

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 Assyrian-Babylonian for Ashurbanipal's library at Nineveh 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 se-

vere 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).

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CLASSICAL CLASSIFICATION: FIRST SPECIFIC DESCRIPTIONS OF MIGRAINE, NOT AURA

In 1st century Rome, Aretaios of Cappadocia 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 *heterocrania* (migraine), *cephalalgia* (mild, infrequent headache), and *cephalea* (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*, *cephalea*) 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 falk 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 10th 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 es-

tablished a pathogenetic classification of *soda* (Arabic from Persian *sardard*, 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 Hildegard 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., Houllier and Fernel [6]) set the stage for the new medicine of the scientific revolution in the 17th century where authors like Harvey and Willis integrated 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 1-1 The Headaches at a Glance

Terms	Age	Risk	Region	Season	Cause	Sign	Evacuation	Regal Cure Full Treatment	Mild Cure	
	Constitution									
1 Soda from heat	Hot	Hot	Hot	Summery	No danger	From taking hot food or drugs or from the sun's heat	Head hot to touch and normal urine and feces	None to do	With rose and sandalwood on the head, and food with grenadine juice	With oil or rose and lemon, and some vinegar on the head
2 Soda from cold	Cold	Cold	Northern	Winterly	No danger	From cold temper of the meninges, from keeping the head bare in cold air	Head cold to touch and improvement from application of warm things	None to do	With a bath and aroma of marjoram, daffodils and musk	A plaster with chamomile, stone clover, calamint and marjoram
3 Soda from hot humor	Warm	Warm	Southern	Summery & of spring	No danger	From blood & yellow bile	If from blood, red face, full veins, great pulse, reddish urine; if from bile, bitter mouth, coarse pulse concentrated urine	Blood letting from the basilica and cephalic vein	Should eat chick-peas and pheasant	With mangel-wurzel and mustard
4 Soda from cold humor	Cold	Cold	Hot	Winterly, autumnal	No danger	From phlegm and black bile	Livid color and congested chest	With jhere pills and cochlearia	With unripe grapes and julep drink, and roborans from unripe grapes	With food of lentils, and baked fish
5 Soda from external heat	Universal	Universal	Universal	Universal	Danger of abscess	From hitting/ beating or from something falling on the head	Throbbing and heaviness and sometimes fever	With blood letting from the cephalic vein and softening enema	Plaster with Armenian lotus, leaves of cypress violets, roses	Plaster with <i>Calamus aronicus</i> , root of grenade, peas and water of roses
6 Soda after evacuation	Dry	Dry	Youthful	Summery	Great danger	From intense blood flow to the nose or flow in the belly	Obstructed bowel movements, sleeplessness, and dryness of the face	None to do	With fat chickens and meat of ram	With soft eggs
7 Hemicranea (sic)	Dry	Dry	Autumnal	Towards old age	Danger for the eyes	From humor of bad quality, cold, or humid	With severe pain extending to the roots of the affected part	With blood letting and expurgation of the inducing humor	Must be brought to sneeze with aroma of marjoram or oil of bitter almonds at the nostril of the affected side	Should anoint for head before onset of paroxysm with oil of daffodils or peonies
8 Soda from the stomach	Hot and humid	Hot	Southern	Senile and adolescent	No danger	From comorbidity of the stomach, or its ascending vapors	It will be mild, with mild stomach trouble, and severe with heaviness of the stomach and vomiting is useful	With vomiting, syrup of acetosella, chalk water	With fried chicken, grenadine juice, and oil of sweet almonds	With the pulp of white bread and sweet grenadine

Translated by H. Isler.

T A C V I N V S XIIII De eo quod multiplicatur in eo de Sola iuxta species ipsius.								
	N O M I N A	C A V S S A	S I G- N V M	E V A cuatio	C V R A regalis	C V R A leuis inuen- tionis		
1	Soda ex caliditate.	Salus, uelti. Regio Tempus Aetas Complectio	Non tumorof. Calida. Actiuum Calida Calida	Excibis calidis stuptis, aut me- dicensis, uel ca- lore solis.	Caliditas ta- ctus capitinis, et æqualis urina & egestio.	Nulla fiat.	Cū rof. & san- dal. sup caput, & cibo cū suc co granati.	Cum oleo rof. aq citrulli, & modico acero super caput.
2	Soda ex frigiditate.	Non tumorof. Serpentrio. Hyemale Frigida	Non tumorof. Meridiona. Actiuum, ueris Calida	Ex frig. cōple- xionis pánicu- los, cerebri, dis- cooptiōe cap. in aére frigido.	Tactus frigidis capitis, & mi- tigatio eius cū rebus calidis applicatis.	Nulla fiat.	Cum balneo, & odore maio- ranæ, narcissi, & musci.	Emplastrēt cū camomillis, co- ro, regia, nepi- ta, & maio- rana.
3	Soda ex humore calido.	Non tumorof. Actiuum, ueris Calida	Non tumorof. Meridiona. Actiuum, ueris Calida	Ex sanguine, & cholera.	Di ex lang. rube- do faciei, reple- tio uenar., ma- gn⁹ pulsus, uri- rusa; si ex chol. os amarii, pul- sus spissus, uri- na intenſa.	Minuatur de- basilica, & ce- phalica.	Cibet iure ci- cerum, aut fa- siiani.	Cum bletsis, & sinapi.
4	Soda ex humore frigido.	Non tumorof. Actiuum, ueris Calida	Non tumorof. Meridiona. Actiuum, ueris Calida	Ex flagmata, & mdacholia.	Liuidus col- or, & strictū pectus.	Cum pillulis yerg, & co- chis.	Cū cibo agre- stis, & potu fu- lep, & rob. a- grestis.	Cū cibo lenti- culæ, & pisci- um ledebeg.
5	Soda ex calid. exteriort.	Non tumorof. Actiuum, ueris Calida	Non tumorof. Meridiona. Actiuum, ueris Calida	Ex percussio- ne, uel alia re- cadente super caput.	Pulsatio, et gra- uedo, & aliqñ do febris.	Cū minutio- ne cephalicæ, & clisteri leni- tiuo.	Emplastrēt lu- to armeno, fo- lijs cipressi, ui olis rof.	Emplastrēt ca- lamo arom.ra- di, granati syl- ueft, pisis, & aqua rof.
6	Soda post euacuationem.	Non tumorof. Actiuum, ueris Calida	Non tumorof. Meridiona. Actiuum, ueris Calida	Ex intenso flu- xu sang. nari- um, & uentris fluxu.	Leuis motus, & uigilia, & ariditas faciei.	Nulla fiat.	Cum gallinis pinguibus, & carnibus arie- tinis.	Cum ouis mollibus.
7	Hemicra- nea.	Non tumorof. Actiuum, ueris Calida	Non tumorof. Meridiona. Actiuum, ueris Calida	Ex hūore ma- la quātitatis, frigido, uel humido.	Dolor fortis, tendens ad ra- dices ipsius partis.	Cū minutio- ne, & purga- tiōe humoris inducentis.	Sternuteēt cū a- ij maioranç, uel oleo amyg. a- maranæ, in nare partis dolētis.	Vngas frons ante aduentū paroxismi cū oleo narcissi, & nardi.
8	Soda cum cō- municatione stomachi.	Non tumorof. Actiuum, ueris Calida	Non tumorof. Meridiona. Actiuum, ueris Calida	Ex cōicatione stōachi in mor- bo, uel ascen- sione uaporis ipsius.	Lene erit, cum lenitate stō achi & grauis cū gra- uedine ipsius. Et confert q̄ uomitus.	Cum uomitu, syrap, acetos. aqua cali, & sale.	Cū galliculo firbeg, aut suc- co granati, & oleo amygda- larū dulciū.	Cū pulte de me- dulla panis al- bi, et succo gra- nati muzi.

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 periostium* [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 deprivations 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 bilious 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 *aurae cujusdam instar ascendens*, 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 pathophysiologic assumptions, there is a hypothesis linking intracranial vasoconstriction 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 Wepfer 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. Wepfer 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, Linné, 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]). Linné, 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 Wepfer, 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, Liveing, 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 sympathetonic vasoconstriction (his face turned “white” in migraine), but Brown-Séquard objected, proposing vasodilation by failure of sympathetic vasoconstriction. In 1867, Möllendorf in Berlin supported this, describing “red” migraine attacks

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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 neurogenic vasoconstriction 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 TRIPTANS

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 adrenolytic properties of ergotamine would counteract the sympathetonic 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 analgesics. They were treated by replacing the analgesics 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 analgesic 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 vasoconstriction, but later evidence indicated that their action on the nervous system is the decisive factor.

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