The Pathophysiology of the Migraine Attack

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PROEFSCHRIFT

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CO-REFERENTEN: Prof. dr. G.W. Bruyn
Prof. dr. A. Staal

The 'Headache Baby' depicted on the cover was presented to the author by Dr. John R. Graham during the author's stay at The Headache Research Foundation in Boston in the summer of 1977. The original of this porcelain statuette was a gift to the Foundation, of which Dr. Graham is the director, by the late Dr. T. Dalsgaard-Nielsen of Copenhagen.
(Photo: G.A.F. Maatje)

'Migraine is not a simple attack, but is a complicated syndrome with diversified accompaniments, and manifold manifestations.'

Henry A. Riley[122] (1932)

in memory of my parents
to Malina and Sven

Preface

> '... our duty is to collect and record facts, in confidence that they will arrange themselves into a theory sooner or later ... and by the accumulation and comparison of accurate records we may hope that the transition from facts isolated to facts linked by the clue of theory will be soon attained.'
>
> Hubert Airy[1] (1870)

There is ample evidence to indicate that migraine was familiar to our ancient ancestors; its first description is said to have appeared in 3000 B.C.[2]! Migraine has accompanied humanity throughout its journey down the ages and its prevalence in modern western society is estimated to range from 15 to 19% in men and from 24 to 29% in women[174]. Bruyn[20] reckons that approximately 6% of the present world population, which means about 180 million, is affected by migraine. One might expect, then, that the origin and methods of treatment of such a common ailment would already have been long established. However, this is not the case and the scientific elucidation of the disorder, and hence the definite solution for its treatment, still lie ahead of us.

The primary purpose of this book is to contribute to this elucidation. My means of achieving this will be twofold: 1. By a presentation of the known data on migraine, or rather the migraine attack, I hope to stimulate scientific consideration of the disorder, as well as genuine interest in both the illness and its sufferers. 2. By accumulating and arranging data available from various fields of clinical and experimental migraine research, I hope to build a systematic framework which unites these data because a mere presentation of facts does not necessarily increase our understanding of the subject unless a cohesive interpretation of these facts is offered.

I have limited the subject of the book to the migraine attack as it is the major manifestation of the disorder. I thought it wise to restrict myself and to try to cover one subject in depth rather than to treat the complex and elaborate subject of migraine as a whole.

The migraine attack has been extensively studied and much is known of the changes in the body which accompany it – data on this are presented in Part I. Part II of the book is devoted to a discussion of my own experimental research on the action of antimigraine drugs. In Part III, an attempt is made to link the various clinical and experimental observations, outlined in Parts I and II, in a framework containing the minimum number of suppositions possible.

The experiments were carried out in the Department of Pharmacology of the Erasmus University Faculty of Medicine, Rotterdam. They were performed in collaboration with P.R. Saxena, *MD,* Professor of Pharmacolo-

gy, and with the assistance of Mrs. W.I. Cairo-Rawlins. In connection with this experimental work I would like to acknowledge the helpful discussions of J. Bruinvels, *PhD,* Professor of Molecular Pharmacology in Rotterdam, G.W. Bruyn, *MD,* Professor of Neurology in Leyden, and A. Staal, *MD,* Professor of Neurology in Rotterdam.

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I am especially grateful to my wife, Malina. The ideas and formulations were discussed with her throughout this work.

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E.S.

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Part I

Observations on the migraine attack

1. Introduction

Migraine, a word of French origin, is a mediaeval corruption of the Greek *ἡμικρανια, hemicrania*[90]. Its etymological meaning, half-headache, indicates two important features of the disorder, the headache and its one-sidedness.

In *classical* migraine, the headache is preceded by an 'aura' of focal neurological symptoms. The symptoms are generally sensory in nature and often involve disturbances of vision, such as scotomas, either dark or luminous, or the scintillating scotoma, also called *teichopsia,* a phenomenon which will be described further in Chapter 3.2. There may also be a sensation of tingling, like 'pins and needles', which often commences in the fingers of one hand, gradually extending up the arm to jump, at a given moment, to the area of the mouth. When this sensory disturbance affects the right side of the body, it may be associated with an aphasic disturbance of speech[49].

However, the classical form of migraine occurs much less frequently than the so-called *common* migraine in which the headache comes on *without* an aura. Except for the presence of an aura in the former, classical and common migraine do not differ essentially from each other[141] and therefore have been placed under the same nosological entity, migraine.

The observations on the migraine attack which will be reviewed in this section, can be roughly subdivided into three groups, *i.e.,* those concerning (i) the circulation of the head, (ii) the gastrointestinal tract and (iii) the chemistry of the body. The circulation of the head — the cephalic circulation — can be subdivided into two compartments, the circulation of the brain — the *cerebral* circulation — and the circulation of the remaining structures of the head which is here referred to as the *cranial* circulation. The two parts of the cephalic circulation will be considered separately because of their distinct significance in the pathophysiology of the migraine attack.

2. Cranial Circulation

A characteristic of migraine is the throbbing quality of the headache which incriminates the vascular system of the head in the generation of the pain. The vessels may either pulsate in an exaggerated way or the pain threshold may be locally decreased, but both mechanisms may also simultaneously be at work. Some observations suggest that in particular the *cranial* part of the cephalic circulation, as distinct from the cerebral circulation, is involved in the generation of the migraine headache. These observations are:

a. During the migraine headache the amplitude of pulsation of the *superficial temporal artery* – the branch of the external carotid artery which supplies the temple (no. 4 in fig. 1) – is increased[167], pressure exerted on the artery diminishes the pain – Parry's compression test[61] – and administration of ergotamine, the most effective drug in the treatment of the migraine headache, leads to a decrease in intensity of the pain simultaneously with a decrease in the amplitude of pulsation of the artery[51] (fig. 2).

b. Increasing the cerebrospinal fluid pressure by intrathecal injection of saline, thereby reducing the amplitude of pulsation of the *cerebral* arteries, does *not* lead to a decrease in intensity of the migraine headache[140], and ergotamine, at least under normal conditions, does *not* affect cerebral blood flow[53] (see also results presented in Chapter 8.2).

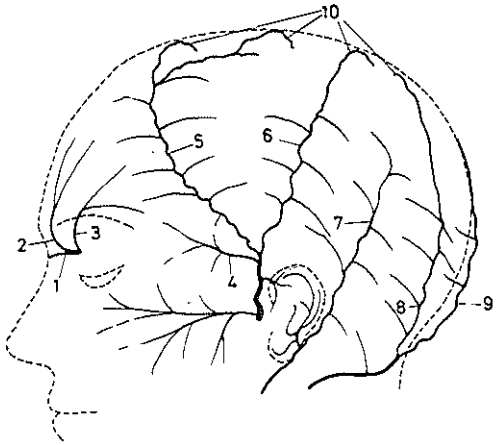

Fig. 1. Blood supply to the cranial structures of the head: 1-3 branches of the internal carotid artery; 4-9 branches of the external carotid artery; 10 anastomoses with the opposite side. (Reproduced from Djindjian and Merland[34].)

2.1. Hemodynamic changes

The studies on the hemodynamic changes in the cranial circulation during the migraine *headache* are summarized in table 1. Not included within this schematic review are the studies on the behavior of the conjunctival vessels[17, 113, 167], and the thermographic studies of Jacobson[73] and Ruegsegger[127]. Jacobson's study dealt with patients suffering from 'vasodilatory headaches' of whom 12 with unilateral attacks showed a skin temperature higher on the affected side than on the healthy side, and nine out of 12

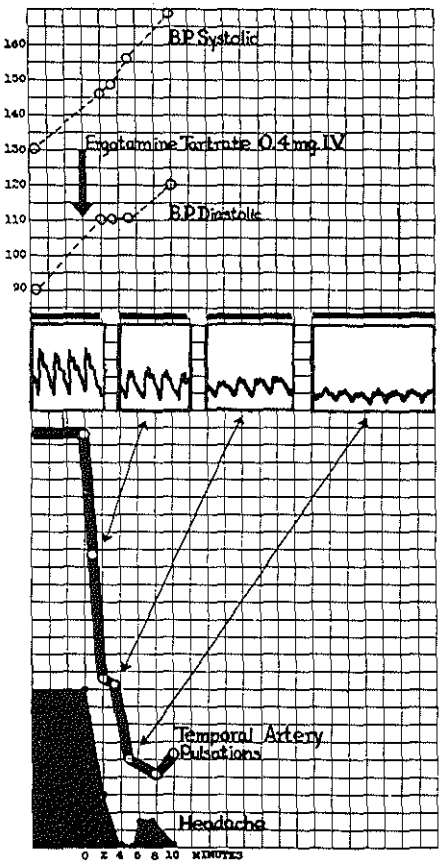

Fig. 2. Administration of ergotamine (0.4 mg i.v.) resulted in a rapid decrease in intensity of the migraine headache which closely paralleled a sharp decrease in the amplitude of pulsation of the superficial temporal artery. (Reproduced from Graham and Wolff[51].)

showed a smaller pupil on the side of the headache. Ruegsegger presented thermograms of two migraine patients but only discussed them vaguely.

In the table it is noticeable that not only multiple techniques have been used, but that they also have been applied to different regions of the cranial circulation. This lack of unity has caused a lot of confusion in current literature. The results of the five studies considered, show that four indicate *in*creased and one *de*creased blood flow to the cranial tissues of the head during the migraine headache. The former four studies are also related by the fact that they focus on the lateral side of the head, whereas the fifth concerns the hemodynamic changes which occur in the forehead. It is evident, then, that the study of Lance and Anthony[86] differs from the others not only in the results obtained but also in the section of the cranial circulation studied, which naturally leads one to conclude that the divergence in the area studied is responsible for the difference in outcome. Thus, it seems that the craniovascular changes accompanying the migraine headache – and which have been suggested to be qualitatively similar to those accompanying cluster headache[157] – consist of increased flow over the lateral side of the head and decreased flow over the forehead. The reason for this difference in vascular changes is not clear but it may be related to the fact that the forehead is vascularized by branches of the *internal* carotid artery – the supraorbital and frontal arteries (nos. 2 and 3 in fig. 1) – while the rest of the cranial circulation is supplied by the *external* carotid artery and its branches.

It is further interesting to note that when the effects of ergotamine or its hydrogenated mate, dihydroergotamine, were studied, an increase in flow was observed when flow was compromised[86] whereas a decrease was observed when flow was exaggerated[37, 61, 167]. It is, therefore, apparently an oversimplification to refer to these ergot compounds merely as cranial vasoconstrictors; they probably exert their beneficial effect in migraine (and cluster headache) through a complex action, possibly at a vascular level.

Müller-Schweinitzer and Stürmer[101] have characterized ergotamine as a partial agonist-antagonist of the α-receptor with a receptor affinity of approximately 350 times that of the endogenous substrate, noradrenaline. Thus, ergotamine's action on the α-receptor depends on the concentration of noradrenaline present in the synaptic cleft which, in turn, depends on the outflow of the postganglionic sympathetic neuron. In the case of a low sympathetic tone, a situation usually compatible with relative vasodilatation, ergotamine will act as an α-agonist to cause the vessels to constrict. On the other hand, when the sympathetic tone is high, in general signifying a state of relative vasoconstriction, ergotamine will act as an α-antagonist to cause the vessels to dilate. Thus, judging from the action of ergotamine, the state of the forehead vasculature in migraine would appear to be one of vasoconstriction associated with a high sympathetic acti-

Table 1. Craniovascular accompaniments of the migraine headache.

Author(s)	*Technique*	*Area or structures studied*	*Findings (interpretation)*	*Laterality related to headache*	*Effect of (dihydro)ergotamine*
Tunis and Wolff[167, 168]	pulse wave registration	superficial temporal artery	↑ amplitude of pulsation (↑ flow)	not stated	↓ amplitude[167]
Elkind *et al.*[37]	^{24}Na clearance	frontotemporal skin	↑ clearance (↑ cutaneous blood flow)	ipsilateral	↓ clearance
Heyck[61]	$CavO_2$, sample from ext. jugular vein	structures drained by ext. jugular v.*	$CavO_2$: ipsilateral < contralateral (arterial blood flow: ipsilateral > contralateral[161])	[161])	↑ $CavO_2$
Lance and Anthony[86]	thermography	forehead	8/13 (62%) skin temperature: ipsilateral< contralateral (↓ flow)		↑ temperature
Sakai and Meyer[130]	^{133}Xe inhalation	lateral side of the head	↑ EFI (↑ cranial blood volume and/or flow)	not stated	not studied

* Approximately 80% of the blood flowing in the external jugular vein is derived from cranial tissues[143].
Abbreviations: $CavO_2$ = arteriovenous oxygen content difference; EFI = extracerebral flow index.

vity, as under these conditions only ergotamine can cause the vascular smooth muscle to relax. However, the vasculature of the forehead, like that of the rest of the cranial circulation, has a very weak (sympathetic) vasoconstrictor nerve supply and in these regions a (sympathetic-cholinergic) vasodilator mechanism predominates[41]. Therefore, the decrease in forehead blood flow as observed during the migraine headache is probably due to a release of vasodilator tone rather than to an increase in constrictor activity, and I am not acquainted with any action of ergotamine which would account for its interference with such a condition.

2.2. Neurokinin

Apart from increased flow in the external carotid territory of the cranial circulation, a local decrease in pain threshold also contributes to the pain of migraine, as shown by Wolff *et al.*[176] Generally speaking, a decrease in pain threshold can be due either to a central (see *e.g.* ref. 156) and/or to a peripheral mechanism.

Evidence for a peripheral mechanism was provided by Chapman *et al.*[25] who showed that subcutaneous perfusates of tender and aching regions of the head contained a substance which possessed, apart from vasodilator properties, the capacity to lower the pain threshold. The concentration of this substance which was provisionally called 'neurokinin', was closely related to the severity of the headache. Further studies revealed that the same substance is released into tissue fluid of the skin during antidromic dorsal root stimulation and during axon reflex flare, and in the dorsal horn of the spinal cord and its rostral extension in the nucleus of the trigeminal tract during (prodromic) sensory nerve stimulation[26]. The neurokinin is released together with its forming enzyme, a proteolytic enzyme, an increase in activity of which has been demonstrated in the cerebrospinal fluid during the migraine headache (see Chapter 5.3a).

Chapman *et al.* were unable to identify the exact nature of the neurokinin but they were able to distinguish it from known substances like acetylcholine, histamine, substance P, bradykinin, oxytocin, *etc.* It has been recently suggested that the neurokinin may well be a mixture of substances, containing both substance P and bradykinin[22].

The increase in flow in the external carotid vascular bed and the presence of neurokinin seem to be related because both correlate with the intensity of the pain[25, 167]. Furthermore, when administration of ergotamine is followed by subsidence of the headache, both external carotid blood flow and neurokinin levels decrease[25, 51, 167]. It is possible that the increase in flow and overdistension of the vessels initiate the release of neurokinin into

tissue fluid of the skin by stimulation of the perivascular nerve endings and activation of the axon reflex. This may also explain the increased proteolytic enzyme activity in the cerebrospinal fluid during the migraine headache because both the neurokinin and its forming proteolytic enzyme are released upon (noxious) sensory nerve stimulation not only in the peripheral tissues but also in the central nervous system *(vide supra).*

3. Cerebral circulation

Changes in the cerebral circulation occur during both the migraine headache and the aura, and will be dealt with here in succession. The relevant studies, with omission of the case reports, are schematically presented in table 2, in which it is noticeable that all studies employed the 133-Xenon clearance technique for the measurement of cerebral blood flow. The technique depends on the measurement of the rate of clearance of a freely diffusible, metabolically inactive isotope from the brain, which is proportional to the capillary blood flow. The radioactive isotope can be administered by inhalation, by intravenous injection, or by injection directly into the *internal* carotid artery. In the studies on migraine, only the first and the last modes of administration have been employed. The major disadvantage of the inhalation method is that the isotope is also introduced into the cranial tissues of the head, leading to inaccuracies in the cerebral blood flow measurements; the major drawback of the intracarotid injection method is, apart from inconvenience to the patient, that no information is obtained on the hemodynamic changes occurring in the perfusion territory of the basilar artery and its branches. This includes the occipital cortex which is thought to play an important role in the generation of the migraine aura (see Chapter 3.2).

3.1. Headache phase

During the migraine headache cerebral blood flow is increased, as shown by all but one study presented in table 2. As explained in the introduction to Chapter 2, changes in the cerebral circulation are probably of minor importance with regard to the generation of the headache. Also, the increase in cerebral blood flow continues beyond the duration of the headache, and it only gradually returns to normal levels[130]. The increase in cerebral blood flow is associated with a loss of autoregulation of the cerebral circulation, *i.e.,* cerebral blood flow is not maintained on lowering of the blood pressure[130], and with a decreased sensitivity of the cerebral vasculature to the dilating effects of CO_2[131]. The increase in cerebral blood flow may be the result of perception of the pain[71] and could outlast the painful stimulus when it is mediated by activation of the ascending reticular activating system (ARAS), *i.e.,* when it depends on a state of increased arousal. The possibility that the cerebral vasodilatation has approached its maximum could explain the decreased sensitivity of the cerebral vasculature to the dilating action of CO_2[131], and the failure of the cerebral vessels to further dilate, and

Table 2. Changes in cerebral blood flow, *i.e.*, Xenon clearance, during the aura and headache phase of the migraine attack*.

Author(s)	*Mode of Xenon administration*	*Aura phase*	*Headache phase*	*Comments*
O'Brien[107]	by inhalation		↓ (± 20%); n = 7**	changes did not correlate with the laterality of the headache
O'Brien[108]	by inhalation	↓ (23%); n = 7	↑ (8%); n = 10	changes during aura were bilateral and occurred diffuse over both hemispheres
O'Brien[109]	by inhalation	↓ (18.5%); n = 6		changes were generalized rather than focal, they outlasted the duration of the aura and did not correlate with the laterality of the symptoms
Skinhøj[152]	by intracarotid injection		5/6 ↑	
Mathew *et al.*[95]	by intracarotid injection	3/3 ↓	↑; n = 13	changes were diffuse over most of the hemispheres
Henry *et al.*[60]	by intracarotid injection		3/6 ↑	
Sakai and Meyer[130]	by inhalation		↑ (31.4%); n = 5 ↑; n = 13	

* Not included are the case reports on the subject, *i.e.*, refs. 36, 54, 105, 149, 151, 152 and 153.

** When the percentage change is presented, it means that the patients were studied both during the attack and in the attack-free period. In all other cases, the values obtained during an attack were compared to the normal values for that laboratory; the ratio refers to the number of patients of the population studied showing the change as indicated by the arrow. Otherwise, statistical analysis has been applied to the mean values.

thus, to further decrease cerebrovascular resistance, on lowering of the blood pressure[130]. Like the cerebral blood flow, the impaired autoregulation of the cerebral circulation also only slowly returns to normal, several days after the attack has resolved.

3.2. Aura phase

As mentioned in the introduction (Chapter 1), the migraine aura often involves symptoms of a visual nature which probably originate in the occipital cortex. A cortical origin of the symptoms is likely, but not necessary, because the disturbance usually involves both eyes in a homonymous way without affecting central vision, and because positive or excitation phenomena can occur among the symptoms[96]. Further evidence of a cortical localization of the process underlying the migraine aura is provided by the electroencephalographic studies of Engel *et al.*[38], in which irregular, slow waves were recorded from the contralateral occipital cortex during homonymous visual field defects in three cases of migraine.

The aura symptom most often referred to in the literature is the scintillating scotoma (see fig. 3). In its classical form, the scotoma begins near the center of vision as a small, gray area with indefinite boundaries. During the next few minutes the gray area slowly expands into a horseshoe, with bright zigzag lines appearing at the expanding outer edge. At first, these lines are small but they grow as the blind area expands and moves outwards, towards the periphery of the visual field. The configuration of the zigzag lines has invoked the comparison with a fortified wall and hence its name, *teichopsia* (τεῖχος, town-wall; ὄψις, vision)[1]. The zigzag lines oscillate in brightness with a frequency of approximately 10 Hz[59,87,96], giving a shimmering impression to the scotoma. This frequency of oscillation may be related to the alpha rhythm of the occipital cortex. The rate of expansion of both the arch formed by the zigzag lines and its associated band of blindness is quite slow, and it takes about 20-30 minutes to reach the limit of the visual field. The expansion of the figure has been shown by Hare to occur in an exponential way[59], and calculations have revealed that the underlying process travels over the striate cortex at a rate of approximately 3 mm/min[87, 121]. This particular rate of propagation led Milner[98] to seek the nature of the process in the spreading cortical depression. The phenomenon of spreading depression as described by Leão[88], is a wave of inhibition which travels over the cerebral cortex at a rate of 2 to 5 mm/min[50], and which is preceded by a short-lasting period of intense neuronal activity[50]. Propagation of the process over the occipital cortex at a constant rate is in agreement with the exponential expansion of the scintillating scotoma, since, towards the periphery, every part of the cortex represents a progressively larger part of the visual field.

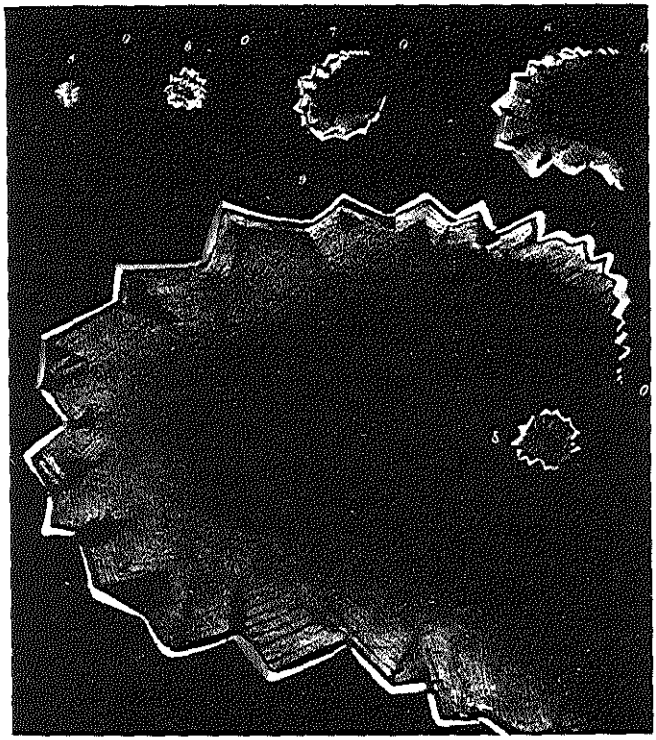

Fig. 3. Progression of a left-sided scintillating scotoma of migraine as seen in the dark, with the beginning of a secondary attack (σ) when the scotoma reached full development. The letter 'O' marks the center of vision in every drawing. (Reproduced from Airy[1].)

It has been suggested that the process underlying the scintillating scotoma is initiated by a local vasoconstriction of the calcarine artery, resulting in ischemia of the occipital cortex near the representation of the macula[96]. This notion is based, to a large extent, on the self-observations of the physicians Cahan (in Schumacher and Wolff[140]) and Hare[59], and on the studies of Marcussen and Wolff[93]. Cahan and Hare studied the effects of the cerebral vasodilator, amylnitrite[154], on their own visual migraine auras, and observed a transient regression of the symptoms after inhalation of the amylnitrite. Marcussen and Wolff[93] studied the effects of another potent dilator of the cerebral vascular bed, CO_2, on the migraine aura of 15 patients during 25 attacks. According to the authors, administration of 10% CO_2 in air resulted, in all cases, in transient clearing of the symptoms, which returned to their former intensity within five minutes after the inhalation of the gas was discontinued.

Although these observations can indeed be best explained by supposing that a vascular event, vasoconstriction, underlies the migraine aura, the question remains as to how this vascular event is related to the above mentioned phenomenon of spreading cortical depression and excitation. It has been suggested that the vasoconstriction and the resultant cortical hypoxia trigger the ionic changes responsible for the initiation of the spreading depression, which, after its initiation, represents a self-propagating process (see *e.g.* ref. 85, p. 164). However, although hypoxia leads to a local depression of the 'spontaneous' cortical neuronal activity, it does not give rise to spreading depression[89]. In addition, the Xenon-clearance studies of the cerebral circulation do not support the notion of a localized decrease in cerebral blood flow as the cause of the migraine aura. They indicate, as shown in table 2, that during the migraine aura the cerebral blood flow is decreased diffusely over both hemispheres despite the focal character and lateralization of the symptoms.

Although hypoxia is apparently not a cause of spreading depression[89], it has been shown to intensify the process[50, 89], and, therefore, possibly also increases the sensitivity of the cortical tissues to its occurrence. The reverse may be true for *hyper*oxia which might slow down the process or even extinguish it and hasten the recovery of cortical neuronal activity from the depression. This could explain the beneficial effect on the aura symptoms of inhalation of CO_2 and amylnitrite, as both agents increase cerebral blood flow, thereby increasing oxygen delivery to the brain. In addition, the generalized decrease in cerebral blood flow which takes place during the aura phase of the migraine attack could be the precipitating factor for the generation of the process which underlies the aura, *i.e.*, the spreading cortical depression heralded by neuronal excitation, in a (genetically determined) susceptible part of the cerebral cortex.

4. Gastrointestinal tract

Symptoms like nausea and vomiting, which frequently accompany the migraine headache, are easily recognizable manifestations of gastrointestinal dysfunction. A concealed consequence of the disturbance in gastrointestinal function during the migraine attack is the delayed absorption of orally administered drugs, as has been recently revealed by the studies of Volans[170, 171] and Orton[111]. Volans[170] studied in 42 patients the absorption of effervescent acetylsalicylic acid (aspirin) during the migraine attack and observed it to be below the 2½% confidence limit for normal individuals in 19 (45%) cases, of which 14 were restudied during the attack-free interval and showed an absorption not significantly different form normal. The latter suggests that the gastrointestinal dysfunction is a feature of the attack rather than a peculiarity of migraine sufferers. Orton[111] reported a similar disturbance in the absorption of ergotamine.

While investigating the relationship between the clinical features of the attack and the disturbed absorption, Volans found that poor absorption became more frequent with increasing severity of both the headache and the nausea. However, the poor absorbers were distributed almost equally between the cases of classical and common migraine.

It has been suggested that the impaired absorption is due to decreased motility of the upper gastrointestinal tract, the latter being shown by the radiological studies of Kaufman and Levine[80] and Kreel[83]. These studies revealed that during the migraine attack there is atony and dilatation of the stomach with contraction of the pylorus, while repeated studies during the attack-free interval demonstrated normally functioning stomachs. The assumption that disturbed motility of the gastrointestinal tract underlies the impaired absorption is supported by the studies with metoclopramide. Metoclopramide is an anti-emetic drug with the unique property of increasing gastric motility and synchronizing antral and duodenal contractions[74], thereby speeding gastric emptying[67]. Volans[171] observed that when the acetylsalicylic acid is administered together with 10 mg metoclopramide i.m., the rate of absorption of the acetylsalicylic acid during the migraine attack is not significantly different when compared to the attack-free interval or to healthy volunteers.

5. Biochemistry

The biochemical data available concern predominantly the headache phase of the migraine attack. This is probably due to the fact that the headache may last from several hours to a few days allowing extensive biochemical investigation, whereas the aura is generally short in duration. Biochemical variables have been studied in the urine, blood and cerebrospinal fluid and will be reviewed here according to the body fluid in which they have been determined. The presentation of the data will be followed by a discussion of their implications (Chapter 5.4).

5.1. Urine

Diuresis is decreased during the migraine headache and increases with subsidence of the pain[104, 138]. The excretion in the urine of 5-hydroxyindoleacetic acid (5-HIAA) and 3-methoxy-4-hydroxymandelic acid (VMA) – the main metabolites of serotonin and of the catecholamines, respectively – is increased (table 3) while the excretion of serotonin is not significantly altered[30, 146]. Kimball and Goodman[82] reported an increase in the urinary excretion of histidine during the migraine headache. However, Sjaastad *et al.*[150] observed no differences in the excretion of the amino-acids, including histidine, in the urine during the headache, when compared to the attack-free interval, and fould all values to be within normal limits. Torda and Wolff[166] demonstrated an increase in the urinary excretion of 17-ketosteroids during the headache phase which was normal during the aura.

5.2. Blood

a. *Serotonin* (5-hydroxytryptamine, 5-HT)

Sicuteri's[148] observation in 1961 of an increase in urinary excretion of 5-HIAA during the migraine headache has directed attention towards the serotonin in the blood. Blood contains approximately 75 ng serotonin per ml, of which 60 ng is stored in the platelets, the remaining 15 ng circulating free in the plasma[115]. The serotonin stored in the platelets is physiologically inactive but is released upon activation of the platelets[97] to participate in the process of platelet aggregation and hemostasis. Whether the free sero-

Table 3. Urinary excretion of amine metabolites during the migraine headache*.

	Author(s)	*Controls*	*HA-free*	*Headache*
5-HIAA (mg/day)	Sicuteri *et al.*[148]		4.0 (0.5-8.6) n = 15	10.6 (2.0-25.5)
	Curran *et al.*[29]	5.61 (3.5-11.2) n = 10	6.94 (0.2-6.9) n = 16	13.1 (1.9-15.4)
	Sicuteri[146]		3.9	5.1
	Kangasniemi *et al.*[79]	3.1 (1.6-4.0) n = 5	3.2 (2.3-3.9) n = 5	3.4 (1.7-5.2)
	Deanovic *et al.*[30]		3.59 (2.5-6.63) n = 13	5.32 (2.71-8.96)
VMA (mg/day)	Curran *et al.*[29]	3.2 (1.1-6.8) n = 10	2.1 n = 5	3.1 n = 9
	Sicuteri[146]		2.7	5.6
	Kangasniemi *et al.*[79]	8.3 (1.6-15.2) n = 6	8.3 (6.0-10.4) n = 5	7.9 (2.0-11.8)

* The data are presented as means with the range given in parentheses.

tonin which is present in the plasma is of physiological significance remains a matter of speculation. Those who regard the serotonin in the blood as an important (causal) factor in the pathophysiology of the migraine attack, ascribe to it a tonic control of the cephalic vascular bed (see Chapter 5.4).

There is a high level of agreement with regard to the changes in blood, plasma and platelet serotonin which occur during the migraine headache. Hilton and Cumings[63] and Rydzewski[128] reported a decrease in the blood serotonin level which is determined by a decrease in both the platelet serotonin content (table 4) and the plasma serotonin level[155]. The decrease in platelet serotonin content seems to result from a change in plasma constitution[8, 10, 35, 100] due to the appearance of a factor with a molecular weight of less than 50,000 daltons[10]. Whether the plasma factor involved affects platelets of migraineurs only and leaves those of non-migrainous subjects untouched, remains a matter of dispute (*cf.* refs. 35 and 100).

Table 4. Changes in platelet serotonin content ($\mu g/10^9$ platelets) during the migraine headache*.

Author(s)	*Controls*	*HA-free*	*Headache*
Curran *et al.*[29]	0.90 (0.34-1.71) n = 21	0.73 (0.19-1.34) n = 28	0.44 (0.05-1.24) n = 21
Anthony *et al.*[7]	0.81 (0.22-1.26) n = 9	0.72 (0.38-0.98) n = 21	0.45 (0.19-0.86)
Hinterberger *et al.*[64]		0.92 ± 0.15 n = 9	0.51 ± 0.27 n = 30
Anthony *et al.*[8]		1.15 (0.53-1.69) n = 8	0.50 (0.18-1.02)
Anthony and Lance[9]	0.98 (0.62-1.49) n = 5	0.50 (0.37-0.72) n = 10	0.35 (0.26-0.62)
Anthony[3]		0.46 ± 0.41 n = 13	0.32 ± 0.23
Anthony and Lance[10]		0.46 n = 30	0.34
Anthony[4]		0.49 n = 20	0.24
Sommerville[155]		0.63 (0.34-0.93) n = 6	0.34 (0.16-0.71)
Rolf *et al.*[123]	0.76 ± 0.17 n = 11	0.68 ± 0.24 n = 16	
Anthony[5]		0.46 n = 10	0.36
Mück-Seler *et al.*[100]	0.55 ± 0.24 n = 25	0.82 ± 0.36 n = 6	0.67 ± 0.26

* The data are presented as means ± standard deviation or the range, the latter being given in parentheses.

b. *Tryptophan*

Tryptophan is the precursor of serotonin and is present in the plasma either free or bound to albumin. Hyyppä and Kangasniemi[70] studied migraineurs during the headache and in the attack-free interval and did not observe any significant changes in the plasma free tryptophan level or in the ratio of

free to total plasma tryptophan. In agreement with this, Salmon *et al.*[132] found that the plasma free tryptophan level was not significantly changed during the headache when compared to the attack-free interval. However, when compared to the control group, the plasma free tryptophan level during the migraine headache was significantly increased. Because this increase in plasma free tryptophan level was not accompanied by any increase in plasma total tryptophan concentration, it indicates a shift from albumin-bound to plasma free tryptophan.

c. *Platelets*

As described above, the platelets lose at least a part of their serotonin content during the migraine headache. With regard to the functional state of the platelets during the migraine attack, it has been reported that their adhesion and aggregation response to ADP (adenosine diphosphate), adrenaline, serotonin or thrombin is enhanced during the aura phase[31]. During the headache phase, platelet adhesiveness remains increased; however, the aggregation response to ADP and adrenaline is decreased while that to serotonin and thrombin remains within normal limits[31]. Hilton and Cumings[63] also reported a normal aggregation response to serotonin with platelets obtained during the migraine headache. Couch and Hassanein[28] and Deshmukh and Meyer[31] studied platelet aggregability to ADP during the attack-free interval and found it to be increased. In addition, both studies revealed a lower threshold for the platelet release reaction, *i.e.*, a secondary aggregation response to ADP was significantly more frequent with platelets obtained during the attack-free interval than with those obtained from healthy controls.

Serotonin is stored in the platelets by forming aggregates with calcium, ATP (adenosine triphosphate) and ADP. The platelet ATP content has been shown to decrease during the migraine headache although the changes never reached the level of statistical significance[8, 64, 129]. The same applies, to some extent, to the platelet ADP content[64, 129].

Upon activation, platelets release, apart from serotonin, ATP, ADP, and several specific and non-specific proteins, including β-thromboglobulin (fig. 4). The plasma level of this platelet-specific protein has been shown by Gawel *et al.*[43] to undergo a significant two-fold increase during the migraine headache.

Platelets do not possess the ability to synthesize serotonin because of the absence of tryptophan hydroxylase activity[99]. They acquire serotonin, which is probably synthesized to a large extent in the enterochromaffin cells of the gut, by active uptake from the plasma. Platelets do, however, possess the ability to inactivate serotonin by oxidative deamination. The responsible enzyme is monoamine oxidase (MAO) which, in human plate-

lets, is mainly of the B-type with a high affinity for tyramine, tryptamine and β-phenylethylamine and less affinity for serotonin. This spectrum of affinities probably relates to the biological function of the platelets, *i.e.*, to store serotonin (and not to destroy it) and to release it upon activation. Upon release from the platelets, the serotonin is very efficiently removed from the circulation by binding and conversion to 5-HIAA[12], probably to a large extent in the lungs[46]. Sicuteri *et al.*[147] were the first to demonstrate that platelet MAO activity is decreased in migraine sufferers, when compared to healthy controls, a decrease which already exists in the attack-free interval[23, 133] and which becomes more pronounced during the headache[47]. The decrease in platelet MAO activity does not, however, reflect a generalized (peripheral) defect in oxidative deamination, as revealed by the normal output of β-hydroxyphenylacetic acid after an oral load of tyramine[177].

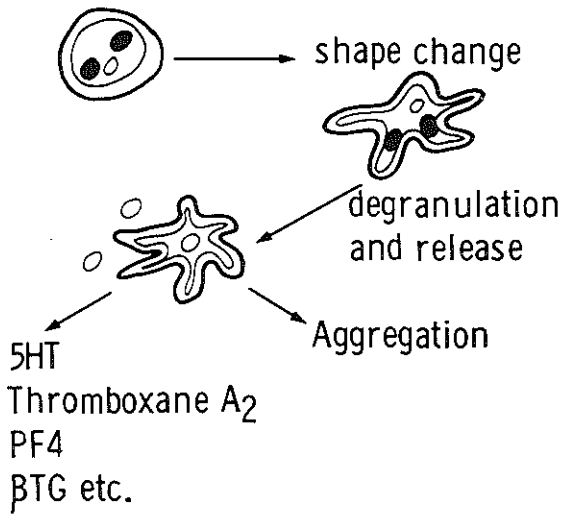

Fig. 4. The platelet release reaction. Upon activation, platelets undergo a change in shape and degranulation which is associated with release of several substances into the plasma, among others, serotonin, ATP, ADP, thromboxane A_2 (a prostaglandin with potent platelet activating and vasoconstricting properties), platelet glandin with potent platelet activating and vasoconstricting properties), platelet factor 4 (PF_4, a heparin neutralizing protein), and β-thromboglobulin (βTG, a platelet-specific protein with prostacyclin inhibitory action). (Reproduced from Gawel et al.[43])

d. *Free fatty acids*

Fatty acids, not esterified by glycerol, cholesterol or lysolecithin, are present in the plasma loosely bound to albumin. With regard to migraine, Anthony showed, in several studies[3-6], that the level of free fatty acids in the plasma increases during the headache. In addition, Hockaday *et al.*[65] and Shaw *et al.* [142] found the plasma free fatty acid level, before and following administration of glucose, to be significantly higher during the migraine headache than during the attack-free interval.

Anthony[3, 4] determined both the platelet serotonin content and the plasma free fatty acid level in 33 migraineurs in order to study the correlation between the changes in the two variables, since certain fatty acids can activate platelets and induce serotonin release[72, 144]. Application of the Chi-square test to Anthony's data reveals that the changes in the two variables are independent (table 5), which makes it unlikely that the rise in free fatty acids in the plasma is responsible for the activation of the platelets and the release of serotonin.

Table 5. Analysis of a possible correlation between plasma free fatty acid levels and platelet serotonin content using the data of Anthony[3, 4]

platelet serotonin content \ plasma free fatty acid level	n.c.	↑	tot.
n.c.	1	8	9
↓	5	19	24
tot.	6	27	33

$$X^2 = 0.42 < X^2_{0.95} = 3.84$$

n.c. = no change; ↑ = increase; ↓ = decrease; tot. = total.

e. *Prostaglandins*

Prostaglandins are products of long-chain unsaturated fatty acids which function as local tissue hormones. In particular, the prostaglandins of the E-series are potent vasodilators, and intravenous infusion of prostaglandin E_1 in man has been shown to lead to a throbbing (vascular) headache[23a]. This prompted Anthony[4] to determine the prostaglandin E_1 levels in cubital venous and arterial blood samples during the migraine headache. However, no significant changes were observed.

f. *Catecholamines*

The plasma adrenaline level does not significantly change during the migraine headache[40]. The plasma level of noradrenaline, however, decreases during the initial phase of the attack, to reach significance 1 to 2 hours before the headache acquires maximal intensity, increasing thereafter[40]. Hsu *et al.*[69] observed a significant increase in plasma total catecholamine levels, *i.e.,* adrenaline plus noradrenaline, in the three hours before awaking with migraine when compared to the similar three hours in migrainous subjects not awaking with headache. The increase in catecholamines was primarily due to the change in the noradrenaline fraction.

The plasma activity of dopamine-β-hydroxylase is, possibly, a better index of the level of sympathetic activity than the plasma cathecholamine level. Dopamine-β-hydroxylase is the enzyme responsible for the conversion of dopamine to noradrenaline and is stored together with noradrenaline in the sympathetic nerve endings. Both are released simultaneously upon nerve stimulation, followed by a rapid re-uptake of most of the released noradrenaline by the adrenergic nerve terminals. In relation to migraine, Anthony *et al.*[6] demonstrated a significant increase in plasma dopamine-β-hydroxylase activity during some stage of the headache phase in 19 out of 20 patients studied. However, migraineurs already exhibit increased dopamine-β-hydroxylase activity during the attack-free interval, when compared to non-migrainous healthy controls, as shown by Gotoh *et al.*[48]

g. *Cyclic adenosine monophosphate (c-AMP)*

Controversy exists with regard to the changes in plasma c-AMP levels which occur during the migraine headache. While Welch *et al.*[175] did not observe any changes, Anthony *et al.*[6] reported a two-fold increase in the plasma level of this nucleotide.

h. *Hormones*

Hinterberger *et al.*[64] determined the plasma levels of 11-hydroxycorticosteroids and found that the levels during the migraine headache were not significantly different from those during the attack-free interval. More recently, Nattero *et al.*[103] measured the plasma levels of two of the 11-hydroxycorticosteroids, cortisol and aldosterone. While the plasma cortisol levels were no different from normal, the 24-hour plasma aldosterone curve showed an inverted profile during the migraine headache (menstrually related), the onset of the pain being followed by a drop in plasma aldosterone level. No changes were noted in the plasma renin activity. Shaw *et al.*[142] measured the plasma insulin levels during the migraine headache and found that the resting plasma levels were not significantly different from those measured during the attack-free interval. However, when the release of insulin from the pancreas was promoted by intravenous infusion of glucose, significantly less insulin was secreted during the headache when compared to the attack-free interval. Plasma prolactin levels during the migraine headache and the attack-free interval remain essentially the same[172].

5.3. Cerebrospinal fluid (CSF)

a. *Enzymes*

Enzyme activity in the CSF has been studied by Chapman and Wolff[27], Barrie and Jowett[13], Kangasniemi *et al.*[78] and Brisied *et al.*[19]. In general, the data on enzyme activity in het CSF during the migraine attack are confusing. However, Chapman and Wolff[27] and Kangasniemi *et al.*[78] seem to agree with regard to the increase in protease (proteolytic enzyme) activity during the migraine headache (see also Chapter 2.2), when compared to the attack-free interval, Kangasniemi *et al.*[78] having recorded an increase in CSF protease activity during the migraine attack from 8.3 to 77.2 nmol/mg protein/hr.

b. *Biogenic amine metabolites*

The data on the CSF levels of 5-HIAA are presented in table 6 from which it can be concluded that no consistent changes in CSF 5-HIAA levels occur during the migraine headache. Kangasniemi *et al.*[79] also determined homovanillic acid (HVA) – the main metabolite of dopamine – levels in the CSF and found no significant differences between migraine sufferers and control subjects, either in the attack-free interval or during the migraine headache.

Table 6. Changes in CSF 5-HIAA levels (ng/ml) during the migraine headache*.

Author(s)	*Controls*	*HA-free*	*Headache*
Kangasniemi *et al.*[79]	26.1 ± 7.3 n = 6	23.0 ± 13.6 n = 8	26.1 ± 13.1 n = 14
Poloni *et al.*[118]	31.1 ± 6.9 n = 5	31.2 ± 2.7 n = 5	25.2 ± 4.5
Hyyppa and Kangasniemi[70]		21.8 ± 14.4 n = 18	27.7 ± 12.7

* The data are presented as means ± standard deviation.

c. *Gamma-aminobutyric acid (GABA) and c-AMP*

Welch *et al.*[175] studied GABA and c-AMP levels in the CSF and found both to be significantly increased during the migraine headache when compared to the attack-free interval.

d. *Lactate and bicarbonate*

Skinhøj[152] measured the levels of lactate and bicarbonate in the CSF during the migraine attack (most patients were in the headache phase) and found the lactate level to be significantly increased and the bicarbonate level significantly decreased. However, when the two patients with severe prodromal symptoms, who were not diagnosed as having classical or common migraine (and probably suffered from complicated migraine), are omitted from the series, the differences are probably no longer significant. In confirmation of this, Schrader and Russell[139] also studied CSF lactate and bicarbonate levels in a group of migraineurs during a typical headache attack and found that the levels were not significantly different, when compared to a control group.

5.4 Discussion

As is evident from the data presented above, several biochemical aberrations already exist in the attack-free interval, which are: increased platelet aggregability with a low threshold of the platelets for the release reaction[28, 31], decreased platelet MAO(B) activity[23, 133] and increased plasma dopamine-β-hydroxylase activity[48]. The aberrations seem to deviate further from normal during the migraine headache, when the platelets undergo a release reaction. The release reaction is partial and results in decreased aggregability of the platelets[31], a reduction in platelet serotonin (table 4), ATP[8, 64, 129] and ADP[64, 129] content and an increase in the plasma β-thrombo-

globulin level[43]. The release reaction is probably restricted to the headache phase and does not occur during the aura. This can be inferred from the fact that induction of a partial release reaction is followed by a decrease in platelet sensitivity to aggregating agents[58] and, while platelet aggregability is high during the aura, it is low during the headache phase[31].

There are no indications that the platelet release reaction and the liberation of serotonin from the platelets are followed by a rise in plasma serotonin level. When the plasma serotonin level was measured during the migraine headache, it was decreased rather than increased[155]. The serotonin released from the platelets is probably rapidly removed from the circulation and converted to 5-HIAA, which is excreted in the urine (table 3). The view is, thus, maintained that the decrease in plasma serotonin level is responsible for the vascular changes in the head which underlie the pain (see *e.g.* ref. 8). This concept is based on the assumption that the serotonin in the plasma exerts a tonic influence on the cephalic vascular bed. If this assumption is correct, the decrease in plasma serotonin level would bring about constriction of the arterioles and dilatation of the larger arteries[55]. The constriction of the arterioles would then result in tissue ischemia and a sterile inflammatory reaction, creating a condition in which the dilatation and overdistension of the larger vessels becomes painful. However, there are no indications that the plasma serotonin level does exert a tonic influence on the cephalic vascular bed, and the changes in the cranial circulation – which are generally believed to be causally related to the headache (see introduction to Chapter 2) – are, apart from their unilateral character, too complex (see Chapter 2.1) to be explained by such a simple humoral mechanism.

The activation of the platelets during the migraine headache seems to be due to the appearance of a factor with a molecular weight of less than 50,000 daltons[10] in the plasma[8, 10, 35, 100]. Many substances would fit into that category, ranging from simple molecules to small proteins. Fatty acids, the levels of which increase in the plasma during the migraine headache[3-6] and which are known to activate platelets and to cause serotonin release[72, 144], have been implicated here. However, when I analyzed Anthony's data on the changes in the plasma free fatty acid level and the platelet serotonin content (table 5), I did not find support for this idea. Therefore, the increase in plasma free fatty acid level has been separated from the platelet activation cascade in the schematic representation of the biochemical changes during the migraine headache (fig. 5). Further support for the independency of the increase in plasma free fatty acid level and the decrease in platelet serotonin content is provided by the observation that raising the plasma free fatty acid level leads to facilitation of the *primary* aggregation response while it does *not* affect the *secondary* aggregation response, *i.e.*, the aggregation response dependent on the platelet release reaction[21].

The increase in plasma free fatty acid level during the migraine headache[3-6] is probably the result of increased activity of the sympathetic nervous system, as indicated by the increase in plasma dopamine-β-hydroxylase activity[6] and the increase in urinary excretion of the catecholamine metabolite, VMA (table 3). Like many other metabolic effects of the catecholamines, the increased lipolysis[142] is mediated through activation of adenylate cyclase and formation of c-AMP. Other observations which support the notion of increased activity of the sympathetic nervous system during the migraine headache are the decreased insulin secretion in response to glucose administration[142] and the tendency to increased heart rate[66]. The platelet activation cascade may also be linked to the increased adreno-sumpathetic activity because both adrenaline[97, 106] and noradrenaline[56, 106] activate platelets, and it is tempting to suggest that the low molecular weight platelet activating plasma factor mentioned above may be a catecholamine.

It is probably also possible to explain the decreased diuresis[104, 138] on the basis of increased sympathetic nervous activity, while the decrease in plasma aldosterone level[103] may be a compensatory reaction to the water retention resulting from the decreased diuresis. The increased ratio of free to total plasma tryptophan[132] is probably related to the increase in plasma free fatty acid level[3-6], as free fatty acids compete with tryptophan for binding to albumin. The decreased platelet MAO activity[47] and the increase in urinary excretion of 17-ketosteroids[166] I am unable to explain and, therefore, they are not included in the framework presented in figure 5. The decreased platelet MAO activity[23, 133], together with the increased platelet aggregability[28, 31] and the increased plasma dopamine-β-hydroxylase activity[48] of the attack-free interval may constitute hereditary traits and/or peculiarities of the migraine sufferer. They may also be the peripheral reflections of the genetically determined 'migraine diathesis'.

The only significant findings with regard to the biochemical changes in the cerebrospinal fluid during the migraine headache are an increase in protease activity[27, 78] and increased levels of GABA and c-AMP[175]. The increased GABA and c-AMP levels have been interpreted by the authors as consequent to the cerebral ischemia which precedes the headache in the migraine attack (see Chapter 3.2), but it should be mentioned that most patients studied by Welch *et al.*[175] suffered from common migraine!

In conclusion, many of the biochemical changes seen in association with the migraine headache may be attributed either directly or indirectly to enhanced adreno-sympathetic activity. A possible interpretation of the available data on this basis is presented in figure 5.

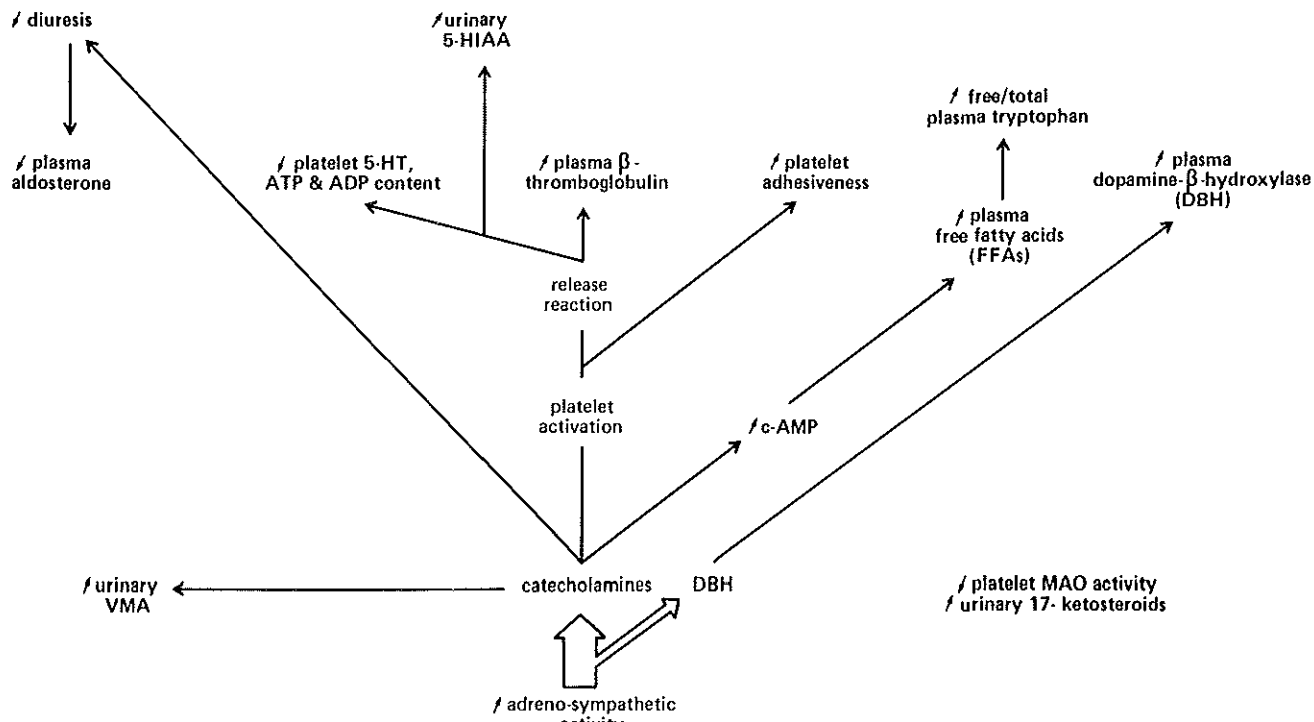

Fig. 5. Biochemical changes during the migraine headache: A sympathetic interpretation. ↑ = increase; ↓ = decrease.

Part II

Experimental data on the action of antimigraine drugs

6. Introduction

The notion that dilatation in the external carotid vascular bed plays an important role in the genesis of the migraine headache has gained general acceptance since Graham and Wolff[51] demonstrated in 1938 that pain relief by ergotamine parallels a reduction in the amplitude of pulsation of the branches of the external carotid artery (fig. 2). Subsequently, the constrictor action of ergotamine on the external carotid vascular bed has been confirmed in the dog[134, 137] and monkey[102]. Saxena and De Vlaam-Schluter[137] compared the effect of ergotamine on the carotid vascular bed with that on the femoral, superior mesenteric, renal, vertebral and coronary beds in the dog, and found the drug to be significantly more potent on the carotid and femoral vascular beds than on the others, a selectivity which may be relevant to its beneficial effect in migraine.

Johnston and Saxena[75] further investigated the vascular selectivity in the action of ergotamine by studying the effect of the drug on the body distribution of cardiac output in the cat, using 15 μm microspheres which were injected into the left atrium. They observed that ergotamine, studied in doses up to 20 μg/kg i.v., significantly decreased the cardiac output by reducing heart rate, while stroke volume remained unchanged. In addition, ergotamine changed the proportional distribution of cardiac output over the various tissues and organs, in such a way that stomach, liver, pancreas, uterus and body skin received a significantly increased fraction of cardiac output, while the lung fraction was significantly decreased.

Because of their double blood supply, the lungs receive microspheres by two ways, *i.e.*, through the bronchial and through the pulmonary arteries, the blood in the pulmonary artery carrying the microspheres which escape entrapment in the peripheral vascular beds by passing through the arteriovenous anastomoses (see Chapter 6.1). Therefore, the authors suggested that the decrease in the fraction of cardiac output reaching the lungs was due to a reduction in the number of microspheres passing through the arteriovenous anastomoses. This assumption was supported by the finding that the number of microspheres in the blood drawn from the external jugular vein at the time of the microsphere injection was decreased after administration of ergotamine.

A selective constrictor action of ergotamine on the arteriovenous anastomoses can indeed explain the above described vascular selectivity in the action of the drug because both head and limbs are rich with regard to the presence of arteriovenous anastomoses. Furthermore, such an action is in agreement with what had been reported on the basis of histological

studies in the rabbit's ear by Stolzenburg[162] in 1937, and it indirectly supports Heyck's view on the pathophysiology of the migraine headache: It is not a simple vasodilatation but, more specifically, the opening of arteriovenous anastomoses that constitutes the basic hemodynamic derangement underlying the migraine headache[61].

The involvement of arteriovenous anastomoses in the pathophysiology of the migraine attack was further studied in the experimental research to be described in Chapters 7 and 8, and therefore, will be dealt with more elaborately here.

6.1 Arteriovenous anastomoses in migraine

Arteriovenous anastomoses, an example of which is shown in figure 6, are sites of communication between the arteriolar and venular sides of the circulation through which blood can bypass the capillary bed. They are morphologically characterized by a clear transition from artery into vein and

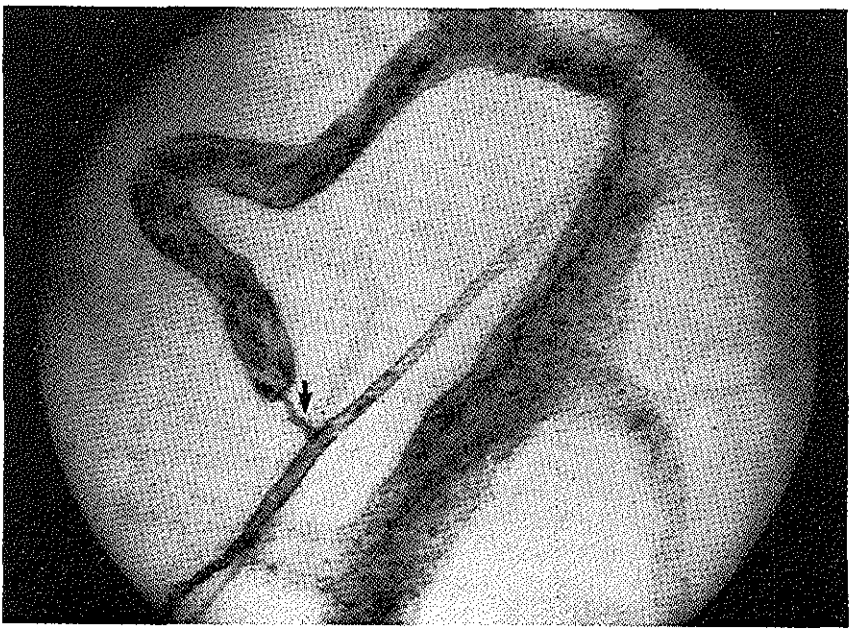

Fig. 6. Example of an arteriovenous anastomosis (arrow), connecting an arteriole (right) with a venule (left), as observed in the human dura mater. (Reproduced form Rowbotham and Little[124].)

possess, at the arterial side, a thick multilayered and sphincter-like musculature with a dense innervation. The diameter of the arteriovenous anastomoses varies but is in general larger than 20 μm[52], which makes the arteriovenous anastomoses wider than the capillaries which measure from 5 to 10 μm[16].

The first to point to the presence of arteriovenous anastomoses in man was Sucquet[163], who provided indirect evidence for the existence of arteriovenous anastomoses as far as the head is concerned, in the lips, nose, forehead, cheeks and ears. Berlinerblau[14] and Hoyer[68], who applied the same resin injection technique as Sucquet, however, failed to confirm his observation. More recent studies on the presence of arteriovenous anastomoses in the human head have not only confirmed Sucquet's findings[24, 94, 116, 119, 165], but also extended them to the deep pial plexus of the brain[125] and to the dura mater[81, 124]. The presence of arteriovenous anastomoses in the forehead and dura mater is pertinent here, the latter being to a large extent vascularized by the middle meningeal artery which is a branch of the external carotid artery.

Opening of arteriovenous anastomoses may conceivably lead to a painful condition like migraine because of an interaction between two mechanisms (see fig. 7): 1. The opening of arteriovenous anastomoses will give rise to a decrease in peripheral resistance leading to exaggerated pulsations in the feeding arteries, and, at the same time, the increased arterial pulse wave will be transmitted, unattenuated, to the venous side of the circulation. 2. As the decrease in resistance occurs at a point prior to the cap-

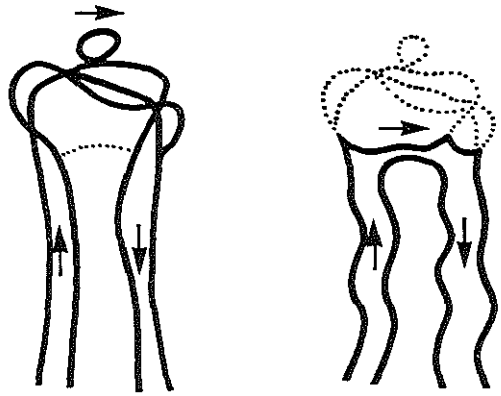

Fig. 7. Heyck[61] hypothesized that arteriovenous anastomoses are intimately involved in the vascular changes underlying the migraine headache, and that, while of minor importance under normal conditions (left), the arteriovenous anastomoses open widely at the onset of the attack (right). (Reproduced from Prusiński[120].)

illary bed, no more blood will enter the (high resistance) capillaries, resulting in tissue ischemia and in the formation of pain-provoking substances, which will render the increased pulsation and overdistension of the vessels painful.

In order to support his above mentioned hypothesis, Heyck measured the arteriovenous oxygen content difference over the cranial circulation by sampling blood from the external jugular vein, which he assumed to be an index of the *proportional shunt fraction.* The data, presented in figure 8, show that the arteriovenous oxygen content difference was significantly lower on the side of the headache, *i.e.,* a greater proportion of arterial blood entered the venous circulation without being submitted to oxygen extraction in the capillary bed, when compared to the nondiseased side. Furthermore, when administration of *dihydro*ergotamine led to subsidence of the headache, this beneficial effect was associated with an increase in the arteriovenous oxygen content difference, thus, according to Heyck, indicating closure of arteriovenous anastomoses.

I have explicitely stated that Heyck assumed the arteriovenous oxygen content difference to be an index of the *proportion,* and not of the total amount, of arterial blood flow shunted through the arteriovenous anasto-

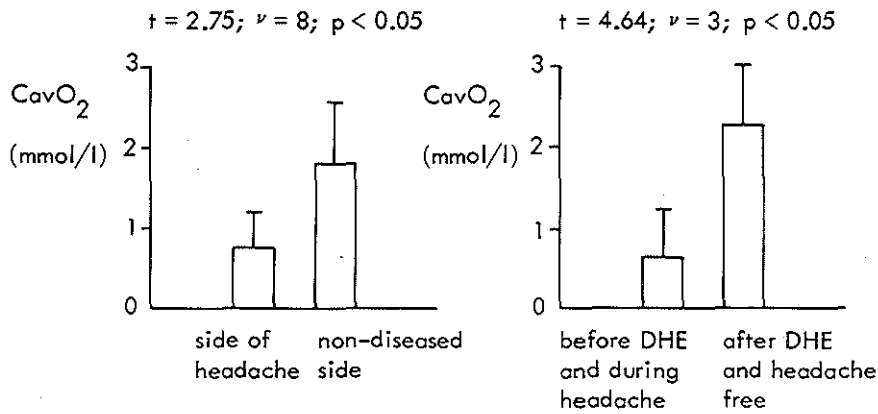

Fig. 8. The arteriovenous oxygen content difference ($CavO_2$) over the cranial circulation, the venous samples having been obtained from the external jugular vein. In the left hand diagram the sides of the head are compared in cases of unilateral headache, and in the right hand diagram the side of the head affected by the pain is studied before and after administration of dihydroergotamine (DHE) and subsidence of the headache. (Data obtained from Heyck[61].)

moses. This is because an increase in the proportional shunt flow is only produced by opening of arteriovenous anastomoses, while an increase in the absolute flow may be a product of either the opening of arteriovenous anastomoses or arterial dilatation. Arterial dilatation, however, leads not only to an increase in flow through the arteriovenous anastomoses, but also to an increase in capillary flow, and it is the supposed *decrease* in capillary flow, despite increased filling of the arteries, which made Heyck postulate the involvement of arteriovenous anastomoses in the pathophysiology of the migraine headache.

As I have pointed out in Chapter 2.1, the decrease and increase in blood flow during the migraine headache occur in different parts of the cranial circulation, and thus, by themselves, form no basis for the implication of arteriovenous anastomoses. Nevertheless, we thought it worthwhile to further investigate Heyck's hypothesis because of (i) the abundance of arteriovenous anastomoses present in the human dura mater[81, 124], (ii) the implication of the vasculature of the dura mater, as part of the external carotid vascular bed, in the genesis of the migraine headache (see introduction to Chapter 2), (iii) the possibility that opening of arteriovenous anastomoses leads to a painful condition like migraine *(vide supra),* and (iv) the pharmacology of the potent antimigraine drug, ergotamine, as presented up till now. We have, therefore, studied the effects of the antimigraine drugs, ergotamine, dihydroergotamine, isometheptene and methysergide, on carotid blood flow, on the distribution of carotid blood flow throughout the cephalic circulation, paying special attention to the arteriovenous anastomoses, and on the arteriovenous oxygen content difference over the cranial circulation, sampling blood from the external jugular vein.

For practical reasons, the experiments were performed in cats. However, one may question the validity of this model for a study of migraine because the cephalic circulation of the cat differs considerably from that of man and obviously cats do not suffer from migraine! In the cat, the internal carotid artery is a vestigial structure, reduced to a fibrotic string, and the brain receives blood from the external carotid artery. The communication between the external carotid artery and the circle of Willis is established through the *rete mirabile conjugatum,* a complex network of fine arteries intertwined in a venous plexus surrounding the internal maxillary artery, not present in man.

While histological studies have shown that the rete *does* contain arteriovenous anastomoses[45], these are quantitatively of minor importance in comparison to those in the facial structures of the cat, as shown by the angiographic studies of Kumar *et al.*[84]. As there is ample evidence for the presence of arteriovenous anastomoses in the same structures in man *(vide supra),* at least with regard to the shunt data, extrapolation from cat to man seems justified.

7. Methods and materials

The distribution of carotid blood flow was studied by means of isotope-labeled plastic microspheres which were injected directly into the carotid artery. The microspheres, when introduced into the arterial circulation, are distributed throughout the tissues in proportion to the local blood flow, provided that blood and microspheres mix homogeneously[57, 62]. Microspheres measuring 15 ± 5 (range) μm in diameter were chosen in order to be able to distinguish capillary flow from flow through the arteriovenous anastomoses. Microspheres which measure 15 μm in diameter will be trapped in the capillaries of the tissues (5-10 μm) but will pass through most arteriovenous anastomoses (> 20 μm) to appear in the venous circulation. The microspheres in the venous blood will ultimately become trapped in the lungs, therefore not re-entering the arterial system in any appreciable amount[39, 76, 173]. This is schematically represented in figure 9. The heart and kidneys were removed and assayed in every experiment to ascertain complete entrapment of the microspheres in the lungs.

7.1. General procedures

Forty mongrel cats with a mean weight of 2.9 ± 0.8 (SD) kg were anesthetized by intraperitoneal injection of a mixture of α-chloralose (60 mg/kg) and urethane (700 mg/kg) in saline. The trachea was cannulated and the animals were allowed to ventilate spontaneously. A cannula was placed in the abdominal aorta through an incision in the left femoral artery and the blood pressure was recorded using a Statham P23AC transducer. The adjacent femoral vein was cannulated for drug administration. The transverse (facial) vein was cannulated in the direction of the left external jugular vein. The left lingual artery was exposed and cannulated retrogradely for the injection of microspheres into the left external carotid artery.

The left common carotid artery was dissected free throughout its course in the proximal part of the neck and side branches of significance, which include the cranial thyroid artery and one or two muscular branches, were ligated. An electromagnetic sine wave flow probe (Skalar, Delft) with an internal diameter of 1.5 or 2.0 mm was placed around the common carotid artery.

The microspheres were obtained from 3M Company (St. Paul, MN), and were labeled with either ^{46}Sc, ^{85}Sr, ^{125}I or ^{141}Ce. They were suspended in saline to which a drop of detergent (Tween 20) had been added to prevent aggregation.

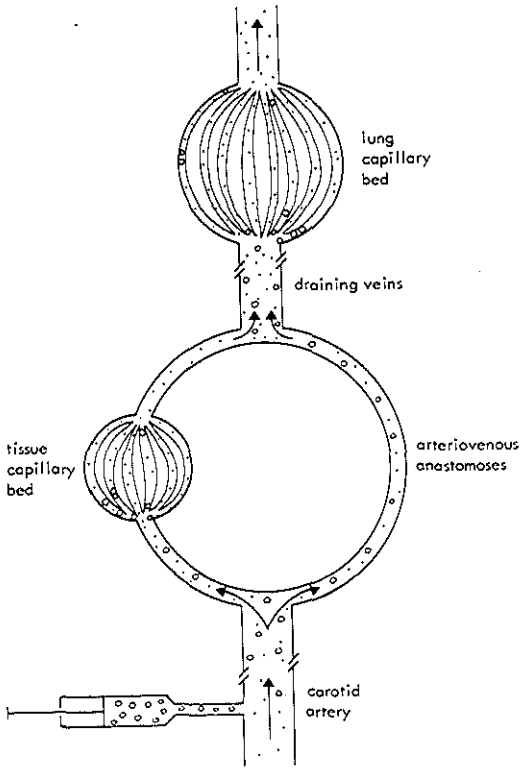

Fig. 9. Schematic representation of the radioactive microsphere technique as it is applied to the study of the distribution of carotid blood flow. The dots represent the red blood cells and the open circles the (15 μm) isotope-labeled plastic microspheres. (Reproduced from Spierings and Saxena[160].)

7.2. Protocol

Approximately 30 minutes after completion of the surgical procedure, the first batch of microspheres was injected to obtain the base-line distribution of carotid blood flow. The subsequent three microsphere injections were made at 30 minutes intervals, *i.e.*, 20 minutes after the administration of increasing doses of either saline (n = 8), dihydroergotamine mesylate (n = 8), ergotamine tartrate (n = 8), isometheptene mucate (n = 8) or methysergide maleate (n = 8). The dosages amounted to 5, 10 and 20 μg/kg for dihydroergotamine, 2.5, 5 and 10 μg/kg for ergotamine, 250, 500 and 1000

μg/kg for isometheptene, and 25, 50 and 100 μg/kg for methysergide, and were attained by accumulation. All drugs were dissolved in saline and administered in a volume of 1 ml.

Ten minutes prior to the microsphere injection the zero flow reference was obtained by occluding the common carotid artery just distal to the flow probe. The zero flow reference served to determine the magnitude of carotid blood flow at the time of the microsphere injection. Five minutes following restoration of carotid blood flow, 2 ml blood samples were drawn simultaneously from the femoral artery and the left external jugular vein. An Oximeter (American Optical Company) was employed for assessing the O_2-saturation of the blood samples after which the samples were returned to the animal via the femoral vein. In addition, a 0.2 - 0.3 ml arterial blood sample was analyzed for pO_2 (mmHg), pCO_2 (mmHg) and pH (ABL2 Acid Base Laboratory, Radiometer, Copenhagen).

Each batch of microspheres contained, on the average, 20,000 spheres and, when warmed up to body temperature, was injected in a volume of 1 ml over a 1 minute period, after thorough vortex and ultrasonic mixing. The sequence of injection of the microspheres carrying the different labels was determined randomly.

Throughout the experiment, the body temperature of the animal was measured rectally and maintained around 37°C by use of a hot water pad.

At the end of the experiment, a blood sample was obtained from the femoral vein for determination of hemoglobin (Hb) by the hemoglobin-cyanide method[77]. On the basis of the Hb values, the O_2-saturation (%) data were converted into O_2-content (mmol/l) data. In every experiment, the flow probe was subsequently calibrated by cannulating the common carotid artery distal to the flow probe and by allowing it to bleed into a measuring cylinder.

7.3. Processing of the microsphere data

The animal was killed with an overdose of pentobarbitone sodium. The various tissues of the head were dissected out separately, weighed and assayed, together with the neck, heart, lungs and kidneys, in a Packard γ-scintillation counter supplied with a multichannel analyzer to distinguish between the different isotopes. The data were processed by a PDP11 digital computer employing the spectral distribution stripping technique[57, 62]. The total number of microspheres injected was calculated from the total amount of radioactivity recovered from the head tissues, neck and lungs, as the microspheres which escaped entrapment in the capillaries of the tissues of head and neck by passing through the arteriovenous anastomoses ultimately became trapped in the lungs.

The fraction of carotid blood flow received by each tissue was calculated as the ratio of the radioactivity recovered from the tissue to the total amount of radioactivity injected. The amount of radioactivity in the lungs, expressed as a percentage of the total dose given, was used to calculate the percentage of carotid blood flow shunted through the arteriovenous anastomoses, *i.e.,* the proportional shunt fraction. The absolute flow values were calculated from the fractional flow values by multiplying them by the corresponding carotid blood flow values.

7.4. Statistical analysis

The data were tested for significance (two-tailed at $\alpha = 0.05$) by means of the Wilcoxon rank sum test and the Spearman rank correlation test. Non-parametric tests were used as some of the variables exhibited skewed distribution and lack of homogeneity of variance. Nevertheless, for reasons of convenience the data are expressed in terms of statistical means $\pm$ standard error of the mean (SEM), unless otherwise stated.

8. Result and discussion

8.1. Analysis of base-line data

Carotid blood flow amounted to 21.1 ± 12.7 (SD) ml/min and was distributed as depicted in figure 10. A large proportion of carotid blood flow – 36.7 ± 15.0 (SD)% – bypassed the capillary bed and entered the venous circulation through the arteriovenous anastomoses. Only 16.0 ± 13.0 (SD)% of carotid blood flow was distributed to the brain, predominantly the ipsilateral hemisphere. Most shunting presumably occurred in the cranial tissues of the head, as shunting of 15 μm microspheres over the cerebral circulation has been reported to amount to less than 2%[39, 92, 126].

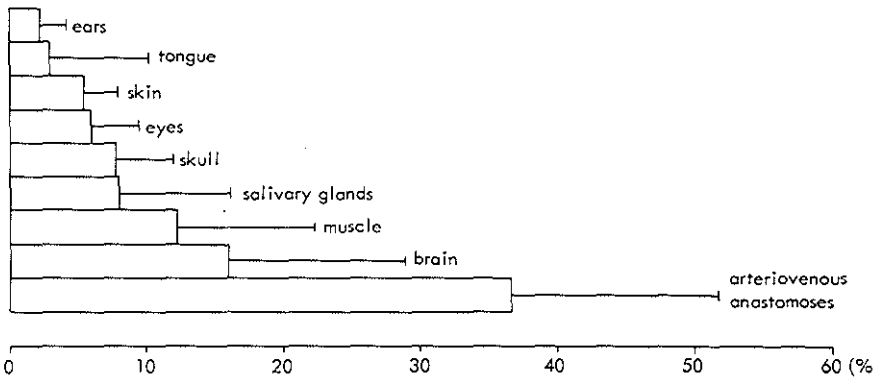

Fig. 10. Distribution of carotid blood flow as determined by direct injection of 15 μm microspheres into the carotid artery. Carotid blood flow averaged 21.1 ± 12.7 (SD) ml/min (n = 40) and 97.4% of the radioactivity recovered from the head was confined to the ipsilateral side. The data are expressed as means ± standard deviation.

The data obtained from the base-line measurements (n = 40) were further analyzed for correlations with the arteriovenous oxygen content difference. In contrast to Heyck's general assumption (see Chapter 6.1) there was no correlation (r_s = -0.23) between the arteriovenous oxygen content difference and the proportion of carotid blood flow shunted through the arteriovenous anastomoses (fig. 11). However, the arteriovenous oxygen content difference showed a significant negative correlation (r_s = -0.62) with carotid blood flow (fig. 12). Multiplication of carotid

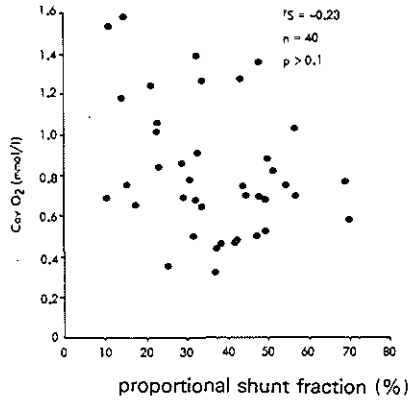

Fig. 11. Scatter diagram in which the arteriovenous oxygen content difference ($CavO_2$) over the cranial circulation with the venous sample drawn from the external jugular vein, is plotted against the proportion of carotid blood flow shunted through the arteriovenous anastomoses. The Spearman rank test was used to calculate the correlation coefficient r_S.

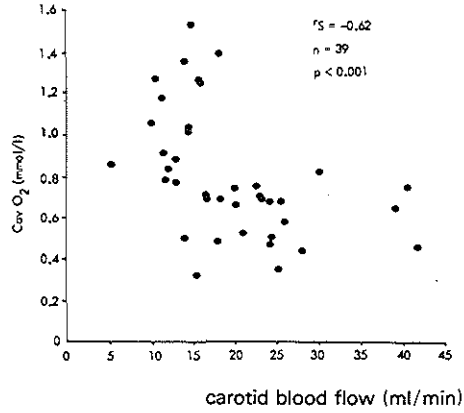

Fig. 12. Scatter diagram in which the arteriovenous oxygen content difference ($CavO_2$) over the cranial circulation with the venous sample drawn from the external jugular vein, is plotted against carotid blood flow. One pair of data (80.7 ml/min, 1.58 mmol/l) has been omitted because of the excessively high carotid blood flow value. The Spearman rank test was used to calculate the correlation coefficient r_S.

blood flow by the shunt fraction in order to obtain the absolute shunt flow decreased the correlation coefficient to -0.51. There was also no significant correlation (r_S = 0.25) between carotid blood flow and the proportional shunt fraction, which indicates that we were probably dealing here with two independent variables.

8.2. **Ergotamine** (fig. 13)

In the cat, as in the dog[134, 137] and monkey[102], ergotamine significantly reduced carotid blood flow, but did not affect the amount of blood delivered to the brain (see also ref. 75). The latter action is similar to what has been reported by Hachinski *et al.*[53] in man using the Xenon clearance technique. Ergotamine profoundly decreased the fraction of carotid blood flow passing through the arteriovenous anastomoses. However, the drug significantly increased the arteriovenous oxygen content difference. The changes induced by ergotamine in the proportional shunt fraction and in the arteriovenous oxygen content difference were not correlated, which further supports the notion that the latter is not an index of the former (see also Chapter 8.1). Ergotamine did not affect the mean arterial blood pressure but slightly and significantly reduced heart rate, an effect which is, at least partially, mediated through an interaction with presynaptic receptors at the postganglionic sympathetic nerve terminals[136].

As ergotamine potently reduces carotid blood flow (present results and refs. 102, 134, 137), the decrease in the proportion of carotid blood flow shunted through the arteriovenous anastomoses, as shown here, might have occurred secondary to the decrease in carotid blood flow, as a compensatory adjustment in order to maintain adequate tissue oxygenation. In support of this possibility, Gewertz *et al.*[44] have demonstrated that a decrease in perfusion flow (and pressure) is associated with a reduction in the proportion of perfusion flow shunted through the arteriovenous anastomoses. In order to further investigate whether the effect of ergotamine on the distribution of carotid blood flow is dependent on the reduction of carotid blood flow *per se,* a series of experiments was performed in which the carotid blood flow was held constant with a peristaltic pump interposed between the femoral and the carotid artery[158]. The effect of ergotamine on the distribution of carotid blood flow over the capillaries and the arteriovenous anastomoses under the condition of a stable perfusion flow is depicted in the lower histogram of figure 14. For comparison, the upper histogram shows the effects of ergotamine obtained in the (flow) experiments described above. It is clear that the effect of ergotamine on the flow distribution over the capillaries and the arteriovenous anastomoses is essentially the same under the two conditions, which suggests that it is in-

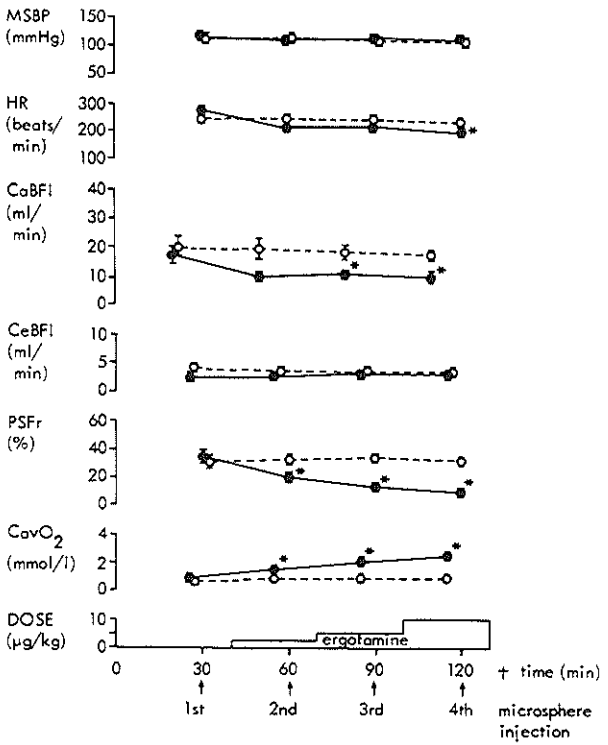

Fig. 13. Effect of ergotamine (2.5, 5, 10 µg/kg) on different hemodynamic variables, depicted as means ± standard error of the mean. MSBP = mean systemic blood pressure (mmHg); HR = heart rate (beats/min); CaBFl = carotid blood flow (ml/min); CeBFl = cerebral blood flow (ml/min), i.e., the amount of carotid blood flow delivered to the brain; PSFr = proportional shunt fraction (%); $CavO_2$ = arteriovenous oxygen content difference (mmol/l). A significant difference ($p \leqslant 0.05$) between the means of the treated (●) and untreated (○) animals is indicated by an asterix and calculated according to the two-tailed Wilcoxon rank sum test. N = 8, except for CaBFl values in the treated group for which one animal had been omitted because of the excessively high flow values (80.7, 47.7, 77.1 and 42.2 ml/min). (Reproduces from Spierings and Saxena[161].)

dependent of the effect on carotid blood flow. This not only adds to our understanding of the vascular effects of ergotamine, but it also indirectly supports Heyck's view on the pathophysiology of the migraine headache (see Chapter 6.1).

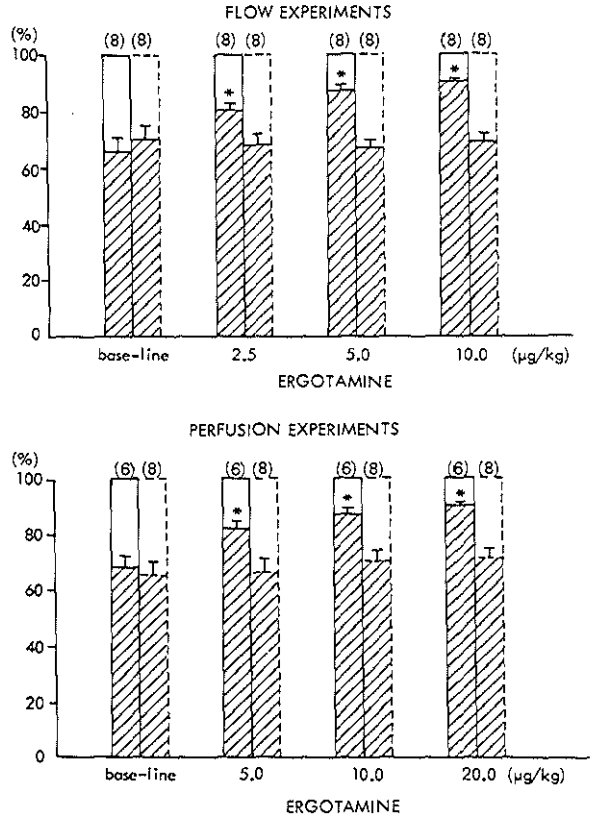

*Fig. 14. The effect of ergotamine, administered intravenously, on the distribution of carotid blood flow throughout the cephalic circulation of the cat. Capillary flow (▨) and flow through the arteriovenous anastomoses (□) are expressed as a percentage of the total amount of radioactivity injected and recovered from head tissues and lungs, respectively. * $p \leq 0.05$, two-tailed Wilcoxon rank sum test vs. corresponding microsphere injection in control (saline) experiments (▨). The number of experiments is given in parentheses. (Reproduced from Spierings and Saxena[160].)*

8.3. Dihydroergotamine (fig. 15)

The pharmacological effect of dihydroergotamine differed quantitatively, rather than qualitatively, from that of its parent compound, ergotamine. Dihydroergotamine, like ergotamine, significantly decreased the carotid blood flow and the proportion of carotid blood flow shunted through the arteriovenous anastomoses, the changes not being correlated. The arterio-

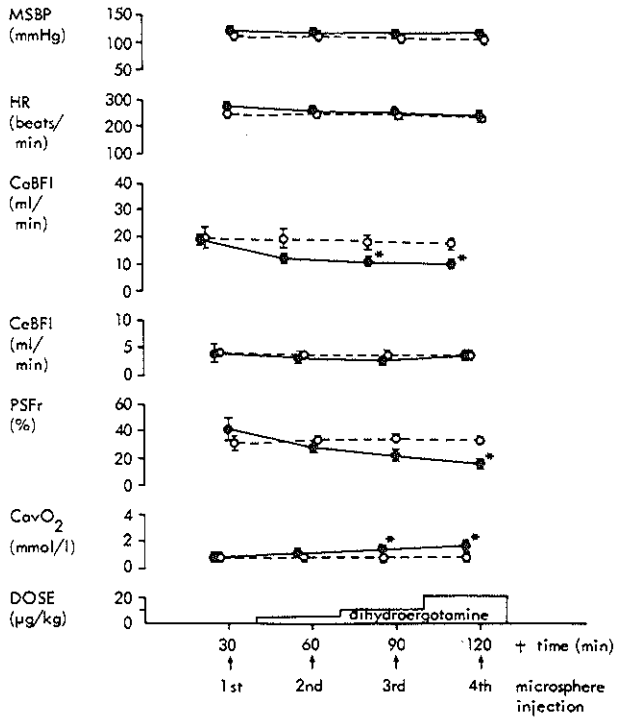

Fig. 15. Effect of dihydroergotamine (5, 10, 20 µg/kg) on different hemodynamic variables, depicted as means ± standard error of the mean. N = 8 for each group. For explanation of the symbols see the legend to figure 13. (Reproduced from Spierings and Saxena[161].)

venous oxygen content difference increased significantly, as shown by Heyck to occur in migraineurs (fig. 8). However, there was no significant correlation between the changes induced by dihydroergotamine in the proportional shunt fraction and in the arteriovenous oxygen content difference.

8.4. **Isometheptene** (fig. 16)

Isometheptene is an indirectly acting sympathomimetic which causes vasoconstriction and stimulation of the heart. It also exerts an antispastic action on those structures that are normally inhibited by sympathetic stimulation[112], and for that reason it has been used in the treatment of spastic conditions which involve the urinary and gastrointestinal tract[117]. With

regard to migraine, isometheptene appears to be effective in the treatment of the acute attack[18, 32, 33, 42, 91, 110, 114, 117, 179, 180], and as a prophylactic agent[18, 114], either alone[18, 33, 42, 91, 114, 117]or in combination with acetaminophen and dichloralphenazone (Midrin®)[32, 110, 179, 180].

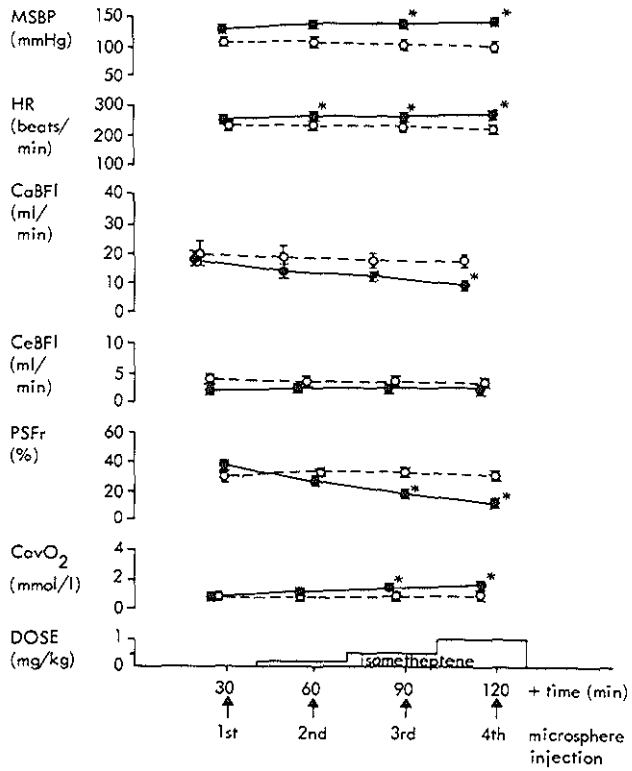

Fig. 16. Effect of isometheptene (250, 500, 1000 µg/kg) on different hemodynamic variables, depicted as means ± standard error of the mean. N = 8 for each group. For explanation of the symbols see the legend to figure 13. (Reproduced from Spierings and Saxena[159].)

In accordance with what is known of the pharmacology of isometheptene *(vide supra)* an increase in blood pressure and heart rate was observed, while carotid blood flow decreased significantly. Due to the increase in blood pressure and the decrease in carotid blood flow, carotid vascular resistance, which is the quotient of blood pressure and carotid blood flow, increased twofold at the highest dose level (being 7.7 ± 0.9, 10.4 ± 1.0, 11.6 ± 1.0, 15.5 ± 2.3 at 0, 250, 500 and 1000 µg/kg, respec-

tively). The amount of cerebral blood flow delivered to the brain was not affected by isometheptene. The effects of isometheptene on the proportion of carotid blood flow shunted through the arteriovenous anatomoses and on the arteriovenous oxygen content difference are similar to those observed with ergotamine and dihydroergotamine.

8.5. **Methysergide** (fig. 17)

Unlike ergotamine, dihydroergotamine and isometheptene, methysergide is effective in migraine only as a prophylactic agent. Among the drugs used for migraine prophylaxis, such as pizotifen, propranolol, amitriptyline, clonidine, *etc.*, methysergide is generally considered to be most effective. Methysergide is a very potent serotonin-antagonist, and for this reason it was introduced in migraine therapy[145].

Saxena[135] studied the effects of bolus injections of methysergide in doses up to 640 μg/kg on different vascular beds in the dog, and reported that methysergide increased femoral and vertebral blood flow, did not affect superior mesenteric and renal blood flow but decreased common and internal carotid blood flow. On the basis of these findings, Saxena suggested that methysergide owes its therapeutic effectiveness in migraine to a selective vasoconstriction of the carotid vasculature. This point of view is supported by the observations of Mylecharane *et al.*[102] in the monkey but not by those of Vidrio and Hong[170] in the dog. The data presented here also do not support such a notion since, except for a decrease in heart rate, no significant hemodynamic changes were observed following administration of methysergide in doses up to 100 μg/kg. The bradycardia induced by methysergide has been shown to be dependent on a central nervous system action of the drug[11, 164].

In conclusion, the studies with the antimigraine drugs confirmed that those agents which are effective in the treatment of the attack, namely, ergotamine, dihydroergotamine and to a lesser extent isometheptene, are potent vasoactive substances which decrease carotid blood flow. In the present series of experiments this could not be confirmed for the prophylactic antimigraine drug, methysergide, for which a purely vascular mode of action has also been proposed[135]. Apart from reducing carotid blood flow, the drugs altered the distribution of carotid blood flow over the capillaries and the arteriovenous anastomoses in favour of perfusion of the capillaries. This not only adds to the vascular effects of the drugs but it also indirectly supports Heyck's view on the pathophysiology of the migraine headache (Chapter 6.1): Opening of arteriovenous anastomoses leads, as a result of capillary steal, to tissue ischemia and lowering of the pain threshold, and to overdistension of the peripheral vessels through transmission of the arterial

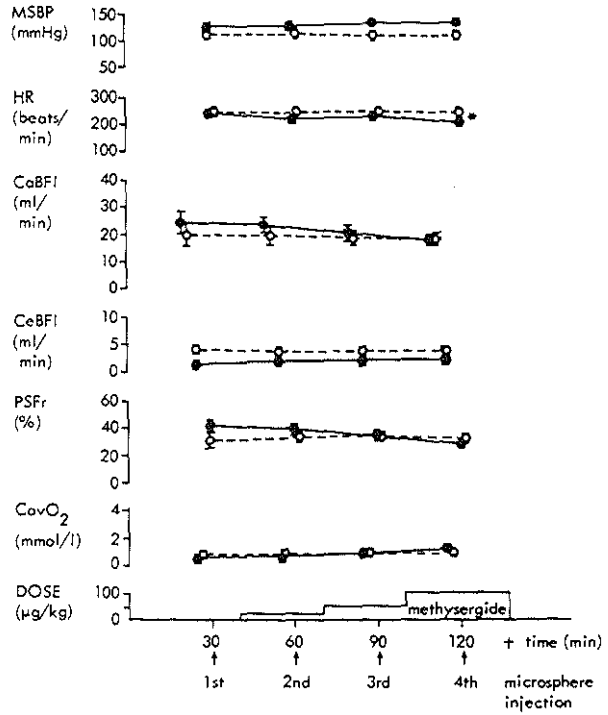

Fig. 17. Effect of methysergide (25, 50, 100 µg/kg) on different hemodynamic variables, depicted as means ± standard error of the mean. N = 8 for each group. For explanation of the symbols see the legend to figure 13. (Reproduced from Spierings and Saxena[161].)

pressure and pulse wave far out into the periphery of the carotid vascular bed. Thus, the drugs exert a direct action at the site of primary vascular derangement, the cranial microcirculation, reversing the increased ratio of shunt to capillary flow, which, in turn, leads to improvement of tissue oxygenation. At the same time, the drugs reduce the carotid blood flow and, as a result, relieve the cranial vasculature of the painfully increased pressure.

However, the experimental data fail to support Heyck's assumption that the arteriovenous oxygen content difference is an index of the proportional shunt fraction, at least in the cat. The correlation between the arteriovenous oxygen content difference and the carotid blood flow would appear to indicate dependence of the former on the latter. If this is also true for man, Heyck's data on the arteriovenous oxygen content difference, as presented in figure 8, can not be used to support a possible role of arteriovenous anastomoses in the pathophysiology of the migraine headache.

Part III

Attempted synthesis

'Reasoning will always be correct when applied to accurate notions and precise facts; but it can lead only to error when the notions or facts on which it rests were originally tainted with error or inaccuracy'.

Claude Bernard[15] (1865)

Migraine can be subdivided into two diagnostic categories, classical and common migraine, depending on the presence or absence of an aura of focal neurological symptoms. The aura symptoms are thought to originate from the cerebral cortex, often the visual cortex or striate area, and they probably depend on the process of spreading depression and excitation as described by Leão[88] and Grafstein[50] (see Chapter 3.2). The coupling of the aura symptoms with the phenomenon of Leão and Grafstein is based on similarity between the rate of the cortical spreading of this phenomenon and the calculated march over the visual cortex of the process underlying the aura symptoms. However, what exactly initiates the spreading depression and excitation remains unclear. It is possible that the *generalized* decrease in cerebral blood flow which accompanies the aura elicits the spreading depression from a (genetically determined) susceptible part of the cerebral cortex, as explained in Chapter 3.2. Then, in common migraine the headache may also be preceded by a phase of decreased cerebral blood flow but *without* initiation of a spreading depression, thus accounting for the vague symptoms which often precede the headache in common migraine, such as irritability, yawning, depression, *etc.*

While so little is known of the migraine aura that only a speculative approach to it is possible, much more data are available with regard to the headache phase of the migraine attack, allowing more solid conclusions. During the migraine headache there is a generalized increase in cerebral blood flow (see table 2) which is associated with a loss of autoregulation – evidenced by a decrease in cerebral blood flow on lowering of the blood pressure[130] – and with a decreased sensitivity of the cerebral vessels to the dilator effect of CO_2[131]. The increase in cerebral blood flow does not play a major role in the generation of the headache (see introduction to Chapter 2) but may occur as a secondary effect, possibly as a result of activation of the ascending reticular activating system (ARAS), because painful stimulation leads to an increase in cerebral blood flow[71]. The dysautoregulation and the decreased reactivity of the cerebral vasculature to CO_2 may be due to the extensive dilatation of the cerebral vessels during the migraine headache.

The hemodynamic changes in the cranial circulation are twofold and consist of a *de*crease in flow within the branches of the internal carotid artery which vascularize the forehead, *i.e.,* the supraorbital and frontal arteries, and an *in*crease in flow within the external carotid artery and its branches which supply the rest of the cranial circulation (see Chapter 2.1). The increase in flow in the external carotid vascular bed probably plays an important role in the generation of the migraine headache, as explained in the introduction to Chapter 2. The pharmacology of the drugs used in the treatment of the attack (see Chapter 8 and refs. 51, 102, 134 and 137) fully supports this notion. However, apart from dilatation of blood vessels, a lo-

cal decrease in pain threshold due to the formation and release of 'neurokinin' seems to contribute to the pain.

The changes during the migraine headache are not restricted to the head, or, as Cervantes wrote in *Don Quixote,* 'When the head aches, all the members partake of the pains'. Thus, the gastrointestinal tract suffers the consequences of the migraine attack, as manifested by decreased motility and atony of the upper part of the gastrointestinal tract[80, 83] and impaired absorption of orally administered drugs[111, 170, 171] (see also Chapter 4). The biochemistry of the body in general is also considerably deranged, as described in Chapter 5. In discussing these biochemical changes, including the changes in platelet biochemistry (Chapter 5.4), I pointed out that one way of explaining them is to assume a heightened activity of the adrenosympathetic nervous system during the migraine headache (see fig. 5). The gastrointestinal dysfunction can also be explained in this way, together with the increased cerebral blood flow. The pain of the migraine headache is probably enough of a threat to account for such a heightened function of this part of the autonomic nervous system, which is so intimately related to stress.

Up till now I have not mentioned the possible role of arteriovenous anastomoses in the pathophysiology of the migraine attack, to which part II of this book is to a large extent devoted. As described in Chapter 6.1, there is evidence for the presence of arteriovenous anastomoses in man in the forehead and dura mater. During the migraine headache the arteriovenous anastomoses probably behave in accordance with the rest of the vascular bed of which they form a part, *i.e.,* they *constrict* in the forehead and *dilate* in the dura mater. It is possible that opening of arteriovenous anastomoses represents the basic vascular change in the dura mater, and it is conceivable that this leads to a painful condition like migraine, as explained in Chapter 6.1. The action on the distribution of carotid blood flow, as revealed by the experiments described in Part II, with regard to the drugs effective in the treatment of the attack, indirectly supports the role of arteriovenous anastomoses in the pathophysiology of the migraine headache. However, they need to be complemented by clinical studies on migraine and, hopefully, such investigations will be prompted by the present work.

Our knowledge of the migraine attack and the relation between the different phenomena as I see it, are schematically depicted in figure 18. I hope that it may serve as a useful framework for further research.

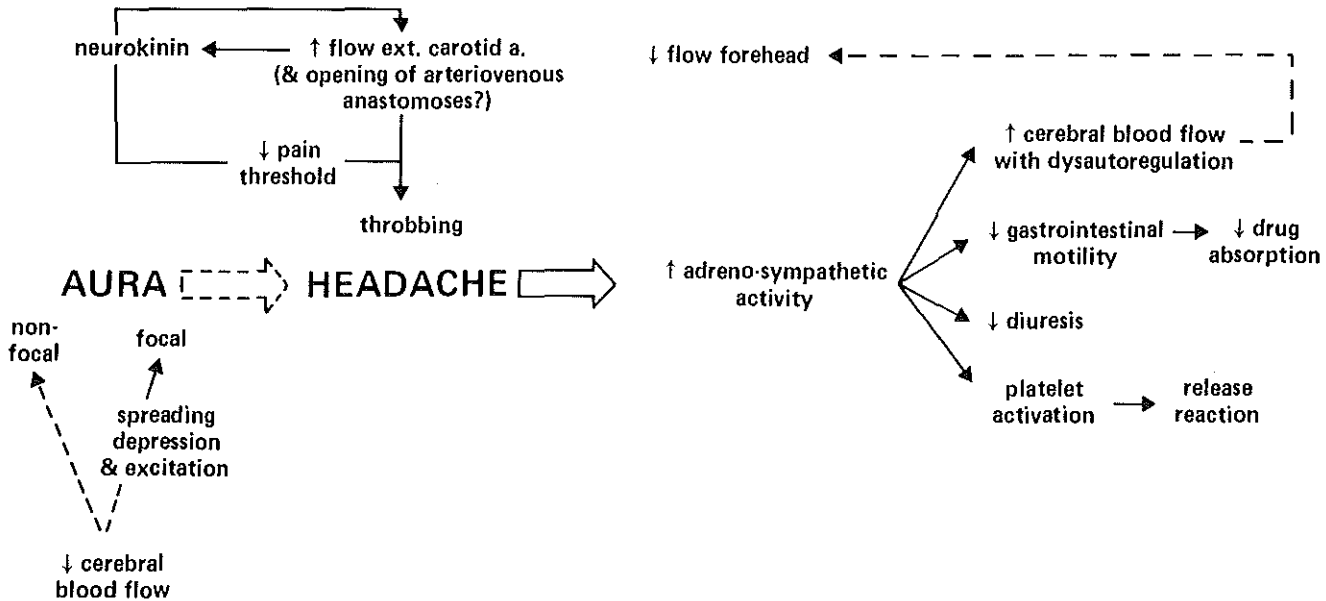

Fig. 18. The pathophysiology of the migraine attack – attempted synthesis. ↑ = increase, ↓ = decrease.

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Curriculum vitae

Egilius L.H. Spierings was born in Helmond, The Netherlands, on August 16th, 1953. Having graduated from college in 1971 he started medical training at the Erasmus University Faculty of Medicine in Rotterdam. In 1974 he became a Bachelor of Medical Sciences, graduating with distinction, and he qualified in medicine in 1978. He passed the Educational Commission for Foreign Medical Graduates' examination in 1977 and the Visa Qualifying Examination, the equivalent of Parts I & II of the National Board of Medical Examiner's examination, in 1978.

In 1974 he was a student research assistant at the Department of Social and Preventive Psychiatry of the Erasmus University, and performed a junior medical rotation in neurology at the Royal Columbian Hospital, Vancouver. From 1975 till 1980 he was associated, first as a research assistant and then, from 1978, as a *PhD*-student, with the Department of Pharmacology of the Erasmus University. In 1975 he performed a senior medical rotation in neurology at the Boston City Hospital, Boston. An elective in headache management he spent at The Headache Research Foundation, The Faulkner Hospital, Boston, in 1977. Since 1980 he functions as a house officer at the Neurosurgery Ward of the Academic Hospital 'Dijkzigt', Rotterdam.

He is a member of the American Association for the Study of Headache, of the Interdisciplinary Society of Biological Psychiatry, and of the Editorial Board of 'Cephalalgia'.

Samenvatting

Migraine is een relatief frequent voorkomende aandoening die zich uit in aanvallen van hoofdpijn, vaak beperkt tot één zijde van het hoofd ('schele hoofdpijn'), al dan niet voorafgegaan door een 'aura'. De aura betreft veelal klachten van visuele aard, zoals het zien van donkere of lichtende vlekken, of het scotoma scintillans, vanwege de kantelenstructuur ook wel teichopsia genoemd. De verschijnselen worden toegeschreven aan een passagère functiestoornis van de cerebrale cortex, i.c. de visuele cortex, mogelijk samenhangend met de vermindering in cerebrale doorbloeding zoals die tijdens de migraine-aura optreedt.

Daarentegen is de cerebrale doorbloeding tijdens de migrainehoofdpijn toegenomen, een toename die waarschijnlijk secundair is aan de pijn. De *oorzaak* van de pijn moet worden gezocht in het vaatbed van de a. carotis externa, waar niet alleen de vaten in versterkte mate pulseren, maar ook de pijndrempel is verlaagd door vorming van 'neurokinine'.

De heilzame werking van ergotamine bij migraine wordt in het algemeen toegeschreven aan een min of meer selective constrictie van de a. carotis externa en haar takken. In experimenten bij katten hebben wij echter kunnen aantonen dat ergotamine, alsook twee andere farmaca met een antimigraine werking, behalve een vermindering in de doorbloeding van de a. carotis, ook de *verdeling* van het bloed over de capillairen en de arterioveneuze anastomosen beïnvloedt, ten gunste van doorbloeding van de capillairen. Arterioveneuze anastomosen zijn vaatstructuren die vóór het capillaire bed het arteriële en veneuze systeem kortsluiten, en via welke het bloed, zonder de capillairen te passeren, direct naar het hart kan worden teruggeleid. In het hoofd komen arterioveneuze anastomosen met name voor in de dura mater, en reeds in de vijftiger jaren is geopperd dat het opengaan van deze vaatstructuren bijdraagt tot, zo niet de oorzaak vormt van, het ontstaan van de migrainehoofdpijn, een veronderstelling die steun vindt in de resultaten van bovengenoemd onderzoek.

Naast veranderingen in de doorbloeding van hoofd en hersenen, treden er tijdens de migrainehoofdpijn ook veranderingen op elders in het lichaam. Zo ondergaan de thrombocyten, die reeds buiten de aanval in verhoogde mate samenklonteren, een reactie die leidt tot het vrijkomen van allerlei stoffen, waaronder serotonine. Ook treedt een functiestoornis op van het maag-darmkanaal, en is de urineproduktie verminderd. Deze veranderingen kunnen, evenals de toename in de cerebrale doorbloeding, worden verklaard door een verhoogde activiteit van het (ortho)-sympathische zenuwstelsel, waarvoor directe aanwijzingen voorhanden

zijn. De hoofdpijn vormt waarschijnlijk voldoende verklaring voor de verhoogde activiteit van dit, zo nauw aan 'stress' verbonden deel van het autonome zenuwstelsel.