SECTION I

General Aspects of the Headaches

Chapter 1

History of the Headache

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ANCIENT MESOPOTAMIA, EGYPT, CLASSICAL GREECE, AND ROME: HEADACHES AS A MAJOR PROBLEM

The earliest accounts of headache in Mesopotamian and Egyptian mythological texts describe magical scenes with dramatic images of suffering:

Headache roameth over the desert, blowing like the wind,
Flashing like lightning, it is loosed above and below;
It cutteth off him who feareth not his god like a reed,
like a stalk of henna it slitteth his thews.
It wasteth the flesh of him who hath no protecting goddess,
Flashing like a heavenly star, it cometh like the dew;
It standeth hostile against the wayfarer, scorching him like the day,
This man it hath struck and
Like one with heart disease he staggereth,
Like one bereft of reason he is broken,
Like that which hath been cast in the fire he is shrivelled,
Like a wild ass... his eyes are full of cloud...

These Sumerian verses were translated into Assyrio-Babylonian for Ashurbanipal’s library at Niniveh in the 7th century BC (23). The clay tablets describe severe diseases as headache, but such symptoms as "flashing like a star" and "eyes full of cloud" may appear in any severe fever. In ancient Mesopotamia, malaria or septic diseases were likely causes of such symptoms. Headache was believed to be provoked by demons, and treated by incantations and strange materials fastened on the head. Some Egyptian descriptions are more specific; there one-sided headache is impressive, especially when the gods Horus and Seth are complaining about their headaches, or when Horus invokes the goddesses Isis and Nephthys, begging them to lower a spare head on him from the sky because he cannot stand his unilateral headache any longer (2).

Prehistorical trepanned skulls found in Egypt are said to have undergone brain surgery for headache. However, there is no evidence to support this claim although scraping the forehead down to the bone was a popular headache remedy among the Fellahin up to the 20th century.

FROM MYTHOLOGICAL TO CLINICAL AND PHILOSOPHICAL OBSERVATIONS

Ancient Greek descriptions range from mythological scenes through clinical groundwork to philosophical critique of medical attitudes.

The Greeks knew headache as a serious complaint. Their Hippocratic corpus presents it as a frequent symptom of dangerous disease with fever, nausea, vomiting, bleeding from the nose, convulsions, and sensory disturbances (25). Zeus, the supreme god, complained of insupportable headache for which he forced Vulcan to split his head with an axe, thus giving birth to Pallas Athene, goddess of learning and strategy (4).

Plato’s dialogue "Charmides" has Socrates promise a headache drug to the hero provided he first undergoes Socrates’ psychotherapy: for you cannot treat the eyes without curing the head, or the head without treating the body, nor the body without treating the soul (19).
2 General Aspects of the Headaches

CLASSICAL CLASSIFICATION: FIRST SPECIFIC DESCRIPTIONS OF MIGRAINE, NOT AURA

In 1st century Rome, Aretaios of Cappadoecia wrote a textbook of neurologic diseases including headache, epilepsy, and hysteria (1). He set the pattern for such textbooks up to the 19th century, and divided the headaches into hemicrania (migraine), cephalalgia (mild, infrequent headache), and cephalae (frequent, severe headache). This early classification survived with the underlying textbook structure. It provided the roots of the 1988 and 2003 international classifications of the International Headache Society, where distinction of migraine from tension-type headache (cephalalgia, cephalaea) is still most important (3,5). In 2nd-century Rome, Galen of Pergamon established the master pattern of what was to become Islamic and European medicine up to the 17th century. He elaborated on Aretaios’ clinical descriptions and pathophysiology (18): migraine is caused by yellow bile irritating the brain and meninges, but the bile, held back by the falx cerebri, affects only one half of the head. Throbbing pain originates from blood vessels, and tension pain from tendons or nerves. Migraine came to us from Galen’s hemicrania through France where the physician Rabelais also used migraine for a fire grenade (12). Galen’s idea of bile from the liver causing migraine is still popular in France where migraine hépatique is attributed to liver disease. Another principal idea lasted up to the middle ages: Aretaios and Galen described Greek scotoma, Latin vertigo: vestibular vertigo with oscillopsia. This was something migraine could turn into, much more dangerous than migraine itself. Nowadays the scotoma of the ancients may be misunderstood as visual aura of migraine because this has also been called scotoma (literally, “shadow-eye”) in the last three centuries.

MEDIEVAL ISLAMIC MEDICINE: RECOGNIZING FUNCTIONAL DISORDER; THE HEADACHES AT A GLANCE

When Islamic medicine attempted a synthesis of Galenic medicine with Aristotelian natural science, the earlier Greek understanding of headache as a functional disorder returned. The Greek medical heritage remained alive in the Byzantine empire and the Islamic countries. In the 6th century, Alexander of Tralleis in Byzantium gave a detailed account of the headaches based on Aretaios and Galen, and on his own practical experience (21). In the 18th century the Persian physician Avicenna integrated Alexander’s concepts in his Greek-based medicine. Avicenna observed that many headaches were not caused by brain damage; the senses were not dulled but unusually acute in that any sound, light, or smell could trigger a headache (22). He established a pathogenetic classification of soda (Arabic from Persian sar dard, or headache). This system was condensed as a table in 11th century Baghdad, and became popular in Europe where it was finally printed, in Latin and German, in the 16th century (11; Table 1-1 and Fig. 1-1), demonstrating the popularity of Arabic teachings in Europe at a time when the final eviction of Islamic medicine from Europe was proposed by Paracelsus.

MEDIEVAL EUROPE: MYTHS, CLINICAL ACUMEN, AND EXPERIMENTAL SCIENCE

European medieval teachings incorporated Islamic concepts, combining the more mystical ideas of various headache saints with clinical impressions such as Hildegar von Bingen’s finding of the comorbidity of migraine and melancholy (13), and the experimental natural science of Albert the Great and his fellow scientists of the 13th century. Hildegard had mystical visions, which have been interpreted as visual aura of migraine: the ornamental frames of her illustrations are suggestive of the zigzag contours of migraine auras. But the content of her visions is far too meaningful, and similar zigzag frames are common in illuminated books of the time. Hildegard was a compassionate clinical observer who found an original explanation for the unilaterality of migraine: nobody could survive this cruel pain if it were on both sides of the head.

RENAISSANCE: CONSOLIDATING THE GALENIC BASIS OF 17TH-CENTURY SCIENTIFIC MEDICINE

In 15th- and 16th-century Galenic medicine (6), pulsatile and tension-like pain are clearly attributed to blood vessels and nerves, respectively. This ancient pathophysiology is still extant in current classification criteria: throbbing pain in migraine, tension-like pain in tension-type headache (3). The clear and orderly Galenic textbooks of this period (e.g., Houlleir and Ferel [6]) set the stage for the new medicine of the scientific revolution in the 17th century where authors like Harvey and Willis introduced their new findings in a similar order.

THE 17TH-CENTURY FOUNDERS OF NEUROLOGY WERE HEADACHE EXPERTS

The founders of neurology—namely, Le Pois, Willis, and Wepfer—were unorthodox professors (7). Expanding Galenic theories they attributed headache to the meninges,
<table>
<thead>
<tr>
<th>Terms</th>
<th>Cause</th>
<th>Sign</th>
<th>Evacuation</th>
<th>Regal Cure Full Treatment</th>
<th>Mild Cure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Soda from heat</td>
<td>From taking hot food or drugs or from the</td>
<td>Head hot to touch and</td>
<td>None to do</td>
<td>With rose and sandalwood on the head, and food with</td>
<td>With oil or rose and lemons, and some vieniger</td>
</tr>
<tr>
<td></td>
<td>sun's heat</td>
<td>normal urine and</td>
<td></td>
<td>granadine juice</td>
<td>on the head</td>
</tr>
<tr>
<td>2 Soda from cold</td>
<td>From cold temper of the meninges, from</td>
<td>Head cold to touch and</td>
<td>None to do</td>
<td>A plaster with chamonile, storz clover, calamin and</td>
<td></td>
</tr>
<tr>
<td></td>
<td>keeping the head bare in cold air</td>
<td>improvement from</td>
<td></td>
<td>marjanam and marjanam</td>
<td></td>
</tr>
<tr>
<td>3 Soda from hot humor</td>
<td>From blood &amp; yellow bile</td>
<td>Blood letting from the</td>
<td>Should eat chick peas and pleasant</td>
<td>With oil or rose and lemons, and some vieniger on the head</td>
<td></td>
</tr>
<tr>
<td>4 Soda from cold humor</td>
<td>From phlegm and black bile</td>
<td>liquid color and</td>
<td>With hore pills and cochlearia</td>
<td>With unripe grapes</td>
<td></td>
</tr>
<tr>
<td>5 Soda from external heat</td>
<td>From hitting/ beating or from something</td>
<td>Throbbing and</td>
<td>With blood letting from the cephalic vein</td>
<td>Plaster with Calamus animus, root of granada, pass and</td>
<td></td>
</tr>
<tr>
<td>6 Soda after evacuation</td>
<td>Obstructed bowel movement, sleeplessness,</td>
<td>Headache and</td>
<td>and softening enema</td>
<td>water of roses</td>
<td></td>
</tr>
<tr>
<td>7 Hemicrania (sic)</td>
<td>From humor of bad quality, cold, or humid</td>
<td>with severe pain</td>
<td>With blood letting and expurgation of the</td>
<td>Should anoint for head before onset of paroxysm with</td>
<td></td>
</tr>
<tr>
<td>8 Soda from the stomach</td>
<td>From comorbidty of the stomach, or its</td>
<td>with severe pain</td>
<td>inducing humor</td>
<td>oil of daffodils or peonies</td>
<td>With the pulp of white broad and</td>
</tr>
</tbody>
</table>

Translated by H. Isler.
FIGURE 1-1. This system of the headaches, printed in Latin in 1532 in Strasbourg, was written in Arabic in 11th-century Baghdad by Abu Ali Yahya ben Isa ibn Gezla, in his book Tables of the Diseases. It would be instantly understood by anybody familiar with Galenic medicine where the relative power of the four humors (yellow and black bile, blood and phlegm) determined the disposition for health and disease, and the “six nonnatural things”—namely, 1) air, or climate, 2) food and drink, 3) movement and rest, 4) emotions or affections of the mind, 5) retentions and excretions, and 6) sleeping and waking—directed the course of health and disease. Migraine, or hemicranea, had special properties, and was to be treated by evacuation of noxious humors from the body.
cranial vessels, and cranial nerves (in Dutch textbooks, the cranial peristium [15]) and observed migraine with aura. Charles Le Pois of Pont-à-Mousson, France, explained epilepsy, hysteria, and migraine as intracranial diseases. He wrote of his own migraine with premonitory symptoms (febricula, "a small fever"), attributing it to the stress and the depressions he had to sustain as a poor student. He described hemicraniae insultus, attacks of migraine with features of stroke, in a girl whom he followed from her 12th to her 17th year. She had a severe left temporal headache followed by bitemporal vomiting. The headache followed after numbness, stiffness, and "straying ants" spreading from her left little finger to the fourth and middle finger and the others, and up the arm auve cujudum instar ascendentis, like some ascending breeze. Later attacks were less severe, often triggered by pleasant smells, such as musk, and always associated with numbness in her left limbs (20).

Thomas Willis of Oxford and London initiated systematic brain research with highly qualified teams. He launched the term neurology in 1664, together with attempts at localization of cerebral functions in autopsies of patients and in animal experiments with intravenous dye injections. At least two of his localizations still prevail: he described the grey cortex as the source of cerebral activity and tracts of white matter as pathways conveying activity to peripheral organs. In 1672 he wrote a textbook of neurophysiology and nervous diseases with two chapters on headache (8). Among many pathophysiological assumptions, there is a hypothesis linking intracranial vasconstriction with subsequent dilatation, not far beyond the old Galenic explanations but already similar to Wolff's 20th-century vascular hypothesis of migraine. He described premonitory symptoms of migraine, the slow proximal ascension of sensory symptoms ("nerve spasms"), and seasonal increase of attacks. Willis found people of any constitution, age, or social standing among headache sufferers. He said that official medicine did not know much about headache, and that empirical knowledge might be more useful. His remedies included at least one which worked: the newly introduced potus cophey (coffee), for which he would send headache patients to taverns instead of pharmacies.

Johann Jakob Wefer of Schaffhausen in Switzerland revolutionized the understanding of the cerebrovascular system. Willis quotes his book on stroke at length, and held him in great esteem. Wefer initiated experimental toxicology with many associates who poisoned all kinds of animals. His descriptions of trigeminal neuralgia, subdural hematoma, basilar migraine, and migrainous stroke are classic (9); he mentioned visual migraine aura and parts of his clinical work survived in leading French and German textbooks of the 18th century.

THE GREAT 18TH-CENTURY SCHOOLS OF MEDICINE: HEADACHE IN TEXTBOOKS OF MEDICINE AND NEUROLOGY

Botanical classifications of disease from Montpellier and Stockholm, and a textbook of neurology from Lausanne prepared the ground for the 19th century.

Herman Boerhaave in Leiden became the "teacher of Europe" through his pupils Haller, Linneé, and Whytt and his brilliant assistant van Swieten, who founded the Vienna School of Medicine, and wrote a commentary to Boerhaave's aphorisms, which was to become the most influential textbook of practical medicine of the century (26). He gave a complete account of episodic cluster headache, the first known up to now (incomplete descriptions occur in Tulp [1641] and others [8,16]). Linneé, Boerhaave's student, classified diseases according to his botanical methods, and François Boissier de Sauvages in Montpellier did the same, including headache and migraine "from the moon" and "from insects." Samuel Auguste Tissot from Lausanne and Pavia, a student of Sauvages and clinical consultant to Albrecht von Haller, wrote a textbook of neurologic diseases, Traité des nerfs et de leurs maladies, which provided the basic pattern for the Parisian neurologists of the 19th century, including detailed accounts of migraine from his own patients but also from Wefer, Willis, and others. Tissot believed that stomach disorder was responsible for migraine (one of Willis' conflicting theories) (14).

THE IMPACT OF 19TH-CENTURY MAINSTREAM NEUROPHYSIOLOGY: CONFLICTING NEUROVASCULAR THEORIES OF MIGRAINE RESULT IN EARLY ERGOT TREATMENT

Experimental neurophysiology inspired clinical research on migraine in 19th-century France, Britain, and Germany.

In Paris, the concept of "ophthalmic migraine" as a separate entity prevailed for some time (Thomas); in London a continuing effort to understand migraine as a seizure-like disorder continued into the 20th century (Sieveking, Living, Jackson, Gowers). Claude Bernard in Paris (1851 to 1853) and Charles E. Brown-Séquard in Philadelphia (1852) showed that section of the sympathetic trunk in animals resulted in atonia of arteries. In 1860, Du Bois Reymond in Berlin explained migraine by sympathotoxic vasocstruction (his face turned "white" in migraine), but Brown-Séquard objected, proposing vasodilation by failure of sympathetic vasocstruction. In 1867, Möllendorf in Berlin supported this, describing "red" migraine attacks
with flushed skin where he had observed retinal vasodilation ophthalmoscopically. In 1868, Woakes in England first recommended ergot against vasodilation by sympathetic failure in migraine (17). A German version followed in 1869, and in 1871 Eulenburg cited Woakes in his German textbook of functional neurology. In the second edition of 1878 he mentioned ergot as routine treatment. Eulenburg tried to reconcile the two conflicting views of sympathetic activity in migraine, and he recommended ergot injections in 1883. His idea of a combination of neuretic actions of ergotamine and vasodilation seems to have survived throughout the 20th century.

20TH-CENTURY PHARMACOLOGY: PURE ERGOTAMINE FUELS MIGRAINE RESEARCH DESPITE CONFLICTING THEORIES; SEROTONIN RESEARCH REPLACES ERGOTAMINE BY TRIPNTANS

In 1906 Dale showed the sympatholytic effect of ergot extract. Ergot again stimulated research on migraine from 1919, culminating in the classic book of H. G. Wolff in 1948 (27), and in the ad hoc classification of 1956. Ergot treatment had been unreliable because of varying alkaloid contents, but in 1919 Stoll at Sandoz in Basel produced pure ergotamine. Rothlin at Sandoz thought that the adrenergic properties of ergotamine would counteract the sympathetic mechanism of migraine, and his colleague Maier in Zürich did a successful trial in 1925, which was confirmed by Trautmann in Germany in 1928, using placebo controls (24). American clinicians were soon convinced, but Horton at the Mayo Clinic believed in the vasoconstrictive effect of ergotamine counteracting the vasodilation of migraine. Graham, Wolff and Tunis in New York demonstrated that ergotamine decreased migraine headache along with the pulse amplitude measured over the temporal artery. But Horton found out that frequent use of ergotamine induced the “ergot cycle,” where vasoconstriction ended up in vasodilation, which required the next dose of ergotamine, an endless cycle causing chronic headache resistant to any treatment except ergotamine withdrawal. Then Sandoz developed a combination of ergotamine and caffeine, which they sold as a specific migraine attack drug, and they also reversed the vasoconstrictor action of ergotamine by using hydrated ergot compounds, which could still stop a migraine attack. In German-speaking countries, many migraine patients suffered from chronic headache with overuse of analogics. They were treated by replacing the analogics by ergotamines, which were thought to be more scientific, and therefore safe, while in the English-speaking countries “ergot cycle” patients had their ergotamine replaced by analogic combinations (10). Meanwhile Sicuteri in Florence and Lance and Anthony in Sydney demonstrated that the neurotransmitter serotonin was involved in the migraine attack, and could abolish it. Sandoz developed methysergide, a serotonin antagonist, as a migraine prophylactic from ergot. The contradictory effects of the ergot drugs were better understood when the divergent properties of serotonin receptors were determined. From 1980 Humphrey, following the demonstration of a cranioselective effect of ergotamine and methysergide on blood flow, used this approach to develop sumatriptan, a specific serotonin receptor agonist and the first of the triptans, which replaced the ergotamines for migraine attacks. The triptans were initially believed to owe their effect to vasoconstruction, but later evidence indicated that their action on the nervous system is the decisive factor.

REFERENCES

22. Rolfinck W. Ordo et methodus medicinae commentatoriae, hoc est en alde cognoscenti et curandi dolorem capitis Jena: Johannes Niemis; 1671.