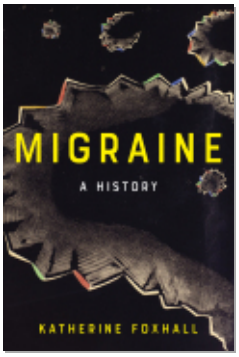
Migraine

Foxhall, Katherine



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"Happy Hunting Ground"

Conceptual Fragmentation and Experimentation in the Twentieth Century

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The Nurse with a Hole in Her Skull, 1936

In 1936, Alfred Goltman, a physician from Tennessee, reported on one of his cases in the prominent medical journal *Allergy*. The patient was a twenty-six-year-old woman with a history of headaches, nausea, and vomiting since childhood. Goltman believed the observations he had made on this patient helped reveal the pathological physiology of migraine. He had first met the woman, a registered nurse, in 1931. He recorded that for as long as she could remember, she had experienced "typical migrainous attacks." A languid feeling warned of the attack's approach before pain, beginning over her right eye, gradually radiated backward until it covered her whole head. The headache would last between one and three days, and, as the pain reached its height, she would vomit. Goltman paid little attention to her family history, but he did note his patient's observation that eating wheat consistently produced an attack. Although wheat had proven to be the principal offending allergen, Goltman's tests also suggested she was sensitive to milk, cheese, seafood, some nuts, fruits and vegetables, feathers, and dust. Measuring her blood count, urine, nitrogen level, blood calcium, and spinal fluid, Goltman found them all to be normal.

Goltman did make one peculiar observation: the nurse had a depression in the left frontal region of her skull. The area, an inch in diameter, also contained a marked concentration of blood vessels. The woman's history revealed that four years before meeting Goltman, she had been admitted to the Memphis Baptist Hospital's neurosurgical service under the care of neurosurgeon Dr. Raphael Eustace Semmes. Semmes was the first neurosurgeon in that city, having been trained at Harvard University by Dr. Harvey Cushing, an Amer-

ican, often known as the father of modern neurosurgery (and, incidentally, the man responsible for suggesting that migraine had been Anne Conway's problem, as we discussed in the previous chapter). In Memphis, Semmes had performed a "craniocerebral exploration" through a burr hole, a small circular opening made in the woman's skull, while she was experiencing a severe headache. As was his usual practice, he performed the operation under local anesthetic. He opened the dura—the thick membrane surrounding the brain and spinal cord—and "a quantity of fluid escaped under increased pressure." Semmes found no evidence of a tumor.[1]

Semmes's procedure drew on decades of excitement about the possibilities of discovering the localization of cerebral function and, related to this, the development of neurological surgery. In the late nineteenth century, British, American, French, and German surgeons competed to open up skulls to treat cranial blood clots, abscesses, tumors, epilepsy, and mental illness, particularly when these had been caused by trauma. Their investigations were aided by technological developments, such as anatomical staining and electrical stimulation, and an enthusiasm for experimenting, using animal studies.[2] Between the 1890s and the 1920s, some surgeons believed brain surgery could cure inherited criminal tendencies and remake a person's social identity by altering their character. Following this theory, some surgeons operated on children who were referred to them by juvenile courts, in an attempt to release pressure on the brain, a procedure with a mortality rate of 42 percent, according to one sample. By the 1930s, the trend of intervening surgically to alter human behavior headed toward its peak with the development of frontal lobotomy as a treatment for mental illness.[3] Semmes's surgical procedure—drilling a hole in the skull of a nurse while she experienced a migraine—marks a moment between what now appear to be two very troubling eras in experimental neuro- and psychosurgery. It is easy to be horrified today by the apparent recklessness and cruelty of lobotomy and procedures related to it, but, at the time, the risks of such surgical interventions were not only accepted in the mainstream—by both patients and physicians— but they were also popular. There were few effective treatments for neurological and psychiatric disorders, and surgery often seemed to work, in a sense, by beneficially changing the patient's personality and restoring their productivity.[4]

Semmes's patient survived the surgery, but her migraine headaches did not stop. When Goltman later observed her healed head, he noticed something interesting: during her headaches, the definite depression that had been left by the skin healing over the hole in her skull began to fill up, "gradually assuming

the appearance of a tumor." The bulge was not tender, nor did it appear as if brain tissue was "protruding through the skull opening." As the migraine attack ended, the swelling would recede and return to a concavity. For Goltman, this added support to the theory, first proposed during the nineteenth century, that migraine headache must be vascular in origin and characterized by dilation of the blood vessels during the attack. Goltman's paper would prove to be influential in the emergence of vascular explanations for the mechanism of migraine during the 1930s, but the combination of experimental surgery, allergic theories, and observations of the brain and vascular system featured in Goltman's paper illustrates how vascular ideas jostled for position among other theories as the international field of migraine research fragmented in the early decades of the twentieth century.

This chapter examines that period's range of medical theories about migraine's causes, symptoms, and definitions. It traces the emergence of the idea that migraine affected not just a particular type of person, based on their gender and social status (as had been common from the late nineteenth century), but a particular type of personality. These debates occurred alongside, as part of, and, in some cases, in opposition to endeavors to find effective treatments. Semmes's procedure on the young woman, and Goltman's later observations about her case, illustrate how migraine came to be seen as potentially fruitful—not to mention frustrating—for a variety of medical specialties in the twentieth century. Ultimately, migraine would be claimed by neurology.

Happy Hunting Ground

In the late nineteenth century, physicians tended to fall into one of two camps—supporting either vascular or nerve-storm theories of migraine—as represented broadly by the ideas of British doctors Peter W. Latham and Edward Liveing, respectively. By the early 1930s, as British neurologists Macdonald Critchley and Fergus Ferguson commented, the condition had become "the happy hunting ground of the theorist . . . attacked by representatives of all branches of medicine."[5] As we saw in the previous chapter, by the early twentieth century, physicians were pessimistic about treatments and disagreed wildly on how to classify and diagnose migraine. In part we can identify the emergence of this situation as early as 1888, in William Gowers's misgivings about either explanation in his *Manual of Diseases of the Nervous System*. In his now classic 1933 textbook of clinical neurology, *Diseases of the Nervous System*, Walter Russell Brain was similarly equivocal, noting that migraine's etiology was a "matter of speculation." For Brain, the most plausible explana-

tion (though he was careful to qualify that this was still hypothetical) was that migraine was due to "arterial spasm followed by dilatation occurring within the distribution of the common carotid artery."[6]

Two decades later, in 1955, Massachusetts physician John R. Graham observed that the field of migraine research had advanced little in two decades. Graham, the founder of the Headache Research Center at Faulkner Hospital in Boston, was becoming an extremely influential figure in migraine research by the 1940s. He was also fond of a good analogy. For him, the best way to represent this professional impasse was with an updated version of the parable of the blind men and the elephant. A cartoon illustrating this appeared as the frontispiece to his little book on the treatment of migraine (fig. 8.1). The original parable came from India, about a group of men who each tried to describe an elephant based on partial knowledge, coming to blows as they disagreed about the others' experience. Graham's version of the fable showed the "ordinary sick headache" elephant surrounded by specialists in white lab coats: a neurologist, a psychiatrist, an allergist, an endocrinologist, an internist, and an ophthalmologist. Each of the men was pulling on a different bit of the elephant. The endocrinologist tugged on the ears, labeled menstrual migraine; the allergist hugged a front leg, designated as cyclical vomiting. The psychiatrist (swinging from a tusk) and the neurologist (peering into the trunk) both appeared to be attempting to tackle classic migraine (migraine with aura). Graham saw the fable as epitomizing the medical profession's attempts to grasp migraine's true nature in the first half of the twentieth century. Each of the elephant's "interesting appendages" had its characteristics, but how these parts were related to migraine as a whole, or shared common physiological rules, remained a mystery. Graham then presented a long list of problems hampering research into migraine pathology and therapies. These included trigger factors, which varied between patients, and observations that migraine often spontaneously remitted or worsened in relation to changing life situations, weather, illness, holidays, or work, "with the result that concurrent medical therapy may receive credit or blame that is not its due." Migraine was notorious for apparently responding to new medicines, and it was greatly influenced by doctor-patient relationships and the placebo effect. Graham felt that trials were being either inadequately carried out or reported. Finally, there was still confusion and disagreement about which headaches should even be included within the diagnosis of migraine.[7]

Before they could determine the shape of the elephant, it seemed, doctors first needed to agree as to which animal they were going to work on. At this

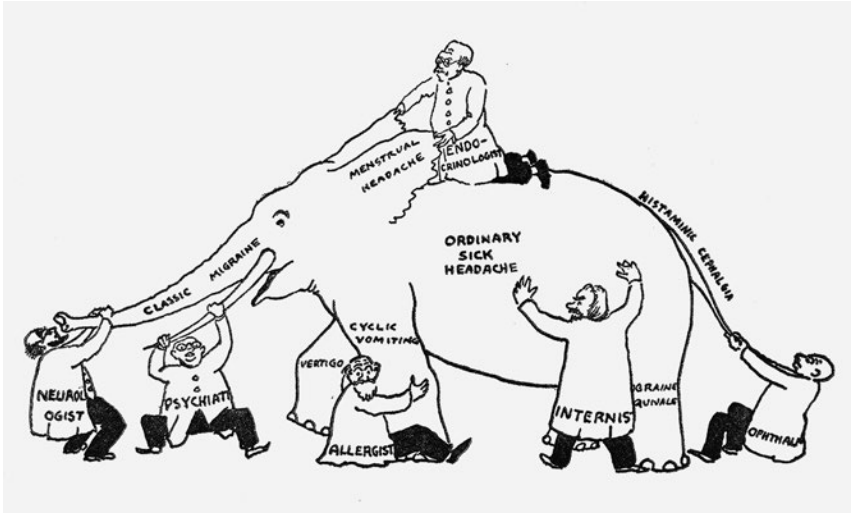

Fig. 8.1. "Ordinary Sick Headache," from John R. Graham, *Treatment of Migraine*, 1956. Courtesy of the Wellcome Library, London, licensed under CC-BY

point, there had been an important shift in the geography of medical authority. Whereas, in the nineteenth century, the main contributions to theories of migraine had come from Europe, by the early twentieth century, many of the most influential researchers in allergy, psychology, and vasculature would be based in the United States.

From Toxins to Allergy

By the turn of the twentieth century, approaches to migraine had embraced theories about uric acid, visual defects, uterine and menstrual disorders, eyestrain, teeth caries, adenoid growths in the pharynx, and abnormalities of the nose.[8] In 1902, J. M. Aikin explained how toxins could be accommodated within Liveing's theory of nerve-storms. The nerve cells, "bathed in their life current," held out against toxins until they were overcome, at which point an explosion—or nerve-storm—occurred. For Aikin, these ideas showed that recent germ theories of disease could also be applied to organisms originating from within the body, which produced disease when they accumulated beyond the body's ability to cope. Aikin proposed treatments to eliminate toxins and restore the processes of digestion through enemas, irrigation, and hot water taken by mouth.[9] Thus it was not much of a leap from seeing migraine as a result of sensitivity to, or poisoning by, toxins in the body to including it within a new and exciting concept of disease, one gaining a great

deal of attention in the early twentieth century—allergy. Moreover, a language based on this idea of sensitivity continued a way of thinking about migraine in relation to nerves, a concept that had emerged in the eighteenth century. In 1906, Austrian pediatrician Clemens von Pirquet had coined the term "allergy" to describe any form of altered biological reactivity. Allergens—including insect stings, pollens, and strawberries—were foreign substances that provoked an immune reaction once they were introduced into a hypersensitive body.[10] During the 1910s, French doctors discussed possibilities for developing desensitizing therapies for a whole range of chronic conditions appearing to originate in hypersensitivity and anaphylaxis, such as arthritis, rheumatism, asthma, and migraine. Factors suggesting migraine might have its origins in allergy included its periodicity, the clear influence of heredity, its early onset in children, and the absence of discernible pathological changes in the body.[11]

George Bray, who worked in the allergy clinic at Great Ormond Street Children's Hospital in London, set out the state of allergy knowledge relating to migraine in 1931. He explained that many migrainous cases also had positive skin tests, often displaying multisensitivity to foods such as wheat, milk, fish, eggs, chocolate, beans, and meats, as well as to inhalants such as feathers and animal hair. Bray suggested that many cases of migraine could be treated solely on an allergic basis.[12] In 1934, influential American allergist Warren T. Vaughan declared that, by using allergic treatment alone, he had helped 50 percent of his headache cases, most of which were migrainous. He was hopeful that future allergic approaches—that is, those advocating the avoidance of particular foods—would provide relief in up to 70 percent of these cases.[13] This was the approach that Goltman had taken with the nurse whose problem opened this chapter, and it seems to have changed very little since the late nineteenth century, when Alexander Haig claimed he had cured his children of migraine by changing their diets. As Matthew Smith has argued, food allergists "were inclined to suspect food allergy as the cause of every chronic health problem encountered in the clinic."[14] Referring to Critchley's happy hunting ground quote, a Danish doctor reflected on how allergists liked to give the impression that they had "captured the prey" of migraine. Nonetheless, by the 1950s, findings of a similar incidence of migraine among allergic and nonallergic persons, and little evidence of a hereditary relationship between it and asthma, were beginning to undermine allergic theories in migraine research, although the significance of food in precipitating migraine attacks was undeniable.[15] The focus on foods and allergy illustrates how Live-

ing's notion of a nerve-storm, decades after *On Megrim* was published, continued to shape the debate by taking it beyond a strictly neural explanatory framework.

In a symposium on migraine held in London in 1963, Vera Walker, a consultant at the Oxford Eye Hospital clinic, described the "continuous stream" of patients with inflammatory conditions who came through the door, of whom at least half had headaches of some sort. Walker recalled that she had begun to take migraine more seriously after discovering Erich Urbach's treatise on allergic diseases, published in 1944. She had become fascinated, to the extent that she "closed the clinic for a month and read everything I could find on the subject of migraine." In 1944, Urbach and Philip M. Gottlieb published *Allergy*, nearly a thousand pages in length. They described migraine as a "symptom complex" and emphasized the importance of eliminating any organic disease before investigating hypersensitivity to foods like wheat and chocolate, or inhaled allergens, such as roses, violets, perfumes, turpentine, naphthalene, and tar. Urbach and Gottlieb proposed that if problem foods couldn't be eliminated, then "deallergization" might be tried. This involved giving the patient minute quantities of the sensitizing foods at first, before gradually increasing the amounts. Walker had learned to suspect an allergy to common foods when a patient reported that their migraine occurred in a definite cycle over the course of days or weeks. "The body can tolerate wheat, milk, eggs, and so on for just so long and no longer," she explained. This time interval could be shortened if some physical shock or nervous tension intervened to precipitate an attack. Walker believed that around half of her migraine patients could be helped by cutting out certain foods, most commonly wheat, cow's milk, cheese, tomatoes, chocolate, fish, and shellfish.[16] In 1962, Macdonald Critchley also talked about migraine as something that built up or became due, to be triggered, for example, by eating chocolate. Critchley recalled Emile du Bois-Reymond's observation from 1860, when, "for some time after an attack, I may expose myself with impunity to certain influences which before would infallibly have induced a seizure."[17]

Endocrine Research

Allergy wasn't the only early twentieth-century discovery that seemed applicable to migraine. In 1905, British physiologist Ernest Starling had given the name "hormone" to the internally secreted compounds produced in glands, including the pituitary, ovaries, and testes, that were carried around the body in the blood. As Chandak Sengoopta notes, these hormones added weight to

the notion of a body regulated by chemicals, rather than the nervous system, and a range of glands maintained hormonal balance, in order for the body to function properly.[18] In 1919, Irving H. Pardee, a physician in the US Army, proposed that "a frontal headache which does not yield to the usual remedies" was one of the earliest symptoms of a malfunctioning pituitary gland.[19] By the 1920s, Sengoopta states, "the glands were seen to possess virtually miraculous powers, not simply over the narrowly sexual aspects of life or behaviours, but over the entire body and mind." With respect to migraine, one theory was that temporary enlargement of the pituitary, rather than hormones per se, put pressure on the cavernous sinuses and caused migraine's distinctive visual and optic disturbances. The hereditary nature of migraine could be explained by an unusually small sella turcica (the depression in the bone in which the pituitary gland is positioned), making a person particularly sensitive to the gland's swelling.[20] In the 1930s, researchers discovered that migraine attacks were preceded by an increased concentration of prolan (a hormone produced in the pituitary that stimulated ovarian follicles) in the urine, and that they could induce headaches by injecting this substance.[21] The authors of one study went so far as to propose that a headache so frequently associated with women's reproductive cycles should be given an endocrine classification.[22]

The availability of a huge range of standardized pure and synthetic hormonal preparations, some of which could be bought in drugstores without a prescription, offered even general practitioners who were interested in migraine an experimental access to the exciting new field of endocrinology. Extracts could either be used individually or in combination, in doses that were entirely up to the clinician to determine. It was completely logical to take a hormone—such as the crystallized ovarian extract theelin, which had been prepared with the restoration of normal sexual function or the treatment of amenorrhea in mind—and apply it to migraine, a disorder that was clearly associated with women's menstrual cycles, or whose symptoms might be explained by a physiological problem located in and around the pituitary.[23]

The possibilities for hormonal experimentation were so broad that Critchley and Ferguson warned of some "pluriglandular therapists" who had brought endocrine therapies into disrepute by being neither "discrete [n]or scientific" in their claims and their use of hormonal products for treating migraine. Critchley and Ferguson were unconvinced by the theory of a swollen pituitary pressing against the sella turcica and observed that "almost all the endocrine organs have been blamed at one time or another for attacks of migraine," but they did accept that practical and theoretical results suggested endocrine

therapies were worth considering for treating menstrual migraine.[24] For instance, E. F. Hartung had recommended using a combination of "anterior and posterior lobe pituitary extract," "whole-gland extract" and "whole powdered gland" in migraine. Other researchers experimented with placental hormone or ovarian follicular hormone (theelin). Critchley and Ferguson recommended theelin and thyroid among a range of treatments that could be administered between attacks.[25] Later researchers proposed that the administration of emmenin (human placental extract) or progesterone might terminate and even prevent attacks.[26] In menstrual migraine, Urbach suggested hormonal substitution therapy, including ovarian, corpus luteum, or pituitary extracts.[27]

California doctor William Moffat described in detail his method for prescribing gonadotropic factor, extracted from the urine of pregnant women (follutein), in cases where migraine was associated with menstruation, a technique he had developed over two years and claimed had worked in all of the seventeen cases of menstrual migraine he had treated. Women would be given a small dose (two to six rat units) between five and seven days after the onset of the menstrual period. The dose was gradually increased over the next ten days, then rapidly increased to a maximum (between 50 and 125 units) on the fourteenth day. Moffat did not know why the gonadotropic factor would work, proposing that it either corrected a previously existing hypofunction, or, giving credence to allergic theories, that the increasing amounts of the preparation desensitized patients and prevented attacks.[28]

Degeneration

In his work on allergy, Urbach quipped that there was only one truly effective prophylactic for migraine: "to persuade an individual suffering from migraine not to marry anyone suffering from the same affliction, or at least not to have any children." Since migraine patients, however, were "quite often talented and highly intelligent personalities," Urbach suggested that this advice would not serve the interests of the community.[29] His statement may have been intended lightheartedly, but it illustrates the continuing importance of a theme that first emerged in chapter 6, when discussions about the relationship between migraine and epilepsy, and the obvious significance of heredity, found migraine a place at the margins of discussions about physical, mental, and social degeneracy. In 1909, in a paper for the *Eugenics Review*, physician and prominent eugenicist Alfred Tredgold had taken long-held ideas about the heredity of nervous disorders a step further.[30] Tredgold warned of the cumulative degeneration that could lead to mental deficiency over subsequent generations.

At first, he argued, the mental change might present itself as migraine or mild epilepsy; later generations might develop insanity or dementia. Over time, the degeneration would become structural, rather than just functional. Eventually, it would produce "actual defect of mind structure—amentia or mental deficiency."[31] For Tredgold, it was vitally important to spot people with "defects" such as migraine, which were at the mild end of the spectrum, to prevent degeneration from progressing far enough over time to impede an entire nation's strength. As Mark Jackson explains, "It was this focus on the degenerative danger of defectives, together with the use of family pedigrees to chart neuropathic constitutions, that linked medical models of feeble mindedness to eugenics, both as a scientific analysis of hereditary difference and as a professional middle-class programme of social and political reform concerned primarily with racial purity and national efficiency."[32] Warnings such as Tredgold's were not just the work of a marginal fringe. In 1913, Britain passed the Mental Deficiency Act, which allowed for the institutionalization of "mental defectives." Ultimately, the eugenicists believed, "some human life was of more value—to the state, the nation, the race, future generations—than other human life."[33] In this light, Urbach's casual comment about breeding takes on a disconcerting significance.

In 1927, British psychologist and epidemiologist Francis Graham Crookshank (a "brilliantly clever, but unstable" man) explained that migrainous men were "thinking introverts" (a phrase he borrowed from psychoanalyst Carl Jung), generally of robust physique, energetic, industrious, and from long-lived families, but with "a certain organ-inferiority" that manifested as facial asymmetry, deviation of the nasal septum, and dental irregularities.[34] The significance of all this, Crookshank suggested, was that "under strain and stress," it was men with these kinds of congenital and acquired inferiorities who had become "functionally blind, deaf, or dumb" during the First World War. Crookshank saw the migrainous brain storm as a "defence and flight and excuse mechanism," analogous to the reactions of men faced with physical danger. Yet it was the psychology of the migrainous person that was most problematic. These were people whose mental state was dominated by repressed rage and humiliation. Sexually jealous as children and maladjusted as adults, such individuals were deeply unhappy, plagued by the need to assert their superiority, not least over the opposite sex. Turned inward, this emotional repression formed the basis of a migraine brain storm. Thus, Crookshank believed, the physician's role was to help a young adult patient—whose life was still before him—"strip himself of his cloak of make-believe" so he could "work out his

own salvation."[35] Crookshank believed he was offering a metaphysical solution to a problem that science could not solve: curing bodily disorder by adjusting the unconscious mind. Crookshank's ideas about the unconscious state of a migrainous person were influenced by the theories of continental psychoanalysts Carl Jung, Sigmund Freud, and, particularly, Alfred Adler, with his work on the inferiority complex. Like many other British doctors, Crookshank took what Tracey Loughran has identified as "a magpie approach," selecting those aspects of continental psychology that seemed most useful.[36]

Freud himself, as has often been noted, had migraine, which he considered to be a tyrant to be rebelled against.[37] In a letter to his wife in 1885, he blamed an attack of migraine on the tartar sauce he had for lunch. He "took some cocaine, watched the migraine vanish at once," and went on writing.[38] We can see in Crookshank's book how a clumsy borrowing of psychoanalytical theories added a new layer to existing understandings of the role of stress and emotions in migraine, but it also shows how the experiences of war had a profound effect on how neurologists, psychiatrists, psychologists, and physiologists understood the relations between mind and body.[39] The postwar context that informed Crookshank's concepts, as well as decades of discussion about migraine as a potential gateway to hereditary degeneration (an association combated by the repeated insistence of many physicians that migraine was a disease of intellect), provide more pieces in the puzzle of how and why migraine's legitimacy became eroded. By drawing on ideas about trauma and neurosis that had informed doctors' responses to the mental and nervous disorders seen in returning soldiers during the First World War, Crookshank was questioning the moral and mental strength of people with migraine.

Migraine Personality

Alongside allergic and hormonal theories, ideas about migraine and personality gained traction during the 1920s and 1930s, particularly in North America.[40] One of the most influential proponents of the concept of a migraine personality was American physician and popular health columnist Walter Alvarez. Much of the discussion about migraine personality took on a very negative tone, but in a self-help book published in 1952, Alvarez presented migraine as a confirmation of his readers' intellectual superiority. Migraine was a plague, perhaps, but at least it was one of "wide-awake, attractive, and well-educated persons." For Alvarez, the typical migraine patient was female, and her headache was only half of the problem. These women had a distinct personality and appearance, so much so that Alvarez claimed one of them

only had to enter the room for him to suspect her trouble. His description was designed to flatter: "such a nice trim figure, such a bright, eager, and intelligent face."[41] When writing for a professional audience, however, Alvarez was less complimentary, describing the women as tense, perfectionist, hypersensitive, easily fatigued, and often depressed or disconnected. Although, in most ways, she would be "decidedly feminine and sexually attractive," there was a masculine element to her nature, "which causes her to act independently and to think dispassionately much as does an able businessman." Many migrainous persons were also allergic, which Alvarez posited as being part of their exaggerated sensitivity in all areas of their lives. In a section that could have been lifted straight out of the nineteenth century, Alvarez explained that many women with migraine had inherited not just a nervous predisposition, but a "frail and sickly body too weak to stand up to the strains of life." While Alvarez did not suggest any outwardly visible physiological inferiority, he did note that these women often had "defective and poorly functioning pelvic organs," dysmenorrhea, and "severe monthly storms."[42]

In 1948, neurologist Harold G. Wolff published *Headache and Other Head Pain*, which would undoubtedly become the most influential study of migraine in the twentieth century. If the previous decades had been characterized by disagreement and fragmentation, Wolff's vascular research galvanized the professional headache community, while his ideas about the "psychobiologic constellation" of migraine also played an important role in cementing assumptions about personality. Wolff collated his observations from a study of forty-six subjects with migraine and found that certain features occurred "with striking frequency." As children, more than half of the migraine patients had been "delicate," shy, withdrawn, and obedient to the desires of their parents. "They were commonly sober, polite, well-mannered children who did their school work conscientiously." But there was another side to this docility; they could be unusually stubborn, or inflexible in certain situations. Overall, Wolff thought, migrainous children were sensitive, but generally trustworthy, energetic, and respected, with the result that they were given responsibilities and special privileges at an early age. By adulthood, their personality traits became distinctive. Tension was an "emotional state common to all," and nine-tenths of the subjects were "unusually ambitious and preoccupied with achievement and success." These were conscientious and hardworking people, perfectionist and exacting. They needed order, and they appeared tireless to others. Their personalities made interacting with others difficult. They were unable to delegate and became inflexible, impatient, and resentful. Although courte-

ous, graceful, and charming, there was little warmth; the migrainous person was cold, aloof, detached. Nonetheless, there were contradictions in Wolff's migraine personality portrait. On the one hand, he observed that these people dressed well, if conservatively, and the women "sometimes sacrificed a degree of attractiveness for austerity or severe neatness," but others, despite having orderly habits of work, were "indifferent about their personal appearance and households."[43] Wolff's diagnosis of the migraine personality was not as overtly gendered as Alvarez's, except in the realm of sex. Among the men, sexual activity was "adequate," but four-fifths of the women expressed sexual dissatisfaction and rarely obtained orgasm. For these women, sex was "at best, a reasonable marital duty."

Wolff described migraine attacks as the result of a failure to adapt to situations in the external environment, such as weekends or vacations, or to an internal bodily state. For "the perfectionist, driving woman," migraine would attack when she refused to acknowledge flagging energy and attempted to perform in her usual manner. Her "essential psychobiologic rigidity" prevented her from making suitable adjustment to changes in her "internal environment."[44] No single characteristic, however, defined the person liable to migraine. Wolff identified a "multiplicity of personality features, life situations, and emotional reactions" as being of importance. He listed so many characteristics that almost anyone might recognize themselves or others as a migraineur.

Wolff's colleague, John Graham, (the author of the elephant parable with which we started this chapter) argued that patients who suffered most from migraine tended to have "a personality that seeks and creates stress and a physiology that handles it poorly." These patients didn't just react over time to an accumulation of stress, they actively sought it out, and even created it. In this statement, we can see how migraine's relationship to stress had evolved from a physiological and hereditary disposition in the nineteenth century to a psychological failing in the twentieth. Accordingly, in addition to the usual prescriptions aimed at restoring and fortifying the nervous body, Graham proposed that treatment needed to be behavioral, by "teaching the patient new attitudes that make it unnecessary to create stresses and easier to withstand those that cannot be avoided."[45] Graham didn't directly discuss the gendered demographics of migraine, but out of thirty illustrative examples in his book, twenty-eight were women. He suspected one forty-year-old woman's story to be "somewhat exaggerated," until a visit to her home verified not only "the prostrating nature of her attacks, but . . . the influence of a schizophrenic

mother and a poverty-stricken life on 'the welfare.'"[46] Graham described a fifty-four-year-old single woman, who was a music teacher and church organist, as rushing and tired, frequently missing meals. It took a conversation with the doctor for her to realize "she was an overly ambitious person who tried to fulfill with too much perfection the requirements of her various jobs." In Graham's examples, migraine appears as a physical and psychological manifestation of the pressures of modern society. A plethora of failings included poor diet; irregular mealtimes; morning deadlines and overcrowded schedules; late awakenings on weekends and holidays, a lack of breaks, failure to take proper vacations or to "get away from their children periodically"; excessive participation in community and church activities; overanxiety about guests, shopping, and vacations; long car journeys; and "acting as chairman (because nobody else will accept)." Migraine patients were particularly unable to delegate, Graham suggested, and "do it all themselves." Evoking once more the nineteenth-century idea of migraine as a nervous storm, or explosion, Graham described all of these failings and deviations from a healthy life as "fuses to the migraine bomb."[47] Education was the most important therapy, and the family physician—the target audience for Graham's book—was the best person for this job. By the late 1960s, it was clear that a major weakness of nearly all the personality studies was that they made no attempt to compare migraine patients with any other group, and they failed to recognize the inherent biases of the self-selecting groups of patients who had sought help from clinics—the population on which the studies were based—rather than representative population samples. Indeed, some physicians were dismissive of the whole genre. "A great deal of nonsense has been written about the lifestyle of migraine sufferers, their personality, attitudes, ambitions, and frustrations," J. B. Foster declared in 1975.[48] As Macdonald Critchley looked back over his career, he admitted that while he had viewed the growth in psychological literature as alarming, later, more nuanced work had been valuable in showing how psychological factors were important as aggravating, rather than causative, factors.[49]

Ergotamine

In addition to their ideas about personality, Harold Wolff and John Graham were key figures in a paradigm shift in understanding the physiological mechanism of migraine. In 1938, a decade before the publication of *Headache and Other Head Pain*, they had published the results of a study that would change the field profoundly, demonstrating unequivocally that the drug ergotamine

had a dramatic effect in treating migraine pain, and that migraine, therefore, had a distinct somatic basis. Perhaps more importantly, they were able to show why ergotamine was so effective.[50] Physiological explanations for the effects of drugs were not incompatible with psychological theories of migraine. Wolff had learned from Adolf Meyer (the psychiatrist responsible for the idea of psychobiology) that psyche, personality, and stress could contribute to physical disease. If personality could be the cause of migraine, then vascular disturbance was the mechanism.[51]

Ergotamine was the only specific drug available for migraine at the time of Graham and Wolff's experiment. Ergot of rye—a common crop disease caused by the fungus *Claviceps purpurea*, in which small, purple-black, elongated ergots replace the grain in the heads of rye and other grasses—had long been known for its ability to stimulate the uterus during childbirth.[52] In 1868, Edward Woakes had recommended the use of ergot extract for migraine, because of its vasodilating effects. By the early 1930s, physicians were regularly reporting on trials of its administration, effects, and complications in medical journals, claiming an efficacy of up to 90 percent.[53] In their study, Graham and Wolff undertook experiments on sixteen subjects over the course of thirty-two migraine attacks. They placed tambours—tiny, drumlike instruments—that could sense the patients' arteries through the skin and attached mirrors to these diaphragms. Rigging up a system of lamps that would throw a beam of light onto the mirror and into the slit of a camera, they were able to record pulsations from the arteries onto a piece of moving bromide paper. They recorded blood pressure at the same time, and the patients—who spent the duration of the experiment "reclining comfortably on a couch"—reported the intensity of their headache. The researchers made initial observations, as controls, before injecting the patients with ergotamine tartrate (Gynergen), produced by the Sandoz chemical company.

One graph from Graham and Wolff's article stood out.[54] It showed unequivocally how the pulsations of the temporal arteries dropped precipitously, either immediately or within a few minutes, after an injection of ergotamine. In ten minutes, the patient reported that the headache had gone. This graph, however, represented only one patient; by no means all responded so dramatically. A second graph showed a much weaker response: a gradual decrease in pain over an hour, accompanied by a similarly gradual overall decrease in pulsation amplitude. In two cases, the pulsations initially decreased and then increased after the administration of ergotamine. In three more, the pulsations increased. Overall, Wolff and Graham reported that across thirty-four

patients, the average reduction in pulsations due to ergotamine tartrate was 52 percent. They also used before-and-after photographs of the forehead of one of their male patients to illustrate the visible constriction of the superficial temporal vessels. They concluded that the most acceptable explanation for ergotamine's ability to end migraine headache was that its vasoconstricting action narrowed the "painfully stretched and dilated" cranial arterial walls, supporting the theory that the pain was due to the distension of these arteries.[55] If psychiatric approaches were designed to prevent the attack from happening in the first place, ergotamine seemed to be the answer once an attack was underway.

British pharmaceutical company Burroughs Wellcome considered developing a new ergot-based drug for migraine in 1948, in response to Sandoz's creation of a product combining ergometrine and caffeine, which promised excellent results.[56] Ergometrine was touted as being even more effective for migraine than ergotamine, and, as one correspondent to the *British Medical Journal* noted, it claimed to avoid the "serious toxic effects" of ergotamine. Moreover, ergometrine could be given by mouth, rather than by injection.[57] In an archival folder of Wellcome Burrough's "developmental rejects," a memorandum reveals discussions about the proposed new product. If caffeine could increase the anti-migraine action of ergometrine, the memo suggested, the combination of ergometrine and caffeine had the potential to be more effective than ergotamine, and have the advantage of considerably greater safety and freedom from side-effects."[58] The proposal seemed promising. "This is interesting—it has possibilities," a scrawled note suggested. Within a month, the Wellcome Chemical Works had been instructed to produce one thousand compressed tablets, to be subjected to a clinical trial. While this particular process appears to have gone no further, Wellcome Burroughs' breakthrough in the migraine market would come in 1956, in the shape of sugar-coated Migril tablets. Migril combined ergotamine with caffeine and cyclizine, a fast-acting antiemetic that prevented nausea, a major side effect of ergot derivatives. Migril's power to avert migraine, if taken as soon as premonitory signs were noticed, gave it an edge over its competitors, notably Sandoz's Cafergot-Q tablets, which promised only "quicker relief" and did not contain cyclizine. Migril was a huge success. By 1961, Migril imitations were available in at least ten countries.[59] By 1967, advertisements in the *British Medical Journal* claimed that over two million migraine attacks per year were being treated with the new drug.

Early marketing campaigns, aimed at physicians, pitched Migril as "today's

master plan against migraine." Leaflets emphasized the importance of cyclizine hydrochloride as a modern breakthrough, making ergotamine bearable in a larger, "truly effective" dose. Migril promised "3D relief": dispelling headache, defeating nausea, and dispersing visual disturbances. For British customers, Migril was available in tablets, while the European market preferred injections. For doctors—ever attentive to their patients' busy professional lives—Migril promised "insurance" with a product that could be taken "anywhere, at any time."[60] The literature implied that simply carrying dosages of Migril improved a patient's life, through the confidence that came from knowing effective "counter-measures" are "now in their hands." Brochures represented men as ballet dancers and jockeys—professions requiring skill, precision, and strength. By 1961, Migril promised to "master" migraine. The imagery was of professional male masters: the hunt master, circus master, schoolmaster, and degree holder (fig. 8.2). These patients could now view their aura not as a threat, but as "a call to prompt and effective action." The brochures depicted men functioning at a high professional level at all times. Their suffering is invisible, internalized, and their professional personas do not betray the inner experiences that require mastering.

Women, on the other hand, were portrayed as sufferers, with their head in their hands, even in leaflets that otherwise used the same language of mastery. When women weren't being shown in pain, they were portrayed as "cured," smiling and able to go on with their colorful social lives. One ad pictured "Mrs. Janice Everett, age 41. Married. Three children. Employed as a bank clerk." Mrs. Everett, in a brightly colored top, getting out of her car, was, of course, smiling (fig. 8.3). In one undated bilingual ad for the South African market, a white woman was shown as half of the doctor's problem: "Migraine is <u>two</u> headaches . . . your patient's and yours" (fig. 8.4). The Migril ads drew on, and perpetuated, highly gendered stereotypes that had emerged about migraine over the preceding century.

We might see the gendered nature of the Migril ads in the context of other postwar pills, like diazepam (Valium), that came to be seen as "mother's little helpers." As David Herzberg has shown for the case of Prozac, advertising for Migril utilized a language of modernity, consumerism, and self-fulfillment, enabling those who took the drug to juggle their modern professional, social, and family lives.[61] There were, however, important differences in how men and women were portrayed. While men appeared nearly as often as women in the brochures' pictures, they were never depicted either with, or as, a problem. They were independent masters, whose engagements with medical prac-

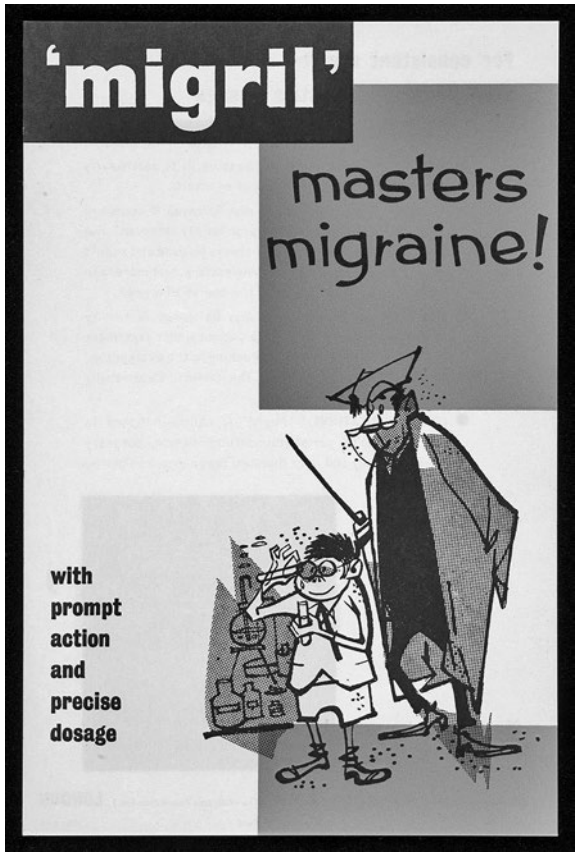

Fig. 8.2. "Migril" Masters Migraine!, Wellcome Burroughs promotional leaflet for migril, 1961, WF/M/PL/199, folder 2. Courtesy of the Wellcome Library, London, licensed under CC-BY

titioners could be seen almost as a professional transaction, procuring insurance and confidence. Women, on the other hand, needed help.

While twenty-first-century marketing materials overwhelmingly portray women, in the 1960s, men were also displayed prominently in the pharmaceutical literature, albeit always as professionals, and always in control of their bodies.[62] All they needed was a little pill-shaped confidence. By 1966, Wellcome Burroughs had updated their approach to marketing Migril, emphasizing speed in addition to mastery. Partly this was a way to help physicians educate their patients. The sooner Migril was taken, the "greater and quicker is the relief of pain," but it also tapped into a lucrative market. Begin-

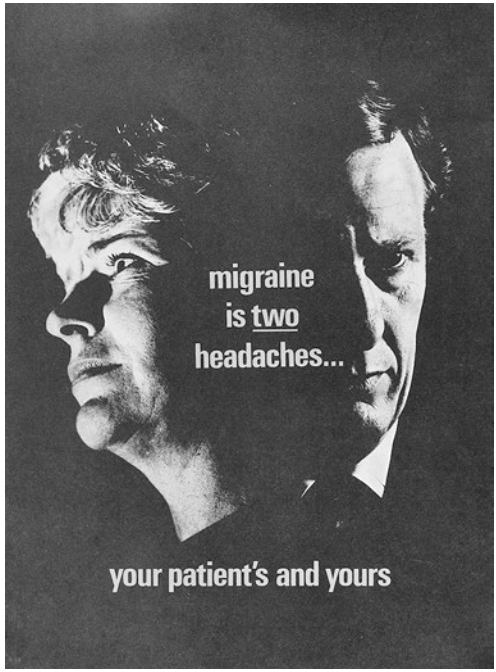

Fig. 8.3. (*left*) "Mrs. Janice Everett, age 41," Wellcome Burroughs promotional leaflet for migril, 1969, WF/M/PL/199, folder 4. Courtesy of the Wellcome Library, London, licensed under CC-BY. *Fig. 8.4.* (right) *Migraine Is Two Headaches*, Wellcome Burroughs promotional leaflet for migril, South Africa, undated, WF/M/PL/199, folder 6. Courtesy of the Wellcome Library, London, licensed under CC-BY

ning in 1968, the advertisements featured a countdown, from "ten" to "stop." The patient described in this campaign was explicitly coded male, gaining protection against "all the symptoms" of migraine, his "confidence restored by the rapidity of effect."[63] It is no coincidence that the idea of the countdown came in the same year that Stanley Kubrick's film *2001: A Space Odyssey* was released. Billed as "a countdown to tomorrow, a roadmap to human destiny," and the "masterwork" of its director, the excitement surrounding this futuristic film tapped into the cultural enthusiasm for space and its exploration. The 1960s had also seen a highly publicized competition to break the land speed record. Speed, modernity, and mastery reflected everything Burroughs Wellcome wanted ergotamine to represent.

The effectiveness of ergot had been widely accepted since the late nineteenth century, but clinical trials conducted in the 1960s gave surprisingly equivocal results. One double-blind controlled trial, conducted on eighty-eight

women and published in the *British Medical Journal* in 1970, suggested ergot was hardly more effective than a placebo. Moreover, the authors found that ergot seemed to aggravate a migraine attack significantly more often than the placebo, and one woman withdrew from the trial because ergotamine made her feel so giddy.[64] Patients' responses to and tolerance for ergotamine were highly variable, whether the drug was given by mouth, injection, or suppository. Overdoses of the drug could result in vomiting, numbness, tingling, and painful cramps, particularly when it was injected. Concern was also growing about the toxic side effects of ergotamine, especially ergotism, a rare but potentially serious condition with symptoms that included convulsions and miscarriage. Ergotamine combined with caffeine was supposedly better absorbed, but the stimulant effect of caffeine might stop patients from sleeping, which was, in itself, often a natural way to end attacks. Other researchers were worried about ergotamine-induced headaches. After prolonged periods of taking ergotamine, the nausea and vomiting of migraine would be absent, but the headache would remain. Further studies reported that ergotamine overuse resulted in constant nausea for between a third and half of the patients. Ergot was dangerous for patients with known vascular disease, liver disease, or pregnancy, and, when taken too frequently, tended to exacerbate the development of the next attack.[65]

In 1956, John Graham had implied that problems of compliance with treatment regimes represented a psychological failing on the part of the patient. In one of his examples, using language highly suggestive of an unhealthy emotional relationship, he described trying to divorce a woman from her ergot with the help of the opioid Demerol and sedatives. Further research on ergot now made it seem much more likely that this was a problem inherent in the drug.[66] In Oxford, Vera Walker was experiencing similar difficulties with patients in her clinic. "The most difficult patients of all are those who report that they have been taking Cafergot, Migril, or Orgraine every 36–48 hours and cannot do without it," she explained. In many cases, migraine drugs appeared to be having a toxic effect. In Walker's experience, the only treatment that worked was similar to one given to chronic alcoholics: a very gradual withdrawal, accompanied by moral support from the physician.[67]

Although ergotamine could be very effective, Jes Olesen remembers that doctors "didn't quite know how to use it." Ergotamine was clearly important, and its action must relate in some way to migraine's pathological physiology, because it had no general sedative or analgesic qualities, but it was a "dirty" drug. It worked on too many receptors and, thus, its mechanisms could not

be used as a way to understand migraine.[68] In 1970, Joseph "Nat" Blau, consultant physician to the National Hospital for Nervous Diseases in London, suggested that if physicians were asked about the drugs they personally took for migraine, it would not include ergot: "They usually admit to taking only a simple analgesic."[69] For all its problems, until the 1980s, ergotamine nonetheless remained the only treatment that *really* worked against migraine attacks, but, compared with specific drugs for other diseases, such as vitamin B12 for anemia or digitalis for heart failure, it simply was not good enough. It frequently failed to relieve attacks, and it did not work for all patients.

There were alternatives, however. Many practitioners continued to use Gowers' mixture, although its pharmacology was not understood.[70] Among the mixture's ingredients, nitroglycerin (which had been William Gowers's drug of choice), amyl nitrite, and histamine all dilated the blood vessels, though this result could be accompanied by unpleasant, even dangerous effects for the patient (as we saw in chapter 5). The promotion of histamine therapy grew out of observations that histamine headache and migraine might be related through a similar vascular physiology. In clinical use, however, it required juggling doses, repeating injections, and even ordering hospitalization, although there seemed to be some evidence that antihistamine might work for some people.[71] At the City Migraine Clinic in London, Marcia Wilkinson reported that sedatives and tranquilizers were often effective if the patient was then able to sleep, a process that commonly ended an attack.[72] Graham shrugged off vitamins as "harmless and a possibly useful adjunct," and he dismissed those who claimed to be able to cure migraine with surgery, comparing them to "the gardener who cuts off the tops of the weeds rather than pull them up by the roots. Sometimes the noxious plants grow again in their original site, and at other times they sprout up again with renewed vigor in new locations."[73] One of the most ardent advocates of combining hormonal and allergic therapies for migraine was British doctor Neville Leyton, at the Putney Migraine Clinic, which opened in February 1950. From the start, the clinic focused on preventive therapy for migraine, rather than acute treatment. In describing the clinic's ethos, E. Harvey Sutherland explained that at Putney, they considered it wrong to send a migraine patient to a neurologist, when "a large number, if not all, of migraine sufferers have some imbalance of the hormones circulating in the body at certain times."[74] The clinic's doctors prescribed hormones to maintain a normal balance in the body and injected or orally administered desensitizing agents. While it might take many months to try the whole range of products, "by far the majority of individuals

who have attended the Migraine Clinic at Putney show very definite improvement," Sutherland claimed. He was highly critical of a medical profession that had been taught migraine was unimportant and untreatable, except with sedatives and ergotamine, as well as of researchers who seemed more interested in the theoretical aspects of headache production than the relief of individuals. "It should seem far more important to patients in general that they should be relieved of their headache than to know just why, scientifically, that headache occurs," he wrote.[75]

Methysergide (later to be marketed as Deseril or Sansert) had been synthesized from lysergic acid (from which LSD is derived) and initially promised "remarkable" results in migraine prophylaxis when its use was introduced by Italian neurologist Federigo Sicuteri in 1959. Most importantly, while ergot had only ever been helpful in ending an attack in progress, methysergide worked as a prophylactic, showing that migraine's cause, as well as its mechanism, must be somatic.[76] The introduction of this drug fundamentally affected how doctors saw their migraine patients, signaling the beginning of the psychological framework's demise. Neil Raskin, an American physician, recalls being quite astonished at how methysergide changed the profession's thinking about the nature of migraine. "Prior to that time, and all through the [19]40s and 50s, migraine was thought to be predominantly psychosomatic," he remembers. "I think back to all those patients that I had sent to psychiatric consultants. . . . Suddenly, patients could take a few tablets of methysergide and within a week they were headache free. No change in their internal milieu. Cured." Even more than ergot had done, methysergide legitimized vascular theories of headache, transforming a psychosocial problem into a scientific one.[77] Unfortunately, unless the drug was used under strict medical supervision, it could produce serious side effects, including nausea, vomiting, diarrhea, insomnia, hallucinations, and retroperitoneal fibrosis, a rare inflammatory disorder affecting the lining of the abdominal cavity. Between the 1960s and the end of the century, tricyclic antidepressants, antiepileptics, beta-blockers, and calcium channel blockers had varying degrees of success in migraine prophylaxis. Nevertheless, some physicians believed a cure-all wonder drug would simply never be found.[78]

Serotonin

The serum vasoconstrictor serotonin (5-hydroxytryptamine, or 5-HT) is one of the most remarkable chemicals in the human body. It is a monoamine neurotransmitter (others include dopamine, noradrenaline, and histamine),

a chemical messenger that performs a fundamental role in the normal functioning of the nervous system. Around 90 percent of the human body's serotonin is found in the gastrointestinal tract, where it regulates intestinal movement. In addition, 5-HT is stored in blood platelets and synthesized in the central nervous system. It regulates sleep, appetite, and body weight, and it is a clotting factor in healing processes. Serotonin affects a person's ability to withstand pain by physically suppressing pain signals. It is linked to mood, and low levels of serotonin are thought to play a role in some mental health disorders, such as depression, aggression, obsessive behaviors, anxiety, and alcoholism.

Serotonin had been named in 1948 by researchers Maurice M. Rapport, Arda Green, and Irvine Page at the Cleveland Clinic, who were working on a newly discovered blood contaminant.[79] In 1953, biochemist Betty Mack Twarog demonstrated the presence of 5-HT in the brains of mammals. Soon, hundreds of papers on serotonin were being published each year. It was clear that serotonin produced an "almost bewildering array" of antidiuretic, vasoactive, psychological, neurological, and gastrointestinal effects throughout the body.[80] For migraine researchers, the possible links between serotonin and migraine were striking, particularly once Wolff and his colleagues had demonstrated that injections of serotonin could produce migrainelike symptoms.[81]

The effectiveness of methysergide, which simulated the effect of serotonin on vascular receptors, strengthened the theory that serotonin must be intimately involved in the biochemical process of migraine headache.[82] Although the drug itself had proven to be problematic, neurologists were convinced that 5-HT played an important role in migraine. In 1961, three researchers from Florence, Italy, drew attention to an increased excretion in urine, during migraine attacks, of 5-hydroxyindoleacetic acid (5-HIAA), a byproduct of serotonin metabolization. Four years later, the Australian-based group of Don Curran, Anthony Hinterberger, and James Lance, working in what had been a "rundown fever hospital" at the University of New South Wales, reported a fall in blood plasma levels of serotonin during migraine headaches. Lance observed that this happened in over 85 percent of their patients.[83] In 1975, Michael Anthony and James Lance proposed that migraine was a "low-serotonin syndrome," caused by some factor in the blood that would lead to a "sudden discharge" of serotonin from storage sites in the body, including the platelets. Edda Hanington's work on tyramine had been particularly suggestive. In 1967, Hanington (who was, at the time, assistant director of the Wellcome Trust in London) had first suggested that a sensitive, localized vascular

response to tyramine (an amino acid derivative thought to be naturally present in many of the common foods implicated in migraine attacks, particularly cheese), might explain some attacks of migraine.[84] By 1981, Hanington and her team were very confident that abnormal platelet behavior (precipitated by stress, hypoglycemia, or dietary or hormonal factors) was inextricably linked with migraine and argued that the disease should be considered a common blood disorder.[85]

Anthony and Lance thought an increase of serotonin in the blood could produce constriction of the intracranial vessels, accounting for mood changes and other neurological phenomena that preceded the headache. As the released serotonin was then excreted or metabolized, its levels in the blood would fall rapidly, causing the vessels in the scalp to dilate and the capillaries in the skin to constrict. Fluctuations in plasma serotonin could also cause nausea and vomiting. As plasma serotonin levels increased, relief would follow.[86] So where did the serotonin go? Some of it would be metabolized as 5-HIAA, as Federigo Sicuteri and colleagues had observed in 1961, while another portion would be excreted unchanged in the urine. Anthony and Lance's theories about the ability of serotonin to simultaneously dilate some blood vessels and constrict others potentially answered one of the major issues Graham and Wolff's earlier work had not addressed: if migraine pain was due to vasodilation, how was one to account for the distinctive pale appearance of many migraine patients during their attacks?[87]

John Cumings emphasized the need for researchers to focus their attention on serotonin. If the cause of the mode of serotonin release and its incorporation into blood platelets could be found, and if researchers could learn how these were controlled, "one would have taken a few steps towards discovering the origin of migraine," he predicted.[88] From the early 1970s, by taking Wolff's observations about distended temporal arteries and Lance's work on 5-HT antagonists as a basis, Patrick Humphrey and his team at the Glaxo pharmaceutical company focused on the pharmacology of methysergide, in order to find out what was unique about its efficacy in migraine. Having identified a new atypical serotonin receptor type (now known as 5-HT_{1B}), localized in cranial blood vessels, Humphrey and his colleagues worked to develop a new drug that would specifically target this receptor.[89]

That drug was sumatriptan, synthesized and patented in 1984. Initial trials proved that it was a highly effective and well-tolerated rescue treatment for migraine patients with and without aura. Marketed as Imitrex, sumatriptan

became available in Holland, Britain, New Zealand, Sweden, Luxembourg, and Portugal in 1991, and a further twenty-five countries by 1993.[90] By the end of the 1990s, there were seven triptans on the global market. For physicians, the results of this drug, the first to be developed specifically for the treatment of acute migraine attacks, appeared to be miraculous. Within minutes, patients' headaches, disability, nausea, and photophobia were significantly reduced.[91] Sumatriptan aborted migraine in half of the patients, and reduced pain in 70 percent. Nevertheless, there were certain concerns about its safety. In 1995, the American magazine *Mother Jones* ran an article by investigative reporter Nicholas Regush, titled "Migrainekiller," reporting the case of Dianne Riley, who had died after being injected with a six-milligram dose of Imitrex. Two months later, her family filed a lawsuit against Glaxo (by then the world's largest pharmaceutical company after its purchase of Wellcome), accusing it of downplaying evidence that the drug could have serious cardiac effects in patients with undiagnosed heart conditions, as well as failing both to label the drug properly to warn doctors of the risks to patients, and to indicate what they should do in case of a negative reaction. The article went on to discuss concerns that Imitrex might have long-term effects on heart vessels, increasing the risk of stroke.[92] Humphrey was well aware of these worries. Ensuring the safety of the drug through studies and emphasizing the importance of diagnosis to physicians was imperative; the possible cardiovascular risks were his "biggest worry for a number of years."[93]

The Neurological Turn

While serotonin was changing how researchers approached pharmacological developments regarding migraine, equally significant changes in classification were taking place. In 1962, the American Ad Hoc Committee on Classification of Headache, chaired by Arnold P. Friedman, MD, and including among its panel members John R. Graham and Harold G. Wolff, had proposed a new classification for headaches. The divisions were based on pain mechanisms and rested on experimental and clinical data, "together with reasonable inference." The committee hoped their classification, although admittedly incomplete, could serve as a diagnostic framework in clinical practice to ensure that patients received proper treatment. While Friedman was a prominent neurologist, the influence of Graham and Wolff's vascular theories on the classification was clear. The committee proposed fifteen categories of headache, of which the first, vascular headache of migrainous type, included five subcate-

gories: classical migraine, common migraine, cluster headache, hemiplegic and ophthalmoplegic migraine, and, finally, lower-half headache. Although the classification was widely used in the years to come, in retrospect Jes Olesen has described it as "completely non-operational." The inclusion of ambiguous words such as "usually" and "commonly" meant that "you could diagnose any kind of headache as migraine according to those criteria if you wanted to."[94]

We might see the ad hoc classification as marking the end of a theoretical era, rather than the beginning of a clinical one. By the 1970s, it seemed increasingly likely that neurological, rather than vascular, processes might be the primary cause of migraine. In America, a new generation of neurologists took over the leadership of the American Association for the Study of Headache, in an effort to transform the field scientifically.[95] In *The Headache and Migraine Handbook*, a guide designed to help members of the general public understand migraine, Nat Blau described how he came to believe "we had been barking up the wrong tree by concentrating on blood vessels alone."[96] He imagined migraine as a symphony with up to five movements: prodrome, aura, headache and other symptoms (the essence of migraine), resolution of headache, and postdrome, or the hangover. Other neurological symptoms of migraine besides aura included photophobia, phonophobia, general irritability, hypersensitivity to vibration and smells, poor concentration, sleepiness, yawning, and even increased libido. Sleep also played a role. This symphony included the entire process of the migraine attack, rather than simply the parts that could be explained by the vascular hypothesis.[97]

In an important paper published in *The Lancet* in 1981, Danish researcher Jes Olesen and colleagues demonstrated that there was no measurable alteration in cerebral blood flow during migraine without aura. This contrasted with classical migraine (migraine with aura), in which they found a wave of diminished blood flow spreading across the brain at approximately two millimeters per minute, a speed that correlated with Leão's theory of cortical spreading depression.[98] Their findings about cerebral blood flow not only undermined a key tenet of the vascular hypothesis, but also posed a significant conceptual challenge for the field by reigniting a fundamental debate about whether migraine was more than one disorder. Olesen and colleagues concluded that the two forms of migraine (classical and common) might have a different pathophysiology.[99] At the City of London Migraine Clinic, Marcia Wilkinson and her team had a number of issues with Olesen's study, not least that it relied on patients whose headaches had been induced with red wine.

Wilkinson argued that comparing spontaneous classical migraine with red wine–induced common migraine was not necessarily valid.[100] Nor did the results account for patients who experienced both classical and common migraine, as Wilkinson herself did. Partly on the basis of the blood flow results, Dewey K. Ziegler proposed that migraine should be thought of as "not one, two, or three illnesses, but several, even a multitude."[101] The ongoing debates about classification also precluded any possibility of accurately understanding migraine at the population level. Into the 1970s, researchers were pointing out that it was not possible to determine migraine prevalence without solving the "important problem" of an accurate definition of migraine, a difficulty that had been raised periodically since the 1930s. In 1975, W. E. Waters and P. J. O' Connor estimated that migraine prevalence in women was roughly twice that of men.[102] In 1980, a community study by researchers in Jerusalem estimated a prevalence of three to one, with an overall prevalence of 10 percent.[103]

The International Headache Society (founded in 1981) published its first *International Classification of Headache Disorders* (*ICHD-1*) in 1988. This was the result of three years' work, with the contributions of twelve subcommittees, and it was the first substantial headache classification to include operational diagnostic criteria. The committee, chaired by Olesen, recognized that there would inevitably be mistakes discovered only through use, but they expressed their hope that the classification would nevertheless inform clinical practice and stimulate interest and research to improve the classification, as well as increase the understanding of headache epidemiology.[104] The committee classified headache into four primary headache groups: migraine (within which, migraine with and without aura were considered to be different types), tension-type headache, cluster headache, and other headaches. Over the following years, *ICHD-1* was accepted widely and translated into more than twenty languages. In the 1990s, the emergence of triptans as a revolutionary new treatment for acute migraine attacks was an important—and successful—early test for these new diagnostic criteria. When combined with the new *ICHD* classification, researchers could follow up with patients much more effectively. For Anne MacGregor, this coincidence is "really incredible."[105] The *ICHD* criteria meant that, for the first time, researchers were able to produce prevalence studies based on internationally accepted and clinically useful criteria. In 1995, the first prevalence study of specific headache types in a general population finally confirmed that women were three times as likely to experience migraine in their lifetime as men.[106]

Conclusion

The twentieth century witnessed the rise and fall of toxic, ocular, allergic, psychological, and vascular theories of migraine. Of all these ideas, the vascular model had proven to be the most enduring, until, by the 1990s, neurobiological explanations of migraine gained the upper hand. Perhaps most significantly, functional magnetic resonance imaging of blood vessels revealed that there was no relationship between the pain of migraine attacks in migraine without aura and abnormal cerebral blood flow. The discovery of serotonin, and drugs that could target its receptors in the brain, was a game changer in the search for effective treatment. The success of triptans that followed had a number of consequences for industrial and academic research on migraine, not all of which were necessarily positive. On a practical level, there was a dramatic effect on the flow of patients to headache and migraine clinics. Anne MacGregor remembers that the "brilliance" of sumatriptan "killed off research on acute patients. . . . Why on earth would they want to not take their triptan, to come along, and be involved in clinical trials when they would then be throwing up in a taxi on the way there?"[107] Triptans also made the pharmaceutical industry reluctant to continue funding research into new drugs because, as Jes Olesen has commented, "people feel that the triptans solve all problems." Then there was the re-ignition of a debate about drug responsiveness and classification. In 1967, Macdonald Critchley had proposed that responsiveness to ergotamine could be considered diagnostic for migraine.[108] The same question came up with triptans. Olesen emphatically rejected any proposal that drug response might be a useful factor in developing a classification, explaining that it would prevent the possibility of testing new drugs.[109] It was clear, however, that while the development of oral triptans represented a real therapeutic breakthrough, as well as a paradigm shift for research, problems related to migraine had not all been solved. A large proportion of patients did not respond to oral triptans, and how they worked remained unclear. Were they acting as a vasoconstrictor on intracranial blood vessels, or acting directly on the neurons in the trigeminal nervous system?[110]

In a 2011 commentary entitled "The Vascular Theory of Migraine—a Great Story Wrecked by the Facts," Peter Goadsby declared that the triumph of neurology in putting migraine "back into the brain," combined with the development of drugs having neuronal, rather than vascular targets, is a victory for patients, freeing them from "any potentially vascular complications of antimigraine therapeutics in the future." Goadsby presented the vascular theory

as a block to medical progress and saw its demise as "ushering a new era."[111] What is striking, however, is how closely this rhetoric of reclaiming migraine for neurology and the brain mirrored discussions from almost a century earlier, proclaiming the triumph of neurosis over biliousness that we saw in chapter 4. Even as migraine has been put back into the supposedly gender-neutral brain, it carries the baggage of history with it.

In particular, the ongoing fascination with, and emphasis on, visual aura has had profound implications for research. The key question of whether the two main types of migraine (with and without aura) are essentially different things remains unanswered. Edda Hanington commented that much of the research published on migraine—including her own on platelet disorder—was based only on subjects who had migraine *with* aura, because it was easy to diagnose accurately. If Hanington's point is relevant to the field as a whole, then it is clear that data obtained from only one group of patients cannot represent the overall migraine population. In particular, it will tend to exclude women whose migraine is related to the menstrual cycle, who may experience the greatest levels of pain, and who form the majority of individuals with the disorder.[112] We simply don't know the extent to which a focus on the recruitment of patients with migraine aura may have skewed the scientific data.