REVIEW ARTICLE

Accepted 7 August 1998
Received 6 January 1998
Indian J. Pharm. Sci., 1998, 60(6) pp. 338-345

The Pathophysiology of Headache Part I

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Headaches can be divided into two broad categories, primary headache disorders and secondary headache disorders. Primary headache disorders include migraine headache, tension type headache and cluster headache. This article discusses the primary headache disorders and their related comorbid conditions.

IT is common folk knowledge that headache is an extremely common symptom in our society. That headache has probably been a burden through the ages is suggested by the fact that a description of what is now called migraine occurs in the work of the early Greek writer Aretaeus and that of the great Greek physician Galen. The frequency of headache is difficult to determine for the population as a whole since the milder cases, which do not come to the attention of the physician are undoubtedly the vast majority. Nevertheless, certain surveys have determined that more than 90% of the population suffers from headache at some time of their life. All headache pains are subjective and many patients are unable to describe it. Additionally they are often unaware of the difference between migraine and other types of headache and may use the term interchangeably. Headache is responsible for large amount of absenteeism from work, and for the expenditure of millions of dollars in medication[2]. Probably more important from a public health aspect are the severe risks run by thousands of patients who are heavily self-medicated to relieve or prevent headache.

THE VARIETIES OF PAIN OF HEAD ORIGIN

Headache and face pain, similar to pain elsewhere in the body, occur in an almost infinite variety of syndromes. Among the many variables that must be documented to define such syndromes are the following :

1. The severity of the pain, a purely subjective decision by the patient, but conveniently estimated on a 1 to 10 scale, 1 being slight discomfort, 10 being unbearable.
2. Location of the pain; that is anterior, lateral part of the head, or upper or lower face.
3. Temporal character of the pain-constant or intermittent. If the later, the frequency and duration of the attacks.
4. symptoms preceding, accompanying, or following the pain; for example, nausea effective states, neurologic phenomena.
5. Precipitating events, for example, emotional, dietary, sleep trauma, menstrual cycle.
6. Methods or procedures found to relieve pain.
7. Life history of headache in terms of age of onset, variations in types of headache (as delineated by the above variables).

Anatomical Origins of Headaches

Headaches are actually referred pain to the surface of the head from very deep structures. Many headaches result from the pain stimuli arising inside the cranium but equally as many probably result from pain outside the cranium. The brain itself is totally insensitive to pain. Cutting or electrically stimulating the brain occasionally causes pain.

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The following are the pain sensitive structures of the head and neck.

1. Soft tissue

Skin, mucous membranes, muscles and other soft tissues of the face, ears, scalp, nose, throat cavity and neck are all pain sensitive.

2. Intracranial vessels

Walls of proximal parts of intracranial arteries were being documented as being pain sensitive. Traction on the veins that pass to the venous sinuses from the surface of the brain and displacement of the great venous sinuses causes pain. Traumatizing crushing or stretching stimulus to the blood vessels of the dura causes pain. Traction on the middle meningeal arteries and also of the large arteries at the base of the brain and their main branches causes pain.

3.The meninges of the brain

Stretching the dura at the base of the brain or damaging the tentorium and the falx of the cranial wall results in pain.

4. Central and peripheral nervous system

Direct pressure by tumor or adjacent tissues on the cranial or cervical nerves containing many afferent pain fibres from the head will also result in pain. When the trigeminal nerve or its ganglion is stimulated, pain is referred to the face or the anterior portion of the scalp.

Areas of the head to which Intracranial Headache is referred

Stimulation of pain receptors in the intracranial vault above the tentorium including the upper surface of the tentorium itself initiates impulse in the fifth cranial nerve and therefore causes referred headache to the front half of the head in the area supplied by the fifth nerve. On the other hand pain impulses from beneath the tentorium enter the CNS mainly through the second cervical nerve which also supplies the scalp behind the ear. Therefore subtentorial pain stimuli cause occipital headache referred to the posterior part of the head.

EPIDEMIOLOGY OF HEADACHE

Migraine occurs in 18% of woman, 6% of men and 4% of children in the U.S. Twenty three million Americans suffer from migraine headache as estimated by American Migraine Society[6,7]. Tension type headache is the most common headache with a lifetime prevalence of 69% in men and 88% in woman. Cluster headache is very rare with a rate of 0.01 to 1.5% in various populations. Prevalence is higher in men than women with a ratio of 5.6:1 and is higher in black than in white patients[8-11]. Although it is known that headache is exceedingly common in populations tested in the United States and Western Europe, whether similar frequency of headache occurs in various segments of the societies has been studied for e.g. between rural and urban populations and a uniformity has been reported.

Headache in children

Severe headache is a frequent complaint in children and it has been estimated that migraine occurs in 1 to 4% of children between ages of 7 to 15 yrs[3]. Some clinical characteristics of childhood headache are different from those in adults. There is an approximately equal sex incidence in contrasts to the female preponderance in adult migraine. Classical migraine is not as common in childhood as in adults but more severe neurological phenomenon associated with headache such as hemiparesis, confusional states and aphasia which are probably due to transient cerebral ischemia occur atleast as frequently and possibly more frequently than in adults. A high percentage of children with migraine have EEG abnormalities, diffuse slowing, focal slowing or paroxysmal changes[4,5].

Classification of Headache

The classification of the primary types of headaches modified from that prepared by the ***American Medical Association's Ad Hoc Committee on Classification of Headache*** is as follows[6] :

1.) Vascular Headache
   a.) Classical Migraine
   b.) Common Migraine
   c.) Cluster Headache
2.) Muscle Contraction Headache

1. Vascular Headache

The Primary cause is dilation of the cranial blood vessels. During the usual state of contraction of the walls of the intracranial blood vessels, cardiac systole is reflected as a minor change in the intracranial pressure. The elastic contracted muscle resist pressure change and absorb the impact. When the vessels are distended the ability of the now hypotonic walls of the vessels to absorb changes in the pressure is reduced and the variations in the pressure within the vessels are thus more directly transmitted to the sensory end organs in and about their walls and to the subarachnoid space. This resulting unusual flood of afferent impulse is interpreted as pain. The impulse formation is largely synchronous with the systolic peak pressure in the vessels and therefore is throbbing in its periodicty in accord with the pulse rate.

After several hours of dilatation, the vessel walls become thickened with edema fluid and they become more rigid and less readily compressible. The artery may be tender to touch. There is excessive loss of plasma through the distended walls with the consequent distention of perivascular tissue spaces. These effects summate to put tension on the pain nerve fibres in and around the vessels which then is recognised by the patient as headache pain[7].

a) Migraine

Migraine is a throbbing recurrent severe headache which usually occurs on one side of the head and is at times accompanied by nausea, vomiting and disability. Migraine is three times more common in women than in men. There is usually a family history of migraine. Although the pain usually is located on just one side of the head in the temple or the eye, it may spread to other areas before diminishing. There are various phases in a migraine attack. Preceding the aura of the classical migraine attack or preceding the common migraine attack the premonitory symptoms may be present e.g. mood swings, craving for food, hyperactivity, apathy and yawning etc. There are few factors which can initiate the aura and some that may trigger the common migraine attack directly or via premonitory symptoms[8].

Migraine attacks can affect the arterial territories other than of the head such as coronary and limb circulation and it can also produce systemic symptoms e.g. mood change or fatigue almost certainly on the basis of systemic or biochemical changes. It is therefore, a systemic disorder which is probably due to an inherited systemic neuromuscular instability. The attack encompasses wide spread neural and vascular abnormalities mediated through biochemical changes of varying intensities[8].

Regional cerebral blood flow (rCBF) was found to be reduced during the aura and this reduction persisted into the headache phase. Arterial spasm is an unlikely cause of decreased rCBF. rCBF was often reduced at the occipital pole before symptoms develop and often persisted after all aura symptoms have disappeared. A primary disorder spreading gradually in the cerebral cortex and causing both hypoperfusion and when severe enough the symptoms must therefore be assumed. In common migraine attack, cerebral hypoperfusion was observed initially but during the fully developed attack rCBF was normal[13].

The field of migraine pathophysiology has been characterized as a battle ground for various elaborate hypothesis: vasospasm, serotonin, blood platelets, central dysnociception, food allergy, cerebral hypoxia, arteriovenous shunts as well as ideas that migraine is entirely psychological. Various theories were proposed to explain the pathophysiology of migraine. They are as follows.

1) Wolff's classic vascular migraine theory

He proposed that the migraine aura was caused by intracerebral vasoconstriction and the headache by painful reactive vasodilatation. This has not been substantiated by the cerebral blood flow (CBF) studies which show a decrease in CBF during migraine with aura but not during migraine without aura. But for spasm of a large artery to reduce rate CBF, it has to reduce the lumen of the artery to more than 5 to 10% because arteriolar dilatation compensates for narrowing of large arteries. With vasospasm the first abnormality observed is an increase in regional blood volume. With more severe vasospasm, rate of CBF will decrease but oxygen consumption and function remained unchanged because of increased oxygen extraction. Only when vasospasm is so marked as to reduce rate of CBF to less than 60% of normal will local metabolism and function begin to suffer. However, there is no positive evidence demonstrating vasospasm during migraine attack. It does not explain the prodromal features of migraine or why some anti-migraine drugs have no effect on the cerebral vasculature[14].

2) Heyck's theory of open arterio-venous anastomoses

It has been suggested that migraine attacks are caused by cerebral or extra cerebral shunting but arteriovenous shunts were found in the brain by few investigators and most anatomists believed that they do not exist. The theory based on reduced arteriovenous oxygen content difference on the headache site suggest that the sudden opening of the shunts would bypass capillary beds and produce tissue ischemia and pain. However, recent studies have indicated that increase in venous oxygen content is not due to shunting of blood but rather to increased tissue perfusion[15].

3) Neurovascular theory

The comprehensive neurovascular theory has replaced these theories and is based on CBF studies, magnetic resonance spectroscopy and magnetoencephalography research. It states that neuronal dysfunction with subsequent vascular changes is responsible for the onset and propagation of migraine. The pain of migraine headaches with aura may be caused and propagated by cortical spreading depression, activation of the nucleus caudalis and subsequent neurogenic inflammation.

Cortical spreading depression (a short lasting wave of neuronal depolarisation spreading forward from the occipital cortex and responsible for the aura) and/or biochemical dysfunction depolarizes perivascular trigeminal fibres. Spreading depression either depolarizes perivascular trigeminal fibres or it changes the metabolism or physiology of the cerebral blood vessels. During spreading depression the concentration of extracellular potassium may reach 60 mM which is sufficient to depolarize trigeminal nerve fibres surrounding pial arteries and cause the release of substance P from the perivascular nerve fibre. The period between the onset of the aura and headache may reflect the time for the propagated wave to reach the ventral brain surface over which the pain sensitive pial arteries course. The pain promoting fibres of the trigeminovascular system would then become activated and a vascular headache would ensue Stimulation of the trigeminal nerve results in the release of substance P and neurokinin A (NKA) that causes neurogenic inflammation and may further enhance neuronal sensitivity, release of calcitonin gene related peptide (CGRP) and nitric oxide promoted blood flow fluctuations in adjacent microcirculatory blood vessels[14-18].

This injury to the blood vessel wall is accompanied by local production or transport of molecules from the circulation that are nociceptive. These substances lower threshold or depolarise sensory nerve fibres by binding to specific receptors on these fibres. Depolarisation is accompanied by local release of neurotransmitter from axonal varicosities and by orthodromic and antidromic conduction. Reaching the brain stem and higher centres orthodromic impulse mediate the perception of pain and provide the efferent limb for trigeminal reflexes. Antidromic conduction is associated with depolarisation induced substance P release into blood vessel wall. Released substance P is postulated to increase vascular permeability and dilate cerebral blood vessels. At higher concentration they degranulate mast cells with local release of histamine. Local inflamation may ensue.

Migraine without aura maybe caused either by a disturbance in the hypothalamic/limbic system involving serotonergic and adrenergic pathways or by a direct effect on the trigeminal nucleus caudalis. The hypothalamus and limbic system affect afferent and efferent, 5-HT and adrenergic pathways. Disturbances in these areas may precipitate the onset of a migraine attack with prodromal symptoms. Subsequently the nucleus caudalis trigeminalis a major relay nucleus for pain in the brainstem may be activated. It is unclear how the nucleus caudilis is stimulated, it may be due to cortical spreading depression and/or biochemical dysfunction which may stimulate the trigeminal nerve endings.

Cortical spreading depression mediated in part by N-methyl-D-aspartate receptor may be caused by an intracellular magnesium deficiency and is further modulated by hypothalamic and limbic 5-HT adrenergic pathways. An imbalance between facilitatory and inhibitory neurons to the nucleus caudalis trigeminalis may render it more sensitive to input that normally would not trigger firing. This may explain why migraine sufferers have an increased susceptibility to head pain even during migraine free periods.

Serotonin plays an important role in the pathogenesis of migraine headaches. A fall in the plasma serotonin occurs at the onset of the migraine attack. This fall in plasma serotonin during the attack is due almost entirely to the loss of the amine from platelets and is specific to migraine and not simply a reaction to headache vomiting or stress.

The fact that reserpine, a potent CNS 5-HT depleting agent precipitates migraine headache and serotonin relieves it, suggests that changes in plasma 5-HT levels are implicated in the mechanism of migraine and are not just interesting association. Behaviour of platelets in migraine subjects basically differs from that of normal controls in that the platelet aggregate more readily after pre-incubation with 5-HT than do platelets of controls, implying that platelet uptake sites accept 5-HT less readily or are less capable of retaining 5-HT than do those of normal subjects. Migraine headaches generally improves with age probably due to a decrease in 5-HT receptors in the brain. Sleep reduces CNS 5-HT neuronal firing and aborts migraine attacks. In addition, plasma 5-HT concentration decreases during a migraine attack and urinary excretion of its metabolites increases. Activation of $5\text{-HT}_{1/D}$ receptors decrease the realease of 5-HT, norepinephrine, acetylcholine and substance P. The inhibitory $5\text{-HT}_{1B/D}$ heteroreceptors on trigeminal nerve terminals block neurogenic inflammation. 5-HT_2 stimulation results in neuronal depolarisation while 5-HT_3 stimulation causes nausea, vomiting and activation of autonomic reflexes[13-16,18]. Other neurotransmitters and mediators are also implicated in the pathogenesis of migraine.

Catecholamines - Migraineurs have an increase in plasma catecholamines before and during the migraine attack. Norepinephrine produces vasoconstriction via the postsynaptic alpha receptors and promotes release of serotonin from platelets. Increase dopamine concentration may be partially responsible for the nausea and vomiting observed during a migraine attack[15,18,19].

Endorphins - They are the naturally occuring opioid polypeptides some of which have potent analgesic properties. The level of beta-endorphins in the spinal fluid of migraineous patients during attacks have been found to be low[20].

Free fatty acids-Emotional stress and alcohol ingestion are factors leading to the release of catecholamines which stimulate beta adrenoreceptors leading to release of free fatty acids. Rise in free fatty acids during migraine could lead to serotonin release from platelets, a function which leads to increase prostaglandin formation, E series of which are known to be powerful vasodilators[17].

Prostaglandins - They play a role in platelet aggregation through the action of their endoperoxides and most probably contribute to the serotonin release and depletion so characteristic of migraine attacks[17].

Other Biochemical abnormalities - Circulating monoamine oxidase has been found to be low in migraine patients in one study at the time of migraine[21] and in another at all times[19]. It has been speculated that this defeciency permits accumalation of various potential vasoactive amines which may initiate the migraine process and several amines have been proposed for this role.

MENSTRUAL MIGRAINE

Migraine also occurs in the premenstrual or menstrual period in women. There are two patterns of menstrual associated headache. In the first, the headache occurs only during the premenstrual and menstrual period and at no other time in the menstrual cycle. In the second pattern, headache may occur at any time, but there is an increase in the occurance and in the intensity of headache in the premenstrual and/or menstrual period. Estrogen is a major factor in these headaches, and estrogen therapy would abort the menstrual migraine while progesterone would not. The following theory has been postulated for the occurrence of menstrual migraine[22].

Catecholamine theory : one of the important metabolic pathways for estrogens is hydroxylation at the 2C-atom of the molecule, 2-hydroxy estrogen or so called catecholestrogens are formed, and during pregnancy their production is greatly increased. Both catecholestrogens and catecholamines are methylated by the same catechol-O-methyl transferase (COMT). Catecholestrogens are superior substrates for (COMT) and are thus extremely effective competitive inhibitors of O-methylation of the catecholamines. The enzymatic methylation and biological inactivation of neurotransmitters of the catecholamine types are therefore strongly inhibited by catecholestrogens. Catecholamine metabolism is thus inhibited by elevated blood levels of estradiol-17-beta. Exogenous steroid administration can both increase and decrease COMT. Thus oral contraceptives influence COMT activity. If it is postulated that catecholamine in the sympathetic nervous system are of pathophysiological importance for the development of migraine attack, the interaction between catecholestrogens and catecholamines might explain both the disappearence of migraine attacks during pregnancy

and the occurrence of such attacks during the interval of treatment with estrogen containing contraceptive pills[22].

b) Cluster Headache

It is probably the most dramatic of all headache types and affect less than 0.01% of the population. As opposed to migraine which occur 3 times more frequently in woman, cluster headache is five times more common in men. A family history is uncommon compared to migraine. The pain of cluster headache is so excruciating that it drives even strongest of men literally to their knees. It is with very rare exception exclusively one sided and located in and around the eye pushing it forward and patients feel as if a red hot poker is being thrust into the eye with immense force and twirled[23].

Clinical Features

The mean age of onset in various series is 31.5 yrs (range 27-37 yrs) with a clear preponderance of the male sex. Sufferers have a masculine physiognomy and physique giving an appearance of hypermasculinism and physical robustness. They have thick coarse skin, wrinkling of the forehead and deep furrows in the face. Female petients too have masculine features[26].

In spite of the hypermasculine appearance, the patients psychological status does not necessarily comply with it and they are said to have personality structure of a mouse[25]. As a result, psychological factors, stress, anxiety, and a feeling of insecurity may trigger the bouts. The attacks are associated with phenomenon such as lacrimation, excessive salivation and nasal secretion, facial flushing and edema of the face[26-29].

Pathogenesis

The pathogenesis of cluster headache has not been well defined. Cluster events may be related to alterations in the circadian pacemaker. It has been observed that the attacks increase following the begining and end of daylight, and there is a loss of circadian rhythm for blood pressure, temperature and hormones including prolactin, melatonin, cortisol and endorphins. Hypothalamic dysfunction causes the loss of circadian rhythm. Neurogenic inflammation, carotid body chemoreceptor dysfunction, imbalance of central parasympathetic and sympathetic tone and increased responsiveness to histamine have been proposed as the cause of cluster headache. The carotid body is the most sensitive chemoreceptor for hypoxemia. Carotid body cells get stimulated by hypoxemia, a lowering of the pH and to some extent hyper capnia. Afferent impulses from the carotid body are mediated through a special branch of the glossopharyngeal nerve, the carotid branch and are conveyed to the posterior medulla namely the nucleus solitarius. The information is processed in the respiratory and cardiovascular centres. The respiratory centre controls ventilation via phrenic or intercostal nerves and the cardiovascular centre controls heart activity via the reticulo spinal fibres. The superior cervical ganglion supplies the carotid body with sympathetic fibres. In the cluster headache there is an inhibition of sympathetic and disinhibition of parasympathetic influence on the carotid body which is thought to diminish peripheral chemoreceptor activity. The cause of the solitary paroxysm is supposed to be oxygen desaturation which leads to hyperactivity in the chemoreceptor and thereby stimulation of the respiratory centre. This via the nucleus solitarius leads to stimulation of the nuclei of the seventh and tenth cranial nerves. A rise in the pO_2 and a decrease in the blood pH may be the factors determining the shut off of chemoreceptor activity which terminates the attack[30,31].

2. MUSCLE CONTRACTION HEADACHE :

It is the most common form of headache and it has been referred to in past as tension headache or scalp muscle contraction headache. There are two distinct disorders :

a) Acute muscle contraction headache : This is often self treated, physicians rarely being consulted. Single attacks are mild, short lived, non-throbbing with a generalised distribution. Attacks last for 2-4 hours and are effectively relieved by simple analgesics. It must be a rare person who has never experienced this type of headache. Attacks last for two to four hours duration and lack associated phenomenon such as nausea, photophobia or autonomic symptoms[32].

b) Chronic muscle contraction headache (CMCH) : Mean age of onset of the headache is 30 yrs with a preponderance in females. The pain is dull in intensity, aching, pressure like constricting or giving a sense of

fullness, location of the pain is frontal, temporal, or frontotemporal[33].

Relationship of CMCH to migraine :

Patients with CMCH are probably constitutionally migrainious and for reasons yet unknown develop daily dull headache several years after the onset of migraine. This condition usually starts after episodes of illness and surgery[34]. Therefore, CMCH diathesis may be dependent on the combination of two intrinsic and constitutional features, migraine and a particular personality complex.

Psychological aspects

Headache is a somatic response arising from a diminished capacity to deal with environmental demands. Patients have poorly repressed hostility, unresolved dependency needs and psychological conflicts. The mechanism may be increased skeletal muscle spasm resulting from psychophysiological expression of anxiety[33,35].

Pathogenesis

It was suggested that the headache was caused by scalp muscle contraction, a consequence of psychohumoral stimulation. Suppresed or repressed emotional conflict that produced skeletal or autonomic discharges are responsible for the stimulation of muscle spasm and vasoconstriction. End organs for pain at these sites are activated thus sending impulses to the brain via afferent nerve pathway. Some studies have proved that ischemia, hypoxia and lactic acidosis associated with muscle spasm did not contribute to pain production[36,37]. It was also shown that contraction of skeletal muscles release pain producing substances. But as it was found that muscle relaxants and anti inflammatory agents have failed in the treatment of CMCH[33], the myogenic mechanism is questionable.

While comparing the baseline EMG activity of headache and nonheadache populations, some have found that it is higher in headache patients whereas, the others have not[38-41]. Surprisingly, biofeedback reduces headache frequency with little change in EMG activity[41] and EMG activity may be significantly reduced in some patients without change in headache[43]. Hence it was concluded that CMCH is not characterised by excessive muscle contraction either during headache or headache free period or in response to stress. Excessive muscle contraction however may cause headache in some patients on certain occassions while conversely it may be secondary to headache in others[44].

CONCLUSION

Today the vasular theory of migraine and muscle contraction theory of tension type headache are no longer tenable. Migraine and tension type headache may be a part of a continum of headache disorders involving the pain control systems and amplified by neurovascular mechanisms, while cluster headache is a distinct entity that may use similar neurovascular mechanisms. Awareness of the presence of comorbid conditions is important as they influence headache treatment. These changing concepts of headache pathogenesis have helped develop new headache treatment.

REFERENCES

1. Waters, W.E., In; Waters W.E., Eds, The Epidemiology of Migraine, Bracknell-Bershire, England, Boehringer Ingelheim, 1974.
2. Graham, J.R., and Wolff, H.G., **Archives Neural Psychiatry,** 1938, 39, 737.
3. Longdon, P.J., and Forsythe, W.I., **Clinical Pediatrics** 1979, 18, 353.
4. Prensky, A.L., **Neurology,** 1979, 29, 506.
5. Ziegler, D.K., Zosa, A., and Zileh, T., **Archives Neurology,** 1965, 12, 472.
6. Closson, R.G. **Neurological and psychological disorders,** 1963, 10, 602.
7. Tauter, M.L., and Ferris, A.J., **Aspirin in modern technology,** 1969, 43.
8. Olesen, J., In; Rose, C.F., Eds., Handbook of Clinical Neurology : Headache, Vol 4, Elsevier Science Publishers B. V., 1986, 59.
9. Cady, R.K., and Shealy, C. N., **J Fam Pract,** 1993, 36, 85.
10. Daliessio, D.J., and Silberstein, S.D., In; Wolff, H.G. Eds., **Headache and other head pain,** 6th Ed, Oxford University Press, New York, 1993, 15.
11. Mathew, N.T., **Neurology,** 1992, 42 (suppl 2), 22.
12. Silberstein, S.D., **CNS Drugs,** 1994, 2, 199.
13. Lauritzen, M., **J. Cerebral Blood Flow Metabolism,** 1983, 3, 254.
14. Daliessio, D.J., and Silberstein, S.D., **Wolff's headache and other head pain,** 1993, 6.157.
15. Mary, L. Wagner., and Stephen, D.S., In; Herfindal, E.T., and Gourley, D.R., Eds., Textbook of therapeutic Drug and Disease Management, 6th Ed, 1996, 983.

16. Olesen, J., and Welch K.M.A., **The headache, Raven Press; New York,** 1993.1
17. Zagami, A.S., **Curr Opin Neurol,** 1994, 7, 272.
18. Silberstein, S.D., **Headache,** 1994, 34, 408.
19. Moskowitz, M.A., **Ann Neurol,** 1984, 16, 157.
20. Bach, F.W., Langemark, M., and Secher, N.H., **Pain,** 1992, 51, 163.
21. Sicuteri, F., and Anselmi, B., **Adv Biochem Psychopharmacol,** 1978, 18, 363.
22. Glover, V., and Sandler, M., **Lancet,** 1977, 1, 391.
23. Olesen, J., In; Rose, C.F. Eds. Handbook of Clinical Neurology : Headache, Vol 48, Elsevier Science Publishers B.V., 1985, 425.
24. Rapoport, A.M. and Sheftell, F., Conquering Headache, Empowering Press, Hamilton, Canada, 1995.
25. Ekbom, K., and Olivarius, Fine, B.D.E., **Headache,** 1971, 11, 97.
26. Graham, J.R., and Rozado, A.Z., **Background to migraine,** 1970, 38.
27. Graham, J.R., **Headache,** 1975, 27.
28. Horton, B.T., **Med. J,** 1961, 10, 178.
29. Sutherland, J.M., and Eadie. M.J. **Headache,** 1972, 13, 401.
30. Lance, J.W., and Anthony, L., **J. Neurology Science.** 1971, 13, 401.
31. Kudrow, L., Mcginity, D. J., and Phillips, E.R., **Cephalagia,** 1984, 4, 33,.
32. Kudrow, L., **Cephalogia,** 1983, 3, 241.
33. Kudrow, L., **O. Appenzeller (Ed) Pathogenesis and Treatment of headache,** 1976, 81.
34. Friedman, A.P., Von Storch, T.J.C., and Merrilt, M.M., **Neurology,** 1954, 4, 773.
35. Mathew, M.J., Stubits, E., and Nigam, M.P., **Headache** 1982, 22, 66.
36. Martin, M.J., and Roma, H.P. **Headache,** 1967, 184.
37. Simons, D.J. Day, E., Goodell, M., and Wolff, H.G., **Ass. Res. Nerv. Dis. Proc.,** 1943, 23, 228.
38. Rodbard, S., **Pain associated with muscle contration headache,** 1970, 10, 105.
39. Rozniak-Patewicz, E., **Headcahe,** 1976, 15, 261.
40. Bakal, D.A., and Kagnov, J.A., **Headache,** 1977, 17, 208.
41. Gannon, L.R., and Haynes, R., **J. Psychosam Res,** 1981, 25, 271.
42. Sutton, E.P., and Bellar, C.D. **Headache,** 1982, 22, 133.
43. Matin, P.R., and Mathews, A.M., **J Psychosom Res,** 1978, 22, 389.
44. Hoffman, E., **Res Commun Psychol Psych Behav,** 1979, 4, 209.
45. **Pikoff, H.,** Headache, 1984, 24, 186.