersion of the body in hot water (Lance, 1973) or by the injection of methacholine (Ostfeld, 1960) is not usually painful, and does not induce other focal features of an attack, such as oedema or tenderness on pressure (Chapman *et al.*, 1960).

Function of the vasomotor innervation – evidence implicating noradrenaline

In 1967, Sicuteri postulated the first event in the genesis of migraine to be a local release of catecholamines with vasoconstriction and increased output of hydroxymethoxymandelic acid (HMMA).

In order to establish the presence of a significant noradrenergic neurogenic control of cerebral blood vessels and its role in migraine, several factors should be demonstrable. (a) There must be an adrenergic innervation of these vessels; (b) the vessels must be capable of responding to the transmitter noradrenaline; (c) the vessels must alter their diameter on electrical stimulation of their innervation; (d) there should be an increase in the plasma concentrations of noradrenaline and dopamine-β-hydroxylase during the constrictor phase of migraine, and increased output of catecholamine metabolites; (e) the reversal of noradrenergic cerebral vasoconstriction should be brought about by α-adrenoceptor blockade if the constriction of cerebral vessels results from the activation of α-adrenoceptors as elsewhere in the periphery.

(a) It is well established that sympathetic nerves make contact with the cerebral vessels (Dahl and Nelson, 1964; Nielsen and Owman, 1967; Falck, Nielsen and Owman, 1968; Iwayama, Furness and Burnstock, 1970; Nelson and Rennels, 1970a, b; Nielsen, Owman and Sporrong, 1971).

Falck *et al.* (1968) demonstrated histochemically that adrenergic vasoconstrictor fibres are distributed only to the larger cerebral vessels outside the brain proper, with few or no axon ramifications along the true resistance vessels. Thus neurogenic vasoconstriction, when it occurs, must reflect lumenal reductions of these larger arteries.

(b) Raper *et al.* (1972) found that the small precapillary pial vessels of the cat, dog, and rabbit were unresponsive to the application of noradrenaline or to electrical stimulation of the ipsilateral superior cervical ganglion. The larger pial arterial vessels of

the cat, however, constricted to noradrenaline applied by micropipettes (Wahl *et al.*, 1972). Marked decreases in cerebral blood flow have been observed in man following intravenous infusion of noradrenaline (Sensenbach, Madison and Ochs, 1953; King, Sokoloff and Wechster, 1952; Moyer, Morris and Snyder, 1954) and scotomata have been induced (Tunis and Wolff, 1953). *In vitro* studies by Nielsen and Owman (1971) in which cat middle cerebral artery constricted in response to noradrenaline or tyramine indicated the possible importance of a contribution by the larger cerebral vessels to changes in blood flow induced by noradrenaline.

Ostfeld and Wolff (1955) drew attention to the phenomenon of increased sensitivity of conjunctival vessels to topically applied noradrenaline during the prodromal phase. This is consistent with the added effect of exogenous noradrenaline superimposed on a transiently increased sympathetic drive. During the headache phase sensitivity of conjunctival vessels to added noradrenaline diminished, consistent with a reduction in neurogenic vasoconstriction.

Increased adrenergic activity due to high circulating catecholamine levels in phaeochromocytoma is associated with vasospastic abdominal and facial symptoms followed by migrainous headache of varying duration (Greene, 1975).

(c) The vasoconstrictor fibre influence on cerebral blood flow is normally small, and the absence of any increase in the cerebral blood flow in the cat or monkey (Meyer, Yoshida and Sakamoto, 1967) on section of the cervical sympathetic might indicate the absence of neurogenic tone in the cerebral vessels of the anaesthetized animal. But one must exercise caution in drawing firm conclusions about the role of the sympathetic on cerebrovascular tone from such experiments in the absence of precise anatomical knowledge of the autonomic innervation to the cranial vasculature and the influence of the operative and anaesthetic procedures employed.

The assumption that the resting cranial vessels are not under signicant neuroconstrictor control does not imply that the vessel diameter cannot be increased further. Absence of neurogenic tone may be combined with the presence of inherent 'myogenic' tone. Such vessels may thus be susceptible to spasmolytic agents such as the nitrites, papaverine or aminophylline or, indeed, acid metabolites.

Electrical stimulation of the cervical sympathetic trunk leads to a 30% decrease in the internal carotid arterial blood flow in the monkey (Meyer *et al.*, 1967) but causes a much greater reduction in the external carotid artery of this species. In the cat, Ingvar (1958) showed that supramaximal electrical stimulation of the nerve fibres increased cerebral vascular resistance by 20–30% and the same seems true for man (Krog, 1964). D'Alecy and Feigl (1972) found that electrical stimulation of the anaesthetized dog stellate ganglion resulted in an average 80% decrease in the continuously measured cerebral blood flow. Decrease in arterial oxygen tension and increase in arterial carbon dioxide tension, and slight pH reduction during stimulation all opposed the observed vasoconstriction which was therefore concluded to be independent of changes in these parameters.

The possible participation of this sympathetic constrictor innervation to the larger cerebral vessels in the genesis of migraine must therefore seriously be considered, especially when no comparable evidence exists for potential monoamine neurotransmitters other than noradrenaline.

(d) When nerve impulses pass along the sympathetic nerves they release noradrenaline and the enzyme dopamine-β-hydroxylase (DBH) from storage vesicles by exocytosis (Schanberg *et al.*, 1974). There is evidence that plasma noradrenaline concentration is more significantly increased during the 3 hr preceding patients awakening with migraine than in the similar 3 hr in those awakening without migraine as recently presented by Hsu *et al.* (1977). Furthermore, plasma catecholamine levels were significantly higher in the 3 hr preceding a migraine than in the corresponding 3 hr when the same subjects did not awaken with migraine. On the other hand, Hsu *et al.* (1977) did not show any differences in plasma concentrations of total and free tryptophan, glucose, insulin, or free fatty acid between patients with or without migraine. The results of Hsu *et al.* are consistent with the autonomic hypothesis in which a noradrenergic vasoconstriction precedes the headache phase. Further evidence favouring an increased activity of the sympathetic nervous system in patients with migraine was provided by Gotoh *et al.* (1976) who showed that DBH activity was significantly higher in serum from untreated migraine sufferers (taken during the headache-free interval) than in serum from normal controls. There were no significant differences in serum DBH activity between patients with classical and common migraine.

Any measurements of plasma noradrenaline or DBH in patients with migraine are suspect if the patient is on medication, especially if the medication includes drugs, such as ergotamine, which possess α-adrenoceptor blocking properties. It is well known that α-blockers (including the ergot alkaloids) increase the amount of noradrenaline and DBH released from sympathetic neurones by actions at receptors on the presynaptic membrane (Rand, McCulloch and Story, 1975; Langer *et al.*, 1975). Thus, in patients on treatment for migraine, a real increase during the prodromal phase could be masked by a drug-induced rise. Alternatively, a

patient withdrawn from therapy (with ergotamine, for example) will probably show no change in plasma noradrenaline concentration during the prodromal phase of a subsequent attack over that seen on medication, because of the abnormally high concentration measured while on therapy. Until more is known of the influence of migraine drugs on plasma noradrenaline and DBH concentrations it seems important that such experiments be restricted to untreated patients.

It might be supposed that the suggested increased turnover of cerebrovascular noradrenaline in migraine should lead to an increase in the urinary output of its metabolite, HMMA. However, the amount of noradrenaline released even by maximal stimulation of the sympathetic innervation of cerebral vessels must be small, and it would therefore seem likely to be masked by the spontaneous variation in urinary HMMA excretion. Despite this, there are several reports of an increased excretion of HMMA during the acute attack (Sicuteri, 1962; Sicuteri *et al.*, 1962; Curran, Hinterberger and Lance, 1965). However, it would seem reasonable first to exclude at least the possibility that this increased HMMA results from stress activation of the suprarenal medulla before concluding it to be of cerebral origin. Yet, if widespread sympathetic stimulation occurs during migraine attacks and vasoconstriction is not confined to the head, then an increased HMMA output would be readily explained. The polyuria and frequency often accompanying migraine might also result from an adrenergic overdrive of this kind. Sympathetic overactivity is commonly associated with hypoglycaemia, a known provoker of migraine in susceptible individuals (Blau and Cumings, 1966; Hockaday, 1975).

(e) If α-adrenoceptor stimulation by neurally released noradrenaline is responsible for the cerebral vasoconstriction and its sequelae in migraine sufferers, then such vasoconstriction should be reversed by α-adrenoceptor blockade.

Cerebral arterial constriction, like peripheral vasoconstriction, can be induced by voluntary overbreathing and is attributed to stimulation of the sympathetic (Corbett, Eidelman and Debarge, 1972). The peripheral vasoconstriction so induced is abolished by the α-blocker thymoxamine (Collier, Nacher and Robinson, 1972) and the same drug given by intravenous infusion to conscious man has been shown to reverse the cortical vasoconstrictor response to hyperventilation. This has been taken as evidence that cerebral adrenergic vascular receptors are largely of the alpha variety (Corbett *et al.*, 1972). Similar receptors have been implicated in the hypocapnoeic constriction of cerebral arteries in rhesus monkeys, which the α-blocker phenoxybenzamine reversed (Fraser, Stein and Pool, 1970). These results were not supported by experiments in baboons in which hypocapnoea-induced vasoconstriction was not affected by α-adrenoceptor blockade with thymoxamine or phenoxybenzamine (Hoff *et al.*, 1972).

An interesting finding by Corbett *et al.* (1972) was that, despite attenuating the hypocapnoea-induced cerebral vasoconstriction, thymoxamine α-blockade produced no significant change in cortical perfusion rates at rest, suggesting that the intracranial vessels are not normally under continuous neurogenic vasoconstrictor tone. This implies that the prodromal vasoconstriction of migraine is possibly due to an abnormal adrenergic drive which ought to prove responsive to α-adrenoceptor antagonism. This abnormal adrenergic drive need not be very marked as atonic vessels are likely to be sensitive to small amounts of noradrenaline. From this it can be predicted that α-blockers given early in the constrictor phase, and in low dosage unlikely to influence vessels normally under sympathetic constrictor tone, will protect against the migraine headache.

Migraine induced by tyramine, reserpine, contraceptive steroids, and other precipitants

Tyramine

In 1967, Hanington noted that foods, especially those containing tyramine and known to interact with monoamine oxidase inhibitors, corresponded with those foods that could precipitate migraine. She postulated that some individuals demonstrate an especially sensitive localized vascular response to amines such as tyramine, and she provided evidence for this by inducing migraine attacks by the oral administration of 100 mg tyramine in patients showing a clear history of migraine provocation by diet. Administration of lactose to the same patients did not induce the attacks. Hanington (1967) and Hanington, Horn and Wilkinson (1970) confirmed that pure tyramine taken by mouth precipitated a migraine attack entirely indistinguishable from the classic migraine of the susceptible subjects concerned.

Youdim *et al.* (1971) provided evidence for defective conjugation of tyramine in migraine patients sensitive to this amine, and this was confirmed by Smith *et al.* (1971) who postulated that the deficiency was in the enzyme responsible for sulphate conjugation. The net result of this defect (as with monoamine oxidase inhibitors) is to potentiate the action of the amine. Tyramine is capable of releasing noradrenaline from sympathetic nerve endings (Davey and Farmer, 1963; Weiner, Draskoczy and Burrock, 1962) causing vasoconstriction. Vasoconstriction of the intra- and extracranial vessels in susceptible individuals is therefore the possible mechanism by which migraine is induced in these patients. Recently, migraine sufferers were found to

be more sensitive to the pharmacological actions of intravenously administered tyramine than matched controls (Ghose, Coppen and Carroll, 1977). In this study, the incidence of post-tyramine migraine was effectively reduced from 46 to 8% by the administration of the α-blocking drug indoramin, indicating that the tyramine-induced vasoconstriction involved the activation of α-adrenoceptors.

Reserpine

Reserpine is well known to deplete the monoamines, noradrenaline and 5HT, from neuronal and extraneuronal sites (Nickerson and Collier, 1975). Kimball, Friedman and Vallejo (1960) induced a migraine-like syndrome in nine out of ten known migraine sufferers by the intramuscular injection of 2·5 mg reserpine. These investigators experienced difficulty in explaining their results in terms of 5HT depletion, as neither this amine nor its precursor, 5-hydroxytryptophan, induced migraine when given intravenously to thirty-five patients. Kimball and Friedman (1961) noted the paradox that although 5HT could not induce migraine attacks in migraine patients, the 5HT antagonist methysergide appeared to be an effective prophylactic. This is highly suggestive that 5HT plays no significant role in the genesis of the migraine attack, despite the findings of an increased excretion of 5HIAA following reserpine injection, or during some spontaneous attacks of migraine (Sicuteri, Testi and Anselmi, 1961).

Not all investigators have shown an increased output of 5HIAA during a migraine attack. Thus, Curzon, Theaker and Phillips (1966) were able to show such a correlation in only two of nine migraine patients, a finding confirmed by Tandon, Sur and Nath (1969), who found no significant difference in the urinary output of 5HIAA before and after the injection of reserpine in migraine subjects. However, Anthony, Hinterberger and Lance (1967) demonstrated that intramuscular reserpine was followed by a fall of total plasma 5HT in ten out of eleven migrainous patients and two normal subjects within 3–5 hr after injection, and the intravenous injection of 5HT restored the plasma 5HT level and alleviated the headache – another finding inconsistent with 5HT antagonism being the mechanism of action of methysergide and related drugs in migraine. Furthermore, Curzon, Barrie and Wilkinson (1969) showed that there was no clear relationship between the time course of the fall in blood-5HT after reserpine and the appearance of the headache.

It has been mentioned already that high urinary excretion of HMMA, the end metabolite of noradrenaline and adrenaline, has been reported in migraine by Sicuteri (1964) and Curran, Hinterberger and Lance (1965). Curzon *et al.* (1969 examined the urinary HMMA changes after reserpine-induced headache. Only those patients in whom reserpine precipitated a migraine attack had marked increased excretion of HMMA (and also 5HIAA) while those in whom no attack was precipitated did not have a significantly increased excretion of the metabolite.

Reserpine-induced headaches closely resemble those of spontaneous migraine, whereas prodromal visual symptoms are rare (Curzon *et al.*, 1969). Vasodilatation, the intensity of which is not simply related to that of the headache, is extremely prominent after reserpine in contrast to the spontaneous migraine attacks in which the patient is usually pale. One explanation of these aspects or reserpine's action might be that the noradrenaline released by reserpine from the nerve endings causes a relatively short-lived vasoconstriction of cerebral and extracranial vessels insufficient in intensity to cause visual disturbances, but enough to cause the accumulation of acid metabolites. The noradrenaline after its surge is metabolized to HMMA, and the neuronal depletion leads to passive vasodilatation which the ischaemic metabolites potentiate by active vascular smooth muscle relaxation. Alternatively, the flushing after reserpine might be related to the concomitant release of 5HT which masks the noradrenergic facial vasoconstriction. Pain-inducing substances produced as a result of the vascular constriction induce the headache, which has a throbbing character due to the pulsatile stretching caused by blood pumping through dilated vessels.

Steroid hormones and oral contraceptives

Migrainous symptoms are associated with the menstrual cycle in about one third of women (Greene, 1975) the majority of attacks occurring pre-, intra-, or post-menstrually. The headache often accompanies fluid retention (e.g. puffiness, weight gain, oedema) and other symptoms of the 'premenstrual syndrome'. Water retention *per se* is not generally accepted to be the cause of menstrual migraine. Certainly the administration of diuretics does not offset the attacks, neither does water retention induced by pitressin or DOCA provoke them (Wolff *et al.*, quoted by Greene, 1975).

Recently, the possibility has been suggested that ovarian steroids interfere with catecholamine metabolism. Endometrial monoamine oxidase activity increases after ovulation, or under the influence of certain oral contraceptives (Southgate *et al.*, 1968; Grant and Pryce-Davies, 1968). Furthermore, the contractile effects of noradrenaline, adrenaline, and tyramine on the rabbit isolated aorta were potentiated by both 17 β-oestradiol and progesterone (Kalsner, 1969). It has been suggested that these steroids exert their action by the inhibition of the enzyme catechol-*O*-methyltransferase, although an

uptake inhibitory mechanism has also been postulated (Iversen and Salt, 1970).

Although the findings that gonadal steroids potentiate the vascular effects of sympathomimetic amines are consistent with the present hypothesis implicating noradrenergic mechanisms in the genesis of menstrual migraine, the progestational increase in endometrial MAO effectively decreasing the effects of catecholamines and the subsequent rebound when, for example, strongly progestogenic oral contraceptives are discontinued, better explains the severe migrainous attacks that occur during the 'pill-free' seven days (Phillips, 1968).

Miscellaneous precipitants

Many dietary precipitants of migraine are known (Hanington *et al.*, 1970). They include chocolate, cheese, citrus fruit, alcoholic drinks, yeast extract, and sea-foods. Despite the fact that very few data on the concentrations of monoamines in different foods are known, those that are available commonly implicate tyramine, which acts by releasing noradrenaline from nerve-endings; chocolate (and some cheeses) contains large amounts of phenylethylamine (Sandler, Youdim and Hanington, 1974). This substance, which stimulates vascular α-adrenoceptors directly (Gonsalves and Johnson, 1977) will precipitate headache in 50% of patients with chocolate-sensitive migraine within 12 hr of administration.

Glyceryl trinitrate is well known to precipitate migraine in susceptible individuals. Campus *et al.* (1967) showed that large increases in HMMA and 5HIAA excretion were noted only in patients who developed headache on glyceryl trinitrate, those suffering no headache showed no change in their output of amine metabolites. Nitrite used as a meat preservative has also been found to provoke headache in a tyramine-sensitive subject (Henderson and Raskin, 1972). The nitrite was considered possibly to be acting through a mechanism common to tyramine. Amphetamine, which has a pharmacological action similar to that of tyramine, may also provoke migraine attacks (Smith, Kellow and Hanington, 1970).

Mechanisms of action of drugs used in the treatment of migraine

It is well known that drug treatment of the acute attack with 'vasoconstrictors' is more likely to meet with success if, paradoxically, it is begun in the prodromal constrictor phase (Today's Drugs, 1963; Rawson and Liversedge, 1975). The more recent observations on the mechanisms of action of antimigraine drugs now permit this paradox to be resolved.

Ergot alkaloids

It is generally believed that ergot alkaloids, such as ergotamine, dihydroergotamine, and methylergotamine, are effective in the treatment of migraine by a constrictor action on scalp arteries (Lance, 1973). That they cause constriction both of arteries and veins of man if the dose is high enough is beyond doubt (Nickerson and Collier, 1975; Aellig, 1976a, b). However, Berde (1971) and Saxena and Vlaam-Schluter (1974) suggested that the degree of vasoconstriction induced by ergot derivatives depends on pre-existing vascular tone. Berde (1971) found that when the arterial resistance of the perfused dog hindlimb was low, ergotamine, dihydroergotamine, and methylergotamine constricted the vasculature, whereas when the resistance was high the drugs had vasodilator actions.

The ergot alkaloids were among the first drugs discovered with α-adrenoceptor antagonist properties. They are also among the most potent agents in this respect, i.e. they are highly effective in antagonizing the effects of noradrenaline on α-adrenoceptors (Table 1). One explanation of the experimental findings of Berde (1971) would be that in the presence of marked neurogenic (noradrenergic) tone the α-blocking action predominates, and a vasodilatation results; in the presence of low intrinsic vascular tone the drug acts predominantly as a constrictor agonist, although whether this is by an action on adrenoceptors (Lance, 1973) or 5-hydroxytryptamine receptors (Aellig, 1976b) remains uncertain. The action of the drugs in migraine, therefore, would be expected to differ in the different phases of an acute attack. In the constrictor phase ergot alkaloids should dilate and thereby prevent the

TABLE 1. Activity of some ergot alkaloids and other drugs in blocking the effects of noradrenaline on the α-adrenoceptors of the guinea-pig isolated aorta. The PA_2 determinations were by the method of Arunlakshana and Schild (1959) and each drug was tested on a minimum of twelve aortae (B. J. Alps and J. Waterfall, Personal Communication; Alps *et al.*, 1972a, b; Collis and Alps, 1973).

Drug	*n*	PA_2
Ergotamine	13	7·20
Methylergotamine	14	7·12
Hydergine	12	7·61
Dihydroergotamine	12	8·18
Phentolamine	14	7·64
Thymoxamine	12	6·93
Indoramin	16	7·38
Chlorpromazine	12	8·30

consequences of the constriction – is this why treatment with these drugs is more often successful when begun early in the prodromal phase? In the dilator phase ergot alkaloids should constrict the vessels, and possibly alleviate some (if any) of the symptoms attributable to vasodilatation. However, since initial vasoconstriction appears to be responsible for the subsequent features of the migraine attack, the use of a selective α-adrenoceptor antagonist lacking vasoconstrictor side effects would appear to be the theoretical treatment of choice for the acute attack in its early phase, or for the prophylactic management of the condition, and would have the additional advantage of obviating the dangers attributable to the peripheral vasoconstrictor property of ergot derivatives.

The vasoconstrictor property of ergotamine and similar drugs should, if the theory is correct, itself induce migraine in susceptible individuals whose vessels are not constricted at the time the medication is taken. The same would be true of vasoconstriction due to inhaled nicotine or parenterally administered noradrenaline. In fact, migraine has reportedly been induced by ergotamine (Wainscott, Volans and Wilkinson, 1974; Grant *et al.*, 1974, 1976), nicotine (Grant *et al.*, 1976) and intravenous noradrenaline has induced the prodromal symptoms (Tunis and Wolff, 1953).

Antagonism of 5-hydroxytryptamine

In addition to blocking α-adrenoceptors and constricting vascular smooth muscle, ergot alkaloids have distinct anti-5HT actions. Thus, ergotamine, methylergotamine, and methysergide all inhibit 5HT-induced oedema of the rat's paw and, in the artery of the rabbit's ear, dihydroergotamine, methysergide, methylergotamine, cyproheptadine, and pizotifen all inhibit the arterial constrictor response to 5HT (Fozard, 1975). Pizotifen and cyproheptadine were also shown to be noradrenaline and histamine antagonists on this preparation, and methysergide and cyproheptadine to be α-blockers on the vas deferens (Görlitz and Frey, 1973). Both pizotifen and cyproheptadine are only slightly less potent than atropine as antagonists of acetylcholine (Fozard, 1975).

Although the mechanism of action of these non-selective drugs in migraine is unknown, it is almost certainly not due to 5HT antagonism (Fozard, 1975). Firstly, the intravenous infusion of 5HT or its metabolic precursor, 5-hydroxytryptophan, does not induce migraine in migraine sufferers (Kimball *et al.*, 1960; Kimball and Friedman, 1961). Secondly, in those patients depleted of the monoamine by treatment with reserpine, intravenous infusion of 5HT alleviated the headache (Anthony *et al.*, 1967). Thirdly, the pharmacodynamic actions of 5HT in man, e.g. constriction of superficial veins, are shared by the antagonists used in migraine, namely, ergotamine, dihydroergotamine, methysergide (Aellig, 1974, 1976a) and pizotifen (Aellig, 1976b).

The suggestion has been made (Aellig, 1976a, b; Mueller-Schweinitzer, 1976) that as the venoconstrictor action of ergotamine as well as 5HT can be antagonized by pizotifen, the ergotamine is acting at least partly by stimulating 5HT receptors. Other interpretations would be that ergotamine is stimulating noradrenaline or histamine receptors which the pizotifen also blocks. This latter explanation is consistent with the additional finding of Aellig (1973) that local infusion of the α-blocker phentolamine inhibits the venoconstrictor effect in man of dihydroergotamine, and phentolamine is devoid of anti-5HT effects (Görlitz and Frey, 1973). However, if we assume that the principal therapeutic benefit of these non-selective compounds results from vasoconstriction during the headache phase of the acute attack the intensity of the symptoms might be reduced, but the attack is unlikely to be aborted. Their vasoconstrictor action is unlikely to be of benefit during the intrinsic prodromal vasoconstrictor phase but, if all the drugs had either α-blocking or other vasodilator property, no matter how weak, on already constricted vessels, then a rationale for their prophylactic use emerges. Yet how much more preferable to have selective vasodilatation unencumbered by agonist activity. The potent inhibitory property of methysergide on the inflammatory response evoked by 5HT (Fozard, 1975) may be relevant to the action of this drug in the headache phase of a migraine attack.

Central α-adrenoceptor stimulation

Clonidine is an antihypertensive drug whose site of action is in the central nervous system (CNS), where it acts by stimulating α-adrenoceptors (Kobinger, 1975). Central α-adrenoceptor stimulation results in a decrease in the number of action potentials passing along the peripheral sympathetic nerves to blood vessels (Schmitt, 1970). This in turn leads to a decrease in the amount of noradrenaline being released from sympathetic nerve endings with a resultant vasodilatation. A decrease in the noradrenaline output might also result from a specific inhibitory action of clonidine at the adrenergic nerve endings (Armstrong and Boura, 1973) possibly due to a stimulant action on peripheral presynaptic α-adrenoceptors (Starke and Altmann, 1973). Ciné-angiographic studies in man have shown that clonidine (75 μg i.v.) speeds up the cerebral circulation time (Lance, 1973) consistent with a vasodilator action. In very high concentrations clonidine also acts as a non-competitive α-adrenoceptor antagonist on

human isolated smooth muscle (Coupar and Kirby, 1972; Kobinger, 1973).

Clonidine is an effective prophylactic agent for migraine for which condition it is active in minute sub-hypotensive doses (Fozard, 1975). The action of clonidine, therefore, provides additional evidence for the involvement of the noradrenergic innervation to the cranial vasculature in the genesis of migraine, and the dosage required for prophylaxis indicates that the increased sympathetic activity must be quantitatively very small indeed. From this it can be predicted that a selective α-blocker would be prophylactic in sub-hypotensive doses.

β-adrenoceptor antagonism

If the increased sympathetic activity results in an increase in the concentration of noradrenaline in plasma then it is possible that vascular β-adrenoceptors will be activated, and the resulting vasodilatation will tend to oppose the constriction due to α-adrenoceptor stimulation. Blockade of the actions of circulating catecholamine on dilator β-receptors has been the rationale for the use of β-adrenoceptor antagonists for migraine prophylaxis (Lance, 1973). However, peripheral β-adrenoceptor blockade is unlikely to explain completely the haemodynamic response to this group of drugs.

Initially β-blockers cause a decrease in cardiac output and a reflex increase in vascular tone (Frohlich *et al.*, 1968) but on continued dosage the vascular resistance eventually decreases and the blood pressure falls. This decrease in vascular resistance with propranolol has been shown in rabbits to result from a decrease in the peripheral sympathetic neuronal activity caused by an action of the β-blocker in the CNS (Lewis, 1975). Thus, prolonged treatment with this β-adrenoceptor antagonist will result not in vasoconstriction, but in vasodilatation, an action entirely consistent with the present hypothesis, and from which one may predict that β-adrenoceptor antagonists by their vasodilator action will be active in preventing the effects of initial α-mediated vasoconstriction. It is also theoretically possible that initial vasoconstriction or decrease in cerebral blood flow in response to drugs such as propranolol or acebutolol (Hares, James and Griffith, 1977) might precipitate an acute migraine attack in susceptible individuals.

It is worth noting that β-adrenoceptor antagonists have been shown to be competitive 5HT antagonists (Schechter and Weinstock, 1974). So, in the headache phase, because they lack intrinsic agonist activity, they could conceivably aggravate the reactive vasodilatation.

Several controlled clinical trials show that propranolol (Webber and Reinmuth, 1971; Widerøe and Vigander, 1974) or pindolol (Anthony and Lance, 1972) reduce the frequency and severity of migraine attacks, but not all agree (Ekbom and Lundberg, 1971; Sjaastad and Stensrud, 1972). The most appropriate dosage regimen and duration of therapy with these drugs remain to be evaluated.

Prediction of drugs likely to be useful for the treatment of migraine

If a vasoconstrictor action of noradrenaline on vascular α-adrenoceptors is the fundamental factor initiating migraine attacks then selective blockade of these receptors provides both the basis for prophylactic therapy of the condition and a clinical challenge for the present hypothesis. The use of α-adrenoceptor antagonists to prevent the initial constriction was suggested by Hanington (1969) as a logical corollary to her discovery of the relationship between dietary tyramine and migraine. The choice of a suitable α-adrenoceptor antagonist for this purpose is however not easy, as it should satisfy the following criteria.

(a) It must be active when taken by mouth; this excludes thymoxamine (White and Richens, 1974).

(b) It should preferably have a duration of action following oral administration of at least 4–6 hr.

(c) It must be a competitive antagonist. The use of an α-adrenoceptor antagonist (including ergot) results in a marked increase in the amount of noradrenaline released from the nerve endings into the synaptic fluid. This is brought about primarily by additional presynaptic actions, common to the α-blockers, of the inhibition of the neuronal reuptake of noradrenaline, and the prevention of synaptic noradrenaline from inhibiting its own release by an action on presynaptic α-receptors (Langer *et al.*, 1975; Rand *et al.*, 1975). This increased amount of noradrenaline is available to compete with the antagonist drug for post-synaptic α-adrenoceptors. However, this it can do only if the antagonist occupies the receptors in a reversible competitive manner.

This is a convenient point at which to counter the common assertion that one consequence of α-blockade is that inevitably there will be troublesome side effects attributable to complete sympathetic transmission failure, like postural hypotension or failure of ejaculation. This view arose probably from the finding of postural hypotension with the irreversible, non-competitive, alkylating agent, phenoxybenzamine (Nickerson and Collier, 1975). However, it would indeed be a strange assertion to make about a competitive α-blocker whose post-synaptic blocking action is attenuated by the ability of the sympathetic innervation to increase its noradrenaline output and so partly reverse the antagonism.

It has already been argued that only very low

doses of drug will be required to overcome the slight increase in the sympathetic activity presently postulated to occur in migraine. Therefore the successful use of a competitive α-blocker in migraine will predictably be with sub-hypotensive doses.

(d) The drug should preferably not cause agonist side effects, such as vasoconstriction, uterine contraction, and tachycardia. This effectively excludes all β-haloalkylamines (e.g. phenoxybenzamine), ergot alkaloids, imidazolines (e.g. phentolamine) and benzodioxans (e.g. piperoxan) leaving only the piperidylethylindoles (e.g. indoramin) which possess intrinsic cardio-inhibitory activity (Alps *et al.*, 1972a, b). If the present theory is correct then titration with sub-hypotensive doses of indoramin (up to 60 mg daily) ought to be prophylactic in migraine, a prediction supported by the recent findings of Wainscott *et al.* (1975).

Other drugs which possess α-blocking properties include the tricyclic antidepressants such as amitriptyline and imipramine (Sugden, 1974) and phenothiazine tranquillizers such as chlorpromazine. On the basis of the present theoretical considerations these drugs ought to benefit some migraine sufferers, as was stated to be the case by Friedman (1972) although those that are more potent as uptake inhibitors than as α-blockers might make the condition worse.

Several antihypertensive drugs pharmacologically related to clonidine have recently emerged (e.g. guanabenz; Baum and Shropshire, 1976) and warrant investigating in migraine, as do a variety of unrelated vasodilator drugs, including the MAO inhibitor phenelzine (Anthony and Lance, 1969) and prazosin that satisfy most of the above-mentioned criteria desirable for the α-blockers.

The hypothalamus and 'spontaneous' migraine

The spontaneous migraine syndrome is associated not only with vascular changes, but also with changes in water balance, food intake, emotional state, and sleep. Herberg (1975) has drawn interesting parallels between the hyperphagia, polydipsia, somnolence and irritability of patients in the pre-headache phase and the identical symptom list associated with experimental lesions of the ventromedial nucleus of the hypothalamus. Herberg reviews evidence which suggests that migraine might be associated with enhanced lateral hypothalamic activity which undergoes a further enhancement (either direct, or by suppression of ventromedial inhibitory activity) at the onset of the migraine attack. Influence on the cranial vasculature is presumably via adjacent posterior hypothalamic neurones. (It should, however, be acknowledged that such increased hypothalamic activity might itself result from altered cortical or subcortical neuronal activity triggered by lumenal changes in hyper-reactive cranial blood vessels, making the migraine primarily a vascular disorder.)

The hypothalamus is strikingly rich in its neuronal monoamine content. Thus dopamine cell groups exist in the dorsal, lateral, dorsomedial, and posterior hypothalamus (Hökfelt and Fuxe, 1972). Noradrenaline is present in cells of the dorsomedial and lateral hypothalamus (Fuxe *et al.*, 1975; Ungerstedt, 1971). Adrenaline occurs in neurones of the arcuate, perifornical, paraventricular, and dorsomedial nuclei (Goldstein *et al.*, 1974). The adrenaline cell system has been considered as playing a role in the antihypertensive action of clonidine (Bolme *et al.*, 1974). Histamine is present in the very high concentrations in all areas of the hypothalamus (Adam and Hye, 1966). In view of the structural similarities of histamine and clonidine and the known antihistamine properties of the imidazoline α-blockers such as phentolamine, it is just possible that clonidine exerts its effects by an action on the histamine receptor. Finally, 5HT is also present in very high concentration in the hypothalamus (Amin, Crawford and Gaddum, 1954; Paasonen and Vogt, 1956) where it follows the pattern for noradrenaline and histamine.

It is just conceivable that currently available antimigraine drugs influence one or other of the hypothalamic amine systems and do not exert their actions primarily by a direct action on the cranial vasculature or its innervation. Migraine inducers such as reserpine might also act centrally or peripherally or both, although tyramine's action would remain at the vascular adrenergic nerve ending, as it does not cross the blood brain barrier to any extent (Oldendorf, 1971). The use of a non-agonist α-blocker such as indoramin, whose central pre- and post-synaptic effects might neutralize one another and result in an action primarily on peripheral post-synaptic vascular receptors (Johnson, 1978) should help to resolve this question. Prazosin, an α-blocker allegedly selective for the post-synaptic receptor (Cambridge, Davey and Massingham, 1977) might also be worth trying in migraine.

But what causes the postulated abnormal hypothalamic activity? Perhaps it is secondary to changes in hypothalamic blood flow due to variations in local ion concentrations, as ascribed to potassium and bicarbonate in rabbits by Cameron and Caronna (1976); cerebral neuronal activity has been shown to be accompanied by an increase in blood flow (Ingvar and Risberg, 1967). Small changes in bicarbonate could be caused, for example, by a different pattern of breathing during sleep. This is consistent with the observation that some patients commonly awaken with established migraine (Hsu *et al.*, 1977).

References

ADAM, H.M. & HYE, H.K.A. (1966) Concentrations of histamine in different parts of brain and hypophysis of cat and its modification by drugs. *British Journal of Pharmacology*, **28**, 137.

AELLIG, W.H. (1973) Studies on the venoconstrictive effect of dihydroergotamine in man. *Naunyn-Schmiedeberg's Archives of Pharmacology*, **279** (Suppl.), Abs. 70 (R.43).

AELLIG, W.H. (1974) Studies on the venoconstrictor effect of ergot compounds in man. In: *Background to Migraine*. The Sixth Migraine Symposium, pp. 15–16. The Migraine Trust, London.

AELLIG, W.H. (1976a) Influence of ergot compounds on compliance of superficial hand veins in man. *Postgraduate Medical Journal*, **52** (Suppl. 1), 21.

AELLIG, W.H. (1976b) Clinical-pharmacological experiments with pizotifen (Sanomigran ®) on superficial hand veins in man. *Abstracts of the Migraine Trust International Symposium*, p. 5, London, September 1976.

ALPS, B.J., BORROWS, E.T., JOHNSON, E.S., STANIFORTH, M.W. & WILSON, A.B. (1972a) A comparison of the cardiovascular actions of indoramin, propranolol, lignocaine and quinidine. *Cardiovascular Research*, **6**, 226.

ALPS, B.J., HILL, MADELINE, JOHNSON, E.S. & WILSON, A.B. (1972b) Quantitative analysis on isolated organs of the autonomic blocking properties of indoramin hydrochloride (Wy 21901). *British Journal of Pharmacology*, **44**, 52.

AMIN, A.H., CRAWFORD, T.B.B. & GADDUM, J.H. (1954) The distribution of substance P and 5-hydroxytryptamine in the central nervous system of the dog. *Journal of Physiology*, **126**, 596.

ANTHONY, M., HINTERBERGER, H. & LANCE, J.W. (1967) Plasma serotonin in migraine and stress. *Archives of Neurology*, **16**, 544.

ANTHONY, M. & LANCE, J.W. (1969) Monoamine oxidase inhibition in the treatment of migraine. *Archives of Neurology*, **21**, 263.

ANTHONY, M. & LANCE, J.W. (1972) A comparative trial of pindolol, clonidine and carbamazepine in the interval therapy of migraine. *Medical Journal of Australia*, **1**, 1343.

ARMSTRONG, J.M. & BOURA, A.L.A. (1973) Effects of clonidine and guanethidine on peripheral sympathetic nerve function in the pithed rat. *British Journal of Pharmacology*, **47**, 850.

ARUNLAKSHANA, D. & SCHILD, H.O. (1959) Some quantitative uses of drug antagonists. *British Journal of Pharmacology*, **14**, 48.

BAUM, T. & SHROPSHIRE, A.T. (1976) Studies on the centrally mediated hypotensive activity of guanabenz. *European Journal of Pharmacology*, **37**, 31.

BERDE, B. (1971) New studies on the circulatory effects of ergot compounds with implications to migraine. In: *Background to Migraine* (Ed. by Smith, R.), Vol. 4, pp. 66–75. Heinemann, London.

BLAU, J.N. & CUMINGS, J.N. (1966) Method of precipitating and preventing some migraine attacks. *British Medical Journal*, **2**, 1242.

BOLME, P., CORRODI, H., FUXE, K., HÖKFELT, T., LINDBRINK, P. & GOLDSTEIN, M. (1974) Possible involvement of central adrenaline neurones in vasomotor and respiratory control. Studies with clonidine and its interactions with piperoxane and yohimbine. *European Journal of Pharmacology*, **28**, 89.

CAMBRIDGE, D., DAVEY, M.J. & MASSINGHAM, R. (1977) Prazosin, a selective antagonist of post-synaptic α-adrenoceptors. *British Journal of Pharmacology*, **59**, 514P.

CAMERON, R. & CARONNA, J. (1976) The effect of local changes in potassium and bicarbonate concentration on hypothalamic blood flow in the rabbit. *Journal of Physiology*, **262**, 415.

CAMPUS, S., FABRIS, F., RAPELLI, A., GASTALDI, L., GAI, V. & NATTERO, G. (1967) Escrezione urinaria di acido 5-idrossiindolacetico durante crisi cefalalgia indotta da trinitroglicerina. *Bollettino della Società di Biologia Sperimentale*, **43**, 1844.

CHAPMAN, L.R., RAMOS, A.O., GOODELL, H., SILVERMAN, G. & WOLFF, H.G. (1960) A humoral agent implicated in vascular headache of the migraine type. *Archives of Neurology*, **3**, 223.

COLLIER, J.G., NACHEV, C. & ROBINSON, B.F. (1972) Effect of catecholamines and other vasoactive substances on superficial hand veins in man. *Clinical Science*, **43**, 455.

COLLIS, M.G. & ALPS, B.J. (1973) The evaluation of the α-adrenoceptor blocking action of indoramin, phentolamine and thymoxamine on the rat and guinea-pig isolated mesenteric vasculature and aortic spiral preparations. *Journal of Pharmacy and Pharmacology*, **25**, 621.

CORBETT, J.L., EIDELMAN, B.H. & DEBARGE, O. (1972) Modification of cerebral vasoconstriction with hyperventilation in normal man by thymoxamine. *Lancet*, **ii**, 461.

COUPAR, I.M. & KIRBY, M.J. (1972) The effect of clonidine on human isolated smooth muscle. *European Journal of Pharmacology*, **17**, 50.

CURRAN, D.A., HINTERBERGER, H. & LANCE, J.W. (1965) Total plasma serotonin, 5-hydroxyindoleacetic acid and p-hydroxy-m-methoxymandelic acid excretion in normal and migrainous subjects. *Brain*, **88**, 997.

CURZON, G., BARRIE, M. & WILKINSON, M.I.P. (1969) Relationships between headache and amine changes after administration of reserpine to migrainous patients. *Journal of Neurology, Neurosurgery and Psychiatry*, **32**, 555.

CURZON, G., THEAKER, P. & PHILLIPS, B. (1966) Excretion of 5-hydroxyindolyl acetic acid (5HIAA) in migraine. *Journal of Neurology, Neurosurgery and Psychiatry*, **29**, 85.

DAHL, E. & NELSON, E. (1964) Electron microscopic observations on human intracranial arteries. *Archives of Neurology*, **10**, 56.

D'ALECY, L.G. & FEIGL, E.O. (1972) Sympathetic control of cerebral blood flow in dogs. *Circulation Research*, **31**, 267.

DALESSIO, D.J. (1962) On migraine headache: serotonin and serotonin antagonism. *Journal of the American Medical Association*, **181**, 318.

DAVEY, M.J. & FARMER, J.B. (1963) The mode of action of tyramine. *Journal of Pharmacy and Pharmacology*, **15**, 178.

DUKE, H.T. & VIETH, R.G. (1964) Cerebral arteriography during migraine prodrome and headache. *Neurology*, **14**, 636.

EKBOM, K. & LUNDBERG, P.O. (1971) Clinical trial of LB46 (d, 1-4-(2-hydroxy-3-isopropylaminopropoxy) indol). Adrenergic beta-receptor blocking agent in migraine prophylaxis. *Headache*, **12**, 15.

FALCK, B., NIELSEN, K.C. & OWMAN, C. (1968) Adrenergic innervation of the pial circulation (abstr.). *Scandinavian Journal of Clinical and Laboratory Investigation*, Suppl. 102, VIB.

FANCHAMPS, A. (1974) The role of humoral mediators in migraine headache. *Canadian Journal of Neurological Sciences*, **1**, 189.

FOZARD, J.R. (1975) The animal pharmacology of drugs used in the treatment of migraine. *Journal of Pharmacy and Pharmacology*, **27**, 297.

FRASER, R.A., STEIN, B.M. & POOL, J.L. (1970) Hypocapnic cerebral arterial constriction, alpha adrenergic blockade. *Circulation*, **42** (Suppl. 3), 120.

FRIEDMAN, A.P. (1972) Migraine headaches. *Journal of the American Medical Association*, **222**, 1399.

FROLICH, E.D., TARAZI, R.C., DUSTAN, H.P. & PAGE, I.H. (1968) The paradox of β-adrenergic blockade in hypertension. *Circulation*, **37**, 417.

FUXE, K., HOKFELT, T., HOLME, P., GOLDSTEIN, M., JOHANSSON, O., JONSSON, G., LIDBRINK, P., LJUNGDAHL, A. & SACHS, CH. (1975) The topography of central catecholamine pathways in relation to their possible role in blood

pressure control. In: *Central Actions of Drugs in Blood Pressure Regulation* (Ed. by Davies, D.S. & Reid, J.L.), pp. 8–22. Pitman Medical, London.

GHOSE, K., COPPEN, A. & CARROLL, D. (1977) Intravenous tyramine response in migraine before and during treatment with indoramin. *British Medical Journal*, **2**, 1191.

GOLDSTEIN, M., LEW, J.Y., MIYAMOTO, T., BATTISTA, A.F., EBSTEIN, R., HÖKFELT, T. & FUXE, K. (1974) The localization and characterization of phenylethanolamine-N-methyl transferase activity in specific regions of the CNS. *Pharmacologist*, **16**, Abs. 257.

GONSALVES, ALEXANDRA & JOHNSON, E.S. (1977) Possible mechanism of action of β-phenethylamine in migraine. *Journal of Pharmacy and Pharmacology*, **29**, 646.

GÖRLITZ, B.D. & FREY, H.-H. (1973) Comparison of the blocking effects of antagonists of adrenaline and 5-hydroxytryptamine on their mutual receptors. *Journal of Pharmacy and Pharmacology*, **25**, 651.

GOTOH, F., KANDA, T., SAKAI, F., YAMAMOTO, Y. & TAKEOKA, T. (1976) Serum dopamine-β-hydroxylase activity in migraine. *Archives of Neurology*, **33**, 656.

GRANT, E.C.G., ALBURQUERQUE, M., STEINER, T.J. & ROSE, F.C. (1976) Oral contraceptives, smoking and ergotamine in migraine. *Abstracts of the Migraine Trust International Symposium*, pp. 8–9, London, September, 1976.

GRANT, E.C.G., CARROLL, J.D., GOODWIN, P. & PRYCE-DAVIES, J. (1974) Hormones and headaches in women. In: *Background to Migraine*, The Sixth Migraine Symposium, p. 7, The Migraine Trust, London.

GRANT, E.C.G. & PRYCE-DAVIES, J. (1968) Effect of oral contraceptives on depressive mood changes and on endometrial monoamine oxidase and phosphatases. *British Medical Journal*, **3**, 777.

GREENE, R. (1975) The endocrinology of headache. In: *Modern Topics in Migraine* (Ed. by Pearce, J.), ch. 7. Wm. Heinemann Medical Books Ltd, London.

HANINGTON, E. (1967) Preliminary report on tyramine headache. *British Medical Journal*, **1**, 550.

HANINGTON, E. (1969) The effect of tyramine in inducing migrainous headache. In: *Background to Migraine, the Second Migraine Symposium* (Ed. by Smith, R.), pp. 10–18, Heinemann, London.

HANINGTON, E., HORN, M. & WILKINSON, M. (1970) Further observations on the effects of tyramine. In: *Background to Migraine, the Third Migraine Symposium* (Ed. by Cochrane, A.L.), pp. 113–119. Heinemann, London.

HARES, P., JAMES, I.M. & GRIFFITH, D. (1977) The effect of acebutolol on the cerebral circulation of man. *British Journal of Clinical Pharmacology*, **4**, 373.

HENDERSON, W.R. & RASKIN, N.H. (1972) "Hot-dog" headache: individual susceptibility to nitrite. *Lancet*, **ii**, 1162.

HERBERG, L.J. (1975) The hypothalamus and aminergic pathways in migraine. In: *Modern Topics in Migraine* (Ed. by Pearce, J.), Ch. 9. Wm. Heinemann Medical Books Ltd, London.

HEYCK, H. (1970) The importance of arterio-venous shunts in the pathogenesis of migraine. In: *Background to Migraine, the Third Migraine Symposium* (Ed. by Cochrane, A.L.), pp. 19–25. Heinemann, London.

HOCKADAY, J.M. (1975) Anomalies of carbohydrate metabolism. In: *Modern Topics in Migraine* (Ed. by Pearce, J.), Ch. 12. Wm. Heinemann Medical Books Ltd, London.

HOFF, J.T., SENGUPTA, D., HARPER, M. & JENNETT, B. (1972) Effect of adrenergic blockade on response of cerebral circulation to hypocapnia in the baboon. *Lancet*, **ii**, 1337.

HÖKFELT, T. & FUXE, K. (1972) In: *Brain Endocrine Interaction, Median Eminence: Structure and Function* (Ed. by Knigge, K. & Scott, D.), p. 181. Karger, Basel.

HSU, L.K.G., CRISP, A.H., KALUCY, R.S., KOVAL, J., CHEN, C.N., CARRUTHERS, M. & ZILKHA, K. (1977) Early morning migraine. Nocturnal plasma levels of catecholamines, tryptophan, glucose and free fatty acids and sleep encephalographs. *Lancet*, **i**, 447.

INGVAR, D.H. (1958) Cortical state of excitability and cortical circulation. In: *Reticular Formation of the Brain*, pp. 381–408. Little, Brown, Boston.

INGVAR, D.H. & RISBERG, J. (1967) Increase of regional cerebral blood flow during mental effort in normals and in patients with focal brain disorders. *Experimental Brain Research*, **3**, 195.

IVERSEN, L.L. & SALT, P.J. (1970) Inhibition of catecholamine uptake by steroids in the isolated rat heart. *British Journal of Pharmacology*, **40**, 528.

IWAYAMA, T., FURNESS, J.B. & BURNSTOCK, G. (1970) Dual adrenergic and cholinergic innervation of the cerebral arteries of the rat. *Circulation Research*, **26**, 635.

JOHNSON, E.S. (1978) Pharmacological consequences of alpha-adrenoceptor antagonism. *Excerpta Medica* (in press).

KALSNER, S. (1969) Steroid potentiation of responses to sympathomimetic amines in aortic strips. *British Journal of Pharmacology*, **36**, 582.

KIMBALL, R.W. & FRIEDMAN, A.P. (1961) Further studies of neurohumoral agents in patients with vascular headaches. *Neurology*, **11**, 116.

KIMBALL, R.W., FRIEDMAN, A.P. & VALLEJO, E. (1960) Effect of serotonin in migraine patients. *Neurology*, **10**, 107.

KING, B.D., SOKOLOFF, L. & WECHSLER, R.L. (1952) Effect of L-epinephrine and L-norepinephrine upon cerebral circulation and metabolism in man. *Journal of Clinical Investigation*, **31**, 273.

KLEE, A. (1968) A clinical study of migraine with particular reference to the most severe cases. *Thesis*, Munksgaard, Copenhagen.

KOBINGER, W. (1973) Pharmacologic basis of the cardiovascular actions of clonidine. In: *Hypertension: Mechanisms and Management* (Ed. by Onesti, G., Kim, K.E. & Moyer, J.H.), pp. 369–380. Grune & Stratton, New York.

KOBINGER, W. (1975) Central cardiovascular actions of clonidine. In: *Central Action of Drugs in Blood Pressure Regulation* (Ed. by Davies, D.S. & Reid, J.L.), pp. 181–193. Pitman Medical, London.

KROG, J. (1964) Autonomic nervous control of the cerebral blood flow in man. *Journal of the Oslo City Hospital*, **14**, 25.

LANCE, J.W. (1973) *Mechanism and Management of Headache*, 2nd edn. Butterworths, London.

LANGER, S.Z., ENERO, M.A., ADLER-GRASCHINSKY, E., DUBOCOVICH, M.L. & CELUCHI, S.M. (1975) Presynaptic regulatory mechanisms for noradrenaline release by nerve stimulation. In: *Central Action of Drugs in Blood Pressure Regulation* (Ed. by Davies, D.S. & Reid, J.L.), pp. 133–151. Pitman Medical, London.

LEWIS, P.J. (1975) Propranolol – an antihypertensive drug with a central action. In: *Central Action of Drugs in Blood Pressure Regulation* (Ed. by Davies, D.S. & Reid, J.L.), pp. 206–214. Pitman Medical, London.

MEYER, J.S., YOSHIDA, K. & SAKAMOTO, K. (1967) Autonomic control of cerebral blood flow measured by electromagnetic flowmeters. *Neurology*, **17**, 638.

MOYER, J.H., MORRIS, G. & SNYDER, H. (1954) Comparison of the cerebral hemodynamic response to aramine and norepinephrine in the normotensive and the hypotensive subject. *Circulation*, **10**, 265.

MUELLER-SCHWEINITZER, E. (1976) Responsiveness of isolated canine cerebral and peripheral arteries to ergotamine. *Naunyn-Schmiedeberg's Archives of Pharmacology*, **292**, 113.

NELSON, E. & RENNELS, M. (1970a) Innervation of intracranial arteries. *Brain*, **93**, 475.

NELSON, E. & RENNELS, M. (1970b) Neuromuscular contacts in intracranial arteries of the cat. *Science*, **167**, 301.

NICKERSON, M. & COLLIER, B. (1975) Drugs inhibiting

adrenergic nerves and structures innervated by them. In: *The Pharmacological Basis of Therapeutics* (Ed. by Goodman, L.S. & Gilman, A.). Macmillan, New York.

NIELSEN, K.C. & OWMAN, C. (1967) Adrenergic innervation of the pial arteries related to the circle of Willis in the cat. *Brain Research*, **6**, 773.

NIELSEN, K.C. & OWMAN, C. (1971) Contractile response and amine receptor mechanisms in isolated middle cerebral artery of the cat. *Brain Research*, **27**, 33.

NIELSEN, K.C., OWMAN, C. & SPORRONG, B. (1971) Ultrastructure of the autonomic innervation apparatus in the main pial arteries of rats and cats. *Brain Research*, **27**, 25.

O'BRIEN, M.D. (1971) Cerebral blood flow changes in migraine. *Headache*, **10**, 139.

OLDENDORF, W.H. (1971) Brain uptake of radiolabeled amino acids, amines and hexoses after arterial injection. *American Journal of Physiology*, **221**, 1629.

OSTFELD, A.M. (1960) Migraine headache. Its physiology and biochemistry. *Journal of the American Medical Association* **174**, 1188.

OSTFELD, A.M. & WOLFF, H.G. (1955) Studies on headache: arterenol (norepinephrine) and vascular headache of the migraine type. *Archives of Neurology and Psychiatry*, **74**, 131.

PAASONEN, M.K. & VOGT, M. (1956) The effect of drugs on the amounts of substance P and 5-hydroxytryptamine in mammalian brain. *Journal of Physiology*, **131**, 617.

PEARCE, J. (1969) *Migraine. Clinical Features, Mechanisms and Management*. Thomas, Springfield.

PHILLIPS, B.M. (1968) Oral contraceptive drugs and migraine. *British Medical Journal*, **2**, 99.

RAND, M.J., MCCULLOCH, M.W. & STORY, D.F. (1975) Prejunctional modulation of noradrenergic transmission by noradrenaline, dopamine and acetylcholine. In: *Central Actions of Drugs in Blood Pressure Regulation* (Ed. by Davies, D.S. & Reid, J.L.) pp. 94–132. Pitman Medical, London.

RAPER, A.J., KONTOS, H.A., WEI, E.P. & PATTERSON, J.L. (1972) Unresponsiveness of pial precapillary vessels to catecholamines and sympathetic nerve stimulation. *Circulation Research*, **31**, 257.

RAWSON, M.D. & LIVERSEDGE, L.A. (1975) The clinical pharmacology of migraine. In: *Modern Topics in Migraine* (Ed. by Pearce, J.), Ch. 14. Wm. Heinemann Medical Books Ltd, London.

SANDLER, M. (1972) Migraine: a pulmonary disease. *Lancet*, **i**, 618.

SANDLER, M., YOUDIM, M.B.H. & HANINGTON, E. (1974) A phenylethylamine oxidising defect in migraine. *Nature*. London, **250**, 335.

SAXENA, P.R. & VLAAM-SCHLUTER, G.M. DE (1974) Role of some biogenic substances in migraine and relevant mechanism in antimigraine action of ergotamine – studies in an experimental model for migraine. *Headache*, **13**, 142.

SCHANBERG, S.M., STONE, R.A., KIRSHNER, N., GUNNELLS, J.C. & ROBINSON, R.R. (1974) Plasma dopamine β-hydroxylase: a possible aid in the study and evaluation of hypertension. *Science*, **193**, 523.

SCHECHTER, Y. & WEINSTOCK, M. (1974) β-Adrenoceptor blocking agents and responses to adrenaline and 5-hydroxytryptamine in rat isolated stomach and uterus. *British Journal of Pharmacology*, **52**, 283.

SCHMITT, H. (1970) Centrally mediated decrease in sympathetic tone induced by 2-(2,6-dichlorphenylamino)-2-imidazoline (ST155, Catapres). In: *Catapres in Hypertension* (Ed. by Conolly, M.E.), pp. 23–41. Butterworth's, London.

SCHUMACHER, G.A. & WOLFF, H.G. (1941) Experimental studies on headache: contrast of histamine headache with headache of the migraine type. *Archives of Neurology and Psychiatry*, **45**, 199.

SENSENBACH, W., MADISON, L. & OCHS, L. (1953) Comparison of the effects of L-norepinephrine, synthetic L-epinephrine and U.S.P-epinephrine upon cerebral blood flow and metabolism in man. *Journal of Clinical Investigation*, **32**, 226.

SICUTERI, F. (1962) L'acido vanilmandelico (VMA), il maggiore metabolita urinario delle catecolamine. *Settimana medica*, **50**, 227.

SICUTERI, F. (1963) Mast-cells and their active substances. Their role in the pathogenesis of migraine. *Headache*, **3**, 86.

SICUTERI, F. (1967) Vasoneuroactive substances and their implication in vascular pain. *Research and Clinical Studies in Headache*, **1**, 6.

SICUTERI, F., ANSELMI, B. & FANCIULLACCI, M. (1974) The serotonin (5-HT) theory of migraine. *Advances in Neurology*, **4**, 383.

SICUTERI, F., FRANCHI, G., MICHELACCI, S. & SALMON, S. (1962) Aumento della escressione urinaria dell'acido vanilmandelico, catabolita delle catecolamine durante l'accesso emicranico. *Settimana medica*, **50**, 13.

SICUTERI, F., TESTI, A. & ANSELMI, B. (1961) Biochemical investigations in headache: increase in hydroxyindoleacetic acid excretion during migraine attacks. *International Archives of Allergy and Applied Immunology*, **19**, 55.

SJAASTAD, O. & STENSRUD, P. (1972) Clinical trial of a β-receptor blocking agent (LB-46) in migraine prophylaxis. *Acta neurologica scandinavica*, **48**, 124.

SKINHØJ, E. (1973) Hemodynamic studies within the brain during migraine. *Archives of Neurology*, **29**, 95.

SMITH, I., KELLOW, A.H. & HANINGTON, E. (1970) A clinical and biochemical correlation between tyramine and migraine headache. *Headache*, **10**, 43.

SMITH, I., KELLOW, A.H., MULLEN, P.E. & HANINGTON, E. (1971) Dietary migraine and tyramine metabolism. *Nature*. London, **230**, 246.

SOUTHGATE, J., GRANT, E.C.G., POLLARD, W., PRYCE-DAVIES, J. & SANDLER, M. (1968) Cyclic variations in endometrial monoamine oxidase: Correlation of histochemical and quantitative biochemical assays. *Biochemical Pharmacology*, **17**, 721.

STARKE, K. & ALTMANN, K.P. (1973) Inhibition of adrenergic neurotransmissions by clonidine: an action on prejunctional α-receptors. *Neuropharmacology*, **12**, 339.

SUGDEN, R.F. (1974) The action of indoramin and other compounds on the uptake of neurotransmitters into rat cortical slices. *British Journal of Pharmacology*, **51**, 467.

TANDON, R.N., SUR, B.K. & NATH, K. (1969) Effect of reserpine injections in migrainous and normal control subjects, with estimations of urinary 5-hydroxyindoleacetic acid. *Neurology*, **19**, 1073.

TODAY'S DRUGS (1963) Drug treatment of migraine. *British Medical Journal*, **1**, 661.

TUNIS, M.M. & WOLFF, H.G. (1953) Studies on headache: long-term observations of the reactivity of the cranial arteries in subjects with vascular headache of the migraine type. *Archives of Neurology and Psychiatry*, **70**, 551.

UNGERSTEDT, U. (1971) Adipsia and aphagia after 6-hydroxydopamine induce degeneration of the nigrostriatal dopamine system. *Acta physiologica scandinavica*, **367** (Suppl. 1), 95.

WAHL, M., KUSCHINSKY, W., BOSSE, O., OLESON, J., LASSEN, N.A., INGVAR, D.H., MICHAELIS, J. & THURAN, K. (1972) Effect of l-norepinephrine on the diameter of pial arterioles and arteries in the cat. *Circulation Research*, **31**, 248.

WAINSCOTT, G., VOLANS, G. & WILKINSON, M. (1974) Ergotamine-induced headaches. *British Medical Journal*, **2**, 724.

WAINSCOTT, G., VOLANS, G.N., WILKINSON, M. & FAUX, G. (1975) Indoramin in prevention of migraine. *Lancet*, **ii**, 32.

WEBBER, R.B. & REINMUTH, O.M. (1971) The treatment of migraine with propranolol. *Neurology*, **21**, 404.

WEINER, N., DRASKOCZY, P.R. & BURROCK, W.R. (1962) The ability of tyramine to liberate catecholamines *in vivo*. *Journal of Pharmacology and Experimental Therapeutics*, **137**, 45.

WHITE, C. DE B. & RICHENS, A. (1974) Thymoxamine and spasticity. *Lancet*, **i**, 686.

WIDERØE, T.E. & VIGANDER, T. (1974) Propranolol in migraine. *British Medical Journal*, **2**, 699.

YOUDIM, M.B.H., BONHAM CARTER, S., SANDLER, M., HANINGTON, E. & WILKINSON, M. (1971) Conjugation defect in tyramine sensitive migraine. *Nature*. London, **230**, 127.