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A. S. Aniskiewicz Lawrence E. Kelly

Major professor

Dr. Albert Aniskiewicz

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NEUROPSYCHOLOGICAL INVESTIGATION OF CLASSICAL AND COMMON MIGRAINE

By

William Mark Hooker

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ABSTRACT

NEUROPSYCHOLOGICAL INVESTIGATION
OF CLASSICAL AND COMMON MIGRAINE

By

William Mark Hooker

Migraine is considered an essentially benign disease but knowledge of the long-term effects of repeated attacks on the brain is limited. Alterations in central nervous system function during the aura of the classical migraine attack have been measured and cases of cerebral infarction during the attack have been documented. A handful of case reports have described progressive cognitive impairment in selected classical migraine patients. Overt neurologic disturbances are absent in the common migraine attack and cases of permanent neurologic sequelae have not been reported. Accordingly, it was hypothesized that a history of classical migraine, but not common migraine, would be associated with permanent and cumulative impairment of higher cortical functioning. A neuropsychological test battery was administered to 16 classical and 15 common migraine outpatients of a university neurology clinic, and 15 normal volunteers. Subjects were matched on sex, age, education, socioeconomic class, and handedness variables, and were free of pain and medication side-effects at the time of testing. Both classical and common migraine groups

demonstrated significantly greater average neuropsychological impairment and reported significantly more cognitive difficulties in everyday functioning than the non-headache control group. Half of the classical migraine subjects exhibited global neuropsychological impairment associated with mild brain damage, a proportion significantly greater than the common migraine or non-headache control groups. The group aggregate neuropsychological data suggests that the classical migraine group had more extensive bilateral anterior and posterior cerebral compromise than the common migraine group. For classical migraine subjects with predominantly lateralized or bilateral neurologic disturbances during the aura, the pattern of neuropsychological impairment was in most cases referable to the neuroanatomically relevant cerebral hemisphere(s). Only weak and indirect support was found for cumulative neuropsychological impairment in the classical migraine group. By contrast, a recency effect was found for the common migraine group, that is, the later the migraine onset and the shorter the history, the greater the average neuropsychological impairment. Though classical migraine presents with transient neurologic disturbance and common migraine with no overt neurologic dysfunction, the present findings demonstrate a continuum of subtle nontransient neuropsychological impairment. This suggests the two migraine disorders are quantitatively related on a pathophysiological dimension which involves a disturbance of cerebral function beyond the attack itself.

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Testing of migraine patients was accomplished at the University of California, San Francisco Department of Neurology under the auspices of Neil Raskin, M.D. I am indebted to Dr. Raskin for his scientific curiosity about the problem I proposed and his willingness to sponsor me. Eleanor Hartman, the administrator of the Neurology Faculty Practice, made me feel welcome and was nothing less than indispensable. Other people who assisted were Elizabeth Bastible, R.N., Terri Badochi, and Leesiza Anderson.

Forty-two migraine patients volunteered to be tested and many more agreed to the selection interview. Without their sacrifices of time and money, hard work, and in some instances, courage, this research would not have been possible. I am very grateful to them.

The difficult job of finding and recruiting matched

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During the last 11 months of the project I also held a full-time job in a research unit of the U.C.S.F. Department of Psychiatry. The director, Reese Jones, M.D., in effect gave me a scholarship to complete my dissertation. This included time off during the day to test subjects and the use of an impressive array of computers for both statistical analysis and word processing. Ronald Herning, Ph.D. provided invaluable statistical advice and good-naturedly tolerated my often erratic work schedule. Kaye Welch lent her word processing expertise and created several tables for me. I am thankful for their support during this busy time.

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CHAPTER I

INTRODUCTION

Migraine is an idiopathic disorder of recurrent paroxysmal disturbance of cerebral function associated with headache and other autonomic and gastrointestinal disturbances. It is considered an essentially benign disorder. However, knowledge of the long-term effects of repeated attacks of migraine on the brain is limited. Sir Charles Symonds postulated over 30 years ago that slight cumulative neurologic damage may occur as a result of repeated migraine attacks (1952). There are no known reports which focus on neuropsychological variables in migraine or which have considered quantifiable, though subtle, behavioral impairment associated with repeated attacks of migraine. The aim of this research project is to investigate the neuropsychological effects of long-term classical and common migraine.

In the common migraine attack no overt neurologic disturbances occur. In the classical migraine attack focal neurologic deficits do occur but are transient and usually resolve quickly and completely. Approximately 10% of the migraine population have classical attacks. In the rare condition of complicated migraine the deficits persist

beyond 24 hours and may become permanent secondary to brain infarction. However, permanent deficits of higher cortical functioning, defined as neuropsychological, may be present in classical migraine as well, though are more subtle and more difficult to detect than are the overt deficits of complicated migraine. The manifest neurologic deficits in classical migraine may clinically resolve, yet more lasting sequelae may be revealed on neuropsychological measures. This has been found to be the case in patients experiencing carotid-distribution transient ischemic attacks (TIA) investigated neuropsychologically 2 to 5 days after the clinical clearing of deficits (Delaney, Wallace, & Egelko, 1980). The guiding hypothesis of the present investigation is that attacks of classical migraine may produce permanent and cumulative, though subtle, neuropsychological impairment. By contrast, attacks of common migraine are not hypothesized to produce permanent or cumulative neuropsychological impairment.

Definition of Migraine

Migraine is actually a group of disorders which have one or more clinical features in common. As no biological markers of migraine have been identified, diagnosis is more or less arbitrary. Most definitions of migraine are merely descriptions of the attack itself.

Traditional classification schemes (Ad Hoc Committee on the Classication of Headache, 1962; World Federation of

Neurology, 1969) consider migraine a primary vascular headache with subcategories of classical migraine, common migraine, cluster headache, hemiplegic migraine, opthalmoplegic migraine, and lower-half headache or facial migraine. The latter category subsumes a number of cranial nerve disorders and cannot be considered exclusively vascular.

Cluster headache, also known as migrainous neuralgia and Horton's histamine cephalgia, shares some clinical features with migraine such as unilateral headpain, similar vascular changes and similar response to symptomatic and prophylactic medication. This has led some authors to suggest a common pathophysiological entity linking the two (Medina & Diamond, 1977; Medina, Diamond & Fareed, 1979; Wolff, 1963). Most authors, however, view the two as distinct due to fundamental differences in epidemiology, attack characteristics, autonomic accompaniments, hormonal and biochemical changes, cerebral blood flow patterns, and response to oxygen inhalation (Ekbom, 1974; Kudrow, 1980; Nelson, duBoulay, Marshall, et al., 1980; Norris, Hachinski & Cooper, 1976; Sakai & Meyer, 1978; Sakai & Meyer, 1979; Sjaastad, 1976).

An enduring traditional concept of migraine is that it is biologically different from muscle-contraction (tension) headache. Challenging this distinction, Raskin (1981) finds the similarities between the two populations more striking than the differences. The sex ratio, age of onset and natural history of the two disorders are similar. Tension

headache patients are susceptible to vascular pain (Krabbe & Olesen, 1980), and migraine headache patients demonstrate as much if not more scalp and neck muscle contraction at rest, or in proportion to pain severity (Anderson & Franks, 1981; Bakal & Kaganov, 1977; Martin & Matthews, 1978). In distinction to migraine, focal neurological dysfunction, nausea and vomiting, and significant changes in cerebral or extracranial blood flow are absent in tension headache patients (Bakal & Kaganov, 1977; Mathew, Hrastnik & Meyer, 1976; Sakai & Meyer, 1978).

Subclassification of migraine is largely an author's prerogative. A most parsimonious scheme consisting of five categories has been presented by Lance (1981). Premonitory migraine consists of variations in mood, alertness or behavior preceding migraine headache by up to 24 hours. This form of migraine has also been termed complete migraine (Blau, 1980). Symptoms experienced an average 10 hours before the headache include elated and depressed mood variations, sleepiness, mental dullness, hunger and craving for sweets, and constipation.

Prodromal migraine includes classical migraine and consists of a focal and reversible neurologic disturbance preceding the headache by 10 to 60 minutes called the aura. Visual disturbance is the most common aura symptom of classical migraine though the entire spectrum of neurologic dysfunction--sensory, motor, cognitive, mnestic--is represented. In Europe such prodromata are described as migraine accompagnée (Bruyn, 1968).

Episodes in which focal neurologic symptoms extend into the headache phase but completely resolve within 24 hours are termed protracted prodromal migraine. Cases which fall in this category include hemiplegic migraine involving transient hemiplegia and unilateral paresthesia (Bradshaw & Parsons, 1964), vertebrobasilar migraine in which there is a slow onset of loss of consciousness lasting 10 to 45 minutes succeeded by throbbing headache (Bickerstaff, 1961), and migraine stupor in which patients remain stuporous or comatose for hours to days with associated transient neurologic symptoms of homonymous hemianopia, ataxia and dysarthria (Lee & Lance, 1977).

Acute confusional states resembling toxic metabolic psychosis observed in a small number of children with migraine belong to the protracted prodromal migraine category as well. Attacks of acute confusional migraine have been reported in five boys and girls between the ages of 5 and 16 in 100 successive cases of children with migraine (Ehyal & Fenichel, 1978). The confusion, disorientation, and agitation lasts an average of several hours and typically terminates in deep sleep from which the child awakens in a normal state.

Nonprodromal migraine is Lance's third category and includes common migraine. Nonprodromal migraine is the most frequent type of migraine. The episodic headache is usually unilateral and associated with anorexia, nausea, vomiting, and photophobia. There are no overt focal neurological disturbances.

Episodes of migraine headache in which focal neurologic disturbances develop concurrent with headache intensification are called interposed migraine. Most cases of opthalmoplegic migraine belong to this group. Opthalmoplegic migraine is rare and typically occurs in young adults with established migraine. It manifests as a unilateral partial 3rd nerve palsy with pupillary involvement (Hedges, 1979), though complete pupillary involvement is not always present (Vijayan, 1980). The headache is usually localized to the ipsilateral orbital or retro-orbital area and is described as especially severe and longer lasting than the average attack.

The migraine equivalent category represents cases in which a gradual onset of transient focal neurologic disturbance occurs but without subsequent headache. Symptoms may be identical to those found in prodromal migraine or may be gastrointestinal, cardiorespiratory, genitourinary, or dermatologic disturbances (Whitty, 1967). Mood and thought disorders have also been described (Catino, 1965; Pearce, 1975).

Another inclusion within the migraine equivalent category are the cases of patients over the age of 40 who experience transient focal neurologic deficits without headache for the first time. Episodes in which the symptoms show a classical migraine buildup, orderly progression, or cross to the opposite side of the body, and after which biomedical tests prove negative, may be transient migrainous accompaniments (Fisher, 1968, 1979, 1980).

The final category, complicated migraine, is reserved for those cases of migraine in which a transient focal neurologic deficit persists beyond 24 hours. Complicated migraine may be the outcome of any migraine disorder other than common migraine. Permanent deficits secondary to infarction of the retina, cerebral hemisphere, or brainstem have been reported (Pearce, 1975). Other noteworthy reports of complicated migraine concern life-threatening (Ferguson & Robinson, 1982), and fatal (Guest & Woolf, 1964) cases.

History of Migraine

Migraine is as old as recorded history. Perhaps the first accounts of migraine are found in Sumerian and Babylonian poems dated approximately 3,000 B.C. Egyptian medical documents contained in the Ebers Papyrus written in 1,550 B.C. or earlier describe migraine headache treatment (Lance, 1982). Hippocrates described a syndrome of periodic headache with visual disturbance and vomiting. The first definitive account of migraine is attributed to Aretaeus of Cappadocia, born around A.D. 81 (Critchley, 1967). Aretaeus used the term heterocrania to describe unilateral or focal headaches associated with nausea, vomiting, and topor. A century later, Galen introduced the term hemicrania, of which the Old English translation was megrim, which translated in French is the current term migraine (Lance, 1982).

The first discription of neurologic deficit in an

attack of migraine was likely recorded by Caelius Aurelianus in his 5th century A.D. medical treatise (Drabkin, 1950, cited in Schiller, 1975). He reported the sudden fogging of vision and the appearance of lines resembling the veins of marble. The first report of transient hemisensory loss and weakness accompanying a severe headache came from Charles Le Pois in 1618 (Riley, 1932, cited in Lance, 1982).

Accounts of migraine and pathogenic theories multiplied in the 18th and 19th centuries. In 1727 the Swiss physician Wepfer proposed that congestion of blood in the cerebral vasculature was the cause of both migraine and epilepsy (Wepfer, 1727, cited in Schiller, 1975). This mechanistic, hydraulic explanation might be considered the first vascular theory of migraine. In the same decade another Swiss physician, Tissot, introduced perhaps the first neurogenic theory. According to Tissot, migraine was a form of supraorbital neuralgia secondary to a "sympathy" between the trigeminal nerve and stomach, gall bladder, or uterus (Tissot, 1783, cited in Bille, 1962).

In 1778 Fothergill reported in detail the visual symptoms of classical migraine and was the originator of the term fortification spectra used to describe the characteristic zig-zag luminesent lines (Fothergill, 1784). In 1824 Wollaston reported the phenomenon of hemianopic scotoma in his own classical migraine attacks (Wollaston, 1824). G. B. Airy (1865) described both visual and aphasic disturbances in his personal migraine attacks. He concluded that the visual symptoms were not retinal but cortical in

origin. Airy's son, Hubert, also a physician and sufferer, hypothesized that the nervous disturbance responsible for the visual symptoms propagated to other local regions of the brain, such as Broca's area, thus causing language disturbances (Airy, 1870).

The clinical documentation of a 3rd cranial nerve palsy during an attack of migraine was first described in 1882 (Saundby, 1882, cited in Kudrow, 1978) though the term ophthalmoplegic migraine is attributed to both Saundby and Charcot (Charcot, 1890, cited in Vijayan, 1980).

The first comprehensive work on migraine was Edward Liveing's treatise, "On Megrim, Sick-Headache and Some Allied Disorders" (1873). Liveing reviewed the many neurologic manifestations of migraine and proposed a neural rather than vascular etiology. Noting the shared characteristics of migraine and epilepsy, Liveing hypothesized a "nerve storm" traversing from the optic thalami to the ganglia of the vagus. John Hughlings Jackson (1876/1932) agreed that migraine was a form of sensory epilepsy due to a "discharging lesion" of the optic thalamus. He believed the headache and vomiting to be "post-paroxysmal epiphenomenon" (p. 153fn.).

William Richard Gowers (1893), a neurologist of equal stature to Jackson in British medicine, regarded the term "nerve storm" as inappropriate though believed that nervous discharge and inhibition processes were in effect in both migraine and epilepsy. He thought the vascular hypothesis incapable of explaining the peculiar and uniform neurologic

disturbances found in migraine.

Paul Julius Moeblus stated the central tenet of the neurogenic theory of migraine succinctly: "Parenchyma is the master, circulation the servant" (1894, p. 97, cited in Schiller, 1975). However, neurogenic explanations of the headache itself were not so facile.

Several vascular theories of migraine were put forward in the nineteenth century. Emil duBois-Reymond, a leading figure in German medicine, believed migraine headache was due to tonic vasoconstriction caused by irritation of the cervical sympathetic nerves (duBois-Reymond, 1860, cited in Bille, 1962). Mollendorf, conversely, thought the pain was caused by vascular dilatation secondary to cervical sympathetic nerve paresis (Mollendorf, 1867, cited in Bille, 1962). P. W. Latham (1872) proposed a vascular cause of the neurologic disturbances, namely cerebral arterial constriction.

The first experimental investigations of migraine were performed by Harold G. Wolff and his colleagues in the 1930s and 1940s. While greatly furthering our understanding of some of the vascular changes associated with the headache phase, Wolff's (1963) studies are certainly not definitive with regard to migraine pathogenesis. Neurogenic, metabolic, and new variants of the vascular theory are proffered in the current migraine literature. As Lance (1982, p. 6) has observed, Gower's conclusion that, "When all has been said that can be, mystery still envelops the mechanism of migraine," remains timely today.

Epidemiology of Migraine

Prevalence

Studies of migraine prevalence have produced notably variable results. This is due to the lack of uniform diagnostic criteria for migraine as well as differences in the populations sampled. Generalizations to the population at large based on highly selected migraine clinic patients is unfortunately a common practice. Not only do biases exist in terms of the severity of the headache and perhaps the presence of other illnesses, but there is evidence that such patients belong to higher social classes and are more intelligent than those with migraine who do not seek medical care (Waters, 1971b).

Furthermore, clinical samples may contain a disproportionate number of psychotherapy patients relative to the general migraine population (Schnarch & Hunter, 1980). Finally, there is evidence to suggest that approximately one-half of those with migraine never consult a physician for it (Waters & O'Connor, 1970). This is also the case for children with severe migraine; in a sample of 73 migrainous children, ages 7 to 13, only 24 had sought medical help (Bille, 1962). Thus, prevalence rates derived from medical patient samples may actually underestimate the true incidence of migraine.

The epidemiological method of employing standardized selection criteria in a survey of the entire population

within a well-defined community has proven valuable in the study of migraine prevalence. Waters (1970) has developed a self-administered questionnaire assessing presence of headache within the preceding year, frequency and severity, unilateral pain distribution, associated nausea or vomiting, and preheadache warning or visual disturbances. The latter three criteria have been found to be significantly associated with headache severity.

In a clinical validational study of these criteria, Waters and O'Connor (1970) surveyed 86% of all the females aged 20 to 64 in a defined area of Glamorgan, South Wales. Of 2,933 women, 78.7% reported a headache in the previous year. Within this group, 29.1% had headache alone; the remainder had one or more of the three migraine features. Random samples of subjects reporting each feature singly or in combination were clinically assessed by a neurologist as having migraine or not. Extrapolating to the entire questionnaire sample, 19% of these women were diagnosed with migraine based on the presence of one of the three clinical features, and 6.1% based on all three features.

Other questionnaire surveys using the criteria of all three clinical migraine features have reported a 7.3% incidence rate in 1,293 randomly selected American adults (Schnarch & Hunter, 1980) and a 5.6% rate in 1,859 adults working in Central London (Henryk-Gutt & Rees, 1973). Three separate surveys of areas in South Wales, South-West London, and the Isles of Scilly, yielding a total of 1,977 men and 2,237 women, report prevalence of at least one clinical

migraine feature in the preceding year to be between 14.9% and 19.5% for men and between 23.2% and 28.7% for women (Waters & O'Connor, 1975). A Migraine Trust survey of 4,965 men and 9,928 women, using unspecified criteria, reported 19.4% and 25.7% prevalence rates, respectively (Green, 1977). Clearly, migraine is more frequent in women than in men in the general population. In large migraine patient series, women account for 60-75% of the sample (Lance & Anthony, 1966; Selby & Lance, 1960).

Age of onset

Bille (1962) studied the prevalence of headache in 9,059 Swedish school children between the ages of 7 and 15. Four percent met the criteria for migraine, including four cases in which migraine was diagnosed retrospectively between the age of 1 and 2-years-old based on symptoms of paleness and attacks of screaming and vomiting. Prevalence rates prior to puberty showed no significant sex differences: boys and girls aged 7 to 9, 2.5% and 2.4%, respectively; ages 10 to 12, 3.9% and 5.4%, respectively. However, the age 13 to 15 group showed a significant sex difference in prevalence: boys, 4.0%, and girls, 6.4%. Similar findings were reported by Dalsgaard-Nielsen's (1970) survey of 2,027 Danish school children in which the modal age of migraine onset was age 10 for boys and age 12 for girls.

In a retrospective study of 84 patients diagnosed with migraine as children, the age of onset ranged from 18 months

to 14 years with an average of seven-and-a-half years (Prensky & Sommer, 1979). A retrospective study of 500 adult migraine patients found the greatest proportion of migraine cases beginning in the second decade (Selby & Lance, 1960). Only 8% of 513 migraine clinic patients reported migraine onset after age 40 (Steiner, Guha, Capildeo, et al., 1980). Onset of severe or disabling headache after age 40 is similarly rare in the non-patient population (Ziegler, Hassanein & Couch, 1977). A study of 513 patients attending a migraine clinic found that migraine onset under age 20 was predominantly of the classical type whereas past age 40 there was a trend toward more common migraine symptomatology (Steiner, et al., 1980).

Natural history

Whitty and Hockaday (1968) studied a group of 92 patients for a period of 15 to 20 years. The 53 women and 39 men had had migraine for 16 to 69 years. Sixty-three patients still had their attacks. There was no clear tendency for attacks to diminish with age; half of the 18 patients over age 64 continued to experience migraine. Advancing age was associated with loss of vomiting and aura, however. Age of onset did not have any bearing on the persistence of the attacks. However, two-thirds of the patients with continuing migraine reported the attacks had become less severe, less frequent, or both. Forty women in the study had undergone menopause. No change in the migraine pattern was experienced by 18 women, and for 6 it

became worse. Only two women had their migraine attacks end. This finding contradicts the widely held belief that migraine ceases or improves after menopause.

Bille (1981) longitudinally studied the 73 children with pronounced migraine identified in the 1955 survey of headache in Swedish school children (Bille, 1962). At a follow-up of 23 years, when the children were all over 30 years old, 38% were still having at least one attack per year. During puberty or as young adults, 62% reported being migraine-free for at least two years. But 22% of this group reexperienced regular attacks of migraine after an average of 5.6 migraine-free years. Adulthood attacks were reported to be milder than those of childhood. In 52% of the cases the attacks were both less severe and less frequent. Forty percent were free of migraine at age 30, significantly more males than females becoming migraine-free (52% vs. 30%).

Familial history

The presence of migraine in the relative of a person with migrainous features often is a factor in the diagnosis of migraine. Such "positive" family histories are commonly reported but have rarely been studied critically. Estimates of familial migraine prevalence are subject to the same biases in all migraine prevalence research. In addition, most studies rely on second-hand reports from probands, not from direct interviews (Ziegler, 1977). Positive family histories of migraine have been reported in 46% to 90% of migraine patient cases in uncontrolled surveys (Dalsgaard-

Nielsen, 1965; Lance & Anthony, 1966; Prensky & Sommer, 1979; Selby & Lance, 1960). Bille's (1962) controlled study of migraine in children found a positive family history in 11.4% of 473 children with frequent though non-paroxysmal headaches and 63.6% of 484 children meeting migraine criteria. However, criteria for the latter group included a positive family history.

Water's (1971b) well-controlled study of 524 first-degree relatives over 21 years old of randomly selected individuals with migraine and individuals without headache in the previous year did not find a significant difference in migraine prevalence. Families of migrainous probands had a 10% prevalence rate whereas non-headache proband families had a 5% rate. The difference reflects a trend of greater familial prevalence of migraine among migrainous individuals but is not nearly as large as reported in other studies. This is likely due to Water's strict definition of migraine (unilateral pain distribution, associated nausea or vomiting, and preheadache warning) and disregard of family history as an inclusion criterion.

Significant sex differences exist in the familial prevalence of migraine. In a non-controlled questionnaire survey of migraine in a non-patient population, Green (1977) found the mother of migrainous individuals was the most frequently cited relative with reported migraine (52-54%). Prensky and Sommer (1979) found migraine to be almost twice as common in the female relatives of children diagnosed with migraine than in the male relatives. In Bille's (1962)

group of 73 children with pronounced migraine, 72.6% of the cases had a mother with reported migraine and 20.5% had a migrainous father.

In a 23-year follow-up of these 73 children (Bille, 1981), 47 had a total of 90 children, evenly divided between daughters and sons, who were 4-years-old or older. Fifteen of these 47 parents (32%) had one child with diagnosed migraine. Thirteen of the 28 mothers and only 2 of the 19 fathers had migrainous children. Ten of the 15 migrainous children were female. Bille (1981) concludes that migraine seems to be more often inherited by girls and more frequently via the mother.

Characteristics of the attack

In a series of 500 migraine patients, over half experienced attacks one to four times a month and two-thirds reported an average attack duration of less than 24 hours (Selby & Lance, 1960). In a controlled study of randomly selected individuals with classical and common migraine, the mean number of attacks per year was eight for both conditions, whereas female migraine clinic patients reported an average of 40 attacks (Henryk-Gutt & Rees, 1973). For men with classical migraine, the mean duration was 13 hours, and for common migraine, 11 hours. Women reported a mean duration of 24 hours and 19 hours for classical and common migraine attacks, respectively. Migraine clinic women reported a mean 31-hour duration. By contrast, the duration of untreated attacks in the 73 children with severe migraine

was usually briefer, in most cases 1 to 3 hours (Bille, 1962).

Attacks are reported to occur most frequently on Saturday or Sunday (Green, 1977). Three-quarters of attacks are reported to occur in the daytime (8 a.m. to 8 p.m.) (Waters & O'Connor, 1971).

In large series of adult migraine patients, unilateral pain distribution is reported in 38% to 68% of cases, and bilateral pain in 38% to 44% of cases (Lance & Anthony, 1966; Olesen, 1978; Selby & Lance, 1960). In one series, 54% of those with unilateral pain reported the same side was invariably involved (Selby & Lance, 1960). The right hemicranium was significantly more often the site of pain than the left in a group of 750 acute migraine attack patients (Olesen, 1978) and the left hemicranium was reported more often in 73 migrainous children (Bille, 1962). A bifrontal distribution of headpain is the most frequent pattern in children (Bille, 1962; Prensky & Sommer, 1979).

Systematic palpation of the chewing and neck muscles revealed mild tenderness in 23% and marked tenderness in 46% of 750 migraine patients during the acute attack (Olesen, 1978). The side of the tenderness was associated with the side of the headache. There was no correlation found between the duration of the attack and the degree of muscle tenderness, but a strong correspondence existed with the presence of vomiting and the history of interictal milder headache. In another survey, scalp tenderness was reported in 65% of 500 cases (Selby & Lance, 1960).

The quality of pain in the acute attacks of 750 migraine patients was reported to be severe in two-thirds, moderate in 30%, and mild in only 2% (Olesen, 1978). The pain was described as throbbing and pulsating in 47% of the cases, and pressing and tightening in 42%. Severe head pain was most often characterized as throbbing and pulsatile.

Abrupt onset of headache occurred in the attacks of over half of the children with pronounced migraine and slow onset was reported in 41% (Bille, 1962). Most of the children described a feeling of exhaustion and sense of well-being shortly after the attack. Over half of the children usually fell asleep.

Nausea and vomiting are very frequent accompaniments of the migraine attack. In Selby and Lance's (1960) series of 500 migraine clinic patients, 87% experienced nausea and 56% experienced vomiting in their attacks. Photophobia was present in 82% of the cases. In another series of 500 patients (Lance & Anthony, 1966), 59% reported both nausea and vomiting, and 16% reported diarrhea in addition. Polyuria during the attack was reported by 29%.

Focal neurological symptoms of all types were found in 64.8% of 500 adult migraine patients (Lance & Anthony, 1966). Visual disturbances reported preceding or during the headache (32.8% of the sample) included fortification spectra (10.2%) and photopsia (26.0%). The two rarely occurred in the same attack. Internal carotid symptoms (e.g., aphasia, paresthesia) were documented in 3.6% of the cases. Symptoms referable to the brainstem and the

vertebrobasilar arterial supply (e.g., diplopia, vertigo, dysarthria, ataxia) occurred in 24.4% of the cases.

Ninety-seven of 500 patients (19.4%) reported some form of impairment of consciousness in a migraine attack (Lance & Anthony, 1966). Syncope, confusion, amnesia, automatism, faintness, faints and epileptic seizures (two patients) were all reported. Of the 324 patients reporting some form of neurologic dysfunction, 24.7% had experienced some change of consciousness during an attack. This is contrasted with only 9.7% describing an alteration in consciousness of the 176 patients who had never experienced a neurologic dysfunction as part of their migraine attack.

Relation to other variables

Variables of general intelligence and social class of non-patient migrainous adults and children have been compared with matched random controls, and no significant differences for either sex have been found (Billie, 1962; Waters, 1971b).

The variables of blood pressure, visual acuity, and proportion wearing spectacles was studied in these same adult migraine and control groups (Waters, 1971b). No significant intergroup differences were detected.

Motion sickness was reported in 54.8% of the children with pronounced migraine and 31.5% of the control children--a significant difference (Billie, 1962). Waters (1972) found migrainous adults reported significantly more childhood bilious attacks and eczema in both sexes, and travel

sickness in men, than in matched non-migrainous adults. Even when an index of degree-of-neurotism was controlled for, these differences remained significant. Interestingly, the control group of non-migrainous headache subjects had prevalences of bilious attacks, travel sickness and eczema intermediate to the non-headache and migraine groups.

Precipitating Factors in Migraine

Certain influences are often identified in the provocation of individual migraine attacks. In fact, headache occurring monthly in association with menses is virtually diagnostic of migraine (Raskin, 1981). Other precipitating influences such as ingestion of wine or cheese are also highly characteristic of the migraine syndrome. However, for most migraine sufferers precipitating factors account for only a proportion of their attacks. Isolating and eliminating such influences or triggers does not necessarily prevent migraine. In most cases, an overall improvement in the course of the migraine history is a likely outcome. Unfortunately, consistent improvement is often impossible because most migraine sufferers experience a changing susceptibility to triggers throughout their migraine years, resulting in repeated exacerbations and remissions (Saper, 1983).

Stress

Stress and emotional conflict are the most commonly reported migraine attack triggers. Sixty-seven percent of

Selby & Lance's (1960) 500 adult migraine patients cited emotional events in the onset of one or more attacks. In another study, 50 migrainous adults prospectively studied their attack precipitants for two months; stress was identified in the attacks of 50% and 56% of the men and women with classical migraine, respectively, and 65% and 45% with common migraine, respectively (Henryk-Gutt & Rees, 1973). Emotional conflict at school or home was identified by 33% of 73 children with severe migraine as the most common trigger of their attacks (Bille, 1962). School work, especially examinations, was the most common precipitant for 59% of the children.

While stress is often implicated in the onset of migraine, it is an ill-defined term and situational factors associated with migraine onset need to be studied (Bakal, 1975). For instance, many patients report migraine following stress, such as the weekend or the first day of a vacation after a stressful work week. Psychological theories of migraine have focused on the interaction between predisposing personality factors and conflictual situations triggering migraine attacks. Another perspective considers such situational factors to be nothing more than ordinary stimuli to which a migraine response indicates an underlying biologic lowered threshold (Raskin, 1981).

Hormonal

Hormonal changes in women, specifically menarche, menstruation and ovulation, are often associated with the

precipitation or worsening of migraine attacks (Saper, 1983). Approximately 60% of women with migraine report attacks occurring in conjunction with their menstrual cycle (Lance, 1982). Waters and O'Connor (1971) found the highest incidence of migraine during the first few days of menstruation, and the next highest incidence during the week following menstruation. In one study of women with migraine, 14% experienced their migraine attacks exclusively before or during menstruation (Epstein, Hockaday & Hockaday, 1975).

Women with menstrually-related migraine are more likely to have onset of migraine at the time of menarche. They are also more likely to experience relief during pregnancy (Epstein, et al., 1975). Somerville (1972b) studied a group of 200 pregnant women and identified 31 women with a pre-pregnancy history of migraine, 77% of whom showed improvement during the pregnancy. In Lance and Anthony's (1966) prospective study of 375 female migraine patients, 120 had a total of 252 pregnancies. Of this group, 63.6% of the women with menstrually related migraine reported migraine relief during pregnancy compared to 48% of the women without menstrually associated migraine.

Some women experience migraine for the first time during pregnancy (Callaghan, 1968). In Somerville's (1972b) study of 200 pregnant women, 7 of the 38 women with migraine had developed their attacks during pregnancy, most commonly during the first trimester. The first week post-partum is often a time of migraine reemergence (Stein, 1981). Fifteen

of 40 randomly selected women on a post-partum hospital ward reported migraine-like headaches the first week following delivery. Nine of 14 women with previous migraine and 6 of 8 women with previous menstrual migraine had post-partum headaches. These are all significant percentages and are contrasted with the only 6 of 26 women without previous history of migraine developing post-partum headaches. The headache was characteristic of mild common migraine--mild to moderately severe bilateral frontal pain with slight photophobia--and occurred most frequently on the fourth, fifth and sixth days following delivery.

The hormonal changes of the menstrual cycle have been investigated in women with migraine. Premenstrual migraine appears to occur during the phase when both plasma estrogen and progesterone fall to their lowest levels. Somerville (1971, 1972a) has shown that it is the drop in plasma estrogen which is influential in the precipitation of menstrual migraine. Women with menstrual migraine were treated with either progesterone or estradiol in the premenstrual phase. Plasma hormonal levels were measured daily. Women treated with progesterone experienced delayed uterine bleeding but their migraine attacks occurred at the regular time in five of the six women. But in women with artificially high levels of estradiol in the premenstrual phase, menstruation occurred at the expected time but the migraine attacks were postponed 3 to 9 days in five of the six women. The sixth woman had a delayed but atypical attack.

Rapidly falling estradiol levels are probably only one factor in the pathogenesis of migraine, and then perhaps only for women with a clear relationship between the menstrual cycle and migraine. Acute attacks of migraine show no clear relation to consistent hormonal flucuations (Epstein, et al., 1975). Nor has the pattern of hormonal flucuations in migrainous women been shown to be different from that of non-migrainous women (Somerville, 1972a). However, Epstein, et al. (1975) have reported significantly higher mean plasma estrogen and progesterone levels in both menstrually and non-menstrually related migrainous patients than in controls during most of the menstrual cycle. They spectulate that these hormonal differences may be related to hypothalamic neurotransmitter abnormalities.

Abruptly falling levels of plasma estrogen occur during both pre-menstrual and post-ovulation phases of the menstrual cycle. This correlates well with the clinical observations of more frequent attacks in the few days preceding menstruation and in the week following (Waters & O'Connor, 1971). During pregnancy plasma concentrations of estrogen are greatly elevated, rising a hundred-fold in the last trimester (Somerville, 1972b). The relief from migraine during pregnancy experienced by most women with menstrually-related migraine is likely due to the steady state or steady rise in estrogen as opposed to the periodic rise and fall of estrogen in the menstrual cycle. Sicuteri (1980) hypothesizes that the improvement of migraine during pregnancy and the often accompanying state of bliss may be

secondary to an increased activity of endorphin neurons and/or an adjustment of an opiate receptor dysfunction inherent in migraine.

The reemergence of migraine in migrainous women post-partum may be explained by the rapidly falling plasma estrogen and progesterone levels or by their indirect influence on serotonin metabolism (Stein, 1981).

Birth control pills, containing varying proportions of progesterone and estrogen, tend to exacerbate migraine, especially during the seven or eight days off the pill each month (Whitty, Hockaday & Whitty, 1966). In one study, 34% of migrainious women taking oral contraceptives considered their migraine to be worse while on the pill (Dalton, 1975b). In a cross-over study of 40 female migraine patients given an oral contraceptive for two months, 28 reported significantly more moderate and severe headaches while on the pill (Ryan, 1978). Interestingly, 12 of the 40 patients reported improvement with the pill. Of 60 migrainous patients taking oral contraceptives, 70% experienced reduced migraine frequency following discontinuation (Kudrow, 1975). A similar finding was reported for women on hormone replacement following reduction and decycling of the hormone therapy. Reduction in migraine frequency was most pronounced for those women suffering the highest frequency of attacks. Improvement began as late as four weeks following discontinuation.

Oral contraceptives increase the risk of stroke independent of other risk factors such as hypertension and

smoking (Collaborative Group for the Study of Stroke in Young Women, 1975). A series of 15 women without migraine who experienced cerebral infarction while taking oral contraceptives has been reported (Gardner, Hornstein & Van den Noort, 1968). In 14 of the 15 a premonitory vascular headache progressively increasing in severity occurred months before the infarct. Nine of these patients experienced throbbing unilateral headache with subsequent neurologic dysfunction compatible with the side of the headache. The authors warn of the increased risk migrainous women face of suffering complicated migraine while taking oral contraceptives.

Dietary

Certain foods and beverages are implicated in the precipitation of some migraine attacks. It is estimated that 5% of those with migraine have exclusively diet-linked attacks (Raskin, 1981). Nevertheless, dietary factors are cited in at least one migraine attack by about 25% of adult migraine patients (Selby & Lance, 1960). In an investigation of food intake prior to a spontaneous migraine attack, Dalton (1975a) recruited 1,147 female volunteers with migraine. During a 3 month period the subjects recorded all food and drink consumed in the 24 hours immediately preceding an attack. A total of 2,313 attacks were analyzed. Cheese was consumed in 40% of the attacks, chocolate in 33%, citrus fruits in 21%, and alcohol in 23%. No dietary factor was identified in only 5% of the attacks.

Most cheese contains tyramine, an amine which was inadvertently discovered to produce headache and raised blood pressure in patients taking monoamine oxidase (MAO) inhibitors. MAO inhibitors depress the enzymatic break-down of tryamine in the digestive system (Hanington & Harper, 1968). Investigating tryamine's role in the triggering of migraine headaches, Hanington and Harper administered capsules of tyramine or lactose placebo to 17 patients with known dietary migraine. The amount of tyramine given was equivalent to three-and-a-half ounces of aged cheese. Headaches of typical character and duration were produced 40 times in 49 administrations of tyramine but only 2 headaches were produced in 26 administrations of the placebo. Among 15 non-dietary migraine patients only 2 headaches were produced in 32 tyramine administrations and this was not significantly different from the placebo administration.

Chocolate, a commonly cited migraine trigger, does not contain tyramine but another vasoactive monoamine, phenylethylamine (Sandler, Youdim & Hanington, 1974). Migraine patients reporting chocolate-induced attacks were administered capsules of phenylethylamine (equivalent to 2 ounces of chocolate) or lactose. In 36 administrations, 18 experienced headache after phenylethylamine ingestion compared to 6 following placebo.

The role of tyramine and phenylethylamine in the provocation of migraine in dietary migraine patients is not universally accepted. In a double-blind and balanced placebo-controlled study, only two of the eight patients

similar to Hanington and Harper's (1968) subjects experienced headache after tyramine and not after placebo (Moffett, Swash, & Scott, 1972). This same research team has administered specially prepared chocolate and matched placebo mixtures to 25 patients with reportedly chocolate induced migraine (1974). Only two subjects consistently developed headache to chocolate. The authors conclude that tyramine and chocolate alone may not be the single factor in the onset of migraine, but in combination with other factors such as alcohol or stress, they may precipitate migraine in susceptible individuals.

The role of diet in migraine has been challenged as well (Medina & Diamond, 1978). Twenty-four migraine patients were randomly assigned to 18 weeks of a diet rich in tyramine, phenylethylamine, nitrate, and levodopa, a diet free of these substances, or a diet with no restrictions. The number of patients who experienced more severe migraine and a higher intake of medication on a particular diet was not significantly different across the three groups. Some headaches were found to be linked to alcoholic drinks and chocolate, but not to cheese. They conclude that foodstuffs do not precipitate new headaches but that alcohol and chocolate may precipitate headaches in susceptible individuals. The mechanism of alcohol's influence in migraine may be its cranial vasodilatation properties (Dalessio, 1980).

Fasting or missing a meal is a commonly identified factor in migraine onset. In Dalton's (1975a) survey of

2,313 spontaneous attacks, fasting, defined as lack of food for five hours during the day of 13 hours overnight, was present prior to 67% of the reported migraine attacks. Medina and Diamond (1978) reported fasting to be the third major migraine precipitant in their study of diet. The mechanism by which fasting provokes migraine is not well understood. Dalton (1972) reports that most migraine patients with fast-induced attacks are not hypoglycemic and have fasting blood sugar levels no lower than controls. However, Dexter and Byer (1981) reported that 118 migraine patients, most of whom had fast-induced attacks, demonstrated either a diabetic (11.9%) or reactive hypoglycemia (88.1%) response to a five-hour 100-gram glucose tolerance test. When a 90-day high-protein, low-sucrose frequent-feeding diet was instituted, 93% of the hyperglycemic group and 69% of the hypoglycemic group showed significant improvement in their headaches.

Sleep

Migraine onset during sleep, nocturnally or daytime nap, is a precipitant reported by some patients. The attack may occur during a dream, and the classical migraine aura may even be incorporated into the dream (Dexter & Riley, 1975). In study of the sleep patterns of seven nocturnal migraine patients, Dexter and Riley (1975) found all attacks were associated directly with rapid eye movement (REM) stage sleep and were not related to a circadian rhythm. In a later study of five patients with complaints of severe

common migraine occurring during daytime napping, Dexter (1979) found all headache arousals were from Stage III, IV or REM sleep. He also observed rapid alterations of platelet-bound serotonin during these three stages and stable serotonin levels during Stage I and II sleep.

Exogenous stimuli

Exposure to glare or stroboscopic light, such as water reflections or motion picture flickering, are among the most common triggers of migraine reported by both adults and children (Bille, 1962; Selby & Lance, 1960). Noise and strong smells may also precipitate an attack. Lance (1982) spectulates a neural relationship between the stimulus and the part of the cerebral cortex which mediates the fast acting response. For example, a patient may develop scintillating scotoma immediately after looking at sunlight reflected from rippling water.

Changes in weather are sometimes reported as preceding migraine attacks. Hot, dry winds are often blamed and some theorize that it is the increased ionization of the air accompanying this weather which is the operative factor in headache provocation (Sulman, Danon, Pfeifer, et al., 1970).

Trauma to the head may produce transient neurologic symptoms identical to the aura of classical migraine followed by headache. This has been reported in atheletes (Bennett, Fuenning, Sullivan, et al., 1980) and in children suffering minor blows to the head (Haas, Pineda & Lourie, 1975).

Nature of the Headpain in Migraine

Site of the headpain

The subjective quality of the headpain in migraine is usually described as severe and compares in intensity with the pain reported by cancer and phantom-limb patients (Hunter & Phillips, 1981). It is equally reported to be throbbing, pulsating and thumping, or steady, pressing and tightening (Olesen, 1978). A third type of pain encountered in migraine is a brief, sudden, sharp jabbing pain called icepick pain. In a series of 100 migraine patients, 42% reported the lancinating pain; half experienced it at least monthly, with or without the usual headache (Raskin & Schwartz, 1980).

The site of these myriad pains can be extracranial, intracranial and acranial. The extracranial vasculature has traditionally been viewed as the site of headache in migraine. Pain results from both distention of the scalp arteries and a local sterile inflammation (Wolff, 1963). A large body of evidence supports this view though recent research casts doubt on the exclusivity of extracranial factors in migraine headache.

Wolff and his colleagues reported that migraine headache could be momentarily abolished or relieved by compression of the common carotid or superficial temporal artery (Graham & Wolff, 1938). Moreover, they found that the amplitude of pulsation of the scalp arteries correlated with the intensity of the headache, and ergotamine relieved

the headache at the same time reducing the pulsations. Indirect measures of intracranial pulsations revealed no such changes. The cause of the pain was hypothesized to be extracranial artery dilatation secondary to increased blood flow. Furthermore, the extracranial arteries of migraine patients, specifically the frontal branches of the superficial temporal artery, were discovered to exhibit greater contractile variability and a larger caliber during both headache and rest than control subjects (Tunis & Wolff, 1953).

Subsequent research on the extracranial vascular hypothesis has produced conflicting results. It may be that extracranial vascular changes contribute to migraine headache in only a proportion of patients. Blau and Dexter (1981) compressed the superficial temporal artery of 50 migraine patients during headache attacks by digital pressure or an inflated blood cuff around the head, and found no change in pain in 21 patients and both a intracranial and extracranial contribution to the pain in 28 of 49 patients. Drummond and Lance (1983) found that headpain was completely or partially relieved by compression of the superficial temporal artery in only 22 of 66 migraine patients.

The Tunis and Wolff (1953) study has been criticized by Blau (1978) who notes that the published arterial pulsation tracings show no change in magnitude between the headache period and the headache-free period 36 to 72 hours before. Nor have the reported differences in superficial temporal

artery pulsation amplitude between migraine patients and normal controls been replicated (Drummond & Lance, 1981; Heyck, 1969). However, Drummond and Lance (1981) reported that the superficial temporal artery pulses of migraine patients during exercise increased in amplitude significantly more on the unilateral headache side than on the unaffected contralateral side. Drummond and Lance (1983) found this pulse amplitude difference significant only for the subgroup of patients who experienced pain relief after superficial temporal artery compression.

Increased extracranial blood flow during headache has been demonstrated by blood flow measures. Sakai and Meyer (1978) found the extracranial circulation clearance of ^{133}Xe was 50% greater in migraine patients during headache than in controls. However, increased blood flow to the scalp and face is inconsistent with the frequent clinical observations of facial pallor and feelings of cold during an attack (Blau, 1978). Thermography studies, which measure changes in skin temperature secondary to changes in cutaneous blood flow, demonstrate both increases and decreases in skin temperature during the migraine attack. Lance and Anthony (1971) found that the skin temperature of the unilateral headache side was lower by about 1 ^{o}C in 8 of 12 patients and higher in 2 of 12 patients as compared with the contralateral side. In the larger Drummond and Lance (1982) study, the one-third of the sample who experienced only "extracranial" vascular pain exhibited increased warmth over the affected areas. Thus, the variation among migraine

patients in skin temperature and facial color during attacks may reflect varying degrees of extracranial artery dilatation.

Intracranial vascular factors also likely contribute to migraine headache, though Wolff (1963) dismissed their role because he found no relationship between headache and the amplitude of cerebrospinal fluid pulsations through a lumbar puncture needle. Nevertheless, migraine patients often report that head movement, coughing, and straining exacerbate the pain. These reactions are consistent with intracranial dilatation and/or traction mechanisms (Lance, 1982). The Valsalva maneuver, a technique of blowing against a closed glottis for several seconds and which results in lowered blood pressure and increased venous pressure, has been found to also accentuate migraine headache, thereby implicating an intracranial rather than extracranial mechanism (Kunkle, 1959; Louis, 1981).

In a series of 50 migraine patients, Blau and Dexter (1981) employed a number of techniques known to reflect intracranial pain mechanisms--coughing, rapid side-to-side head rotation and breath-holding for 30 seconds. Nearly all the patients (49 of 50) reported that at least one of these actions exacerbated their headache. Drummond and Lance (1983) reported that of the 40 patients who did not experience pain relief from temporal artery compression, pressure on the ipsilateral common carotid artery relieved headache partially or completely in 19. No benefit was gained by compressing the contralateral common carotid

artery. The site of the pain was inferred to be the intracranial arteries of the middle meningeal or cerebral arteries.

It is well established that there is a striking increase in cerebral blood flow during migraine headache (Edmeads, 1977; Mathew, Hrastnik & Meyer, 1976; Skinhoj, 1973). However, there is no evidence that the increased cerebral blood flow is the cause of the headache. The hyperperfusion usually persists beyond the termination of headache and shows no spatial relationship to the headpain (Edmeads, 1979). Also, the headache may be relieved by injection of ergotamine tartrate (Hachinski, Norris, Cooper, et al., 1978; Norris, Hachinski & Cooper, 1975) or codeine (Sakai & Meyer, 1978) during persistent cerebral hyperperfusion.

Intracranial nocieptive nerve endings are found in the meninges, the proximal sections of the major arteries and the veins at the base of the brain (Dalessio, 1980). Blau (1980) argues that migraine headache arises from the meningeal vessels, particularly the dural venous sinuses. Such a site is consistent with the deep throbbing nature of the pain and its exacerbation by maneuvers which raise or suddenly alter the intracranial venous pressure.

Another possible intracranial site of migraine headache is suggested in the syndrome of <u>carotidynia</u> (Raskin & Prusiner, 1977). The wall of the carotid artery at its bifurication may produce referred pain in the scalp, jaw, gums or face if stimulated electrically. In a series of 74

migraine patients, Raskin and Prusiner found 38 had tender carotid arteries which were almost always ipsilateral to the headpain. In these patients the headache may be secondary to some abnormality of the carotid artery.

A third site of pain in migraine headache are the neck and jaw muscles (Olesen, 1978). Pain trigger areas exist in the muscles of the scalp, jaw, neck and chest (Hay, 1979). They are the source of both referred pain and local pain. Olesen (1978) speculates that the myogenic pain may actually be the cause of common migraine pain.

Central versus local origin of pain

The early observations of Graham and Wolff (1938) of pulsating cranial arteries led to a simple mechanistic theory of migraine pain: pulsating waves knocked on the dilated extracranial arteries. Later experiments demonstrated that vasodilatation alone was not sufficient. For example, dilatation by immersion in hot water was not associated with pain in normals or those with migraine (Wolff, 1963). However, when blister fluid was injected around the dilated vessels headache developed. Specimens of periarterial fluid collected during headache were found to belong to the polypeptide group and resembled bradykin and kallidin. This substance was called neurokinin (Wolff, 1963). When neurokinin was introduced into human skin it produced vasodilatation, lowered the pain threshold, increased capillary permeability and increased tissue vulnerability to injury. Wolff's (1963) hypothesis of

headache included both extracranial arterial distention and a local sterile inflammatory reaction to neurokinin release.

Hypotheses of local biochemical processes at the site of the migraine headache have attributed the pain to the release of "vasoneuractive" substances which directly stimulate pain receptors (Sicuteri, 1976). Substances studied which have influence on the microvasculature and pain-production include histamine (Anthony & Lance, 1971; Sicuteri, 1963), bradykinin and kallidin (Keele & Armstrong, 1964), prostaglandin E_1 (Carlson, Ekelund & Oro, 1968), and serotonin or 5-hydroxytryptamine (5-HT) (Sicuteri, Fanciullacci, Franchi, et al., 1965). Sicuteri, et al. (1965) found that 5-HT greatly potentiated the pain induced by bradykinin and speculated that the release of both substances may be operative in migraine pain.

The role of serotonin in the pathogenesis of migraine has received much attention and will be discussed in a later section. In brief, during the migraine attack plasma serotonin levels fall (Anthony, Hinterberger & Lance, 1967; Lance, Anthony & Hinterberger, 1967) and urinary excretion of the serotonin metabolite, 5-hydroxyindoleacetic acid (5HIAA), increases (Curran, Hinterberger & Lance, 1965; Sicuteri, Testi & Anselmi, 1961). Low plasma 5-HT may release tonic vasconstriction and produce dilatation of scalp arteries, thereby setting in motion the involvement of other pain producing substances at the peripheral level.

More recently, Sicuteri has hypothesized that the pain in migraine is not essentially peripheral but central in

origin (Sicuteri, 1972, 1976; Sicuteri, Anselmi & Fanciullacci, 1974). Migraine is viewed as an expression of central dysnociception. The reasoning is that the serotonin release from blood platelets during migraine attack reflects the release and depletion of monoamines in the central nervous system. Since inhibition of transmission in the pain pathways by enkephalins is regulated by serotonergic neurons originating in the brainstem (Lance, 1981), a disorder in the turnover of serotonin, and perhaps other neurotransmitters, results in hypersensitivity to vascular receptors and a general overactivity of central pathways mediating pain perception. This hypothesized brainstem disorder of the "pain integration-modulation-inhibition" system may be genetic (Sicuteri, 1976).

Nature of the neurologic dysfunction in migraine

The neurologic dysfunctions evidenced in classical migraine or migraine accompagnée can be divided into four broad functional categories: sensory, motor, cognitive, and arousal/consciousness/orientation. Clinical reports of each category will be reviewed. These disturbances are almost always transient and seemingly completely reversible though this is open to debate because of the paucity of longitudinal and neuropsychological studies. The relatively rare cases of permanent neurologic sequelae will be discussed, with particular attention to those reports with physical findings of structural damage.

Transient neurologic deficit

In accordance with Lance's (1981) classification scheme, "transient" will be considered as a duration of 24 hours or less. The vast majority of neurologic episodes in migraine are paroxysmal and last 60 minutes or less.

Visual symptoms are the most frequent neurologic disturbance in classical migraine for both children and adults (Bille, 1962; Lance & Anthony, 1966). The visual symptoms are quite diverse but tend to be distinct and stereotyped for each individual (Hachinski, Porchawka & Steele, 1973). A highly characteristic feature of classical migraine and no other pathological process is the preheadache scintillating scotoma. As described by Aring (1972) in his personal attacks, the attack begins with a sudden visual inefficiency, as though there were lessened illumination. Near or at the center of one visual field a tiny flickering light evolves into a zig-zag horseshoe-shaped formation. The serrated edges appear as the walls of pre-20th century fortifications as seen from above, thus the term, fortification spectra (Fothergill, 1784). This scintillating shape increases in size gradually and progresses regularly toward the peripheral visual field. It usually leaves behind a band of blindness. The rate of expansion to the peripheral field takes 20 to 30 minutes and is remarkably consistent from attack to attack. The scotoma may present as quadratic hemianopia, inferior or superior, or complete homonymous hemianopia. The headache usually follows and is contralateral to the scotoma.

Airy (1870) was the first to recognize the significance these visual phenomena held for understanding neural functioning. Lashley (1941) estimated that his own fortification spectra expanded at a rate of 3 mm per minute. He assumed the propagation rate was constant and the perception of the arcs expanding with greater speed as they grew larger was explained by the fact that there are progressively fewer neurons in the visual cortex moving from the central region to the outer margin. Recent research on the electrophysiological topography of the visual field in the human occipital cortex supports Lashley's hypothesis, showing a 3.3 mm per minute propagation wave (Richards, 1971).

The other common visual disturbance in migraine is photopsia, the sensation of unformed flashes of light. This may be experienced as sparkling, dazzling or flickering lights, spots, circles, stars, or little white things moving around (Fisher, 1980). Lance and Anthony (1966) reported photopsia occurred more frequently than fortification spectra, but both were rarely experienced by the same patient. Whether photopsia is referable to disturbed function in the occipital cortex or is secondary to constriction of the ophthalmic artery is not known. Incontrovertible evidence for the cortical rather than retinal origin of a variety of migrainous visual symptoms is presented in one case of a classical migraine patient without eyes (Peatfield & Rose, 1981).

Other visual disturbances besides photopsia and

scintillating scotoma occur in migraine but are much less common. Klee and Willanger (1966) described in detail the visual hallucinations of eight migraine patients. Disturbances of perception included metamorphopsia, in which objects appear to have distorted contours, and macropsia and micropsia, in which the objects appear to increase or decrease in size without the perception of a change in distance from the object. Other disturbances involve the perception of movement, the apparent movement of stationary objects, or the apparent increase or decrease in the rate of movement, or jerky movements of the object. Diplopia, polyopia, reduction in discrimination of contrast, dimness of vision and visual perseveration were also reported.

Atkinson and Appenzeller (1978) reported a bizarre case of a woman artist with protracted prodromal migraine who experienced complex formed visual hallucinations for 5 to 60 minutes preceding the headache. She had several drawings of these hallucinations on display at an art gallery! Lewis Carrol reportedly recorded his migrainous visual hallucinations in creating "Alice in Wonderland" (Kudrow, 1978).

Disturbances of auditory perception appear to be nearly nonexistent. Bille (1962) reported in his series of 73 migrainous children one child who heard an echo after every sound.

Paresthesia, or the sensation of numbness and/or tingling, is second only to scintillating scotoma in frequency of transient neurologic disturbances in migraine.

In many instances the numbness will "march" or slowly spread over the fingers, migrating to the hand and elbow, then "skipping" up to the ipsilateral side of the face and tongue in a period of 10 to 30 minutes. In other cases, multiple paresthesias may appear simultaneously (Fisher, 1968) or the paresthesia will cross to the opposite hand and side of the face during the attack (Fisher, 1980). Involvement of the leg is very rarely reported (Heyck, (1973). Most episodes of paresthesia fall in the cheiro-oral distribution (Bruyn, 1968). This may be a reflection of the more extensive and organized cortical representation of the hands and mouth region (Heyck, 1973).

Hemiplegia or unilateral motor weakness presents in a similar fashion and is often confluent with hemiparesthesia. A dichotomy of hemiplegic migraine into sporadic and familial types has been proposed by Whitty (1953). In sporadic hemiplegic migraine the transient weakness and numbness usually develop in a few minutes and resolve in 30 to 60 minutes, subsiding before onset of the headache. This pattern conforms to the classical migraine syndrome and the family history of these patients is no different from common or classical migraine patients (Heyck, 1973). It has been estimated that 33% of migrainous patients visiting a clinic experience transient unilateral limb symptoms on at least one occasion (Bradshaw & Parsons, 1965).

Sporadic hemiplegic migraine usually occurs in the course of a common or classical migraine history. In Heyck's (1973) series of 45 hemiplegic migraine cases, two-

thirds had well-established migraine attacks before their first hemiplegic attack. The remaining patients' first and only form of migraine was hemiplegic. Migraine attacks other than hemiplegic were cited as far more frequent. Visual disturbances were common percursors; in 35 of the 45 cases, the hemiplegic attack was reportedly initiated by scintillating or simple scotomas.

The severity of limb weakness and numbness varies from mild to severe. In Bradshaw and Parson's (1965) series of 75 hemiplegic migraine patients, there was a tendency for the longer lasting episodes (over 1 hour) to be associated with more profound weakness. In about 75% of the patients the attacks were confined to the same side; in the remaining patients the unilateral symptoms alternated sides. Heyck (1973) reported that in three-quarters of his hemiplegic migraine cases, the side of the headache correlated with the laterality of the brain dysfunction (i.e., contralateral to the limb symptom). Findings of focal EEG abnormalities were reported in 13 of his 45 patients. The lateralization of the EEG abnormality was more consistent with the hemiplegic symptoms; in 12 of the 13 abnormal records, the reduction in alpha activity and phase reversal findings were localized in the cerebral hemisphere contralateral to the symptoms.

Familial hemiplegic migraine has similar symptomatology to sporadic hemiplegic migraine but is far more rare and has three distinguishing characteristics according to Pearce (1975). The weakness recurs always on the same side, the weakness lasts hours or days and surpasses the headache, and

the syndrome is striking in its familial pattern: the weakness is present on the same side among affected relatives. Just a handful of such cases have been published: Whitty (1953) presented 4 patients, Symonds (1952) reported 2 cases, Blau and Whitty (1955), 9 cases, Bradshaw and Parsons (1965), 6 cases, Heyck (1973), 2 cases, and Glista, Mellinger, and Rooke (1975), 10 cases.

Alteration in the level of consciousness preceding headache is another form of transient neurologic dysfunction found in migraine. Bickerstaff (1961) reported a syndrome predominantly affecting migrainous adolescent girls, involving impairment or loss of vision bilaterally, dysarthria, vertigo, tinnitus, ataxia and bilateral parethesia of the hands, feet, mouth and tongue. These symptoms lasted 10 to 45 minutes and resolved before a throbbing headache occurred. Of 32 patients under age 23, 8 also experienced a disturbance of consciousness in one or more of their attacks. The onset of unconsciousness was, unlike syncope, always slow, and was never so profound that the patients were unrousable. There were no epileptic features. Bickerstaff termed this form of migraine <u>basilar artery migraine</u> and hypothesized vasoconstriction of the vessels supplying the brainstem, in particular the reticular formation and/or its cortical connections.

In a later report, Lee and Lance (1977) presented seven patients, age 10 to 52 years, who were stuporose, in addition to other brainstem disturbances, for periods ranging from 2 hours to 5 days. Four patients were also

reportedly confused, aggressive or hysterical. They posited ischemia of the midbrain or the hypothalamus.

The syndrome of confusion, disorientation and agitation without loss of consciousness in migrainous children was reported by Ehyal and Fenichel (1978). They argue that acute confusional migraine is not a brainstem disturbance but is cortical in origin. Its apparent rarity in adults relative to children may be due to maturational differences in the levels of cortical organization.

A related disorder, transient global amnesia (TGA), has been reported in migraine. TGA is defined as a single isolated episode of confusion and amnesia characterized by the inability to form new memories, repetitive queries, retrograde amnesia and absence of other neurologic signs and symptoms (Bender, 1956). Caplan, Chedru, Lhermitte, et al. (1981) have presented six common and six classical migraine patients with TGA. In half the subjects abnormal EEG findings were reported, with a left hemisphere or bilateral focus. In three patients the TGA occurred in conjunction with the classical aura. The authors postulated a vascular disturbance in the dominant posterior cerebral artery territory.

Olivarius and Jensen (1979; Jensen & Olivarius, 1980) reported TGA in eight women, seven of whom had classical migraine. In five patients with EEG data, four had abnormalities, with slow wave activity in the left temporal region found in three of the patients. Three patients had typical vertebrobasilar migraine and in three other patients

there was evidence of previous transient neurologic dysfunction compatible with the vertebrobasilar arterial territory. The amnesia lasted 2 to 24 hours and was accompanied by headache in half of the cases. TGA is possibly a result of transitory ischemia in the mamillohippocampal formation supplied by the posterior cerebral artery circulation, which is fed by the basilar artery.

Difficulties in attention, concentration, thinking, language comprehension, word finding, verbal fluency, short-term memory, spatial orientation, time estimation, etc. during the migraine aura, headache or post-headache phases have been reported by migraine patients themselves (e.g., Aring, 1972) and by treating clinicians (e.g., Barolin, 1972). As Raskin and Appenzeller (1980) have noted, these cognitive impairments seem to be out of proportion to the level of pain experienced and are undoubtably cortical in origin. No known formal neuropsychological assessment studies have been performed during the acute phases of migraine and thus quantification of these transitory neurologic disturbances is not available. A handful of psychometric tests performed between attacks will be presented below.

Transient aphasia, involving both receptive and expressive aspects, commonly accompanies right hemiplegia in the classical aura. Several published cases of aphasic disturbance associated with migraine are so unusual they deserve mention. The exceedingly rare syndrome of alexia

without agraphia has reportedly occurred in two migrainous individuals (Bigley & Sharp, 1983; Fleishman, Segall & Judge, 1983). The theorized mechanism accounting for this syndrome is a lesion(s) which interrupts both right and left calcarine cortex outflow channels to the dominant angular gyrus (Geschwind, 1965). The two patients, a 35-year-old man with several previous classical migraine attacks and a 60-year-old woman with a intermittent history of common migraine, experienced approximately 30 minutes of alexia during which time their visual fields were full, there was no hemiplegia or parethesia and auditory comprehension was normal. In both reports the authors postulate a highly localized area of ischemia in the occipital lobe.

The rare aphasic syndrome of muteness with sparing of written language function (aphemia) was reported in a 25-year-old woman with hemiplegic migraine (Jenkyn & Reeves, 1979). In annual attacks her right leg became paralyzed, followed by an inability to speak for 30 minutes. No other limbs were involved. Language comprehension and writing were reportedly left intact though no formal testing was conducted. Left monocular blurring and severe left hemicranial pain followed. A tentative mechanism proposed by the authors was ischemia of the dominant supplementary motor area supplied by the anterior cerebral artery.

Prolonged and permanent neurologic deficit

Migraine aura status (Sacks, 1970) is a condition of recurring cycles of neurologic dysfunction such as

paresthesia or scotoma which persists for days or even weeks. Haas (1982) reported two classical migraine patients who experenced visual disturbances lasting several minutes or less but which reoccurred several times an hour for 2 to 5 weeks. All neurological and visual field examinations were normal during this period. Cases of familial hemiplegic migraine have been reported in which signs of a upper-motor neuron lesion with hemiparesis, hemiparesthesia, hyperreflexia and altered superficial reflexes, and abnormal EEG records, last for 10 days to 2 weeks, well after the headache had subsided (O'Connor, 1973; Whitty, 1953). In these cases the neurologic deficits and associated EEG abnormalities appear to resolve completely.

In the most extreme cases of complicated migraine there is incomplete remission of the prolonged neurologic symptoms (Klee, 1968). The deficits are permanent. In these instances the inescapable conclusion is that structural damage has occurred, most likely due to brain ischemia. Infarctions can occur in the retina, in the cerebral cortex or the brainstem. Connor (1962) reported 18 cases of complicated migraine: 5 retinal lesions, 10 hemispheric and 3 brainstem cases. In half of these patients the typical transient neurologic symptoms experienced during the aura never resolved. One case of <u>benign orgasmic cephalgia</u> (Paulson & Klawans, 1974) which resulted in permanent neurologic deficit has been reported (Levy, 1981).

Hemianopia is the most frequent permanent sequel of complicated migraine. Davis-Jones, Gregory, and Whitty

(1973) have reported nine cases of permanent visual field defects, Cohen and Taylor (1979) one case, and Bousser, Baron, Iba-Zizen, et al. (1980) one case. Permanent residual symptoms of hemiplegia, hemisensory loss, and cranial nerve pareses have been reported in five cases by Boisen (1975), and by Dorfman, Marshall and Enzmann (1979) with two cases. In the latter report, one patient also had residual mild dysphasia.

Long histories of hemiplegic migraine resulting in cumulative global cognitive impairment or dementia have been reported by Symonds (1952), Bradshaw and Parsons (1965), O'Connor (1973), and Glista, et al. (1975). Evidence suggesting heightened vulnerability of the young brain to complicated migraine insult has been presented by Verret and Steele (1971) who reported on eight cases of children with onset of hemiplegic migraine in infancy (age 3 months to 3 years). Half of these children sustained permanent neurologic deficits: two were moderately retarded and one dyslexic. All four had movement disorders such as restlessness, choreo-athetosis, or dystonic posturing of the limbs.

Ferguson and Robinson (1982) presented the case of a 13-year-old girl who experienced repeated complicated migraine attacks, at times resulting in unconsciousness and decorticate posturing, over the course of 8 months. With near complete recovery 8 days after one episode she reported incomplete retrograde amnesia for the preceeding 3 years and almost total amnesia for the preceeding 3 months. Symptom-

free for the next 18 months, she continued to be amnestic for the period of attacks and exhibited a stabilized deterioration of her mathematical ability.

Several psychometric investigations of cognitive functioning in classical migraine have been conducted and may have relevance to the clinical reports of cognitive impairment in complicated migraine. In Bille's (1962) study of 73 children with pronounced migraine, no differences in general intellectual test performance were found in comparison to matched controls but the boys did perform more poorly on several visuoperceptual tests and the girls scored significantly lower on the Critical Flicker Fusion test, a non-specific measure of higher cortical functioning.

Klee and Willanger (1966) reported that in a series of eight patients with classical migraine, six demonstrated slight intellectual impairment as determined by a small battery of tests measuring abstraction ability and verbal memory (Nielsen, Peterson, Thygesen, et al., 1966). The authors proposed that the intellectual reduction had developed gradually in association with the increasing severity of their migraine attacks.

In a comparison of 29 migraine patients with 35 ulcerative colitis patients on the Wechsler Adult Intelligence Scale (WAIS), Schuchman and Thetford (1970) found no difference in overall IQ but the migraine patients scored significantly lower on the Digit Span subtest, a measure of short-term memory. For what it's worth, self-reported memory problems were found to be more frequently

cited by migraine patients than by non-headache medical and psychiatric patients in two questionnaire studies (Mahrer, Mason & Rosenshine, 1966; Rogado, Harrison & Graham, 1973).

Pathological evidence of structural damage

The etiology of strokes in otherwise healthy young adults is often not known (Abraham, Shetty & Jose, 1971; Fisher, 1971). Migraine appears to be a risk factor in cases of cerebral infarction. In one retrospective study of 15 consecutive young stroke victims, 4 patients or 27% had a history of classical migraine (Spaccavento, Solomon & Mani, 1981). There is a statistical link between migraine and hypertension and heart disease (Leviton, Malvea & Graham, 1974). It was also found that both men and women with migraine tended to die younger than people without migraine. The mechanisms underlying these associations are not well understood.

An early theory of why certain migraine patients developed permanent neurologic sequelae was the presence of cerebral vascular anomalies (O'Connor, 1973). But this does not seem to be the case. In a series of 40 complicated migraine patients, Pearce and Foster (1965) reported the carotid or indirect vertebral angiography findings performed in 33 of the patients. Only two arteriovenous malformations (AVM) were detected. Anatomical variations in the circle of Willis were found in three other cases but their significance was considered doubtful.

In 220 angiographically-proven cases of AVM recorded in

the files of Blend and Bull (1967), 12 patients, or 5%, were found to have a history of migraine. This is approximately the population incidence of migraine. Conversely, of 3,736 normal carotid angiograms undertaken for various suspected causes, 202 or 5.4% were patients with migraine. Interestingly, of the 12 cases with angiomata, 4 cases were suitable for surgery and 3 did have their AVMs clipped. Two of the patients experienced migraine relief for at least 4 years of follow-up, whereas the third patient suffered remission after 1 year. The authors conclude that radiologic investigation of suspected vascular anomalies in migraine is apt to be fruitless, but in those rare cases of coexisting structural (AVM) and migraine conditions, the two may be interdependent.

The permanent neurologic deficits of complicated migraine are likely the result of infarction. In recent years the CT-scan investigations of complicated migraine have verified zones of infarction compatible with the symptomatology (e.g., Bousser, et al., 1980; Cohen & Taylor, 1979; Dorfman, et al., 1979). Nevertheless, CT-scans may be normal in the face of neurologic deficits and abnormal EEG activity in the corresponding brain region (e.g., Levy, 1981).

The several postmortem studies in cases of fatal complicated migraine conclusively demonstrate brain infarction secondary to ischemia. Buckle, duBoulay, and Smith (1964) reported the case of a 16-year-old girl who was normal prior to a course of six severe complicated migraine

attacks over 4 months time, the last of which resulted in coma and death. Histological examination revealed cortical ischemia confined to the territories supplied by the circle of Willis. There was complete sparing of the cerebellum and brainstem.

Guest and Woolf (1964) reported the case of a 28-year-old man with a 2 year history of severe migraine attacks. The fatal attack resulted in right hemiparesis and a semicomatose state which deepened and ended in death some 20 hours later. Brain examination showed extensive ischemic changes and small hemorrhages throughout the left cerebral hemisphere, particularly in the superior and middle frontal gyri. Discrete regions of the brainstem also showed ischemic damage and this was the likely cause of death. The internal carotid and anterior and middle cerebral arteries were normal.

Reduction in regional cerebral blood flow during the migraine aura is well documented and will be discussed in the next section. What the prime mechanism is in cerebrovascular insufficency and infarction in migraine is not known. Prolonged spasm of the large intracranial arteries has been the traditional explanation (Wolff, 1963). Angiographic studies conducted during the migraine aura (e.g., Symonds, 1952; Whitty, 1953) and the postmortem findings of normal carotid and cerebral arteries (Buckle, et al., 1964; Guest & Woolf, 1964) have not demonstrated arterial spasm. But Dukes and Vieth (1964) reported a progressive decrease in caliber and filling of the internal

carotid system with reflux into the vertebral system in serial angiograms during the aura of a classical migraine patient. After the aura resolved they observed reversion to normal flow. This is the only known authenticated case of serial observations of intracranial vasoconstriction during migraine aura.

Several subsequent angiography studies have been reported in which the absence of filling in a vessel was attributed to arterial spasm, but these observations have not been serial or were conducted post-infarction (e.g., Dorfman, et al., 1979; Heron, 1966). There is also the possibility that arterial spasm during angiography is iatrogenic; precipitation of hemiplegic migraine attacks shortly after carotid angiography have been reported (Blau & Whitty, 1955).

If occlusion of the large intracranial vessels due to migraine-induced spasm is questionable, perhaps it is the smaller arteries that are involved. Symonds (1952) proposed that permanent neurologic deficits were due to small thromboses in the terminal arterioles during spasm. Vessels which have occluded may be too small to be discerned individually. This may explain the discrepancy between clinically positive infarctions in complicated migraine and negative CT-scan results (e.g., Dorfman, et al., 1979).

The rapidly resolving prodromal symptoms of classical migraine are compatible with the putative effects of temporary arterial vasospasm, but how does the vasospastic model explain prolonged but completely reversible neurologic

deficts? Wolff (1963) believed that another pathological process must be involved. A number of authors have suggested that focal brain edema, secondary to ischemia, would account for the prolonged neurologic signs but without the development of cell death (Blau & Whitty, 1955; Rosenbaum, 1960; Speed, 1964; Whitty, 1953).

An alternative vascular model of ischemic brain changes in migraine aura is that of arteriovenous shunting (Heyck, 1969, 1970). Arteriovenous anastomoses (AVA) or shunts are sites of interconnection between the arterial and venous sides of the circulation through which blood can bypass the capillary beds. AVAs play an important role in cerebral circulation regulation and are prominent in the dura mater. Under normal conditions the flow through AVAs is low, not exceeding an average of 2% of cerebral blood flow (Spierings, 1982). In migraine, Heyck hypothesizes that there is a pathological opening of the AVAs, accounting for both the prodromal symptoms and the dilatation and increased pulsation of the superficial vessels on the painful side of the head. Cerebral ischemia may be the product of the resulting capillary steal.

Heyck (1969) reported that measurement of the arteriovenous oxygen content differences over the cerebral circulation during the prodromal phase of migraine in two patients showed that a significantly greater proportion of blood entered the venous circulation without being submitted to oxygen extraction in the capillary bed than when compared to the normal state. Corresponding lateralized differences

over the cranial circulation during migraine headache have been found as well. The role of AVA shunting in migraine has been reviewed by Saxena (1978).

Reduction in regional cerebral blood flow during the migraine aura may be the secondary event of some primary neuronal process and consequently not the primary cause of the prodromal neurologic dysfunctions. The spreading depression of Leão (Leão, 1944, 1947) may be one such primary neuronal event. Leão documented an enduring reduction of spontaneous electrical activity after stimulation in the rabbit cerebral cortex. The depression of neuronal activity spreads at a uniform rate in all directions, much like the ripples in a pond after a stone has been dropped. Recovery takes some 5 to 10 minutes. The spreading wave traverses the cortex at the approximate rate of 3 mm per minute. The exact mechanism of spreading depression is not yet known but recent research demonstrates that extracellular ionic variations in nerve and glial cells occur and that the brain is capable of both establishing and recovering from local ionic inhomogeneities (Kraig & Nicholson, 1978). Milner (1958) was the first to note the correspondence between Leão's work and Lashley's (1941) observations of his own migrainous scintillating scotomas. This association has since been amplified by others (e.g., Basser, 1969; Gardner-Medwin & Skelton, 1982).

The observation made by Heyck (1973) and others that the march of symptoms in migraine auras/accompaniments often follow a neuroanatomical pathway not related to any one

vascular territory lends support to a neuronal process. For example, visual disturbances may progress to hemisensory deficits and then to hemiplegia. These symptoms are referable to sequential involvement of the occipital, parietal and frontal lobes, and these regions are subserved by several vascular territories.

In a high-resolution ^{133}Xe intraarterial measurement study of regional cerebral blood flow (rCBF) during normal, prodromal and headache phases of classical migraine attacks, Olesen, Larsen and Lauritzen (1981) reported changes consistent with spreading neuronal depression. In half of the six patients there was initial focal hyperemia. During the aura all patients displayed occipitoparietal regional reduction which spread anteriorly over 15 to 45 minutes. In four patients the entire cortex was involved. It was concluded that alterations in neuronal functioning better explained the symptoms than arterial spasm, and that the reduced rCBF may be secondary to lowered metabolic requirements of the depressed cells.

Similar changes in cortical blood flow have been demonstrated experimentally in the rat brain after elicitation of a single spreading depression (Lauritzen, Diemer, Jorgenson, et al., 1982). In the affected hemisphere blood flow increased approximately 250% at the point of the spreading depression in the first two minutes. Subsequent blood flow values decreased to 80% of control values and remained low for 60 minutes.

Biologic Changes Associated with Migraine

Biochemical, vascular, electrophysiological, and neuroanatomical changes have been observed during migraine attacks. Biologic differences between migraine patients in a headache-free interval and normal controls have also been measured. Links between the many biologic changes and their relation to migraine etiology remain obscure and spectulative. Raskin and Appenzeller (1980) caution that all these changes may be central to the mechanism of migraine or may be the epiphenomena of some central process. Known biologic changes associated with migraine will now be reviewed.

Biochemical changes

Serotonin (5-HT) has been extensively studied in migraine, beginning with the observation that urinary levels of the serotonin metabolite, 5-hydroxyindoleacetic acid (5-HIAA) were increased during migraine attack in some patients (Sicuteri, 1961). Plasma serotonin decreases an average 60% during migraine headache in most migraine patients and is not a specific reaction to stress or the presence of headache alone (Anthony, Hinterberger & Lance, 1967; Curran, Hinterberger & Lance, 1965). This association has not always been found and such discrepancies remain unexplained (Ziegler, Hassanein & Wood, 1976).

In classical migraine attacks it has been demonstrated that plasma 5-HT increases significantly during the aura and decreases significantly during the headache (Lance, Anthony

& Hinterberger, 1967). The platelets contain virtually all the 5-HT present in the blood (approximately 8% of all the 5-HT in the body). Platelet function tests performed during the classical migraine attack show significantly greater platelet adhesiveness to glass beads during both aura and headache phases, and significantly increased aggregation to naturally occurring aggregating agents such as adenosine diphosphate (ADP), epinephrine, thrombin and serotonin during the aura, but significantly decreased aggregation during the headache (Deshmukh & Meyer, 1977).

These changes in platelet aggregability parallel the plasma serotonin changes reported by Lance, et al. (1967). Evidence that the platelet release reaction--the release of 5-HT, thromboxane and a number of enzymes which promote further aggregation and release or active substances--occurs during the migraine attack comes from the measurement of significantly increased serum concentrations of Beta Thromboglobulin (BTG), a specific protein secondary to the platelet release reaction (Gawel, Burkitt & Rose, 1979).

Assays of platelet 5-HT concentration in migraine patients and controls show a significant decrease in platelet 5-HT during the attack compared to the headache-free period (Mück-Šeler, Deanovic & Dupelj, 1979). Platelets collected from the headache-free migraine group and incubated with the platelet-poor plasma taken from migraine patients experiencing an attack produced an average 22% reduction in 5-HT content. No reduction in 5-HT resulted in the platelets of the control group, or when

platelets were incubated with headache-free migraine plasma.

These results suggest that a 5-HT releasing factor is present in the plasma during the migraine attack, and that migraine patients have some form of platelet abnormality. Studies of platelet response to ADP, epinephrine and serotonin in migraine patients between attacks show a significantly greater aggregability compared to matched controls (Couch & Hassanein, 1977; Deshmukh & Meyer, 1977; Kalendovsky & Austin, 1975). The concentration of circulating microemboli is significantly lower in migraine patients and this suggests an excessive platelet aggregation to the minimal trauma of the venipuncture procedure (Deshmukh & Meyer, 1977).

Platelet hyperaggregability and plasma hypercoagulability characterize complicated migraine patients following an attack (Kalendovsky & Austin, 1975) and patients with a history of migraine who have sustained cerebral infarctions (Kalendovsky, Austin & Steele, 1975). The authors suggest that chronic platelet hyperaggregability may represent a genetic disorder associated with migraine and puts migraine patients at risk for recurrent arterial occlusions. This may account, in part, for the epidemiological findings of increased risk of stroke and heart attack in the migraine population (Collaborative Group for the Study of Stroke in Young Women, 1975; Leviton, et al., 1974).

Whether the putative platelet abnormality in migraine is a primary, inherited defect of the platelets themselves

(Hanington, 1978), or is secondary to exogenous factors affecting platelet function is unknown. Primary exogenous factors proposed include plasma free-fatty acids which are elevated during the headache (Anthony, 1976), a complement immune reaction (Lord & Duckworth, 1978), and a non-specific circulating platelet-damaging humoral agent also causing a transitory deficit of platelet monoamine oxidase activity (Sandler, 1977, 1978)

Cerebral spinal fluid (CSF) studies of the role of brain serotonin in migraine are inconclusive (Welch, 1982). In animal research, CNS serotonin depletion follows experimentally produced transient cerebral ischemia (Welch, Gaudet, Wang, et al., 1977). The authors suggest that brain ischemia is one factor which may produce altered CNS serotonin metabolism during the migraine attack and may lead to increased pain sensitivity.

Intracerebral lactate-acidosis has been found in the CSF of both classical and common migraine patients during an attack (Skinhoj, 1973). Its presence is indicative of anaerobic cerebral metabolism and may underlie the reactive hyperperfusion observed following the migraine aura.

Gamma-Aminobutyric Acid (GABA) has been detected in the CSF of migraine patients during the attack, but not in attack-free intervals or in tension headache patients (Welch, Chabi, Bartosh, et al., 1975). GABA in the CSF is abnormal and may reflect disordered CNS GABA metabolism. It has been detected in the CSF of patients with recent onset of cerebrovascular disease and within 48 hours of

vertebrobasilar insufficency episodes (Welch, Chabi, Neil, et al., 1976). Another substance in the CSF of patients with recent thromboembolic occlusive episodes, is 3',5'-cyclic adenosine monophosphate (cyclic AMP), which has been detected in the CSF of migraine patients within 48 hours of an attack.

It is concluded that the similarities of the CSF findings of detectable GABA and cyclic AMP found in both migraine and stroke patients preclude these substances being related to the cause of migraine (Welch, Chabi, Neil, et al., 1978). Their presence could be related to disturbances of cerebral energy metabolism secondary to cerebral anoxic ischemic conditions, or may be secondary to the slow potential changes accompanying the spreading depression of Leão (Welch, 1982).

Vascular changes

Cerebral blood flow changes in migraine have been measured using clearance measures of ^{133}Xe. The radioactive isotope is delivered to the cerebral vasculature through inhalation of an air mixture or by intracarotid injection. The flow of radioactively-tagged blood is monitored extracranially with scintillation detectors, 8 to 254 per hemisphere.

Early inhalation studies showed a global, bihemispheric reduction in cerebral blood flow during the classical migraine aura (O'Brien, 1967, 1971a). This reduction was around 20% below the levels of headache-free migraine

patients and did not appear to be the result of altered CO_2 tension or blood pressure.

Unfortunately, these early inhalation regional cerebral blood flow (rCBF) studies did not account for extracranial circulation and were of relatively poor resolution. Later intracarotid ^{133}Xe injection studies (Edmeads, 1977; Hachinski, Norris, Cooper, et al., 1977; Hachinski, Olesen, Norris, et al., 1977; Norris, Hachinski & Cooper, 1975; Olesen, Larson & Lauritzen, 1981; Simard & Paulson, 1973; Skinhoj, 1973; Skinhoj & Paulson, 1969) and modified ^{133}Xe inhalation studies (Matthew, Hrastnik & Meyer, 1976; Olesen, Lauritzen, Tfelt-Hansen, et al., 1982; Sakai & Meyer, 1978) have afforded greater spatial and temporal resolution of the rCBF changes during classical aura, prolonged neurologic deficit, and the headache phase of both classical and common migraine.

Reductions of rCBF during the classical prodromal phase range from 20% to 67% below normal flow values, with some studies reporting zones of reduced flow falling below the ischemic threshold of 20 ml of blood per 100 grams of brain tissue per minute (e.g., Hachinski, Norris, Cooper, et al., 1977). No such prodromal rCBF reductions have been found in common migraine patients (Hachinski, Olesen, Norris, et al., 1977; Olesen, et al., 1982). Flow reductions are usually hemisphere-wide and focal zones of even greater rCBF decrements have been correlated with the ongoing neurologic deficit (e.g., Skinhoj, 1973), except in cases of neurologic symptoms referable to the vertebrobasilar arterial system

(Hachinski, Norris, Cooper, et al., 1977). If the prodromal symptoms persist into the headache phase, associated cortical zones exhibit continued low rCBF values (Mathew, Hrastnik & Meyer, 1976).

In the highest resolution study of rCBF changes in classical migraine conducted (Olesen, Larsen & Lauritzen, 1981), an initial focal hyperemia preceded the prodromal rCBF reductions in the occipitoparietal region. The subsequent reduced flow values (oligemia) were found to spread anteriorly at the approximate rate of 2 mm per minute over the course of 15 to 45 minutes. The authors suggest that this localized hyperemia of short duration is compatible with the observation of Leao (1944, 1947), of momentary heightened neural activity preceding the spreading depression and is not consistent with an arterial spasm. This phenomenon may have been overlooked in previous rCBF studies which are hindered by noncontinuous measurements.

During the headache there is an accompanying bihemispheric significant increase in rCBF. This is a universal finding in classical migraine but is a variable finding in common migraine (e.g., Sakai & Meyer, 1978), some studies finding no rCBF changes (Hachinski, Olesen, Norris, et al., 1977; Olesen, et al., 1982). Two theories have been forwarded to explain this so-called "luxury perfusion." The hyperperfusion may be secondary to a cerebral metabolic acidosis state secondary to ischemic hypoxia (Lassen, 1966; Skinhoj & Paulson, 1969). This condition is likely present in the classical migraine case. The second theory proposes

that increased rCBF is a reflection of increased brain metabolism secondary to pain perception of the headache itself (Ingvar, 1976). This view is supported by Sakai and Meyer's (1978) finding that lessening of headache severity by codeine reduced hemisphere blood flow bilaterally, but to the greatest extent in the hemisphere contralateral to the hemicranial pain, and not in the brainstem or cerebellar regions. On the other hand, Edmeads (1979) points out that hyperperfusion outlasts the headache by hours or days.

Impaired cerebral circulation autoregulation has been demonstrated in migraine. Cerebral blood flow regulation resides in the intrinsic tone of the cerebral vessels which are subject to both metabolic and neurogenic control (Raskin & Appenzeller, 1980). Changes in the pressure of CO_2 and O_2 readily alter the caliber of cerebral blood vessels in a counteractive fashion, though the effects of O_2 tension are much less in magnitude. Hyperventilation decreases CO_2 tension (hypocapnia) and reduces CBF secondary to vasoconstriction. Increased CO_2 tension (hypercapnia) produces vasodilatation and increased CBF. Neural control of the cerebral blood vessels is less well understood but a dense network of adrenergic and cholinergic fibers and receptors surround the vessels (Purves, 1978).

Autoregulation is the ability to maintain blood flow despite changing perfusion pressures and has been found to be defective in classical migraine and cerebrovascular occlusive disease (Edmeads, 1977; Raskin & Appenzeller, 1980). The normal cerebral vasodilator effect of CO_2 is

abolished bihemispherically during the aura and headache (Sakai & Meyer, 1979; Simard & Paulson, 1973). Impaired autoregulation has also been demonstrated in some common migraine patients and may be present in headache-free migraine patients as well (Sakai & Meyer, 1979).

Cerebral functional impairment during the classical aura may be secondary to cerebral vessel dysautoregulation (Olesen, et al., 1981). Behavioral activation (i.e., language, psychomotor activity) studies conducted during this period show impaired or absent neural activation vis-a-vis increased rCBF. The authors suggest an underlying uncoupling of the link between cerebral function, cell metabolism and rCBF.

The associated migraine symptoms of dizziness, vertigo and motion sickness reported by migraine patients significantly more often than tension headache and non-headache controls (Kuritzky, Ziegler & Hassanein, 1981; Raskin & Knittle, 1976) and the high proportion (80%) of vestibular abnormalities detected by electronystagmography (Kuritzky, Toglia & Thomas, 1981) may be explained by impaired central cerebral vasomotor autoregulation (Sakai & Meyer, 1978).

Systemic vasomotor changes observed clinically and experimentally during the headache-free period support the hypothesis of a generalized vasomotor dysfunction in migraine. Clinical observations such as episodic cold hands and feet, and facial pallor or flushing and blotching of the skin may actually serve as biological markers of migraine

(Appenzeller, 1978). Experimental production of headache in migraine patients but not normal controls by oral nitroglycerine (Kaneko, Shiraishi, Inaoka, et al., 1978) or intravenous histamine (Krabbe & Olesen, 1980), and frequently reported "ice-cream headache" (Raskin & Knittle, 1976), lend evidence of a extracranial vasomotor dysfunction.

Psychophysiological measures of autonomic vasomotor function in migraine have produced confusing and often conflicting results. Training of autonomic relaxation responses produced decreased temperature in the temporal artery region (vasoconstriction) in migraine patients and increased temperature (vasodilatation) in controls (Price & Tursky, 1976). In one study, measures of head and hand temperature showed significantly warmer temperatures in migraine patients than in matched controls across a variety of behavioral tasks (Cohen, Rickles & McArthur, 1978). In two other studies, head and hand temperature, as well as heart rate, blood pressure, forehead and forearm muscle tension, and skin resistance were found to be equal for migraine and matched tension headache and non-headache control groups both at rest and during self-control and stressful procedures (Anderson & Franks, 1981; Andrasik, Blanchard, Arena, et al., 1982a).

Most psychophysiological research in migraine has studied the "heat-dilation reflex" (Kerslake & Cooper, 1950). This is the normal response of increased blood flow in the extremities in response to momentary heating of the

trunk. A number of studies have reported a defective vasodilator response to this stimulus in migraine patients (Appenzeller, Davison & Marshall, 1963; Appenzeller, 1969, 1978). The authors have hypothesized an underlying abnormal continuous excessive vasoconstrictor tone and/or the presence of vasoconstrictor substances, which interfere with the autonomic conditioning of decreased sympathetic vasoconstrictor effects. But replication of Appenzeller's experiments have found normal vasodilatation in response to body heating among migraine patients no different from carefully matched controls (French, Lassers & Desai, 1967; Hockaday, MacMillan & Whitty, 1967). Morley (1977) has critically reviewed the evidence concerning abnormal general vasomotor control in migraine and concludes rigorous experimentation does not support the hypothesis. The rationale for biofeedback treatment of migraine is thus also open to question. This will be discussed in the treatment section.

Electrophysiological changes

EEG abnormalities in migraine are several times more common than the estimated 5% to 10% incidence in the general population (Parsonage, 1975). The high incidence of EEG abnormalities in the migraine population was first reported by Dow and Whitty (1947), who found persistently abnormal records in 59% of 51 cases. Since then, large surveys have reported persistent EEG abnormalities in 30% of 459 migraine patients (Selby & Lance, 1960), 61% of 560 cases (Hockaday &

Whitty, 1969), and 73% of 64 migrainous children under the age of 14 (Prensky & Sommer, 1979). Higher than expected EEG abnormalities have not been reported in all EEG studies, however, of migrainous children (Bille, 1962) or adults (Boudin, Pepin, Barbizet, et al., 1962; Lauritzen, Trojaborg & Olesen, 1981).

The most commonly found EEG abnormalities are non-specific dysrhythmias and reduction or loss of alpha rhythm and an increase in the slower rhythms in the theta and delta range. In addition, a growing number of studies have reported visual evoked potential abnormalities (e.g., Gawel, Connolly & Rose, 1983). The EEG abnormalities may have only statistical significance; there is no uniform EEG pattern in migraine. The non-specific deviations are seen in varying types of cerebral pathology as well as in the "normal" population. Whether the EEG abnormalities reflect cerebral damage caused by the migraine attacks, or denote the presence of an underlying constitutional brain abnormality remains an open question.

EEG abnormalities have been reported during the migraine attack and between attacks. Focal positive findings during the aura were first described by Engel, Ferris and Romano (1945), who reported transient low-voltage theta activity in the occipital lobe contralateral to the visual field scotoma in their patients. Subsequent studies have reported focal delta wave, theta wave, and spike-like changes compatible with the on-going neurologic deficits of classical, hemiplegic and accompagnee migraine patients

(Christiani, Volker & Soyka, 1980; Matthis, Perriaud, Jeklel, et al., 1980). Focal EEG slowing and flattening may be secondary to ischemia, as has been measured with experimental clamping of the carotid artery during continuous EEG recording and intraarterial ^{133}Xe injection (Trojaborg & Boysen, 1973), or secondary to a neuronal depression process (Basser, 1969).

The prolonged neurologic deficits of familial hemiplegic migraine are accompanied by long-lasting EEG abnormalities which return to normal days to weeks after attack onset (Bradshaw & Parsons, 1965; Rosenbaum, 1960; Whitty, 1953). However, in complicated migraine with permanent neurologic deficit, the EEG abnormalities persist (Engel, Hamburger, Reiser, et al., 1953). In the latter case, the EEG changes are similar to those produced by cerebral infarction.

In the spectrum of EEG abnormalities in migraine, focal changes are rare and usually only present during the on-going neurologic deficit. Far more common are generalized dysrhythmias and non-specific slow activity which are present interictally. A persistent EEG pattern of abnormally slow-wave and high-voltage paroxysmal activity, once termed <u>dysrhythmic migraine</u> (Weil, 1952), was reported in 42% of 144 common migraine cases, 36% of 245 visual aura classical migraine cases, and 45% of 171 lateralized motor, sensory and cognitive deficit classical migraine cases (Hockday & Whitty, 1969).

Dysrhythmic and other non-specific EEG abnormalities

have not been found to be correlated with the headache, medication use, frequency of attacks, or duration of migraine history (Hockaday & Whitty, 1969; Slevin, Faught, Hanna, et al., 1981). These findings contradict Slatter's (1968) hypothesis that abnormal EEG findings are the result of the migraine attack itself. However, patients developing migraine under the age of 20 were significantly more likely to have an abnormal EEG record than those developing migraine after age 20, and the EEG abnormality most often associated with young migraine onset is dysrhythmia (Hockaday & Whitty, 1969).

These findings suggest that the changes found in the EEG of migraine patients represent in part the underlying pathophysiology of migraine, especially in those patients developing migraine in youth. Children with migraine show a significantly higher percentage of 14 and 6/second positive spike phenomenon than children with seizures (12.2% vs. 4.3%) (Jay, 1982), and significantly lower "coherence," a spectral derivation of the degree to which two cortical sites influence each other or are collectively influenced by a common pacemaker in response to photic stimulation, than matched control children (Simon, Zimmerman, Sanderson, et al., 1983). These positive findings may serve as markers of autonomic instability in children with migraine.

Studies of photic stimulation in migrainous adults have found highly significant differences from normal controls, suggesting some form of cortical dysregulation. Golla and Winter (1959) reported an extension of the flicker response

to flash rates above 20/second, termed the "H-response" in 108 of 113 migraine patients and in only 8 of 50 controls. Similar findings have been reported by Slatter (1968), Smyth and Winter (1964), and Townsend (1967).

Studies of hemispheric asymmetries in the evoked potential of visual stimuli have shown differences of 50% or less in normal subjects but classical migraine patients exhibit hemispheric asymmetries between attacks of 150% and as great as 500% during attacks (Regan & Heron, 1970). This method can effectively separate classical migraine from common migraine patients, and among classical migraineurs, separate those during the attack from those between attacks (MacLean, Appenzeller, Cordaro, et al., 1975).

Components of the visual evoked potential in headache-free migraine patients have been found to be significantly different from normal controls. In response to single unpatterned flashes, female migraine patients exhibit an average lower positive second component and later negative third component (Richey, Kool & Waggoner, 1966), and both sexes exhibit a larger negative first component and overall longer latencies to brighter flashes (Gawel, et al., 1983). Similar waveform differences have been reported in response to a reversing checkerboard stimulus (Kennard, Gawel, Rudolph, et al., 1978). These differences may represent a failure of sensory input modulation due to either lack of inhibition or excessive excitation.

Migraine and epilepsy

Beginning with Liveing (1873) and Gowers (1907), a postulated link between migraine and epilepsy has been explored. The two disorders share the clinical features of paroxysmal onset and, in some cases, the march of symptoms pattern. Lennox (1960) believed migraine was "autonomic epilepsy." He reported that 11.1% of 1,610 epileptics had migraine versus 6.3% of 956 controls, and 6.5% of 415 migraine patients had seizures compared to 0.5% of the general population. Basser (1969) reported that 5.9% of 1,830 migraine patients and 1.1% of 548 tension headache patients had epilepsy, a highly significant difference. However, a large prospective survey found no significant differences between these two patient groups (Lance & Anthony, 1966).

Several forms of relationship may account for this statistical link between migraine and epilepsy. Two opposing positions view the relationship as either coincidental (Lance & Anthony, 1966) or as mistakenly associated--some forms of epilepsy responsive to anticonvulsant medication also underlie recurrent headache (Riley & Massey, 1980). Another explanation posits that repeated migraine attacks cause epileptogenic lesions. Slatter (1968) reported two cases in which focal brain damage caused by migraine might have been responsible for later epileptic changes. But in a large study of 560 migraine patients, 126 of whom reported personal or family history of migraine (a case selection bias, not a true

measure of epilepsy incidence in a migraine population), there was no tendency for epilepsy to be commoner in the patients with a long history of migraine or in patients with a constantly lateralized stereotyped aura (Hockaday & Whitty, 1969). Furthermore, in over half of the patients with both migraine and epilepsy, the first seizure occurred before or within the first year of migraine onset. Only in a few cases did epilepsy develop late in the migraine course.

Another explanation proposes an underlying pathophysiological state which may be manifested as either migraine or epilepsy, or in rare cases, both (Basser, 1969). Such a pathophysiological condition may be genetically associated (Dow & Whitty, 1947). Barolin (1970) reported similar EEG abnormalities in the non-migrainous family members of 17 migraine patients. Lennox (1960) reported that 23.9% of epileptics have a family history of migraine, a percentage significantly higher that that of normal controls.

Neuroanatomical changes

Computerized axial tomography (CT) studies of migraine have produced some unexpected positive findings. The first CT-scan investigation of migraine began with the serendipitous finding of focal cerebral edema shortly after the migraine attack of one of the staff who volunteered to test the recently installed CT-scanner (Baker, 1975). In studies of selected patients with severe migraine, CT

abnormalities have been reported in the range of 24% (Cala & Mastaglia, 1980) to 76% (Cala & Mastaglia, 1976). In a study of 129 consecutive migraine patients less disabled than those reported in previous studies, 25% exhibited CT abnormalities (Sargent, Lawson & Solback, 1979).

CT investigations of several hundred migraine patients have revealed four types of abnormality: low densitometric zones, ventricular enlargement, cortical atrophy, and infarctions. The low densitometric zones reflect cerebral edema, likely due to alteration in the blood-brain-barrier. Cerebral edema is maximum 3 or 4 days after an ischemic insult and may last for 2 weeks (Mathew, Meyer, Welch, et al., 1977). Studies performed within days of the attack have reported low densitometric zones and later reexamination has shown resolution (e.g., Baker, 1975; Cala & Mastaglia, 1976; Mathew, et al., 1977). Studies performed after the acute stages infrequently find low density areas (Sargent, et al., 1979). One study, however, has not confirmed acute changes in cortical density (Masland, Friedman & Buchsbaum, 1978).

CT findings of ventricular enlargement, cerebral atrophy and cerebral infarction are highly correlated with the severity and presence of migrainous neurologic symptoms. In one study of 13 complicated migraine patients, 11 had at least one of these abnormalitiess (Hungerford, duBoulay & Zilkha, 1976). Other studies reporting permanent CT abnormalities corresponding to clinical symptomatology include Baker (1975), Cala & Mastaglia (1976, 1980), and

Mathew (1978).

The meaning of cerebral atrophy in migraine remains unclear, however. It may represent the end result of repeated episodes of focal or multifocal ischemia (Mathew, et al., 1977; Cala & Mastaglia, 1980). On the other hand, Masland, et al. (1978) found cerebral atrophy in only 10% of 136 patients with classical, common and complicated migraine, compared to 25% of 8,000 patients consecutively screened for various reasons unassociated with headache who exhibited enlarged ventricles and cerebral atrophy. The authors conclude that positive CT findings in migraine are incidental.

Pathogenic Theories of Migraine

The pathogenesis of migraine remains unclear but this is not due to a shortage of theories. All pathogenic theories are incomplete and rely on varying degrees of speculation. For the present time being, almost any conceivable theory linking neurotransmission, humoral changes and vascular reactivity is plausible (Lance, 1981). A comprehensive theory must be able to explain the signs and symptoms, the underlying vascular, biologic and neuronal changes, the function of vasomotor innervation to the affected vasculature, the mechanisms of action of migraine attack triggers, and the basis for the mode of action of different therapeutic agents. Raskin and Appenzeller (1980) state that migraine may not be a unitary disorder and suggest that

its multivariate features and precipitants may be due to several underlying disordered mechanisms.

Genetic theories

Genetic theories of migraine are perhaps the most speculative. Reports of familial history of migraine range from 10% of a randomly selected migraine sample (not significantly different from the 5% familial incidence in a non-migrainous sample) (Waters, 1971b), to 90% of a migraine patient series (Dalsgaard-Nielsen, 1965). For certain forms of migraine, most notably familial hemiplegic migraine (Bradshaw & Parsons, 1965; Whitty, 1953), the hereditary link appears strong. Theories of transmission include recessive inheritance with 70% penetrance (Goodell, Lewontin & Wolff, 1954) and autosomal dominant inheritance with incomplete penetrance (Raskin & Appenzeller, 1980). One recent hypothesis associates sinisterality, immune disease, learning disorders and migraine with delayed growth of the left hemisphere secondary to excessive testosterone secondary to some gene complex abnormality controlling the development of brain asymmetry and immunity (Geschwind & Behan, 1982).

Ziegler (1977) has stressed the need for controlled studies of the inheritance of physiologic patterns of response to external stimuli leading to migraine headaches. At the present time genetic theories have not furthered our understanding of migraine.

Systemic metabolic/humoral disorder theories

The modern version of the classical vascular theory assumes that cranial blood vessels overreact to one or more circulating agents independent of the autonomic control of the vasculature involved. In Wolff's (1963) two-step vascular theory the primary event is cerebral vasospasm which causes the neurologic symptoms of the aura, followed by reactive hyperemia in the the intra- and extracranial vessels. The headpain is caused by dilatation of the extracranial vessels plus the local exudation of a polypeptide substance called neurokinin which produces a sterile inflammation around the vessels.

A more recent vascular pathogenic theory proposes that the opening of arteriovenous anastomoses causes both the aura symptoms and the headache (Heyck, 1969). Blood is shunted from the cerebral capillary beds, producing ischemia and neurologic dysfunction, and the direct transfer of blood from the arteries to the veins causes extracranial vascular distention and accompanying pain. Support for this theory comes from recent evidence that ergotamine, a common abortive medication, favors the capillary circulation by closing arteriovenous shunts (Spierings & Saxena, 1980).

There are objections raised with these vascular theories of migraine. In the common migraine attack rCBF evidence of decreased blood flow prior to the headache is lacking, a necessary component in both theories (Olesen, et al., 1982). The neurologic symptoms of the classical migraine aura do not necessarily correspond to the cortical

zones supplied by any one vascular territory presumably being influenced by vasospasm or capillary bed steal. Bruyn (1968) takes exception to cortical involvement in the migraine aura and proposes brainstem participation, specifically the regions of the posterior limb of the internal capsule, thalamic ventroposterolateral nuclei, and the lateral geniculate body.

Wolff (1963) and Heyck (1969) left open the question of what sets the vascular changes in motion. Circulating vasoactive substances have been extensively studied in this regard. Serotonin or 5-HT is a biogenic amine which may have an important role in the pathogenesis of migraine. During migraine attacks urinary levels of the serotonin metabolite 5-HIAA rise (Sicuteri, et al., 1961) and platelet-bound and free plasma serotonin levels fall in most patients (Lance, et al., 1967). This has been confirmed by Mück-Seler, et al., 1979). One theory postulates a serotonin-releasing factor in the blood which causes the platelets to release their serotonin, resulting in the initial cerebral vasoconstriction, extracranial vasodilatation and increased platelet aggregation (Anthony, Hinterberger & Lance, 1969). A later modification proposes a concurrent liberation of histamine and proteolytic enzymes from mast cells, which, with the released serotonin, increase capillary permeability and the production of the pain substance plasmakinin (Fanchamps, 1974).

Serotonin is known to be the most potent vasoconstrictor amine in the cerebral circulation (Raskin &

Appenzeller, 1980) but blood-born serotonin cannot cross the blood-brain-barrier (BBB) (Lance, 1982). This fact challenges the circulating serotonin theory. Harper, MacKenzie, McCulloch, et al. (1977) circumvent this problem by proposing a transiently defective BBB in migraine patients which would allow serotonin and other vasoactive substances to enter the cerebral circulation. At the present time, however, there is no way to prove the existence of a leaky BBB in migraine patients (Amery, 1982).

Hanington (1978) proposes that the platelet release of serotonin is not the effect of some outside stimulus but rather an indication of a primary abnormality of platelet function which causes the migraine attacks. Evidence indirectly supporting this hypothesis are the findings of a platelet release action (Gawel, Burkitt & Rose, 1979), platelet aggregation (Couch & Hassanein, 1977; Deshmukh & Meyer, 1977), and plasma hypercoagulability (Kalendovsky & Austin, 1975) in headache-free migraine patients. Nevertheless, direct evidence that migraine is a blood disease is lacking (Lance, 1982).

Another vasoactive substance receiving attention for its possible role in migraine pathogenesis are the prostaglandins (i.e., PGE_1), long-chain unsaturated free-fatty acids synthesized by virtually all the body tissues. PGE_1 is capable of intracranial vasoconstriction and extracranial vasodilatation (Welch, Sprira, Knowles, et al., 1974). PGE_1 intravenously infused into normal subjects produces vascular headache, nausea, and even a visual aura

in some subjects (Carlson, et al., 1968). Sandler (1972) proposes that a pharmacologically active triggering agent such as tyramine may cause the release of prostaglandins from the lungs into the arterial circulation. In one study, however, plasma levels of PGE_1 have not been found to change during the migraine attack (Anthony, 1976). But PGE_1 may be released locally at the arterial wall in response to neural or chemical stinuli (Raskin & Appenzeller, 1980). Prostaglandin synthesis in the blood vessel walls has been found to be stimulated by prolactin, serotonin and angiotension (Horrobin, 1977). Horrobin (1977) believes that a PGE_1-like substance is the final common cause of migraine, and its synthesis can be associated with sleep, stress, fluid and electrolyte retention, renal disease and dietary factors--common triggers of the migraine attack.

Central nervous system disorder theories

The neurogenic hypothesis assumes a primary neural stimulus which induces a vasomotor response. For years controversy has existed regarding the role of neural factors in the control of cerebral blood flow, but recent evidence demonstrates that stimulation of the hypothalamus or cervical sympathetic ganglia can alter the caliber of pial and cerebral vessels (Purves, 1978). The neurological phenomenon of the spreading depression of Leão (Leão, 1944, 1947), well documented in the animal laboratory (Gardner-Medwin & Skelton, 1982; Kraig & Nicholson, 1978; Lauritzen, et al., 1982), finds application in neurogenic hypotheses of

migraine based on its clinical correspondence to the aura march of symptoms (Milner, 1958) and the pattern of observed rCBF changes (Olesen, et al., 1981).

Other lines of evidence supporting a neurogenic hypothesis are the occurence of prodromal symptoms such as appetite changes, thirst, sleep disturbances, temperature dysregulation and emotional alterations, implicating the hypothalamus and autonomic ganglion of the head (Blau, 1978; Herberg, 1975), prolonged but reversible neurologic deficits incompatible with a temporary arterial spasm, the significantly greater incidence of EEG abnormalities (Parsonage, 1975), and vasomotor dysregulation, including postural symptoms (Raskin & Knittle, 1976), impaired response to CO_2 (Sakai & Meyer, 1979) and behavioral stimulation (Olesen, et al., 1981), and generalized vasomotor dysfunction (Appenzeller, 1978), though this latter finding has been inconsistently replicated (Morley, 1977).

Two theories recast the classical vascular pathogenic theory into separate neuronal processes. Johnson (1978) proposes that the initial vasoconstriction is caused by the transiently increased release of noradrenaline from sympathetic nerve endings acting on the vascular alpha-adrenoceptors. Burnstock (1981) suggests that the vasodilatation following cerebral vessel spasm is mediated by the neurogenic release of adenosine triphosphate (ATP) and its breakdown products, adenosine monophosphate and adenosine. ATP and its products are potent cerebral

vasodilators, and may additionally be involved in pain production and platelet aggregration abnormalities.

Brain serotonin is a inhibitory neurotransmitter located in nerve circuits (serotonergic) near the midline regions of the medulla, pons and upper brainstem (Raskin & Appenzeller, 1980). Speculation that changes in plasma serotonin during the migraine attack parallel brain serotonin changes has guided several neurogenic theories.

Sicuteri (1976; Sicuteri, et al., 1974) proposes that the pain in migraine is due to a central lowering of the pain threshold caused by a disorder of the integration-modulation-inhibition of pain system mediated by the brainstem. Brain serotonin is believed to be a pain-modulating neurotransmitter. Modification of serotonin turnover in the brainstem is observed during changes known to be associated with migraine attacks: ovulation, menstruation, pregnancy, stress and sleep deprivation. Control of serotonin turnover may be genetically deranged in migraine.

Raskin and Appenzeller (1980) state that serotonergic circuits may serve to dampen overreaction to internal and external stimuli. In an extension of Sicuteri's model, they propose that modulation of serotonin release in the raphe neurons is defective, resulting in sporadically low synaptic serotonin levels and secondarily increased neuronal firing rates. Increased serotonergic activity could account for the dysregulation of cerebral circulation, desuppression of pain perception, as well as changes in the regulation of

sleep, body temperature, endocrine function, and the effects of stress.

Integrative theories

One theory which goes a long way in explaining the multivariate data of migraine is Amery's (1982) brain hypoxia model. The key event hypothesized in all migraine attacks is brain hypoxia which "unleashes a whirlpool" of biochemical, vascular and hematological changes underlying the attack signs and symptoms. Different mechanisms may set off hypoxia, the most common cause likely being increased brain metabolism with accompanying oxygen needs which cannot be adequately met. Increased metabolism could be a product of autonomic nervous system overactivity associated with frequent triggers of migraine attacks, such as emotional stress, REM sleep, and certain exogenous substances like tyramine and phenylethylamine. For unknown reasons, individuals with migraine are more susceptible to the development of brain hypoxia, or react in an exaggerated or abnormal way to brain hypoxia.

A spreading wave of cortical depression may be initiated by brain hypoxia. Amery finds the ionic shifts that occur in spreading depression identical to hypoxic processes. A reciprocal relationship may exist in which the neuronal activation preceding the inhibition phase increases the oxygen needs of the brain tissue, and thus exacerbates the pre-existing hypoxia. Amery argues that brain hypoxia/spreading depression would produce the neurologic

signs and symptoms of the prodrome and aura, and cause the release of humoral mediators previously discussed in other theories, including serotonin, catecholamines, prostaglandins, and ADP and ATP. The individual and collective influence of these substances account for the headache, nausea and vomiting of the acute attack. The unilaterality of the neurologic deficit and headache may be due to individualized brain asymmetry: one area of the brain is somehow more at risk for developing hypoxia.

Lance (1982) proposes an extremely complex neurovascular model which links cortical and subcortical activity in the pathogenesis of migraine. The individual with migraine is believed to possess an inherited pattern of monoamine metabolism which leaves him/her more susceptible to stress which causes the release of monoamines and consequent neural and vascular changes known clinically as a migraine attack. Hypothesized mediation of monoamine transmission is conducted by the hypothalamus, which in turn, is influenced by an internal rhythm mechanism (biological clock) and afferent impulses from the cortex and thalamus. The biological clock rhythms might account for the often cyclical attacks of migraine (e.g., menstrual or sleep cycle). The clock could also be overridden or reset by emotional stress, physical injury or threshold-breaking stimuli (e.g., glare, noise).

Descending impulses from the hypothalamus project to serotonergic circuits of the raphe nucleus and noradrenergic circuits of the locus ceruleus in the brainstem.

Hyperactivity of these circuits could cause constriction of the cortical microcirculation and induce ischemia or the spreading depression of Leão. Vasodilatation in the extracerebral circulation is mediated by the parasympathetic pathway of the 7th cranial nerve. Electrical stimulation of the locus ceruleus in the cat and monkey produces these exact changes and are usually ipsilateral to the stimulation (Lance, Lambert, Goadsby, et al., 1983).

Other factors such as the secretion of catecholamines from the adrenal gland and perhaps release of free-fatty acids mobilized by noradrenaline release might act on platelets directly to release platelet-bound serotonin which, in conjunction with bradykinin and histamine, would sensitize vessel walls of the extracranial and meningeal vasculature to distention and cause local pain. Concurrently, depleted monoamines would disrupt the endogenous pain control system and open the afferent gateway from the senses, increasing sensitivity to light, sound and smells.

Psychogenic theories

Psychological etiology in migraine was once the predominant view (psychosomatic) but is no longer seriously entertained. A brief review of the psychogenic theory of migraine will be presented primarily for historical interest. Psychological factors in migraine are presently viewed by most experts in the field as a generic trigger of a pathophysiological process, probably mediated by autonomic

nervous system activity (Raskin & Appenzeller, 1980).

Psychological theories of migraine can be classified by the form of relationship posited between the physical symptoms of migraine and the personality of the individual. Psychological factors can be viewed as causal, as reactions, or as interactively related to biological factors in the production of a migraine attack.

The "pure" psychogenic theory of migraine is psychoanalytic in origin and continues to influence popular notions about the "migraine personality." The stereotypic migraine sufferer is variously described as ambitious, perfectionistic, compulsive, rigid, and inhibited in the expression of anger and aggresssion. The theory contends that unconscious hostility toward loved ones is the primary conflict for such individuals and that headache occurs in situations in which the dominant emotion is anger, though unexpressed, or guilt following expression. Obsessive-compulsive personality characteristics, such as perfectionism, orderliness and inflexibility, are viewed as reaction formations to the repressed hostility and resentment.

The data base for the psychodynamic theory has been the psychiatric interview and the retrospective analysis of selected patients (Alvarez, 1947; Engel, Hamburger, Reiser, et al., 1953; Friedman, von Storch & Houston, 1954; Fromm-Reichmann, 1937; Wolff, 1937). Harrison (1975) has cautioned the uncritical acceptance of these studies because of observer bias, inadequate diagnostic criteria and the

lack of control groups. A less obvious note of caution comes from Barolin (1972) who notes that this conception of the migraine personality is predominantly an Anglo-American one. By contrast, the older German literature postulated a link between hysteria and migraine, and the French literature characterized the "migrainic" as a "bon vivant" personality who likes to dine and to love!

Experimental support of the psychoanalytic account of migraine has relied on the projective testing of fantasy material and has proven inconclusive. Formal scoring of the Rorschach response has found no differences between migraine and tension headache groups (Cooper & Friedman, 1954), more popular responses, faster reaction times and better control of affect in a migraine group compared to a duodenal ulcer group (Kaldegg, 1952), and more delay of response and whole response scores in a migraine group compared to a "superior" normal group (Ross & McNaughton, 1945).

Psychogenic explanations of migraine have generally lost support in recent years, perhaps because of the clinical impression that migraine patients in psychotherapy usually do not lose their migraines (Friedman, 1975). Controlled psychotherapy trials are needed to conclusively determine the import of psychological factors in the pathogensis of migraine.

Hypotheses about the existence of psychological disturbances in migrainous individuals resulting from the physical pain of migraine, as has been found in certain chronic pain conditions (Sternbach & Timmermans, 1975), or

somehow interactively contributing to the migraine syndrome, remain tenable and debated in the current literature. Evidence comes from various self-report instruments such as adjective check lists and objective personality inventories like the Minnesota Multiphasic Personality Inventory (MMPI). From these studies one finding is clear: individuals with headache generally describe themselves as more "neurotic" than do non-headache controls (Harrison, 1975).

Randomly selected non-patients with classical or common migraine were found to score significantly higher on the Neurotic scale of the Eysenck Personality Inventory than matched non-headache controls, but significantly lower than migraine clinic patients (Henryk-Gutt & Rees, 1973). The same finding was reported using patient controls (Maxwell, 1966). However, in another random non-patient sample of women with migraine or non-migrainous headache, no differences were found on the neurotic items of the Cornell Medical Index (Waters & O'Connor, 1971) and migraine and cluster headache patients scored within the normal range on the Freiburg Personality Inventory, a German personality test (Cuypers, Altenkirch & Bunge, 1981).

Neurotic self-perceptions among migraine suffers may begin early. In Bille's (1962) study of 73 migrainous children, both boys and girls described significantly more symptoms of anxiety, tension and nervousness in school situations than did matched control children. Interestingly, these attitudes matched the attitudes of their parents regarding their children, thus further

complicating the question of cause and effect.

Self-reports of behavior associated with hostility, aggression, guilt and depression are variable across studies. Using the Buss-Durkee scales, Henryk-Gutt and Rees (1973) found that classic migraine but not common migraine males reported significantly more hostile behavior than did control males whereas only female migraine clinic patients reported more hostile attitudes. Neither sex showed between-group differences on self-reported guilt. In a poorly validated questionnaire study, Bihldorff, King and Parnes (1971) found that migraine patients scored lower on a self-reported direct expression of anger factor and higher on a factor of anxiety and guilt following expression of anger than did tension headache and non-headache controls.

Self-reported depression has not been found to significantly vary among migraine patients and other headache patients and matched controls on the Beck Depression Inventory (Andrasik, et al., 1982c). However, in a non-controlled study using the Zung Self-rating Depression Scale, a weak but significant correlation was found with severity of migraine (Couch, Ziegler & Hassanein, 1975). Depression was found to be unrelated to pain and gastrointestinal symptoms of migraine but was highly correlated with the focal neurologic disturbances found in the classical migraine patients.

The most objective psychological studies of migraine are those using the MMPI, an instrument with response-set correction features and non-transparent items (Harrsion,

1975). MMPI studies carefully differentiating groups of migraine, tension and mixed vascular-tension headache patients find a continuum of neurotic pathology, with migraine patients displaying the more normal profiles (Andrasik, et al., 1982b; Kudrow & Sutkus, 1979; Sternbach, Dalessio, Kunzel, et al., 1980). The tension headache groups generally display the greatest degree of psychological disturbance. This may be due to the "pain density" of their condition (i.e., few pain-free intervals) (Sternbach, et al., 1980).

In studies using either matched controls or a large standardization sample of general medical patients as a control group, statistically significant differences have been found for scales 1, 2, and 3, the so-called neurotic triad, which indicate a preoccupation with somatic symptoms and bodily concerns of a vague and diffuse nature. In most studies the scale elevations found for the migraine patients are within the normal range and are not clinically different from patients receiving outpatient medical care (Andrasik, et al., 1982c; Sternbach, et al., 1980), though in one study of migraine clinic patients there was significant psychopathology due to a tendency to "fake bad" (Rogado, Harrison & Graham, 1973).

The statistically significant but clinically unimportant MMPI neurotic triad elevation may simply reflect the life situation of one exposed chronically to the risk of sudden intense pain and the role of prolonged patienthood with the inherent qualities of increased dependency and somatic

preoccupation (Harrison, 1975).

Treatment of Migraine

Migraine is a chronic condition and its present treatment is limited to management not cure. Elimination or reduction of common migraine triggers marks the beginning of treatment. This might involve correction of dental and visual problems, reducing coffee and alcohol intake, normalizing sleep and eating patterns, and stopping medications such as birth control pills, nitroglycerin and vitamin A. Diet is rarely a significant factor in migraine (Medina & Diamond, 1978). To conclusively rule out a dietary influence, a strict trial of ingredients never reported to provoke migraine such as distilled water, vegetables, potatoes, cottage cheese, and chicken, is recommended (Raskin & Appenzeller, 1980).

Treatments often tried but not demonstrated effective are transneural stimulation and treatment of temporomanibular joint (TMJ) dysfunction (Saper, 1983). Accupuncture is reported to be effective (Kajdos, 1975) but there is no evidence of relief beyond the acute stage (Lance, 1982).

The mainstay of treatment in the acute stages of the attack is pharmacological (Diamond & Dalessio, 1978). What is beneficial in the long-term treatment of migraine remains unsettled, though several longitudinal studies of prophylactic drug therapy demonstrate substantial long-term

effectiveness (Mathew, 1981; Raskin & Schwartz, 1980). Studies of behavioral treatment also report significant long-term benefit and will now be discussed.

Behavioral treatment

Outcome of formal psychotherapy and psychoanalysis in migraine has never been carefully studied. Impressions of its efficacy differ; Friedman (1975) concludes after 30 years experience that it is not useful, whereas Fine (1969) suggests, upon review of the case material literature, that it is.

Training in behavioral self-management and cognitive reappraisal procedures shows promise in migraine treatment. A comprehensive package of training in problem analysis, self-monitoring, goal setting, muscle and mental relaxation, self-evaluation, thought stoppage, covert and overt rehearsal, etc. was found significantly more effective in reducing the frequency of migraine attacks relative to two control groups practicing self-recording and self-monitoring of antecedent stimuli (Mitchell & White, 1977). At the 3 month follow-up the three subjects participating in the entire training regimen over a 60 week period exhibited an average 83% reduction in attack frequency. Unfortunately, the small number of subjects precludes generalization.

The substantial length of time devoted to the training in the above mentioned cognitive-behavioral treatment may account in part for its long-term success. In another study, Rational Emotive Therapy (RET) training was not found

to be effective compared to a waiting-list control (Lake, Rainey & Papsdorf, 1979). The authors conclude that the RET training (three 40-minute sessions) was not an adequate test of the treatment.

The two primary behavioral interventions practiced in migraine treatment are biofeedback and relaxation training (Blanchard & Andrasik, 1982). Forms of relaxation training include variations of Jacobson's (1939) progressive relaxation procedures (e.g., Lance, 1982, pp. 115-119), autogenic training (Schultz & Luthe, 1969), and passive relaxation and meditation. Types of biofeedback include thermal self-regulation from feedback sites at the finger or temple, cephalic blood-volume pulse feedback to constrict the cranial arteries, and electromyograph frontalis (EMG) feedback to reduce the level of muscle tension in the forehead.

Muscle relaxation training has long been advocated as the treatment of choice for muscle contraction headache (MCHA) but migraine patients have been shown to demonstrate chronic high levels of tension in muscles of the head and neck, sometimes exceeding that of patients with diagnosed MCHA (Bakal & Kagnov, 1977). Review of the treatment literature suggests that both relaxation and biofeedback training are equally effective for migraine and MCHA (Cohen, 1978).

In a controlled randomized treatment study, after 4 weeks of baseline and 2 weeks of treatment, a progressive relaxation with home practice treatment group demonstrated

significant reductions in headache intensity and duration, and intake of medications compared to a waiting-list control; the improvement was maintained at a 3 month follow-up (Blanchard, Theobald, Williamson, et al., 1978). Combining muscle relaxation training with classical conditioning to the word "relax" in an uncontrolled study, Warner and Lance (1975) reported substantial improvement in 7 of 12 migraine patients after four weekly training sessions and 6 months of daily home practice. Transcendental meditation was found to have limited effectiveness in an uncontrolled treatment study; after 4 months, only 6 of 17 migraine patients were judged to be improved (Benson, Klemchuk & Graham, 1974).

In biofeedback training auditory or visual signals provide information about the status of a physiologic response such as rate of blood flow (as measured by skin temperature or plethysmographic changes) or muscle tension (as measured by electrical discharge changes). By trial and error the individual learns to manipulate the physiologic response in the desired direction. Voluntary vasomotor control has been cited as proof of the specificity of autonomic learning (Miller, 1973). Bidirectional changes in digital skin temperature can be reliably self-regulated in normals (Taub & Emurian, 1973).

The utility of biofeedback training in migraine treatment was incidentally discovered during experiments of hand warming- induction by autosuggestion (Sargent, Green & Walters, 1972). A subject experienced spontaneous recovery

from a migraine attack in conjunction with voluntary finger vasodilatation. In a subsequent uncontrolled study of 62 migraine patients, the authors reported that 74% experienced headache activity improvement after thermal biofeedback training in vasodilatation and the use of autogenic phrases emphasizing relaxation and passivity.

Digital vasodilatation alone was thought to be the operative factor in the thermal biofeedback treatment of migraine (Turin & Johnson, 1976), but in more recent studies, substantial and equal clinical improvement has been demonstrated when migraine patients were trained in digital vasoconstriction (Kewman & Roberts, 1980; Largen, Mathew, Dobbins, et al., 1981). Successful treatment has also been reported in the biofeedback training of temporal artery vasoconstriction (Bild & Adams, 1980; Friar & Beatty, 1976). In a comparison of the effects of training in skin temperature warming and cooling at finger and scalp sites, Gauthier, Bois, Allaire, et al. (1981) found significant reductions in migraine activity and drug usage at 4 weeks and 6 months post-treatment for all four randomly-assigned treatment groups; furthermore, the magnitude of the change was not significantly different across the groups.

By what mechanism does vasomotor biofeedback, via vasodilatation or vasocontriction, at finger or scalp sites, influence migraine activity? One study working with both normal subjects and migraine patients found hand warming after digital thermal biofeedback training led to reliable decreases in supraorbital and superficial temporal artery

pulse-volumes confluent with increases in digital pulse-volume (Sovak, Kunzel, Sternbach, et al., 1978). However, finger temperature increases lagged behind the blood perfusion of the arm and hand tissue. The authors argue that feedback of the digital temperature is irrelevant to the subject's current physiological state and may not be the operative element in learning volitional vasodilatation. When digital vasodilatation was induced by externally warming the subjects' hands, digital pulse-volume again increased in all subjects but cranial pulse-volume increased in normals but decreased in the migraine patients. The authors conclude that the observed redistribution of cardiac output cannot explain the mechanism of biofeedback therapy because otherwise migraine could be treated with warm water immersion of the hands.

Sovak et al. (1978) and Dalessio, Kunzel, Sternbach, et al. (1979) postulate that what is learned in biofeedback is not a single autonomic response such as digital vasodilatation but a generalized decrease in tonic sympathetic autonomic nervous system outflow. This view is in accord with the earlier notion of turning off excessive sympathetic activity in thermal biofeedback (Sargent, Walters & Green, 1973). The "adaptation-relaxation reflex" (Dalessio, et al., 1979) is the antithesis of the "orienting reflex" (Sokolov, 1963) in which peripheral vasoconstriction is associated with generalized arousal.

In the adapatation-relaxation reflex model therapeutic effects are mediated centrally. Approaching the phenomenon

from a different perspective, Gauthier, et al. (1981) propose a model of peripheral control of sympathetic activity. The finding of treatment efficacy with either hand or cephalic vasodilatation or vasoconstriction suggests a common mechanism of teaching the patient to stabilize the cerebral and peripheral vascular system by providing a physiologic condition incompatible with extreme vasomotor activity. Teaching bidirectional temperature control might therefore be more effective in teaching vasomotor stability than training in any one direction alone (Blanchard & Andrasik, 1982).

Reviews of the short-term treatment efficacy of relaxation training, autogenic training, thermal biofeedback and cephalic vasomotor feedback show the behavioral interventions to be equally effective and superior to mere headache monitoring and to pharmacological placebo (Adams, Fenerstein & Fowler, 1980; Blanchard & Andrasik, 1982). It is suggested that all behavioral treatments are successful to the degree to which the patient develops the ability to relax. The earlier emphasis on digital vasodilatation as the operative factor in migraine relief may more accurately reflect the process of relaxation, through peripheral or central mediation of sympathetic outflow. Some support for this view comes from Surwit, Shapiro, and Feld's (1976) finding that leaving normal subjects alone in the lab during long baseline periods produced digital temperature increases as effectively as biofeedback training in vasodilatation.

Information about the long-term effectiveness of

behavioral interventions is limited to a 1 year prospective follow-up of 18 patients randomly assigned to thermal biofeedback or relaxation treatments (Silver, Blanchard, Williamson, et al., 1979). Both groups demonstrated average reductions in headache frequency of approximately 50%, a level similar to reductions immediately after treatment.

Pharmacological treatment

Antimigraine drugs have two applications: symptomatic relief and prophylaxis. Ergot derivatives and analgesics are used in symptomatic treatment if the patient's headache frequency is less than one to two attacks a week and general health (i.e., absence of coronary artery disease, severe hypertension, peripheral or cerebrovascular disease, peptic ulcer) or other medication use (e.g., anticoagulant use) does not contraindicate their use (Saper, 1983).

Ergotamine tartrate has been in use for over 50 years and is considered to relieve pain in about 70% of patients and to greatly reduce the duration of the attack if taken immediately upon attack onset (Lance, 1982). Graham and Wolff (1938) first reported its effect of decreasing the pulsation amplitude of scalp arteries and concommitant reduction of headache intensity. Ergotamine tartrate has been demonstrated to vasoconstrict the external carotid artery and its branches (Saxena, 1972), and to redistribute blood from arteriovenous anastomoses to capillaries (Spierings & Saxena, 1980), but to have little effect on the internal carotid branches (Sakai & Meyer, 1978).

One mode of ergotamine tartrate's action is stimulation of peripheral receptor sites in arterial walls, producing vasoconstriction (Saper, 1983). However, it has been hypothesized that its effect may in fact be on central brain mechanisms, specifically the depression of firing of serotonergic neurons in the brainstem (Raskin & Appenzeller, 1980). Agonism of serotonin is hypothesized to occur at the presynaptic autoreceptor and/or the postsynaptic receptor sites.

Ergotamine tartrate comes in many preparations, including tablet, sublingual, aerosol, suppository and injection forms, and in differing combinations with caffeine, phenacetin, acetaminophen, and anticholinergic and antiemetic alkaloids.

Prophylaxis is attempted when the headache frequency is greater than one to two headaches a week, and symptomatic therapies have failed or are medically contraindicated (Saper, 1983). Interval therapy includes the use of tricyclic antidepressants (e.g., amitriptyline or Elavil), monoamine oxidase inhibiting antidepressants (e.g., phenelzine or Nardil), beta blockers (e.g., propranolol or Inderal), and methysergide (Sansert). The putative action of these drugs is blockage of the biological events leading up to a migraine attack. All have a range of adverse side effects varying from dry mouth to retroperitoneal fibrosis. All may cross the blood-brain-barrier and serve as serotonin agonists (Raskin & Appenzeller, 1980).

In a retrospective non-randomized follow-up study of

interval treatment, Raskin and Schwartz (1980) obtained self-reports of headache activity from 146 patients treated with propranolol, amitriptyline, ergonovine, methysergide, ergotamine, phenelzine, papaverine, and cyproheptadine in sequential fashion. The mean follow-up period was 35 months for both this group and an age-matched sample of 85 migraine patients who chose non-drug treatments. Substantial improvement of 1 year or more in duration was reported by 55% of the drug treatment group and 26% of the control group. Improvement of two years or longer was reported by 31% and 12%, respectively. These intergroup differences were significant. The authors conclude that prophylactic migraine therapy provides substantial long-term benefits to some patients.

Comparison of behavioral and pharmacological interventions

Several studies have addressed the relative long-term efficacy of behavioral and drug interventions in migraine treatment. In a study comparing hypnotherapy and relaxation with the prophylactic drug prochlorperazine (Stemetil), 47 migraine patients were randomly assigned to either condition for a 2 month treatment period followed by a 3 month follow-up (Anderson, Basker & Dalton, 1975). Complete remission was reported in 10 of the 23 patients receiving hypnotherapy and only 3 of the 24 patients on drug therapy, a significant outcome difference.

A combination of thermal biofeedback, autogenic training, and relaxation treatment was compared to a drug

treatment condition of propranolol with occasional analgesic use in a randomized study of 58 female migraine patients (Sovak, Kunzel, Sternbach, et al., 1981). At the end of treatment, there were significantly fewer drop-outs in the behavioral treatment group (Blanchard & Andrasik's (1982) calculation) and a nonsignificant trend for the behavioral treatment group to show more improvement (53.6% vs. 45%).

In the largest treatment study to date, Mathew (1981) randomly assigned 340 migraine patients to individual treatment with propranolol, amitriptyline, biofeedback (EMG and thermal training), or some combination of the three, or to a control group that received ergotamine and analgesics. Results were reported in terms of percentage of improvement in headache activity between the pretreatment measure and a 4 to 6 month follow-up measure. Behavioral treatment alone was superior to the control condition (35% improved vs. 20%) but had a significantly higher percentage of drop-outs (Blanchard & Andrasik's (1982) calculation: 35.4%) than the other conditions and was not as effective as the drug condition. Propranolol alone was significantly superior to amitriptyline alone (62% improvement vs. 42%). The most effective treatment was propranolol plus biofeedback with an average 74% improvement rate.

The discrepancies among these outcome studies pave the way for future drug-behavioral therapy interaction studies in migraine treatment (Blanchard & Andrasik, 1982).

Proposed Study

Three subject groups with at least 15 subjects each will be recruited. The groups will consist of classical migraine, common migraine, and non-headache subjects. The latter two groups will serve as controls for the classical migraine subjects. Subjects will be matched on sex, age, education and handedness factors. A specialized neuropsychological test battery will be administered to assess higher-cortical functioning variables. The battery and testing procedures will be discussed in Chapter II.

Rationale of the experimental design

The rationale for the two control groups is as follows: the majority, if not all the classical migraine subjects experience significant psychological stress as a consequence of their episodic severe headpain and allied symptoms. Such stress may be secondary to the pain itself, the changes induced in their interpersonal environment due to frequent periods of incapacitation and increased dependence, and the disruption of their everyday activities and responsibilities. The common migraine group is intended to control for these influences. The experience of migraine for the common migraine subjects is comparable to the classical migraine subjects minus the repeated attacks of neurologic dysfunction.

A second factor controlled for by the common migraine group is that of medication use. The majority of both classical and common migraine subjects have undertaken

varying regimens of antimigraine and analgesic medications and are currently either pursuing experimental trials or have settled upon a treatment plan. Subjects in the two groups are treated with virtually the same prophylactic and abortive antimigraine and pain-killing drugs. Both groups of subjects may have additionally sought relief through such non-pharmacologic avenues as biofeedback, acupuncture or psychotherapy. Information about past and current treatment is elicited but will not be considered in the analysis; it will be presumed to be a random factor between the two groups.

The non-headache subjects will serve as a control for the above factors which characterize both migraine groups. The non-headache subject group will serve as a normal reference group by which the effects of repeated attacks of neurologic dysfunction and episodic severe headpain, psychological stress and medication use will be controlled for.

Regarding the anticipated relevance of this study to the migraine population at large, a precautionary note must be stated. The migraine groups consist of patients from a department of neurology clinic. This guarantees that the sample contains a high proportion of cases with complex symptomatology and history; in other words, this is a highly selected sample of individuals with migraine. The results of this study are therefore not intended to be readily generalized to populations other than migraine clinic patients.

Hypotheses

The long-term consequences of repeated migraine attacks on higher cortical functioning is unknown. Alterations in central nervous system function during the aura of the classical migraine attack have been measured but are incompletely understood. Cases of brain damage in the course of migraine attacks have been documented. On the basis of the similarities between classical and complicated cases of migraine, and lacking evidence of a pathogenic difference between the transient neurologic dysfunction of classical migraine and the permanent neurologic deficit of complicated migraine, it is proposed that the two disorders differ only on a quantitative dimension. Furthermore, the handful of case reports and psychometric studies suggesting slight neuropsychological dysfunction in selected classical migraine patients lead to the hypothesis that classical migraine is associated with cumulative and permanent, though subtle, neuropsychological impairment which is measurable. Accordingly, the proposed controlled investigation of classical and common migraine will test the following hypotheses:

Hypothesis I: The classical migraine group will show significantly greater average neuropsychological impairment and a greater percentage of tests scored in the impaired range than the common migraine and control groups.

Hypothesis II: Length of migraine history, frequency, and severity of the migraine attacks will be significantly positively correlated with the average neuropsychological

impairment rating and percentage of tests scored in the impaired range within the classical migraine group.

Hypothesis III: The predominantly lateralized transient neurologic symptoms of classical migraine subjects will correspond with significant neuropsychological impairment referable to the contralateral cerebral hemisphere.

CHAPTER II

Method

Subjects

Thirty-one migraine patients of the U. C. San Francisco Department of Neurology and 15 non-patient adults from the Medical Center and the San Rafael First Methodist Church served as voluntary subjects. Migraine subjects were divided among classical (n = 16) and common (n = 15) diagnostic groups. In the classical migraine group, the 13 women and 3 men ranged in age from 21 to 65 years (M = 41.9) and in education from 12 to 23 years (M = 15.9). The common migraine subjects consisted of 13 women and 2 men and ranged from 23 to 61 years of age (M = 41.1) and 12 to 19 years of education (M = 15.6). The 13 women and 2 men serving as control subjects were between the ages of 21 and 62 (M = 41.9) and had 12 to 22 years of education (M = 15.7). Left-handed subjects in the classical, common and control groups numbered one, four, and one, respectively. All subjects were of middle to upper-middle socioeconomic status. Most of the subjects resided in the San Francisco Bay Area; a few of the patients had traveled from outside of California.

Criteria for selection was as follows:

Exclusion criteria

Table 1 displays the exclusion criteria applied to all subjects. The disorders listed are not exhaustive but representative of the conditions excluded in this study. There are many conditions other than migraine which cause headache or are associated with headache (Diamond & Dalessio, 1978; Friedman, 1974; Saper, 1983). Disorders such as epilepsy and certain systemic diseases have known detrimental effects on brain function and were therefore excluded. Psychological disturbance also led to exclusion because the behavioral changes found in the major psychological disorders often influence the results of neuropsychological testing.

Inclusion criteria

Table 2 specifies the inclusion criteria for the three subject groups. The headache-free control group consists of subjects experiencing six or less mild headaches a year. This is considered an average frequency of headache in a healthy population (Andrasik, Blanchard, Arena, et al., 1982c). Mild headaches (Grade I severity (Olesen, Krabbe, and Tfelt-Hansen, 1981)) are defined functionally as the ability to carry out normal everyday activities.

The common and classical migraine groups were selected in a two-step process. First they were diagnosed by a board-certified neurologist (Neil H. Raskin, M.D.) based on presenting signs and symptoms, history, and neurological exam. In some cases, biomedical tests (e.g., spinal tap,

Table 1

Subject Exclusion Criteria

I Central Nervous System Disease/Trauma

- A. Seizure history
- B. Head injury with loss of consciousness
- C. Cerebrovascular occlusive disease

II Cranial Nerve Disease/Trauma

- A. Trigeminal neuralgia
- B. Glossopharyngeal neuralgia
- C. Postherpetic neuralgia

III Peripheral Nervous System Disease/Trauma

- A. Motor/sensory damage to upper extremities
- B. Thoracic outlet syndrome
- C. Carpal tunnel syndrome
- D. Peripheral vascular disease

IV Systemic Disease

- A. Juvenile onset diabetes
- B. Chronic obstructive pulmonary disease
- C. Renal disease
- D. Chronic alcohol abuse
- E. Opiate dependence

V Extracranial Pain Conditions

- A. Dental pain
- B. Temporo-mandibular joint disease
- C. Otolaryngological disease
- D. Cervical disk disease
- E. Ocular disease

VI Headache Other than Defined by Inclusion Criteria

- A. Primary vascular headache with secondary nontransient neurological disorder
  1. Complicated migraine
  2. Hemiplegic migraine
  3. Ophthalmoplegic migraine

Table 1 (Continued)

B. Other primary vascular headache
   1. Cluster headache

C. Secondary vascular headache
   1. Systemic infection and fever
   2. Hypoxia
   3. Hypoglycemia
   4. Toxic rebound
   5. Post-concussive

D. Traction headache
   1. Intracranial mass lesion
   2. Increased intracranial pressure
   3. Intracranial hemorrhage

E. Inflammatory headache
   1. Subarachnoid hemorrhage
   2. Meningitis

F. Muscle contraction headache
   1. Presence of 3 or more of the following:
      a. headache frequency more than 3 times a week
      b. headache usually described as bilateral and beginning in the occipital, sub-occipital, or back of neck region
      c. headache described as usually feeling like a tightness or external pressure on head
      d. headache usually described as a continual dull ache

VII Psychological Disorder

A. Conversion cephalgia
B. Major depression
C. Primary thought disorder

CT-scan, EEG) were conducted to rule-out other pathological processes. However, there is no biomedical test to rule-in migraine.

In the second step the more detailed inclusion criteria were considered with regard to each patient diagnosed with classical or common migraine. The criteria, discussed below, are based on well known classification schemes (Ad Hoc Committee on Classification of Headache, 1962; World Federation of Neurology: Information, 1969). In addition, the more refined research criteria developed by Olesen, et al. (1981) in migraine prophylactic drug research was incorporated.

Inclusion criteria for the common migraine group are recurrent headache one to six times a month lasting no longer than 24 hours each. The attack is associated with anorexia, sometimes with nausea and vomiting, and with at least one of the following: unilateral pain location, pulsating pain quality, and photophobia or phonophobia. The pain intensity is described functionally as preventing normal everyday activities and/or necessitating bed rest (Grades II and III, respectively (Olesen, et al., 1981)). No well defined neurologic aura can be present. This does not exclude vague and nondistinct emotional, gastrointestinal, and autonomic disturbances preceding the headache such as depression, irritability, hunger, or fatigue.

A maximum of one <u>interval</u> headache per week was allowed (Olesen, et al., 1981). This is defined as a mixed

Table 2

Subject Inclusion Criteria

I All Subjects

A. Both sexes
B. Ages 18 to 65
C. Pain-free and symptom-free at time of testing
D. Alert and motivated to do best
E. Informed consent

II Headache-Free Control Group

A. 6 or less mild headaches per year (Grade I: Able to carry out normal work activities)

III Common Migraine Control Group

A. Recurrent idiopathic attacks of headache
B. Often familial
C. Associated with anorexia, sometimes nausea/vomiting
D. Associated with one or more of the following:
   1. Unilateral pain location
   2. Pulsating pain quality
   3. Photophobia or phonophobia

E. 1 to 6 attacks per month
F. At least a 2 year history
G. 24 hours or less usual duration
H. Pain intensity medium or severe (Grade II: Unable to perform usual work but bed rest not necessary. Grade III: bed rest necessary)
I. Maximum of 1 weekly interval headache defined as mixed vascular-muscle contraction headache of mild intensity or moderate intensity without nausea
J. If prodrome present, various vague and nondistinct autonomic, gastrointestinal, and emotional disturbances but no well defined focal neurologic disturbances

Table 2 (Continued)

IV Classical Migraine Experimental Group

A. Recurrent idiopathic attacks of transient, reversible neurologic dysfunction preceding or concurrent with headache, though occurrence of headache is not inevitable
   1. Neurologic dysfunction usually 60 minutes or less in duration
   2. Symptoms include one or more of the following:
      a. Visual changes: scotoma, fortification spectra, photopsia
      b. Somatosensory changes: hemiparesthesia
      c. Motor changes: hemiplegia
      d. Cognitive changes: aphasia, spatial deficits, memory deficits, confusion, disorientation

B. Often familial
C. Associated with anorexia, sometimes nausea/vomiting
D. Associated with one or more of the following:
   1. Unilateral pain location
   2. Pulsating pain quality
   3. Photophobia or phonophobia

E. 1 to 6 attacks per month
F. At least a 2 year history
G. 24 hours or less usual duration
H. Pain intensity medium or severe
I. Maximum of one weekly interval headache defined as common migraine headache or mixed vascular-muscle contraction headache

vascular-muscle contraction headache which does not interfere with everyday activites, or if the pain intensity is sutficient to interfere with normal functioning, then nausea cannot be present.

The subject must have had at least a 2 year history of common migraine.

The inclusion criteria for the classical migraine group were identical to the common migraine group with the exception of the specification of the aura. In the classical migraine group there must be recurrent attacks of transient, reversible neurologic dysfunction preceding or concurrent with the headache. Within each case, the headache phase itself does not have to invariably occur. The aura may stand by itself.

The neurologic dysfunction will usually last 60 minutes or less and may involve visual changes, somatosensory changes, motor changes, and/or cognitive changes.

Procedure

Subjects were approached through direct contact at the Medical Center or by phone call. Neurology outpatient consultations are conducted twice a week by Dr. Raskin. New outpatients diagnosed with migraine thought appropriate for the study were referred to the investigator immediately following their appointment. Outpatients with known migraine diagnoses on a return visit were approached prior to their appointment by the investigator. The majority of

potential migraine subjects were identified through review of their medical chart; approximately 2,050 records of patients consulting Dr. Raskin prior to March, 1983 were reviewed. Patients meeting the rudimentary criteria for selection were then contacted by phone and further interviewed.

Control subjects were recruited by direct appeal to U. C. staff and students, and through the newsletter of the San Rafael First Methodist Church.

All potential subjects were given an explanation of the research project but were not informed of the hypotheses to be tested. Confidentiality was assured through the use of code numbers with the subject code key kept separate from all test results. Furthermore, no record of their participation or nonparticipation was entered in the medical record. No subject was paid or reimbursed for their time though they were promised a short report of the study at its conclusion.

Having met the criteria for one of the three groups and upon agreement to participate, a 3 hour appointment was scheduled. An appointment card and project description memo was given to the subject. This letter is located in Appendix A. It was emphasized that the subject must be feeling his/her best on the day of testing. Cancellation was encouraged if this was not the case.

The testing session was conducted in a private faculty neurology office in the outpatient clinic. Throughout the session it was the investigator's aim to establish an

interpersonal climate that was non-threatening and comfortable for the subject, and was at the same time standardized so that each administration of the tests was as much like every other administration as possible. All questions and concerns of the subject were addressed directly at the onset. A brief presentation of the type and nature of the tests was given. To help the subject do his/her best, supportive reassurance was given when appropriate. If necessary, breaks were taken to insure the subject's sustained effort and interest. At the end of the session feedback on the test results was offered.

To promote standardization, the tests were given in the same order and identical instructions were communicated. The investigator is well familar with the tests and protocol of neuropsychological assessment, having administered similar batteries over 200 times to brain-damaged, psychiatric, and normal subjects in the past 3 years.

A potential criticism of this study is that the examiner is not blind to the subjects' backgrounds and diagnoses. However, these tests have rigorous administration and scoring criteria; there is little room for examiner judgement. While use of a "blind" technician to administer the test may be the best protection against examiner bias, investigations of the examiner characteristics in neuropsychological testing indicate that an experienced and supportive examiner facilitates the subject's best performance and may outweigh the advantages of a less experienced technician (Parsons & Prigatano,

1978).

Prior to the interview and testing, an informed consent form was read and signed by the subject. This form is contained in Appendix B.

The standardized interview form is located in Appendix C. Note was made of such historical predictor variables as age, sex, race, education, occupation, and handedness. The medical history of the subject and family of origin was briefly obtained. An exhaustive description of the headache disorder was elicited, including the type and locus of pain, intensity, frequency, duration, associated symptoms, prodromata, and precipitating factors.

The time course of the headache disorder, such as age of onset, remissions and exacerbations, and time of the last attack, was gathered. Medication history and current treatment plan was obtained.

Observations on the subject's use of language, affect, and orientation (time, person, place) were also noted.

Measures

The neuropsychological test battery consists of a series of standardized and objective behavioral measures of sensory-perceptual and motor skills, language, verbal and nonverbal reasoning, and auditory and visual memory functions. The tests are designed to allow differentiation of the sensory and motor modalities involved in the perception and execution of the task from the inherent

are all well founded in previous neuropsychological research and are psychometrically sound. Many of the tests belong to standardized neuropsychological test batteries (i.e., Halstead-Reitan Neuropsychological Test Battery (Boll, 1981; Filskov & Goldstein, 1974; Reitan, 1979); Revised Lafayette Clinic Adult Neuropsychological Battery (1977); Michigan Neuropsychological Test Battery (Smith, 1975)).

The battery constructed for the present research represents a compilation of those tests, in the investigator's experience, which offer the most time efficient assessment of higher cortical function which may be compromised in migraine. Certainly a more comprehensive battery could have been used but the net gain in information was judged to be minor with respect to the increase in time to administer (two to three times longer). This battery represented a reasonable concession to the time constraint of the clinical setting.

The neuropsychological test materials are located in Appendix D and are organized in the order of administration. The battery required approximately 3 hours to complete. Each test will now be discussed.

The Patient's Assessment of Own Functioning Inventory

This measure was developed to objectify a patient's complaints of disability (Heaton, Chelune, and Lehman, 1981), though reliability and validity data are lacking. The 34-item questionnaire broadly investigates the range of

neuropsychological dysfunction. The subject is requested to answer each question on the basis of current functioning between headache attacks. Responses are on a 6 point scale, incremented from "almost always" to "almost never." This measure was included as a quantified indication of the self-perceived state of neuropsychological functioning as defined by the sensory-perceptual, motor, cognitive, and memory demands of everyday life (e.g., "How often do you forget something that has been told you within the last day or two?"). The results will be considered with regard to group membership and neuropsychological test results.

Sensory-Perceptual examination

The visual, auditory, and tactile sensory-perceptual examinations require initial determination that the subject can perceive unilaterally presented stimuli on each side of the body. Upon confirmation of unilateral perception, stimuli are presented in a bilaterally equal and simultaneous manner in order to test for the suppression of one of two competing stimuli.

The visual field exam (Reitan, 1979) provides an estimation of the area of the visual fields and tests for suppression of a stimulus upon bilateral simultaneous stimulation. Unilateral stimuli are first presented at three different eye levels, followed by bilateral presentation of stimuli at each level. The subject is instructed to look directly at the examiner's nose while sitting knee-to-knee and to say "left" or "right" upon the

movement of the examiner's index finger in the appropriate peripheral field. The subject is not informed that bilateral simultaneous movement will follow the unilateral presentations. A total of 12 suppressions is possible for each visual field.

The auditory exam (Reitan, 1979) consists of both unilateral and bilateral simultaneous auditory stimuli. The examiner stands behind the patient and makes barely audible finger movements in each ear. Upon successful identification of unilateral stimuli ("left", "right"), bilateral simultaneous and unilateral stimuli are interspersed. The subject is not instructed about the simultaneous bilateral stimulation trials. A total of four suppressions are possible for each ear.

The single and double simultaneous (face-hand) stimulation test (SDSS) (Western Psychological Services: W-156A) (Centofanti & Smith, 1979) is a measure of the subject's ability to perceive both single and double simultaneous tactile stimuli applied to both cheeks and both hands in all possible permutations. The tactile stimulus is applied by a brisk, light stroke of the examiner's forefinger while the subject's eyes are shut. The subject is instructed to indicate where he/she was touched by pointing to the spot. A total of 12 suppressions are possible for each cheek and each hand.

The finger agnosia test (Reitan, 1979) is a measure of tactile perception and recognition. Light tactile stimuli (touch of a pencil eraser) are applied to the distal segment

of each finger, beginning with the dominant hand, while the subject's eyes are closed. The order of the finger touching is standardized; each finger on each hand is touched four times. A system is worked out with the subject for reporting which finger is touched. The thumb is labeled number 1, the index finger number 2 and so on to number 5 for the small finger. A total of 20 errors for each hand is possible.

The finger agraphesthesia test (Reitan, 1979) is a measure of tactile perception of numbers written on the ball of the fingertips. The numbers "3", "4", "5", and "6" are each written four times on each hand in a standard order beginning with the dominant hand. The subject is instructed to close his/her eyes and report which numbers are written. A sample of the four numbers are written on a larger scale on the subject's palm prior to the fingertip writing. A slightly blunted pencil is used. A total of 20 errors are possible on each hand.

Motor examination

The motor strength of the upper extremities is measured with the Smedley Hand Dynamometer (Lafayette Instrument Company: Model #78010) (Reitan, 1979). After adjustment for hand size, the subject is instructed to grip the dynamometer with arm extended toward the floor and to squeeze as hard as possible. The dominant hand is tested first, followed by the nondominant hand. Two trials are performed. The effort is registered in kilograms of force. The mean value of the

two trials provides the score for each hand.

The Finger Oscillation (Tapping) test (Halstead, 1947; Reitan, 1979) is a measure of upper-extremity motor speed in which the subject depresses the lever of a manual counter with the index finger. The apparatus consists of a board-mounted digital mechanical counter with a telegraph key-like lever attached (Reitan Neuropsychology Laboratory: Manual finger tapper for adults). The subject's hand rests on the board with only the index finger raised to move the lever. No other movement of the hand or arm is permitted. The subject is instructed to tap the lever down as rapidly as possible. After a practice trial with each hand, 10-second trials are conducted beginning with the dominant hand and alternating to the nondominant hand. The mean number of taps achieved in 5 trials for each hand is the recorded score.

The finger tapping test appears to be predominantly a pure motor speed measure. It is one of the few measures demonstrated to discriminate multiple sclerosis patients from patients with other neurological diseases (Matthews, Cleeland, & Hopper, 1970). In addition to speed of performance, the pattern of lateralization (the difference between rate of speed for each hand) is of interest. The optimal degree of lateralization is estimated by Reitan (1974, p. 46) to be a 10% decrement in nondominant hand rate from the dominant hand rate. Lateralization in excess of this difference or lack of lateralization may relate to cerebral pathology. Lateralization on the finger tapping

test appears to be free of variation from such factors as age, sex, and handedness (Andrew, 1981).

The Grooved Pegboard test (Lafayette Instrument Company: Model #32025) measures fine motor speed and coordination of the upper extremities. It consists of 25 holes with randomly positioned slots. Pegs with a key along one side must be rotated to match the hole before they can be inserted. The subject is permitted a practice row with each hand. Instructions are to place the pegs, one at a time, as quickly as possible into the holes. The first trial is with the dominant hand, the second with the nondominant hand. Number of seconds to insert all 25 pegs provides the score for each hand.

The grooved pegboard has been found to be a rather complex task requiring a larger number of sensory and motor components than most other motor tests. In a comparison of normal controls and patients with right or left hemisphere tumors on a variety of motor tasks, Haaland, Cleeland, and Carr (1977) found the grooved pegboard to differentiate the groups whereas other less complex motor tasks, such as the finger tapping test, did not. Furthermore, subjects with left hemisphere damage demonstrated bilateral grooved pegboard impairment whereas right hemisphere damaged subjects showed only contralateral impairment. Haaland, et al. (1977) conclude that the complexity of this task reveals a left hemispheric asymmetry of sensory-motor control in right-handed brain damaged patients.

Aphasia screening

The Aphasia Screening Test (Reitan Neuropsychology Laboratory: Aphasia Screening Test) (Wheeler & Reitan, 1962) is designed to survey a broad range of possible aphasic symptoms and related deficits. It also samples spatial-constructional skills. It is a modification of the Halstead-Wepman Aphasia Screening Test (Halstead & Wepman, 1949). The subject is required to name, spell, and draw geometric shapes, name common objects, identify individual numbers and letters, read and write words and sentences, comprehend spoken language, perform calculations and mental arithmetic, identify body parts, and differentiate between right and left. Wheeler and Reitan (1962) demonstrated the test to be sensitive to the presence and laterality of cerebral dysfunction in a heterogeneous set of brain-damaged patients compared to a non-brain-damaged control group.

The test was not designed to be scored psychometrically but rather used as a qualitative survey of specific deficits in language behavior. Scoring criteria developed by Russell, Neuringer, and Goldstein (1970) permit quantification of the test and were used in this study. All items of the test, excluding the drawing responses, are scored with different weights; failure of a relatively easy item (e.g., "name square"), contributes more to the total error score. A total error score of 75 is possible.

Russell, et al. (1970) provide criteria for scoring the copy drawings of the Greek cross item of the Aphasia Screening Test as well. The subject draws two crosses to

match a sample. Each drawing is scored on a 1 to 5 rating scale based on accuracy and symmetry. If the WAIS-R Block Design test (to be discussed below) is scored below the other WAIS-R subtests (with the exception of the Object Assembly and Digit Symbol subtests) then 2 points are added to the drawing scores. The sum of these scores makes up the Spatial Relations score.

Memory examination

The Russell (1975) revision of the Wechsler Memory Scale (WMS) (Wechsler, 1945) was used in the test battery. The WMS (The Psychological Corporation: Model #8987-307 (Form I)) is the most commonly used memory test in clinical neuropsychology but is no longer considered an adequate measure of memory. This is so because of its underlying assumptions of memory as a unitary function and brain damage as a unitary process. Guided by factor analytic studies of the WMS, Russell retained only the Logical Memory and Visual Reproduction short-term memory subtests and added a long-term memory measure by readministering the two subtests 30 minutes later.

The Logical Memory section consists of two action-packed stories segmented into discrete elements. The examiner reads the story and immediately asks the subject to recall, word for word, as much as possible. The dictated stories are recorded verbatim. A total of 46 elements may be recalled by the subject; this represents the short-term semantic score. The Visual Reproduction component consists

of displaying a printed geometric figure for 10 seconds, removing it, and having the subject draw it from memory. A total of four designs are displayed (one each on two cards and two designs on the third card). A total of 14 elements may be correctly reproduced.

The subject is not informed of the repeat administration in 30 minutes. He/she is asked to recall each story and draw each drawing in the greatest detail possible. If necessary, prompts are given but the prompted elements are not included in the score. In the test battery the 30 minute recall is conducted after administration of the Raven Standard Progressive Matrices-Short Form test. Six scores are derived: the short-term semantic and figural memory scores, the long-term semantic and figural memory scores, and the semantic and figural percentage retained scores.

Russell (1975, 1978) found the scoring revision to reliably and validly separate brain damage from normal, and right hemisphere damage from left hemisphere damage cases. The verbal recall tests are related to the left cerebral hemisphere and the figural recall tests to the right cerebral hemisphere. The new scoring method also demonstrated a graded measure of memory impairment that was significantly correlated with total brain damage impairment in the Halstead-Reitan battery.

In a subsequent validational study, Russell (1982) subjected the first 4 scales of the revised WMS along with 13 subtests from the Wechsler Adult Intelligence Scale

(WAIS) and Halstead-Reitan Neuropsychological Test Battery to a principle components factor analysis. Five types of memory were isolated. Both short-term and long-term figural memory scores loaded on the first factor, along with WAIS Block Design, the Category test, and Trails B. Semantic short-term and long-term scores loaded exclusively on the second factor. WAIS Digit Span, an immediate memory task, did not load on either factor. Russell concludes that the presentation of both semantic and figural types of memory requires so much time that long-term and short-term memory processes are utilized. Thus, while an individual subject may score differentially on the short and long-term recall tests, both performances evidentially belong more to the area of long-term memory than short-term memory.

Trail Making test

This test (Reitan Neuropsychology Laboratory: Trail Making Test for Adults) has two parts. Trails A consists of 25 circles distributed over a notebook-sized piece of paper. The circles contain the numbers 1 to 25. The subject is instructed to connect the circles with a pencil in numerical order as quickly as possible. Part B also consists of 25 circles but contains both numbers and letters. The instructions are to connect the circles in order, alternating between numbers and letters (1-A-2-B, etc.). Before each part a practice page is presented. During the timed tests any mistakes are immediately corrected by the examiner; such delays become part of the final score--the

number of seconds to complete the task.

Both parts require fine motor speed and coordination, visual scanning, and the ability to progress in sequence. Trails B requires the additional ability to maintain and integrate two simultaneous sets of symbols while alternating between them.

The Trail Making Test was originally part of the Army Individual Test and first reported by Armitage (1946) to be an indicator of brain damage. Reitan (1955b, 1958) demonstrated highly significant differences in the performances of a group of heterogeneous brain damaged subjects matched to a group of control subjects. In further investigations (Fitzhugh, Fitzhugh, & Reitan, 1963) it was found that patients with acute lesions of the left cerebral hemisphere performed less well on Part B relative to performance on Part A than did patients with acute right cerebral or non-lateralized cerebral lesions. No such effect of lateralization was present for groups with chronic brain damage.

Wisconsin Card Sorting Test

The Wisconsin Card Sorting Test (WCST) (Wells Printing Company, Madison, Wisconsin: Original WCST) consists of four stimulus cards which are placed in front of the subject, placed left to right. The cards show a red triangle, two green stars, three yellow crosses, and four blue circles. The subject is given a deck of 64 cards, each card a unique combination of the three characteristics of color, form and

number. The subject is instructed to place each consecutive card in front of the stimulus card he/she thinks it belongs with. The only response from the examiner after each card placement is "right" or "wrong." It is up to the subject to get as many correct as possible. The object of the test is to successfully sort 10 consecutive cards based on the card sorting principle the examiner is adhering to. Upon successful sorting of 10 cards, a new principle is instituted. The order is: color-form-number-color-form-number. The subject is never informed of the principle or when it is changed. The test is completed when all six categories are achieved or two decks of 64 cards have been exhausted.

The WCST (Berg, 1948; Grant & Berg, 1948) was designed to measure flexibility in thought and to identify perseveration (i.e., continuing a class of response previously labeled incorrect). Milner (1963) administered the WCST to patients undergoing brain operations for intractible epilepsy. All had static, atrophied lesions. She reported that patients with dorsolateral frontal lobe surgical excisions committed significantly more perseverative errors than did patients with other cerebral sites of excision. Furthermore, no more than three of the the six sorting categories was achieved in this group. Milner hypothesized that these test results may be referable particularly to left frontal lobe function because left dorsolateral lesions were consistently smaller than right frontal lesions in this patient population.

Drewe (1974) studied the WCST performances of subjects with focal lesions of diverse etiology. As Milner, she reported significantly more perseverative errors in the frontal lesion groups. In contrast, she found a trend for the right frontal cases to be more impaired than the left frontal cases on the WCST.

Robinson, Heaton, Lehman, and Stilson (1980) also investigated WCST perseverative responses and frontal lobe lesions in conjunction with the Halstead-Reitan Neuropsychological Test Battery. Consistent with the previous two studies, they reported the frontal groups to be significantly more impaired than the non-frontal groups, even when general neuropsychological impairment was controlled for. Supporting Drewe's (1974) results, they found the right combined frontal groups scored significantly higher on the perseverative measure. While successfully distinguishing frontal from non-frontal lesions, the number of perseverative errors did not separate focal frontal lesions from diffuse lesion cases. They recommend that the WCST is most effective in conjunction with a comprehensive neuropsychological test battery.

In the current use of the WCST, number of correct categories achieved, total number of errors, and perseverative errors were recorded. Perseverative errors are defined as a response which would have been correct on the immediately preceding category, or, in the first stage, as a continued response based on the subject's initial preference (Milner, 1963). In previous studies it has been

found necessary to reduce the skewness of the perseverative error data by a log transformation (Grant & Cost, 1954; Milner, 1963). The transformation y=log(x-3), where x is the original score and y is the analyzed score was used (Robinson, et al., 1980, p. 608).

Raven's Standard Progressive Matrices-Short-Form

The Raven Standard Progressive Matrices test (SPM) (The Psychological Corporation: Model #9686-767) was designed as a measure of Spearman's g which would provide an index of intellectual capacity relatively free from cultural and educational influences (Raven, 1938/1975). It tests an individual's capacity to apprehend meaningless figures, to form comparisons, and reason by analogy (Raven, Court, & Raven, 1977). There are 60 items divided into five sets. The 12 problems within each set are slightly overlapping and become progressively more difficult. In a sense, the order of the items provide training in the type of analysis needed to successfully complete the set. Each item consists of a single pattern (Set A), a 2 X 2 matrix (Set B), or a 3 X 3 matrix (Sets C, D, E) of geometric figures with the lower right section missing. The subject has the choice of six (Sets A, B) or eight (Sets C, D, E) alternative sections to fill the missing section (i.e., to complete the pattern). The test is untimed and does not require verbal response.

Raven, et al. (1977) cite numerous international studies of the reliability and validity of the SPM. Some 30 studies of internal consistency show a modal split-half

coefficent of r = .91. Test-retest coefficents derived from some 20 studies range from about r = .90 for a 1 week interval, decreasing to about r = .80 for an interval ranging from 1 month to 3 years.

Of the many validity studies conducted, only a few will be mentioned. Correlations of the SPM with the Stanford-Binet and Wechsler scales range from r = .54 to r = .88 for English speaking children, adolescents and adults. Factor analytical studies tend to confirm its measurement of general intellectual functioning or *g*. Loadings of up to .83 on *g* have been found in large studies of children and adults. In addition, most studies have not found loadings on verbal-educational or numerical ability factors. One study (Burke, & Bingham, 1969) found the SPM to load significantly on a factor of general intellectual functioning heavily determined by verbal content. This may reflect the strategy of some subjects to verbalize the steps involved in solving the problems. Surprisingly, a small loading of the SPM on a visual-spatial factor has been a consistent finding in the factor analytical studies.

The single greatest disadvantage of the SPM is the length of administration--sometimes extending to two hours. Encouraged by high split-half corrected reliability coefficents (e.g., r = .96 (Burke, & Bingham, 1969)), Berker, Zubrick, Javornisky, Whelan, Whitten, and Smith (1979) developed a short form of the SPM. The 30-item form was derived by a step-wise, item-total correlation procedure applied to each set of 12 items. Six items per set were

retained. Regression analysis of a clinical sample of 114 subjects produced a correlation between the SPM and SPM-SF of $r = .98$ with a standard error of 2.2. Cross-validation on 115 clinical subjects showed a shrinkage of approximately 2%. A new regression analysis was performed on the combined samples and provided the predicted SPM scores for the SPM-SF scores. Internal and construct validity studies further suggest that the shortened SPM results in little loss of validity (Berker, et al., 1979).

Wechsler Adult Intelligence Scale-Revised Subtests

The Wechsler Adult Intelligence Scale-Revised (WAIS-R) (The Psychological Corporation: Model #8991-713) is an updated Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 1955) with new norms based on a stratified sample of 1,880 adults tested between 1976 and 1980 (Wechsler, 1981). Much of the WAIS content was retained though some items were changed or deleted to reflect contemporary society. The WAIS was the standard instrument in intellectual assessment and it is expected the WAIS-R will continue the tradition. WAIS reliability and validity studies are too numerous to mention but are fully described in Matarazzo (1972) and Klove (1974).

The full WAIS-R (11 subtests) was not administered in the present study. Four subtests were selected: Digit Span, Block Design, Digit Symbol, and Similarities. The rationale for the abbreviation is three-fold. First, time. The WAIS-R requires one-and-a-half hours; this amount of time could

not be realistically accomodated. Second, these four subtests are the most sensitive of the WAIS-R battery to cerebral dysfunction and are considered "don't hold" tests (Wechsler, 1958). The Digit Symbol and Block Design tests have been selected for an abbreviated Halstead-Reitan neuropsychological screening battery for this reason (Erickson, Calsyn, & Scheupbach, 1978). Third, these four subtests were used in a regression formula estimating overall recent intellectual deterioration from a demographically predicted premorbid IQ (Wilson, Rosenbaum, & Brown, 1979; Wilson, Rosenbaum, Brown, Rourke, Whitman, & Grisell, 1978). This formula and its use will be discussed in detail below.

In the Digit Span test random digits are read at the rate of one-a-second until the subject fails to successfully repeat two trials of an item. Items range in length from 3 digits to 9 digits. In the second half of the test, the subject repeats the spoken digits in backward order. The items range from 2 to 8 digits in length. This test measures auditory attention and immediate memory, as well as the ability to manipulate mentally the digits in reverse order while maintaining the memory.

The Block Design test consists of nine blocks colored red on two sides, white on two sides, and red/white on two sides, which are manipulated to form two-dimensional designs to a model. There are 10 designs which increase in difficulty; the first 6 designs require only 4 blocks, the last 4 designs require all 9 blocks. Each design is timed;

bonus points are added for speed. This test is the best WAIS-R measure of visuospatial organization and visuoconstructive ability.

The Digit Symbol test is a symbol substitution task consisting of four rows containing a total of 100 blank squares each paired with a randomly assigned number from 1 to 9. At the top of the test sheet is a key that pairs each number with a different symbol. The subject is to write in the blank square the symbol which belongs to the number printed above the square. The subject is given 90 seconds to complete as many squares as possible. The Digit Symbol test is consistently the most sensitive of the WAIS-R subtests to brain damage, irrespective of localization. It is dependent on a large number of functions, including sustained attention, motor speed, and visual-motor coordination.

The Similarities test assesses verbal concept formation. The subject is instructed to explain what each pair of words (e.g., apple-orange, boat-automobile, praise-punishment) has in common. The test increases in difficulty and is discontinued after four consecutive failures. Responses are scored 1 or 2 points depending on the degree of appropriate abstraction. The scoring criteria includes examples. Similarities appears to be the best overall measure of verbal ability since it is independent of memory function and least influenced by the subject's background and experience of all the WAIS-R verbal subtests. It is also the most sensitive to brain damage, irrespective of

localization, of the verbal subtests.

All WAIS-R subtest raw scores are converted to scale scores with a mean of 10 and a standard deviation of 3. Age-scaled score transformations are also available.

Tactual Performance Test

The Tactual Performance Test (TPT) (Reitan Neuropsychology Laboratory: TPT (10 hole board) for adults) consists of several components, each with its own score. The TPT is a Sequin-Goddard form board (Arthur, 1947) modified by Halstead (Halstead, 1947; Reitan, 1979). The board contains spaces for 10 differently shaped blocks and is held semi-vertically in a stand placed before the blindfolded subject. The blocks are placed on the table in front of the stand. The subject is never permitted to see the board or the blocks; however, the subject's hands are guided over the board and blocks for initial familiarization. The subject's task is to insert the blocks as quickly as possible with first the dominant hand, followed by the nondominant hand and then both hands. Each trial is timed. Typically a 30% to 40% decrease in time is expected from trial to trial.

After the three trials, the board and blocks are removed and the subject's blindfold taken off. On a blank piece of paper the subject is instructed to draw a diagram of the board and its shapes. Both the shape of the blocks and their relative location on the board are to be recalled. The Memory component is based on the number of blocks

correctly reproduced and the Localization component is based on the number of blocks correctly located in their approximate spatial position relative to one another. If a shape is drawn unlike any of the actual blocks but is verbally described as one of the blocks, credit is given.

The TPT is a complex tactual discrimination test and appears to assess motor speed, use of tactile and kinesthetic cues, learning, and incidental memory. An impaired performance on any of the six components (dominant, nondominant, both hands, and total times, memory, localization) is generally associated with brain damage. The test appears to be especially sensitive to parietal lobe dysfunction but there are conflicting reports about this (Lezak, 1976).

Data Preparation and Reduction

Summary Measures

Certain demographic and self-report information obtained in the interview were reduced to summary measures. An indice of the frequency and severity of the subject's migraine attacks was calculated by summating the duration of the attack in hours times the severity of the attack for an average month based on the past 12 months (# hours of headache attack * severity rating * # attacks in an average month). Severity was functionally defined as follows: Still able to carry out normal work activity (Grade I); Unable to perform usual work but bed rest not necessary (Grade II);

Bed rest necessary (Grade III) (Olesen, et al., 1981)) This is termed the Headache Index.

The five demographic variables of age, sex, race, education, and occupation were used in the estimation of a Premorbid Intelligence Quotient. This index was employed in two ways. First, as a check on the successful matching of subjects on age, education, sex ratio, and handedness ratio. Second, it was used in conjunction with the Deterioration IQ to provide a Deterioration Quotient or estimate of recent intellectual decline. Each of these indices will be now be defined.

A premorbid IQ can be estimated in two ways: present performance on tests thought to be relatively insensitive to brain dysfunction or from demographic information. Wechsler's "hold" tests (Information, Vocabulary, Picture Completion, and Object Assembly WAIS subtests) (Wechsler, 1958) have been found to be ineffective in premorbid IQ estimation because these measures are not impervious to brain dysfunction (Matarazzo, 1972).

Wilson, et al. (1978) reported a method of estimating the WAIS Full Scale IQ from demographic information by regressing the Full Scale IQs of the 1955 WAIS standardization sample (n = 1,700) on age, sex, race, education, and occupation. The R^2 was .54.

In a later study, Wilson, et al. (1979) compared the utility of Wechsler's (1958) deterioration quotient with their demographic variables formula in assessing intellectual decline. Both methods employ Wechsler's (1958)

"don't hold" tests (Digit Span, Block Design, Digit Symbol, and Similarities) as an index of intellectual impairment, which, in conjunction with a estimated premorbid IQ, provide a Deterioration Quotient. Demographic data and WAIS age-corrected subtest scores were collected on 140 neurologically impaired subjects and 140 non-neurologically impaired subjects. Using discriminant analysis, this diagnostic dichotomy was regressed on the two sets of predictors. The rate of correct classification of cases in the first run was 71.8% for the demographic variable formula and 63.2% for Wechsler's formula. On a subsequent double cross-validational procedure, there was an 11% improvement in classification accuracy for the demographic estimate over Wechsler's present ability index (72.8% vs. 61.8%)

The regression formula is as follows: Premorbid IQ = .172(age) - 1.53(sex) - 11.33(race) + 2.44(education) + 1.01(occupation) + 74.05. This formula takes into account the aggregate increase in educational attainment from the 1955 sample to the level (median of 12.3 years) reported by the U.S. Bureau of Census in 1976 (Wilson, et al., 1979). In the equation, male = 1, female = 2, white = 1, and non-white = 2. Occupational categories as defined by Wechsler (1955) are assigned the following scores: Professional, technical, and kindred workers (5); Managers and administrators, except farm (7); Sales workers (7); Clerical and kindred workers (7); Craftsmen and kindred workers (6); Operative, except transport (3); Transport equipment operators (3); Laborers, except farm (1); Farmers and farm

managers (1); Farm laborers and farm foremen (0); Service workers except private household (5); Private household workers (3); Homemakers (4); Unemployed persons last worked 1959 or earlier (0); Students (10).

The Deterioration IQ is calculated by summing the age-scaled scores of the four Wechsler "don't hold" tests (Digit Span, Block Design, Digit Symbol, and Similarities), multiplying by 1.25 and adding 50.

The Deterioration Quotient is calculated as follows: Predicted Premorbid IQ - Deterioration IQ/ Predicted Premorbid IQ. This is interpreted as a measure of overall recent change in intellectual functioning.

Three composite scores are derived from various tests previously described. The Sensory-Perceptual Examination score (Russell, et al., 1970) is calculated by counting all suppressions of double simultaneous stimulation in the tactile, auditory, and visual modalities and multiplying by 1.5. If three or four single stimulations show a loss of perception in any modality, then the suppression is not counted. This sum is added to the total number of finger agnosia and finger dysgraphesthesia errors of both hands.

The Aphasia composite score is the sum of the weights of each item missed. Scoring rules regarding what is counted correct or incorrect are outlined in Russell, et al. (1970, p. 110).

The Spatial Relations composite score is the sum of the two Greek cross scores. Scores are assigned by comparison of the drawings with five sets of comparison drawings scored

1 to 5 (Russell, et al., 1970, pp. 113-118). If the WAIS-R Block Design score is lower than the other WAIS-R subtest scores, with the exception of Digit Symbol, then 2 points are added to the sum of the drawing scores.

In conclusion, summary measures used were the Headache Index, the Premorbid Intelligence Quotient, the Deterioration Quotient, the Sensory-Perceptual Examination, Aphasia, and Spatial Relations composite scores.

Impairment ratings

Because of the large number of variables relative to the number of subjects, the data was further reduced. A single score of total brain damage or impairment was derived. Two types of impairment ratings were employed. The Average Impairment Rating (Russell, et al., 1970) is P. M. Rennick's modification of the Halstead-Reitan Impairment Index (Reitan, 1955a). Rather than dichotimize each subtest making up the index as impaired or unimpaired, Rennick placed each test score on a five-point scale, 0 to 4. Russell, et al. (1970) have extended the scale to six categories. A 0 rating represents a high normal performance; 1 is normal; 2 indicates mild impairment; 3, mild to moderate impairment; 4, moderate to severe impairment; and 5 indicates severe impairment.

In Rennick's standardization sample, a score of 1 generally included the first standard deviation on either side of the mean for normal controls. Increasing degrees of impairment were set according to the number of standard

deviations from the mean for normal controls for most of the tests. The three composite scores, Aphasia, Spatial Relations, and Sensory-Perceptual Examination, were scaled on an inferential basis by Rennick. Ratings of 2 and above represent increasing degrees of brain damage.

The Average Impairment Rating (AIR) is the sum of 12 tests scored 0 to 5 and divided by 12. The 12 tests are the Halstead Category test, the Halstead Tactual Performance Test components of Total time, Memory, and Location, Seashore Rhythm test, Halstead Speech Perception test, Tapping test (worst performance), Trail Making B test, WAIS Digit Symbol subtest, and the Aphasia, Spatial Relations and Sensory-Perceptual Examinations. On the basis of a series of validity studies reported by Russell, et al. (1970), an AIR of 1.55 or greater is considered indicative of brain damage.

A modified AIR was calculated in the present study. The Halstead Category, Seashore Rhythm and Halstead Speech Perception tests were not included. The Revised Wechsler Memory Scale semantic and figural short-term memory scores were added to the remaining nine tests. The 11 tests making up the AIR have raw score rating equivalents located in Russell, et al. (1970, pp. 108-109) and Russell (1975).

The second impairment rating method consists of the percentage of the tests with a numerical rating in the impaired range or with a score exceeding the impairment cut-off score. This rating is termed the Percent Impaired Index. Table 3 contains the impaired range cut-off scores

Table 3

Normative Data

Test	Impaired Range
Grip Strength (kg)[a]	
males- dominant	<35
males- nondominant	<30
females- dominant	<25
females- nondominant	<22
Finger Tapping (mean/10 sec)[a]	
males- dominant	<50
males- nondominant	<44
females- dominant	<46
females- nondominant	<41
Grooved Pegboard (sec)[a]	
dominant	>66
nondominant	>66
Wechsler Memory Scale- Revised[b]	
short-term semantic memory	<24
long-term semantic memory	<20
semantic percentage retained	<85
short-term figural memory	<10
long-term figural memory	< 9
figural percentage retained	<84
Trail Making Test (sec)[c]	
Part A	>33
Part B	>87
Tactual Performance Test[c]	
dominant hand (min)	> 8.2
nondominant hand (min)	> 4.5
both hands (min)	> 2.7
total (min)	>15.6
memory	< 6
localization	< 5

Table 3 (Continued)

Test	Impaired Range
Aphasia Screening Test composite score[c]	
Impairment rating	> 1
raw score	> 6
Spatial Relations composite score[c]	
Impairment rating	> 1
raw score	> 3
Sensory-Perceptual Examination[c]	
Impairment rating	> 1
raw score	>12
Wisconsin Card Sorting Test[d]	
perseverative error responses	≥20
number of categories achieved	≤ 3
Raven Standard Progressive Matrices- SF[e]	
predicted long form score	≤ age-normed 25th percentile
Wechsler Adult Intelligence Scale- Revised[f]	
Digit span	< age-scaled score of 8
Digit symbol	
Block design	
Similarities	

[a]Revised Lafayette Clinic Adult Neuropsychological Battery Norms (1977)

[b]Russell (1975)

[c]Russell, Neuringer, & Goldstein (1970)

[d]Milner (1963); Robinson, Heaton, Lehman, & Stilson (1980)

[e]Berker, Zubrick, Javornisky, Whelan, Witten, & Smith (1979); Raven, Court, & Raven (1977)

[f]Wechsler (1981)

for the 30 tests in this study's battery.

Degree of Lateralization Index

This index consists of a number of test score comparisons based on a set of rules developed by Russell, et al. (1970, pp. 158-161). It serves as a summary measure of the degree, if any, of lateralized cerebral dysfunction in the presence of indicated overall brain damage (AIR $\geq$ 1.55). The index is considered in relation to those classical migraine subjects with predominantly lateralized transient neurologic dysfunction and all migraine subjects with predominantly hemicranial pain.

Test score pairs in which the right side of the body is compared with the left side are: Finger Tapping score, TPT time score for each hand, finger agnosia and finger dysgraphesthesia errors, auditory, tactile, and visual suppressions, and presence of homonymous hemianopia. The Aphasia composite score (considered an indicator of left cerebral hemisphere dysfunction) is compared to the Spatial Relations composite score (considered an indicator of right cerebral hemisphere dysfunction).

As a modification of the Russell, et al. (1970) lateralization key, only the WAIS-R Similarities and Block Design subtest scores were compared. A 3 or greater age-scaled point difference was considered indicative of left cerebral hemisphere dysfunction (Similarities lower) or right cerebral hemisphere dysfunction (Block Design lower).

CHAPTER III

Results

The hypotheses will first be reviewed in light of the data in general terms; in later sections statistical treatment of the data will be presented in detail.

As postulated in Hypothesis I, the classical migraine group had a significantly greater Average Impairment Rating than did the control group. However, contrary to the hypothesis, the classical migraine group did not exhibit significantly greater average impairment when compared to the common migraine group. In fact, the common migraine group had a significantly higher AIR than did the normal control group. Both the classical and common migraine groups scored a higher percentage of tests in the impaired range than did the control group, but this difference was not significant at the .05 alpha level.

As postulated in Hypothesis II, a high positive correlation was found between both the classical migraine group AIR and the Percent Impaired Index with the length of migraine history, but no significant relationship was found with the Headache Index. However, upon correction for age of the subjects, the significant correlations between the impairment indices and history duration were reduced to

nonsignificance.

Hypothesis III postulated that lateralized neuropsychological impairment would be contralateral to predominantly lateralized transient neurologic symptoms, and was of course dependent on the number of classical migraine subjects with AIRs equalling or exceeding the brain damage criterion (AIR $\geq$ 1.55). Of the eight subjects with measurable brain damage, four had neuropsychological impairment lateralized to the right cerebral hemisphere, one subject demonstrated left cerebral hemisphere lateralized impairment, and the remaining subjects exhibited diffuse impairment. The neurological symptoms present in the classical aura were lateralized to the left side of the body in three subjects and were bilateral in the other five subjects. Three of the four subjects with neuropsychological impairment referable to the right cerebral hemisphere had exclusively left-sided neurologic symptoms. All three subjects with measured bilateral impairment presented with bilateral neurologic disturbances. One subject each with right and left lateralized impairment had bilateral disturbances during the classical aura. While the correspondence between the Lateralization Index and the aura signs and symptoms was strong, the small number of subjects precluded statistical significance.

Group means and standard deviations for the impairment indices, summary scores, headache characteristics, and all tests in the battery are presented in Table 4. Probability values in the table are for the Student-Newman-Keuls post-

hoc comparison test and were included only for the one-way ANOVAs performed on the 3 subject groups which were significant at the .10 alpha level.

Subject matching

Subject matching across the three groups was successful. One-way analysis of variance (ANOVA) conducted on the variables of age, $F(2, 43) = .02$, $p < .983$, education, $F(2, 43) = .04$, $p < .962$, and predicted premorbid IQ, $F(2, 43) = .15$, $p < .866$, indicated no significant differences between the three groups. Chi-square analyses performed with the variables of sex, $\chi^2(2, N = 46) = .24$, $p < .888$, and handedness, $\chi^2(2, N = 46) = 3.64$, $p < .162$, showed no significant differences.

Summary of attack characteristics

Characteristics of the headache attack in the classical and common migraine subjects were examined and found to not differ significantly between the two groups except for frequency of attacks. Classical migraine subjects had significantly fewer attacks per month than did common migraine subjects, $F(1, 29) = 4.73$, $p < .038$.

About one-third of both classical and common migraine subjects reported a prodrome of approximately 24 hours duration. Changes described included ill-defined mood changes such as a "feeling of strangeness" or "unreality," fatigue, and cravings for salts or sweets. About half of the subjects reported photophobia preceding or during the attack. Several subjects from each group reported

Table 4

Comparison Of Groups On All Measures

	Classical[a]		Common[b]		Control[c]	
Measures	M	SD	M	SD	M	SD
AIR	1.30_{y}	.54	1.19_{y}	.49	$.78_{y}$	.43
Percent Impaired	34.37_{x}	20.39	31.33_{x}	18.68	19.55_{x}	16.47
Predicted IQ	111.55^{x}	6.37	110.78^{x}	6.23	112.13^{x}	7.98
Deterioration IQ	102.34_{x}	7.94	105.75	8.06	109.58_{x}	8.57
Deterioration Quotient	$.08_{y}$	.05	.05	.05	$.02_{y}$	.07
Functioning Inventory	47.25_{z}^{y}	22.38	39.20	20.66	25.27_{z}^{y}	12.83
Age of Onset (Yrs)	17.69	12.05	23.40	8.40	--	--
History Duration (Yrs)	24.19	13.15	17.73	9.51	--	--
Time Post Attack (Days)	42.44	52.51	14.47	30.00	--	--
Duration (Hours)	22.83	15.49	21.07	16.21	--	--
Severity (Grades I-III)	2.67	.45	2.57	.50	--	--
Frequency (Attacks/Mo)	2.80_{y}	3.23	9.27_{y}	11.42	--	--
Headache Index	173.73^{y}	214.49	300.13^{y}	281.81	--	--
Grip Strength (kg)						
Dominant	33.16	11.40	31.85	6.67	34.37	9.85
Nondominant	29.33	10.63	27.68	7.82	30.30	9.42
Finger Tapping (M/10s)						
Dominant	43.49_{y}	7.15	46.52	5.06	48.77_{y}	4.91
Nondominant	40.61^{y}	6.48	42.38	5.66	43.90^{y}	5.15
Grooved Pegboard (sec)						
Dominant	69.44_{y}	13.75	59.33_{y}	8.62	60.47_{y}	8.08
Nondominant	77.00_{x}	17.85	66.40_{x}	11.15	65.80_{x}	10.84

Table 4 (Continued)

	Classical		Common		Control	
Measures	M	SD	M	SD	M	SD
Wechsler Memory Scale-R						
Short-term Semantic	21.06_{x}	5.18	21.53_{x}	5.98	26.07_{x}	7.60
Long-term Semantic	17.94_{x}	5.03	17.87_{x}	6.70	23.33_{x}	7.72
% Semantic Retained	85.17_{x}	8.76	80.63_{x}	12.64	88.42_{x}	8.74
Short-term Figural	10.13	2.31	10.53	2.33	11.53	2.33
Long-term Figural	8.13	3.91	7.73	2.91	10.13	3.18
% Figural Retained	79.93	31.61	73.59	19.38	86.11	20.66
Trail Making Test						
Part A	26.81	10.07	23.80	9.38	23.67	7.76
Part B	86.31_{x}	66.06	64.20	19.39	50.07_{x}	17.30
Tactual Performance Test						
Dominant (min)	6.40_{y}	2.38	6.57_{y}	2.49	4.35_{y}	1.58
Nondominant (min)	4.98_{y}	2.65	5.59_{y}	2.71	3.64_{y}	2.02
Both (min)	2.76	2.27	3.61	2.06	2.51	1.72
Total (min)	14.14_{x}	6.46	15.76_{y}	6.42	10.50_{xy}	4.63
Memory	7.31_{x}	1.85	7.73_{y}	1.16	8.07_{xy}	1.16
Localization	4.13	2.47	3.60	2.80	5.00	2.56
Aphasia Screening	3.94_{yz}	3.00	2.00_{y}	2.07	1.20_{z}	1.52
Spatial Relations	4.06_{x}	1.06	3.47_{y}	1.13	3.13_{x}	1.06
Sensory Perceptual Exam	6.03_{x}	2.67	6.57_{x}	4.36	3.77_{x}	3.39
Wisconsin Card Sorting Test						
# Categories	5.13	1.82	4.80	1.93	5.60	.91
Total Errors	23.06	18.62	28.13	17.61	19.80	15.28
Perseverative Errors	13.19	11.08	13.33	7.51	12.20	9.06

Table 4 (Continued)

Measures	Classical M	Classical SD	Common M	Common SD	Control M	Control SD
Raven SPM-Short-Form						
Predicted Long-Form	45.31	6.37	41.60	9.12	46.33	6.92
Percentile	82.81	15.05	73.00_{x}	24.33	88.67_{x}	11.87
WAIS-R						
Digit Span	9.94	1.61	10.40	2.32	10.40	2.61
Age-Corrected	10.13	1.67	10.87	2.26	11.00	2.78
Block Design	9.19	2.95	9.33	2.69	10.40	2.41
Age-Corrected	10.13	2.39	10.67	2.29	11.80	2.51
Digit Symbol	9.31_{x}	3.11	10.47	2.26	11.67_{x}	2.56
Age-Corrected	10.94_{y}	2.79	11.73	2.28	13.07_{y}	1.62
Similarities	9.81	2.40	10.67	2.97	11.40_{y}	2.56
Age-Corrected	10.69	2.15	11.53	3.02	11.80	2.62

Note. -- = Not applicable.

Note. All probability values are from the Student-Newman-Keuls test.

Note. Means having the x subscript are significantly different at $p < .10$.

Note. Means having the y subscript are significantly different at $p < .05$.

Note. Means having the z subscript are significantly different at $p < .01$.

$^{a}n = 16$. $^{b}n = 15$. $^{c}n = 15$.

phonophobia; one classical migraine subject described auditory distortions in which words sounded elongated during the aura. Nausea and/or vomiting during the attack was reported by almost all of the common migraine subjects and half of the classical migraine subjects.

All of the classical migraine subjects reported aura visual disturbances; 9 reported scotomata; photopsia phenomena were reported by 10 and fortification spectra by 7 subjects. Symptoms referable to brainstem involvement, including ataxia, drop attacks, dizziness, light-headedness, clumsiness and dysarthria were reported by five classical migraine subjects. Eight subjects reported paresthesia of the hand, lower arm, face, or tongue. In five of these subjects the numbness "marched" from hand to the lower arm, then up to the ipsilateral cheek and side of the tongue. In one subject the hand paresthesia was bilateral and in another subject the numbness characteristically progressed from one hand to the other. In three of the subjects with unilateral upper limb paresthesia, motor weakness and incoordination were also reported.

Cognitive impairment during the aura and occasionally persisting into the headache phase was reported by five subjects. The most common complaint was slowed mentation and reduced mental efficiency. Short-term memory deficits were described by seven subjects. Aphasic manifestations, including impaired comprehension, dysnomia, dysgraphia, and literal paraphasic errors were reported by five subjects. One subject reported several episodes of impaired cognitive,

mnestic and language abilities surpassing the migraine attack by days to 2 weeks.

A surprising number of common migraine subjects reported brainstem and higher cortical disturbances during their migraine attacks. Three subjects reported vertigo, ataxia, or dysarthria; two subjects described cognitive difficulties; three reported short-term memory deficits; and two subjects reported dysnomia.

Precipitating influences were reported by all migraine subjects to be highly variable, and three classical migraine and five common migraine subjects were unable to identify any triggers for their attacks. Nine women, two classical and seven common migraine, reported attacks in association with their menstrual cycle. Half of subjects in both groups reported some foodstuff precipitants. Red wine, chocolate, and citrus fruits were the most frequently mentioned substances. Psychological stress was a reported factor in the attacks of two classical migraine subjects and five common migraine subjects. Triggers less frequently reported included organic and perfume odors, fatigue, fasting, high altitudes, and wind on the face.

Eight of the classical migraine and seven of the common migraine subjects reported a migrainous parent, the mother in 12 cases, the father in 2 cases, and in 1 case, both parents.

Indices of Impairment

Significantly more classical migraine subjects scored in the brain-damaged range of the AIR (AIR $\geq$ 1.55) than did the common migraine and control subjects: 8 of the 16 classical migraine subjects compared to 3 of the 15 common migraine subjects and 1 of the 15 normal control subjects, $\chi^2(2, N = 46) = 7.97$, $p < .019$.

A one-way ANOVA of the AIR for all three groups was significant, $F(2, 43) = 4.81$, $SS_b = 2.33$, $SS_e = 10.41$, $p < .013$. A Student-Newman-Keuls post-hoc multiple comparison test was performed utilizing the harmonic mean of the three group ns ($N_h = 15.33$). Both the classical and the common migraine groups had significantly higher AIRs than the control group, $p < .05$. The two migraine groups were not significantly different on the AIR.

The percentage of tests performed in the impaired range was not significantly different between the three groups, $F(2, 43) = 2.70$, $SS_b = 1872.93$, $SS_e = 14919.59$, $p < .079$. Post-hoc comparison showed the classical and common migraine groups' Percent Impaired Index was nonsignificantly greater than the control group, $p < .10$. The two migraine groups did not have a significantly different Percent Impaired Index.

The Deterioration Quotient, a measure of recent intellectual decline, was significantly different between the three groups, $F(2, 43) = 4.33$, $SS_b = .030$, $SS_e = .147$, $p < .019$. The Deterioration Quotient of the classical migraine group was significantly higher than the control

group, $p < .05$, but not significantly higher than the common migraine group. The common migraine group Deterioration Quotient was not significantly different from the control group.

A Deterioration Quotient of .11 or greater is considered indicative of central nervous system compromise. The mean Deterioration Quotient of the classical migraine group falls short of this threshold ($M = .082$). Five of the classical migraine subjects, one common migraine subject, and two of the control subjects demonstrated Deterioration Quotients equalling or exceeding .11, though this group difference was not significant, $\chi^2(2, N = 46) = 3.51$, $p < .173$.

The only attack characteristic that significantly differed between the two migraine groups was frequency per month. Therefore, this variable was introduced as a covariate in an analysis of covariance for each of the three impairment indices. The adjusted F-ratio of the AIR dependent variable was increased but remained nonsignificant, $F(1, 29) = 1.95$, $p < .174$, as was true of the Percent Impaired Index F-ratio, $F(1, 29) = .93$, $p < .343$. However, the Deterioration Quotient F-ratio was increased significantly, $F(1, 29) = 7.27$, $p < .012$; the adjusted means for the classical and common migraine group Deterioration Quotients were .091 and .039, respectively.

Impairment Indices and attack characteristic correlations

Table 5 contains correlation coefficients between the relevant measures for all three groups. In the second hypothesis, the AIR and Percent Impaired Index were postulated to be positively associated with the duration of the migraine history and frequency-severity of the attacks among the classical migraine subjects. That is, the longer and the more extreme the migraine attacks, the greater the expected neuropsychological impairment. One of the subjects was excluded from the following analyses because he did not experience headaches in his attacks (i.e., migraine accompagnée). The Pearson correlation coefficients between history duration and the AIR, $r(N = 15) = .598$, $p < .014$, and the Percent Impaired Index, $r(N = 15) = .609$, $p < .012$, are significant. Correlations between the Headache Index and AIR, $r(N = 15) = .318$, $p < .247$, and Percent Impaired Index, $r(N = 15) = .234$, $p < .402$, were of the hypothesized direction but were not significant. However, a significant positive correlation was found between the Headache Index and the Deterioration Quotient, $r(N = 15) = .682$, $p. < .005$.

Linear regression using the history duration and Headache Index variables as predictors of the AIR showed a significant fit, $F(2, 12) = 4.68$, $p < .032$, $R^2 = .438$, with history duration explaining a significant amount of the variance, $t(1) = 2.68$, $p < .020$, compared to the Headache Index, $t(1) = .741$, $p < .473$. Regression onto the Percent Impaired Index produced similar results: $F(2, 12) = 4.83$, $p < .029$, $R^2 = .446$, history duration, $t(1) = 2.91$, $p < .013$,

Table 5

Intercorrelations Between Headache and Impairment Measures

	2	3	4	5	6	7	8
1. Headache Index							
Classical[a]	-.16	.25	-.29	.32	.23	.68**	.57*
Common[b]	.05	.34	.19	.36	.44	.02	.07
Control[c]	--	--	--	--	--	--	--
2. Age of Onset							
Classical	--	-.31	.07	.36	.42	.08	-.12
Common	--	-.22	.19	.66**	.71**	.51*	.66**
Control	--	--	--	--	--	--	--
3. History Duration							
Classical		--	-.35	.60**	.61**	.14	.42
Common		--	.36	.08	.23	-.32	-.52*
Control		--	--	--	--	--	--
4. Time Post Attack							
Classical			--	-.23	-.15	-.34	.15
Common			--	-.02	.14	.04	.22
Control			--	--	--	--	--

Table 5 (Continued)

	2	3	4	5	6	7	8
5. Average Impairment							
Classical				--	.96***	.56*	.52*
Common				--	.91***	.61*	.34
Control				--	.89***	.33	-.20
6. Percent Impaired							
Classical					--	.46	.53*
Common					--	.49	.42
Control					--	.18	-.11
7. Deterioration Quotient							
Classical						--	.54*
Common						--	.56*
Control						--	-.14
8. Assessment Inventory							
Classical							--
Common							--
Control							--

Note. -- = Not applicable.

$^{a}n = 16$. $^{b}n = 15$. $^{c}n = 15$.

* $p < .05$. ** $p < .01$. *** $p < .0001$.

and the Headache Index, $t(1) = .310$, $p < .762$.

However, the history duration variable is highly correlated with age, $r(N = 15) = .624$, $p < .010$, as is the AIR, $r(N = 15) = .817$, $p < .0001$, and the Percent Impaired Index, $r(N = 15) = .882$, $p < .0001$. Therefore, partial-whole correlation coefficients were performed, partialling-out the influence of the age variable. The adjusted correlations between history duration and the AIR was $r(N = 15) = .197$, $p < .464$, and with the Percent Impaired Index, $r(N = 15) = .161$, $p < .553$. In conclusion, Hypothesis II was not supported.

Examination of the relationship of the history duration variable in the common migraine group reveals a different pattern. No association seemingly exists between history duration and the AIR, $r(N = 15) = .079$, $p < .780$, or the Percent Impaired Index, $r(N = 15) = .234$, $p < .401$. However, age was found to correlate significantly with history duration, $r(N = 15) = .683$, $p < .005$, the AIR, $r(N = 15) = .563$, $p < .029$, and the Percent Impaired Index, $r(N = 15) = .729$, $p < .002$. The correlation coefficient between history duration and AIR with age partialled-out was $r(N = 15) = -.506$, $p < .055$, and with the Percent Impaired Index, $r(N = 15) = -.528$, $p < .043$, a significant correlation.

This is in a direction opposite to that found for the classical migraine group. That is, for the common migraine group, the shorter the migraine history, the greater the measured neuropsychological impairment.

A related variable, age of onset, was similarly

considered for the two groups. Among classical migraine subjects the age of onset ranged from 5 to 52 years (M = 17.7), and among common migraine subjects, onset occurred between the ages of 12 and 39 years (M = 23.4); the two groups do not differ significantly, $F(1, 29) = 2.31$, $p < .139$.

Onset age of the classical migraine group does not significantly correlate with the AIR, $r(N = 16) = .356$, $p < .176$, or the Percent Impaired Index, $r(N = 16) = .546$, $p < .029$. Partialling-out the influence of age, the resultant correlation with the AIR was $r(N = 16) = -.186$, $p < .490$, and with the Percent Impaired Index, $r(N = 16) = -.152$, $p < .574$. These correlations are in the hypothesized direction (i.e., the earlier the onset, the greater the neuropsychological impairment), but fall well short of significance.

In the common migraine group, onset age is significantly correlated with the AIR, $r(N = 15) = .660$, $p < .007$, the Percent Impaired Index, $r(N = 15) = .711$, $p < .003$, and with age, $r(N = 15) = .561$, $p < .030$. Partialling-out age, the onset age correlation with the AIR is $r(N = 15) = .503$, $p < .056$, and with the Percent Impaired Index, $r(N = 15) = .533$, $p < .041$. In summary, the correlations between age of onset of common migraine and the impairment indices decline only slightly when the mutual influence of age is accounted for. The Percent Impaired Index is significantly positively correlated with age of onset, that is, the later the onset of common migraine, the

greater the measured neuropsychological impairment. This is contrary to the relationship found among the classical migraine subjects.

The elapsed time since the last migraine attack was considered in relation to the impairment indices for both groups. For the classical migraine group, a negative but nonsignificant correlation was found between days elapsed since the last attack and the AIR, $r(N = 16) = -.232$, $p < .387$, and the Percent Impaired Index, $r(N = 16) = -.155$, $p < .567$. For the common migraine group, the respective correlations were $r(N = 15) = -.016$, $p < .956$, and $r(N = 15) = .140$, $p < .618$. In conclusion, time elapsed was not significantly associated with the impairment indices though for classical migraine subjects the negative association was in the hypothesized direction (i.e., the more recent the attack, the greater the neuropsychological impairment).

Lateralization

A total of 12 subjects had AIRs scored within the brain-damaged range. The one control subject and three common migraine subjects with significant AIRs demonstrated a diffuse pattern of neuropsychological impairment. The common migraine subject with the highest AIR, a score of 2.09, indicating mild-moderate brain damage, also presented with the most profound neurologic disturbances of the common migraine subjects, including cognitive, aphasic, mnestic, and upper-motor speed and coordination deficits during her headache attacks without any preheadache disturbances.

Among the eight classical migraine subjects with significant AIRs, three had diffuse impairment, four subjects showed lateralization of impairment, one strongly, to the right cerebral hemisphere, and one subject had weak left cerebral hemisphere lateralization.

As planned in Hypothesis III, a comparison was made between the Lateralization Index and the laterality of the neurologic deficits present during the classical aura of the subjects with significant AIRs. Three of the four subjects with right hemisphere lateralization reported exclusively left-sided symptoms (e.g., left homonymous hemianopia, left-hand paresthesia). The three subjects with diffuse impairment reported bilateral neurologic disturbances. Unexpectedly, two subjects, one each with right or left hemisphere lateralized impairment, also reported bilateral symptoms. A simple frequency count of subjects with symptomatology contralateral to the lateralized impaired cerebral hemisphere or bilateral in accordance with diffuse impairment was conducted. The statistic showed a trend in the hypothesized direction, $\chi^2(2, N = 8) = 4.80$, $p < .091$.

In a further examination of the AIR and the classical aura symptoms, the neurologic disturbances were dichotomized into pronounced and mild categories, the latter consisting of visual disturbances only. Seven of the classical migraine subjects had pronounced aura symptomatology and an AIR in the brain-damaged range, and three subjects had mild symptomatology and within-normal-range AIRs. However, the remaining six subjects had cross-classifications: five with

pronounced symptomatology but normal AIRs and one with mild aura but significant AIR. The frequency count was not significant, $\chi^2(1, N = 16) = 1.33, p < .248$.

The relationship of impairment lateralization and headache locus was investigated in the eight classical migraine and two common migraine subjects with significant AIRs and nonalternating lateralized or bilateral headache. Six subjects reported right hemicrania: three with right cerebral hemisphere lateralized impairment, one with left cerebral hemisphere lateralized impairment, and two with diffuse impairment. All three subjects with left hemicrania had diffuse impairment. One subject had both bilateral headache (holocrania) and diffuse impairment. The frequency statistic was not significant, $\chi^2(4, N = 10) = 4.44$, $p < .349$.

The relationship between the laterality of the classical aura symptoms and headache locus was investigated in 15 classical migraine subjects (excluding the one migraine accompagnée subject). Included were three subjects who reported alternating lateralized neurologic disturbances which were always followed by contralateral headache. Of the two subjects with left hemicrania, one had right lateralized symptomatology and one bilateral. Of the eight right hemicrania subjects, two had left lateralized disturbances, five bilateral, and one right. Of the two holocrania subjects, one had right-sided symptoms and one bilateral. The frequency statistic was significant, indicating a general association between the neurologic

disturbances in the aura and the subsequent headache, contralateral in cases of unilateral symptomatology, and bilateral in cases of bilateral symptomatology, $\chi^2(9, N = 15) = 18.21$, $p < .033$.

Measures differentiating the three groups

The dominant hand Finger Tapping test was significantly different between the three groups, $F(2, 43) = 3.21$, $p < .050$. Post-hoc comparison shows the classical migraine group performed significantly more poorly than the control group, $p < .05$. Other group comparisons were not significant. The mean number of taps produced by the classical migraine group ($M = 43.49$) falls in the mild impairment range.

The Grooved Pegboard measure was performed in the impaired range by the classical migraine group, the dominant hand mean ($M = 69.44$) showing mild impairment, and the nondominant hand mean ($M = 77.00$) registering mild-moderate impairment. Significant group differences were found for the dominant hand performance, $F(2, 43) = 4.30$, $p < .020$, and for the nondominant hand performance, $F(2, 43) = 3.27$, $p < .048$. The classical migraine group performed significantly more poorly with the dominant hand compared to both the control group, $p < .05$, and the common migraine group, $p < .05$. On the nondominant hand measure, the classical migraine group performed more poorly than the common migraine group and the control group, but the difference fell short of significance, $p < .10$.

On the short-term semantic memory scale of the revised Wechsler Memory Scale measure, the group differences approached significance, $F(2, 43) = 2.92$, $p < .066$. Post-hoc comparison indicated the classical and common migraine groups performed more poorly than the control group, $p < .10$. Both migraine groups means (classical: $M = 21.06$; common: $M = 21.53$) fall in the mild impairment range. Both migraine groups also showed mild impairment on the long-term semantic memory scale (classical: $M = 17.94$; common: $M = 17.87$). Group differences on this measure were significant, $F(2, 43) = 3.48$, $p < .040$; the two migraine groups performed more poorly than the control group, $p < .10$.

Both the classical and common migraine groups performed with mild impairment on the long-term figural memory scale ($M = 8.13$; $M = 7.73$, respectively), but no significant group difference was found, $F(2, 43) = 2.19$, $p < .124$.

The Trail Making Test, Part B performance group differences approached significance, $F(2, 43) = 2.98$, $p < .061$. Post-hoc comparison showed the classical migraine group performed more poorly than the control group, $p < .01$. The classical migraine group mean ($M = 86.31$) was on the borderline of mild impairment.

The Tactual Performance Test dominant hand performance was significantly different across the three groups, $F(2, 43) = 4.82$, $p < .013$. Both classical and common migraine groups performed significantly more poorly than the control group, $p < .05$. The TPT nondominant hand and both hands performances were scored in the mild impairment range for

both classical and common migraine groups, though neither group performed significantly more poorly than the control group. TPT total time performance was significantly different across the groups, $F(2, 43) = 3.13$, $p < .054$, and post-hoc comparison showed the common migraine group performed more poorly than the control group, $p < .05$, whereas the classical migraine group-control group comparison was less significant, $p < .10$. The common migraine group had a total TPT time performance ($M = 15.76$) in the mild impairment range.

On the Aphasia Screening test the three groups scored significantly differently, $F(2, 43) = 5.85$, $p < .006$. The classical migraine group produced significantly more errors than both the control group, $p < .01$, and the common migraine group, $p < .05$. However, the classical migraine group mean ($M = 3.94$) fell within normal limits.

On the Spatial Relations test the groups demonstrated a trend toward significant difference, $F(2, 43) = 2.94$, $p < .063$. The classical migraine group scored more poorly than the control group, $p < .10$. The mean of the classical migraine group ($M = 4.06$) is within the mild impairment range.

On the Sensory-Perceptual examination the difference between the groups approached significance, $F(2, 43) = 2.68$, $p < .080$. On post-hoc comparison, the classical and common migraine groups made more errors than the control group, $p < .10$. However, the group means (classical: $M = 6.03$; common: $M = 6.57$) fall within the normal range.

On the Raven Standard Progressive Matrices test, the group differences approached significance, $F(2, 43) = 2.96$, $p < .062$. The common migraine group exhibited a lower predicted age-adjusted percentile than did the control group, $p < .10$.

On the WAIS-R Digit Symbol subtest corrected for age, the group differences were significant, $F(2, 43) = 3.38$, $p < .043$. The classical migraine group scored significantly lower than did the control group, $p < .05$.

Assessment of own functioning inventory

Total mean scores on the AOFI were significantly different across the three groups, $F(2, 43) = 5.19$, $p < .010$. Upon post-hoc comparison, the classical migraine group scored significantly higher on the inventory than did the control group, $p < .01$.

Within the classical migraine group, the AOFI was significantly positively correlated with the AIR, $r(N = 16) = .518$, $p < .040$, the Percent Impaired Index, $r(N = 16) = .526$, $p < .036$, and the Headache Index, $r(N = 15) = .569$, $p < .027$.

Correlations between these variables within the common migraine and control groups were not significant; these correlations are presented in Table 5.

With the AOFI of the classical migraine group serving as the dependent variable, a linear regression procedure produced the best fit with the predictor variables of headache duration, frequency, time elapsed since the last

attack, and education (negative), $F(4, 10) = 3.93$, $p < .036$, $R^2 = .611$. Individually, the variables explained the AOFI variance as follows: frequency, $t(1) = 2.85$, $p < .017$, duration, $t(1) = 2.29$, $p < .045$, education, $t(1) = -2.25$, $p < .048$, and time post-attack, $t(1) = 1.58$, $p < .146$.

For the common migraine group the best linear fit of predictor variables was migraine history duration (negative), age, and education (negative), $F(3, 11) = 8.95$, $p < .003$, $R^2 = .709$. The individual variable contributions to AOFI variance were: migraine history duration, $t(1) = -4.06$, $p < .002$, age, $t(1) = 3.22$, $p < .008$, and education, $t(1) = -2.29$, $p < .043$.

Analysis of variance across the three groups for each of the 33 AOFI items revealed significant group differences for six items. For item #11, "How often do you have difficulties understanding what is said to you?", $F(2, 43) = 4.56$, $p < .016$, both the classical and common migraine group means were significantly greater than the control group mean, $p < .05$. For item #15, "When you speak, are your words indistinct or improperly pronounced?", $F(2, 43) = 8.91$, $p < .001$, , the classical migraine group mean, $p < .01$, and the common migraine group mean, $p < .05$, were significantly higher than the control group mean. For item #16, "How often do you have difficulty thinking of the name of things?", $F(2, 43) = 4.05$, $p < .024$, the classical migraine group mean was significantly higher than the control group mean, $p < .05$. For item #25, "How often do

your thoughts seem confused or illogical?", $F(2, 43) = 3.29$, $p < .046$, the classical migraine group mean was significantly higher than the control group mean, $p < .05$. For item #32, "Do you have more difficulty than you used to in following directions to get somewhere?", $F(2, 43) = 3.42$, $p < .042$, the classical migraine group mean was significantly higher than the control group mean, $p < .05$. And for item #33, "Do you have more difficulty than you used to in following instructions concerning how to do things?", $F(2, 43) = 5.63$, $p < .007$, the classical and common migraine group means were greater than the control group mean, $p < .01$, and $p < .05$, respectively.

The final question of the inventory required a "yes," "no," or "I don't know" response to the question, "Do you think you are as 'bright' now as you were before your present illness?" Control subjects were instructed to respond in terms of how they assessed their "brightness" now compared to an earlier time of their lives. A response of "no" was made by five classical migraine subjects, four common migraine subjects, and one control subject. Eleven subjects responded with "I don't know": four classical, five common, and two control subjects. A frequency count of the "yes" and "no" responses for the three groups was not significant, $\chi^2(2, N = 35) = 4.43$, $p < .109$. However, a significant difference was found comparing classical migraine and control subjects, $\chi^2(1, N = 25) = 3.95$, $p < .047$, but not common migraine and control subjects, $\chi^2(1, N = 23) = 3.47$, $p < .063$.

CHAPTER IV

Discussion

Summary of findings

Half of the classical migraine subjects exhibited neuropsychological impairment associated with mild brain damage, a proportion significantly greater than the matched common migraine or non-headache control subjects. The average performance on the 11 tests of the neuropsychological test battery used to determine the presence and degree of brain damage was not significantly different between the classical and common migraine groups, though both migraine groups demonstrated significantly greater average impairment than the non-headache control group. The group means of the Average Impairment Rating are more representative of the individual AIR scores than are frequency tallies of the number of subjects scoring at or above the brain damage criterion score. The discrepancy in results between the two approaches to the same data is explained by the fact that five classical migraine subjects scored exactly at the brain damage cut-off score (i.e., AIR $\geq$ 1.55).

The classical migraine group had a significantly greater recent decline in intellectual ability, as

determined by the Deterioration Quotient, than did the control group, or the common migraine group, when the frequency of migraine attacks were statistically equated.

When all 30 tests of the battery were given equal weight, the three groups did not differ significantly in the percentage of tests performed in the impaired range. However, a number of individual tests did significantly differentiate the subject groups.

Sensory-perceptual functioning was within normal limits for all three groups. Dominant hand motor speed and coordination of the classical migraine group showed mild impairment and was significantly poorer than both the common migraine and control group dominant hand performances. The dominant hand performances of both classical and common migraine groups on a complex tactual discrimination and manipulation task were significantly poorer than the control group performance. The nondominant hand and both hands performances of the two migraine groups showed mild impairment. The overall performance on the Tactual Performance Test was within normal limits for the classical migraine group, but mildly impaired for the common migraine group and significantly poorer compared to the control group.

Aphasia screening showed the classical group committed significantly more errors than did the common migraine and control groups. Nevertheless, all group means on the Aphasia Screening Test were within normal limits. Visuospatial and visuoconstructive performance of the

classical migraine group was mildly impaired and significantly poorer than either the common migraine or control group performances.

The immediate recall of orally-presented digit strings and the incidental memory recall of tactually-perceived shapes was performed within normal limits by all groups. The normal WAIS-R Digit Span performance is not in accordance with prior research showing a significantly lower score by migraine patients compared to matched controls (Schuchman & Thetford, 1970). However, short-term and long-term memory of semantic material, and long-term memory of visually-presented figures, was found to be mildly impaired for both classical and common migraine groups. The mildly impaired verbal memory finding replicates the report by Klee and Willanger (1966), though the tests used are not entirely comparable.

One conceivable explanation of why both migraine groups demonstrated mildly impaired short- and long-term memory is that subjects in both groups were prescribed propranolol (Inderal), a drug with alleged iatrogenic properties, namely, memory impairment. Controlled studies of the behavioral toxicity of this drug have yet to be conducted, however. To rule-out this factor, medication history was examined in detail. As expected, the types of medication and the extent of their use was approximately equivalent between the two groups. No single pattern of medication use was discernible for those subjects with memory impairment or global neuropsychological impairment. Inderal was

prescribed for approximately one-quarter of the subjects within each group and appeared to be randomly distributed with regard to the variables of interest. Furthermore, no subject taking Inderal reported recent memory problems in association with its use.

Tests of concept formation and perseveration, and verbal and non-verbal analogous reasoning were performed within the normal range by all groups. No significant differences separated the migraine groups and the control group. This finding contradicts an earlier finding of impaired abstraction ability among six of eight classical migraine patients; however, the study used unstandardized measures of abstraction ability and was uncontrolled (Klee & Willanger, 1966).

Two complex tests involving symbol substitution and the simultaneous integration of two sets of symbols, and which require many discrete abilities (e.g., sustained concentration, visual-motor coordination, sequential processing, short-term memory) in order to be performed successfully, were performed significantly more poorly by the classical migraine group than the normal control group. Both the WAIS-R Digit Symbol test and the Trail Making Test, Part B, have consistently proven to be extremely sensitive to brain damage, irrespective of localization.

Classical migraine subjects were hypothesized to show cumulative neuropsychological impairment. Accordingly, the length of migraine history was examined after correction for the confounding factor of age. History duration was

positively correlated with the impairment indices (i.e., the longer the history, the greater the overall neuropsychological impairment) but the association was not statistically significant. An unexpected association was found for the common migraine group: the shorter the migraine history, the greater the proportion of impaired neuropsychological test performances.

Previous EEG research has found EEG abnormalities more prevalent the earlier the onset of migraine among both classical and common migraine patients (Hockaday & Whitty, 1969). Therefore, age of migraine onset was examined. The corrected correlation between onset age and the impairment indices of the classical migraine subjects was nonsignificant but in the hypothesized direction (i.e., the younger the migraine onset, the greater the impairment). Hockaday and Whitty (1969) reported that migraine onset before or after age 20 was associated with a significant split in the proportion of patients with abnormal EEG records as adults. Among the present sample of eight classical migraine patients with significant neuropsychological impairment, half reported migraine onset before or at age 20. In summary, no relationship was discernible between degree of neuropsychological impairment and age of migraine onset.

For the common migraine subjects a significant association was found between onset age, corrected for age, and neuropsychological impairment: the older the age of migraine onset, the more impairment measured. Indeed, all

three common migraine subjects with significant neuropsychological impairment reported migraine onset after age 20.

The time elapsed post-attack has been found to be an important factor in CT-scan findings of cerebral edema (Mathew, 1978). Therefore, the elapsed time since the last migraine attack was examined. For common migraine subjects no relationship existed with the impairment indices. Among classical migraine subjects, the association was in the expected direction (i.e., the more recent the attack, the greater the measured neuropsychological impairment), but was not statistically significant. This suggests that neither migraine group was suffering from the acute effects of an attack preceding the testing.

Migraine attack characteristics of severity, duration and frequency were subsumed in the Headache Index. It was hypothesized that the Headache Index score would indirectly reflect the magnitude and extent of both an underlying pathophysiological process and the psychological distress secondary to the pain. The Headache Index of the classical migraine group was not significantly correlated with either of the two summary impairment indices, but it was significantly positively correlated with the Deterioration Quotient, that is, the more frequent, more prolonged, and more severe the migraine attack, the greater the intellectual decline from predicted premorbid levels. The common migraine group did not exhibit any significant relationship between the Headache Index and the impairment

indices or the Deterioration Quotient.

The Assessment of Own Functioning Inventory (AOFI) total score for the classical migraine group was best explained by the attack variables of frequency and duration. The AOFI was also significantly and positively associated with the impairment indices. Classical migraine subjects reported a significantly greater incidence of dysnomia, confused or illogical thoughts, and difficulty following directions to get somewhere than did control subjects.

For the common migraine group, only the Deterioration Quotient was significantly and positively correlated with the AOFI. Among the demographic and attack characteristic variables, the common migraine AOFI was best explained by length of migraine history (the shorter the history, the higher the AOFI total score) and age (the older the subject, the higher the score).

Both classical and common migraine subjects reported significantly more occurrences of impaired verbal comprehension, dysarthria, and difficulty in following instructions in how to do something than control subjects. No significant differences in self-reported memory difficulties were detected, thus not supporting the questionnaire findings of significantly greater complaints of memory difficulties among migraine patients compared to matched controls (Mahrer, et al., 1966; Rogado, et al., 1973). An equal number of classical and common migraine subjects reported not being as "bright" now as before their migraine onset, or were not sure.

The reported aura neurologic disturbances of the classical migraine subjects were examined in relation to the headache and neuropsychological test findings. A significant association was found between lateralized neurologic symptoms and contralateral headache, and bilateral neurologic symptoms and holocrania. This replicates Heyck's (1973) observation of contralateral headache in hemiplegic migraine, and is congruent with the report of premonitory vascular headache contralateral to the subsequent permanent neurologic deficit in women on birth control pills who suffered cerebral infarctions (Gardner, et al., 1968).

Correspondence between neuropsychological impairment referable to one cerebral hemisphere and contralateral aura neurologic disturbance, or diffuse neuropsychological impairment and bilateral symptomatology, was found. Unfortunately, the small number of subjects precluded statistical significance.

A straightforward ipsilateral correspondence between lateralized neuropsychological impairment and the headache locus was not established. Similar findings of only a loose correlation between lateralized regional cerebral blood flow patterns during migraine headache and ipsilateral hemicrania have been reported (Sakai & Meyer, 1978).

Interpretation and conclusions

The most unexpected finding of the study is the significantly greater average neuropsychological impairment

evident for the common migraine subjects relative to the normal control subjects. On nearly every measure of the battery the common migraine group performances were intermediate to the classical migraine and control group performances. This fact raises anew the long-standing controversy about whether migraine is actually a number of separate diseases with separate pathophysiological underpinnings, or is a single disease, the differing clinical manifestations representing a pathophysiological continuum.

Implicit in the reasoning of Hypothesis I was that complicated and classical migraine were quantitatively, not qualitatively, different. Common migraine was viewed as a separate syndrome because overt signs and symptoms of neurologic dysfunction were absent. The present results serve to discard this view, and suggest that classical and common migraine are quantitatively related on a number of neuropsychological variables associated with higher cortical functioning. Presumably, common migraine and complicated migraine anchor the endpoints of a pathophysiological continuum, with classical migraine positioned intermediate.

Several lines of evidence suggest that classical and common migraine are biologically more similar than they are different.

Electrophysiological data is suggestive of a common pathophysiology; interictal EEG recordings show slow-wave and high-voltage paroxysmal activity in equal proportions of classical and common migraine patients (Hockaday & Whitty,

1969).

Cerebral blood flow studies report both similarities and differences between the migraine disorders. Some report hyperperfusion during the common migraine headache identical in pattern and magnitude to that observed in classical migraine (Sakai & Meyer, 1978; Skinhoj, 1973); others report no rCBF changes preceding the headache (Hachinski, Olesen, Norris, et al., 1977) or during the headache (Olesen, Lauritzen, Tfelt-Hansen, et al., 1982). One case of decreased occiptial rCBF and impaired reading activation during a severe common migraine attack has been reported (Olesen, Larsen, Lauritzen, et al., 1981). Common migraine patients have been shown to exhibit cerebral vasomotor dysregulation similar to classical migraine patients during both headache and post-headache phases (Sakai & Meyer, 1979).

Biochemical abnormalities have been detected in both disorders. Increased lactate, GABA, and cyclic AMP values in the CSF during or shortly after the attacks of both common and classical migraine patients have been reported (Skinhoj, 1973; Welch, et al., 1978). The presence of these substances has been interpreted as evidence of hypoxic brain metabolism during the migraine attack.

CT-scan abnormalities have been found in common migraine patients as well (Sargent, et al., 1979). Abnormalities include low densitometric zones, ventricular enlargement, and mild cortical atrophy (Mathew, et al., 1977; Mathew, 1978).

In the present investigation, both migraine groups were found to be mildly impaired on short-term and long-term semantic memory, and long-term figural memory tests, and on a tactual discrimination and manipulation task. Both groups similarly reported episodes of dysarthria, impaired verbal comprehension, and difficulties in following instructions. In both groups an equal proportion of subjects reported not being as "bright" now as before their migraine onset.

In some tested abilities, the migraine groups significantly differed: classical migraine subjects exhibited slower dominant hand motor speed and less dexterity, more aphasic errors, greater visuospatial and visuoconstructional dysfunction, and greater intellectual decline from predicted premorbid levels.

At the risk of over-interpreting the group aggregate data, it appears that the classical migraine pattern of neuropsychological deficits implicate a larger zone of brain involvement than does the common migraine pattern of deficits. Specifically, and more spectulatively, the common migraine deficits are associated with predominantly posterior cerebral compromise and the classical migraine deficits are referable to both posterior and anterior cerebral compromise.

The developmental course of neuropsychological impairment may be different for the two migraine disorders. A cumulative effects model was hypothesized for the classical migraine subjects. In other words, it was expected that the degree of neuropsychological impairment

present would be the cumulative result of the repeated migraine attacks on the brain over the migraine history. A trend in the relationship between the impairment indices and the duration of the migraine history was suggestive of cumulative neuropsychological impairment but was not significant and therefore remains tentative. The possibility that the measured neuropsychological impairment reflects the underlying pathophysiology of the brain associated with the migraine syndrome cannot be ruled-out.

The opposite--and significant--relationship between migraine history and degree of neuropsychological impairment was found for the common migraine group. In comparison to the natural history of classical migraine, common migraine begins later (Steiner, et al., 1980) and continues longer (Whitty & Hockaday, 1968). In the present sample, the later and more recent the onset of common migraine, the greater the neuropsychological impairment. Whether this is the result of a rapidly evolving pathophysiological process, or represents the end product, that is, the clinical manifestation, of a long-term disease process is unknown. In the latter case, a threshold model may be applicable, that is, the signs and symptoms of migraine become manifest once some pathophysiological threshold is breached. Conceivably, the threshold for the expression of common migraine is lowered in susceptible individuals as their brains age.

Analysis at the level of the migraine attack reveals a different pattern for the two migraine groups. An index of

the magnitude and extent of the migraine attack was strongly associated with recent intellectual decline for the classical migraine subjects. This suggests that the degree of incapacitation caused by the classical attack is linked to a lower than expected intellectual ability.

The common migraine attack, reported to be approximately of the same severity and duration as the classical migraine attack, but more frequent, does not appear to be linked to measured neuropsychological impairment. Speculating that both migraine groups experience the same "quantity" of psychological distress secondary to their attacks, it is proposed that the psychological variable contribution to the measured neuropsychological impairment is controlled for between the groups. Consequently, an inference can be made that the experience of the severity, duration, and frequency of the classical migraine attack is related in some unknown way to the underlying pathophysiology and associated higher cortical disturbance, and that the latter is not simply a psychological reaction to the pain and disruption caused by the headache alone.

In conclusion, this investigation challenges the prevailing assumption that migraine is an essentially benign disease. Higher cortical functional impairment was detected in a significant proportion of migraine subjects who were free of pain and the residual effects of previous attacks at the time of testing. Both classical and common migraine subject groups demonstrated average neuropsychological

impairment significantly exceeding the non-headache control group average. The measured neuropsychological impairment had real-life correlates: migraine subjects reported a number of neuropsychological difficulties in everyday functioning significantly more often than control subjects.

Overall neuropsychological impairment of the classical migraine group was in the borderline mild range. The group patterns of neuropsychological deficits suggest that the classical migraine group had more extensive bilateral anterior and posterior cerebral compromise. For classical migraine subjects with predominantly lateralized or bilateral neurologic deficits during the aura, the pattern of neuropsychological impairment was in most cases referable to the neuroanatomically relevant cerebral hemisphere(s). These results suggest that permanent higher cortical dysfunction is associated in a lawful way to the classical stereotyped neurologic deficit of the aura which is putatively transient.

It is hypothesized that common migraine, like classical and complicated migraine, involves a disturbance of cerebral activity. Complicated migraine presents with permanent neurologic deficit, classical migraine with transient neurologic dysfunction, and common migraine with no overt neurologic disturbance. Sensitive testing of higher cortical functioning has demonstrated a continuum of nontransient and subtle impairment in approximate proportion to these clinical manifestations. Quantitative, not qualitative differences appear to separate common and

classical migraine, and presumably complicated migraine. This is not a new conceptualization of migraine; the present evidence of relative neuropsychological impairment lends support to the single pathophysiology theory of migraine.

Questions of the pathological processes of classical and common migraine could not be answered in the present investigation. Only weak, indirect support was found for a cumulative effects model in classical migraine. The discovery of a recency effect for neuropsychological impairment in common migraine remains unexplained. Lack of information about change over time is a major weakness of this type of experimental design. Future neuropsychological investigations of migraine conducted longitudinally would make important advances in the understanding of the evolving nature of the migraine pathophysiology and its behavioral consequences.

APPENDICES

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

BERKELEY • DAVIS • IRVINE • LOS ANGELES • RIVERSIDE • SAN DIEGO • SAN FRANCISCO SANTA BARBARA • SANTA CRUZ

Description of Research Project

Dear research participant:

The problem of migraine is undoubtly familiar to you. Eight to 12 million Americans are estimated to suffer from migraine. What causes migraine headache and its associated symptoms is not well understood. Medical research is proceeding along several lines of inquiry (psychological, neurological, physiological, biochemical) into this problem. One approach, termed "neuropsychological," seeks to explain brain-behavior relationships. The source of data in this type of research comes from behavioral tests. Inferences can be made about brain functioning from the results of these tests.

The research I am conducting is a neuropsychological investigation of migraine. There are clues from previous research that this type of testing may shed some light on the brain processes underlying migraine episodes. The specific hypotheses of the study cannot be disclosed at this time but a report will be available at the study's conclusion, sometime in Spring.

Your participation will involve taking a number of tests measuring many different variables of mental functioning, such as verbal and spatial abilities, memory, and problem-solving styles. None of these tests are painful or pose any degree of risk. The entire session will last no longer than three hours.

Because the tests do require concentration and sustained effort, it is vital that you come to the appointment alert and pain-free. If you are not feeling your best on that day please call and cancel. We can always reschedule.

Enclosed is a consent form which needs to be read and signed. Please bring it with you. Also, if you wear reading glasses, please bring them as well.

Thank you very much for your help. I will see you at room 882, Ambulatory Care Building.

Sincerely,

William D. Hooker

William D. Hooker, M.A.
681-8080 x471

APPENDIX A

Letter To Prospective Subjects

MICHIGAN STATE UNIVERSITY
Department of Psychology

DEPARTMENTAL RESEARCH CONSENT FORM

1. I have freely consented to take part in a scientific study being conducted by WILLIAM M. HOOKER, M.A. under the supervision of NEIL H. RASKIN, M.D., Professor, Department of Neurology, University of California School of Medicine.

2. The study has been explained to me and I understand the explanation that has been given and what my participation will involve.

3. I understand that I am free to discontinue my participation in the study at any time without penalty.

4. I understand that the results of the study will be treated in strict confidence and that I will remain anonymous. Within these restrictions, results of the study will be made available to me at my request.

5. I understand that my participation in the study does not guarantee any beneficial results to me.

6. I understand that, at my request, I can receive additional explanation of the study after my participation is completed.

Signed: _____

Date : _____

Code #: _____

APPENDIX B

Informed Consent Form

CODE #: _____ SEX: _____ AGE: _____ RACE: _____ EDUC: _____

OCCUP: _____ RATING: _____

HAND DOM: _____ PRPHRL M/S DAMAGE: _____

HEAD INJURY, SEIZURE: _____

OTHER MED PROBS: _____

TYPE(S) HEAD PAIN: _____

_____

INTENSITY: _____

FREQUENCY: _____

DURATION: _____

LOCUS: _____

COURSE: _____

_____

ASSOC SX: _____

_____

PRODROMATA: _____

_____

PRECIP FACTORS: _____

_____

AGE OF ONSET: _____

TIME POST-ATTACK: _____

FAM HX: _____

_____

MEDS: _____

_____

DIAGNOSIS: _____

LANGUAGE: _____

AFFECT: _____

ORIENTATION: _____

APPENDIX C

Standardized Interview Form

PATIENT'S ASSESSMENT OF OWN FUNCTIONING INVENTORY

Instructions: Please answer each of the following questions by placing a check next to the response which most accurately describes the way you have been recently.

1. How often do you forget something that has been told you within the last day or two?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

2. How often do you forget events which have occurred in the last day or two?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

3. How often do you forget people whom you met in the last day or two?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

4. How often do you forget things that you knew a year or more ago?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

5. How often do you forget people whom you knew or met a year or more ago?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

APPENDIX D

Neuropsychological Test Battery

Patient's Assessment of Own Functioning Inventory

6. How often do you lose track of time, or do things either earlier or later than they are usually done or are supposed to be done?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

7. How often do you fail to finish something you start because you forgot that you were doing it? (Include such things as forgetting to put out cigarettes, turn off the stove, etc.)

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

8. How often do you fail to complete a task that you start because you have forgotten how to do one or more aspects of it?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

9. How often do you lose things or have trouble remembering where they are?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

10. How often do you forget things that you are supposed to do or have agreed to do (such as putting gas in the car, paying bills, taking care of errands, etc.)?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

11. How often do you have difficulties understanding what is said to you?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

3

12. How often do you have difficulties recognizing or identifying printed words?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

13. How often do you have difficulty understanding reading material which at one time you could have understood?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

14. Is it easier to have people <u>show</u> you things than it is to have them <u>tell</u> you about things?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

15. When you speak, are your words indistinct or improperly pronounced?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

16. How often do you have difficulty thinking of the names of things?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

17. How often do you have difficulty thinking of the words (other than names) for what you want to say?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

4

18. When you write things, how often do you have difficulty forming the letters correctly?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

19. Do you have more difficulty spelling, or make more errors in spelling, than you used to?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

20. How often do you have difficulty performing tasks with your right hand (including such things as writing, dressing, carrying, lifting, sports, cooking, etc.)?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

21. How often do you have difficulty performing tasks with your left hand?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

22. How often do you have difficulty feeling things with your right hand?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

23. How often do you have difficulty feeling things with your left hand?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

5

24. Lately do you have more difficulty than you used to in seeing all of what you are looking at, or all of what is in front of you (in other words, are some areas of your vision less clear or less distinct than others)?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

Note: If you are having this kind of trouble with your vision, is it more difficult to see things located to your right or to your left?

( ) to the right
( ) to the left
( ) cannot tell whether one side is worse than the other

25. How often do your thoughts seem confused or illogical?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

26. How often do you become distracted from what you are doing or saying by insignificant things which at one time you would have been able to ignore?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

27. How often do you become confused about (or make a mistake about) where you are?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

28. How often do you have difficulty finding your way about?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

6

29. Do you have more difficulty now than you used to in calculating or working with numbers (including managing finances, paying bills, etc.)?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

30. Do you have more difficulty now than you used to in planning or organizing activities (that is, deciding what to do and how it should be done)?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

31. Do you have more difficulty now than you used to in solving problems that come up around the house, at your job, etc.? (In other words, when something new has to be accomplished, or some new difficulty comes up, do you have more trouble figuring out what should be done and how to do it?)

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

32. Do you have more difficulty than you used to in following directions to get somewhere?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

33. Do you have more difficulty than you used to in following instructions concerning how to do things?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

34. Do you think you are as "bright" now as you were before your present illness?

( ) yes
( ) no
( ) I don't know

VISUAL:

SUPPRESSIONS

Above eye level
Eye level
Below eye level

RV LV

R ___/12

L ___/12

AUDITORY:

Right Ear-Left Ear - RE LE

R ___/4

L ___/4

SOMATOSENSORY:

1. RC-LC°			11. RH-LH			RC	/12
2. RC-RH			12. LC-RH			LC	/12
3 LH			13. LH			RH	/12
4 LC-RH			14. RH			LH	/12
5. RC			15. RC-LC				
6. LC-LH			16 LC-LH				
7 RH			17. RC-RH				
8. RC-LH			18. LC				
9. LC			19. RC-LH				
10 RH-LH			20. RC				

FINGER AGNOSIA:

ERRORS

	1	2	3	4	5		
Right:						R	/20
Left:						L	/20

FINGER DYSGRAPHESTHESIA:

Right:	4 6 3 5	3 5 4 6	6 5 4 3	5 4 6 3	6 3 5 4	R /20
Left:						L /20

MOTOR:

RH	Dynamometer	LH
1)		1)
2)		2)
$\bar{X}$ =		$\bar{X}$ =

RH	Tapping	LH
1)		1)
2)		2)
3)		3)
4)		4)
5)		5)
$\bar{X}$ =		$\bar{X}$ =

RH	Pegboard	LH
1)		1)

APHASIA SCREENING TEST

Form for Adults and Older Children

Name:_____ Age:_____ Date:_____ Examiner:_____

1	18. Repeat TRIANGLE 1
2. Name SQUARE 4	19. Repeat MASSACHUSETTS 1
3. Spell SQUARE 1	20. Repeat METHODIST EPISCOPAL 1
4. Copy CROSS	21. Write SQUARE 3
5. Name CROSS 4	22a. Read [illegible]VE?
6. Spell CROSS 1	22. Repeat SEVEN 5
7.	23. Repeat/Explain ME SHOUTED THE WARNING. 4/2=4
8. Name TRIANGLE 2	24. Write ME SHOUTED THE WARNING. 2
9. Spell TRIANGLE 1	25. Compute 85 - 27 = 48 - 25 = 9 - 16 = 2
10. Name BABY 4	26. Compute 17 X 3 = 8 x 6 = 3 x 4 = 2
11. Write CLOCK 3	27. Name KEY 4
12. Name FORK 4	28. Demonstrate use of KEY 4
13. Read 7 SIX 2 3	29.
14. Read M G W 3	30. Read PLACE LEFT HAND TO RIGHT EAR. 2
15. Reading I 2	31. Place LEFT HAND TO RIGHT EAR 2
16. Reading II 1	32. Place LEFT HAND TO LEFT ELBOW 3

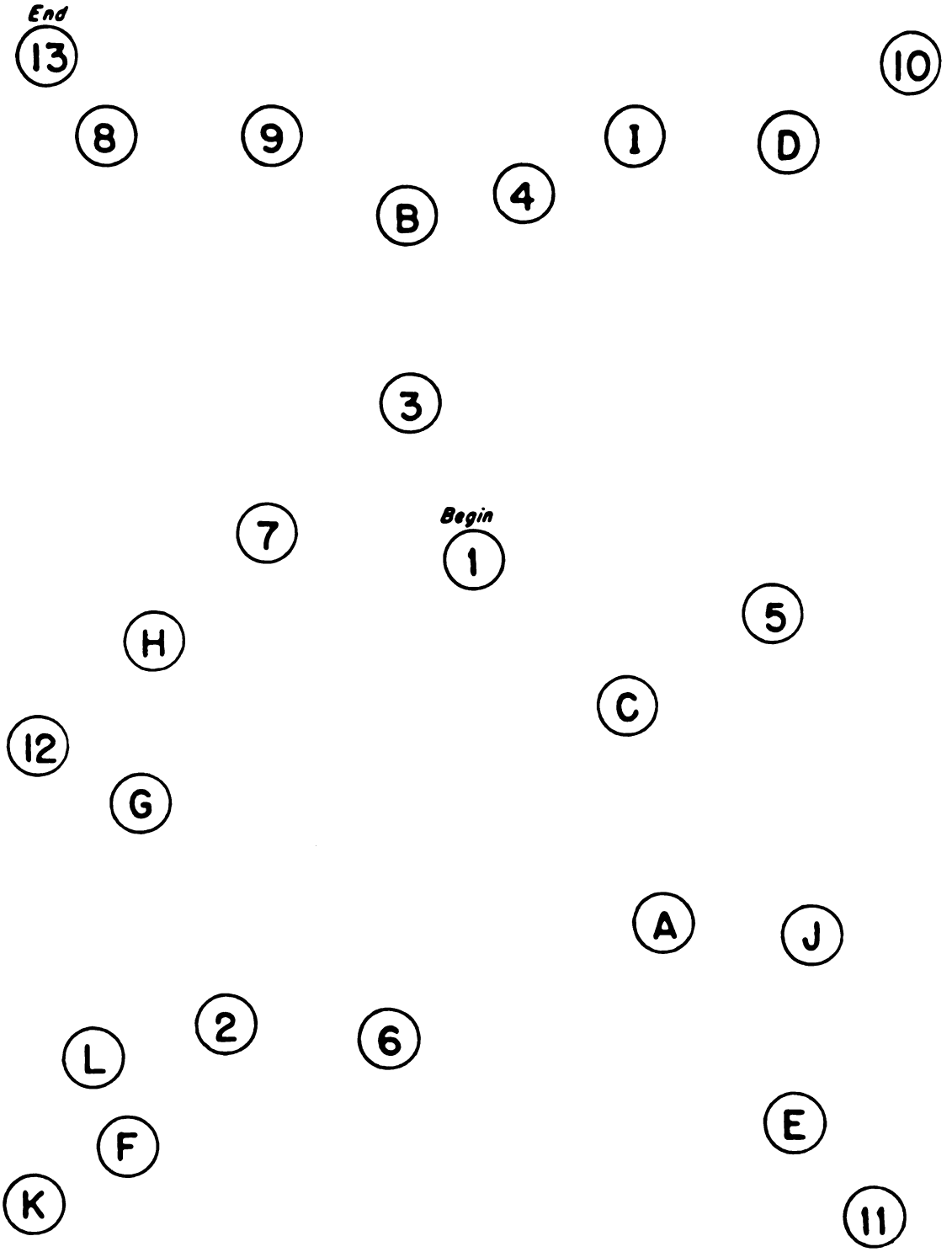
A

B

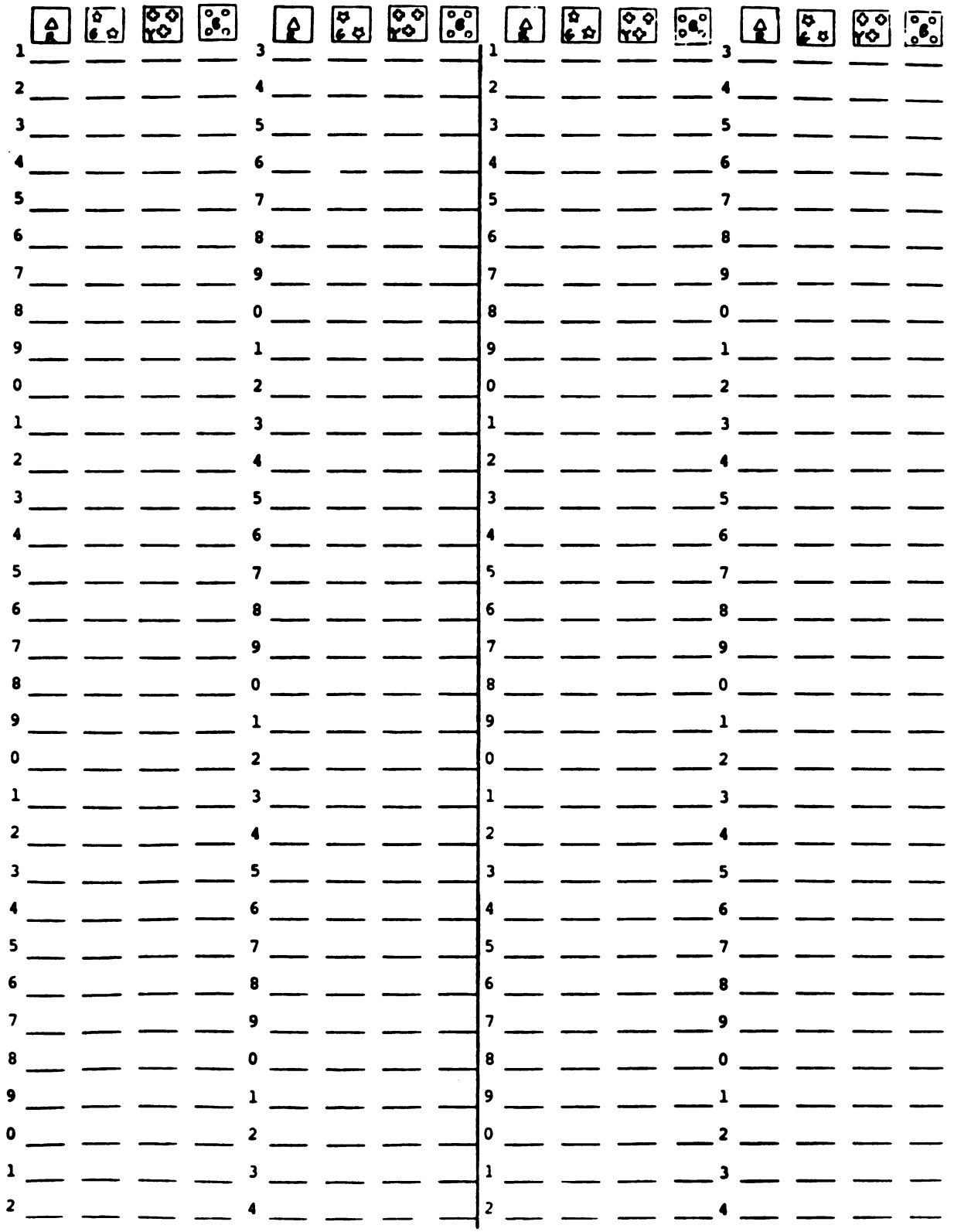
C-1,C-2

Anna Thompson/ of South/ Boston/ employed/ as a scrub woman/ in an office building/ reported/ at the City Hall/ Station/ that she had been held up/ on State Street/ the night before/ and robbed/ of fifteen dollars/. She had four/ little children/ the rent/ was due/ and they had not eaten/ for two days/. The officers/ touched by the woman's story/ made up a purse/ for her/.

The American/ liner/ New York/ struck a mine/ near Liverpool/ Monday/ evening/. In spite of a blinding/ snowstorm/ and darkness/ the sixty/ passengers including 18/ women/ were all rescued/ though the boats/ were tossed about/ like corks/ in the heavy sea/. They were brought into port/ the next day/ by a British/ steamer/.



Trail Making Test, Part B



Wisconsin Card Sorting Test

SHORT FORM OF RAVEN STANDARD PROGRESSIVE MATRICES

Name _____ Date _____ Examiner _____

Age _____ Sex _____ Education/Highest grade level in school _____

Site of Lesion _____ Date of lesion onset _____

Hand Used: Right Left

Time started _____ Time finished _____

A			B			C			D			E		
2		C	6		R	3		RC	2		R	4		LC
3		L	8		R	4		R	3		RC	6		L
4		C	9		L	5		RC	4		RC	8		LC
5		R	10		R	6		R	5		R	9		RC
7		R	11		L	7		L	6		LC	10		LC
9		L	12		C	8		L	7		L	11		R

Errors: _____ _____ _____ _____ _____

Score: 30 - _____ = _____ approximating long form score of _____

Percentile based on long form score approximation _____

Error Pattern:

Spatial Distribution of Items Missed

a) On left side _____ (8 errors possible)

b) On right side _____ (10 errors possible)

c) Center _____ (12 errors possible)

Note: Additional data for standardization will be welcomed.
Neuropsychological Laboratory, Univ. of Michigan, 1111 Catherine St. Ann Arbor, MI 48109
February 3, 1979

3. DIGIT SPAN Discontinue after failure on BOTH TRIALS of any item. Administer BOTH TRIALS of each item, even if subject passes first trial.

	DIGITS FORWARD	Pass-Fail	Score 2, 1, or 0
1.	5-8-2		
	6-9-4		
2.	6-4-3-9		
	7-2-8-6		
3.	4-2-7-3-1		
	7-5-8-3-6		
4.	6-1-9-4-7-3		
	3-9-2-4-8-7		
5.	5-9-1-7-4-2-8		
	4-1-7-9-3-8-6		
6.	5-8-1-9-2-6-4-7		
	3-8-2-9-5-1-7-4		
7.	2-7-5-8-6-2-5-8-4		
	7-1-3-9-4-2-5-6-8		
	Total Forward		Max=14

	DIGITS BACKWARD*	Pass-Fail	Score 2, 1, or 0
1.	2-4		
	5-8		
2.	6-2-9		
	4-1-5		
3.	3-2-7-9		
	4-9-6-8		
4.	1-5-2-8-6		
	6-1-8-4-3		
5.	5-3-9-4-1-8		
	7-2-4-8-5-6		
6.	8-1-2-9-3-6-5		
	4-7-3-9-1-2-8		
7.	9-4-3-7-6-2-5-8		
	7-2-8-1-9-6-5-3		
	Total Backward		Max=14

*Administer DIGITS BACKWARD even if subject scores 0 on DIGITS FORWARD

[ ] + [ ] = [ ] Max=28
Forward Backward Total

6. BLOCK DESIGN Discontinue after 3 consecutive failures.

Design	Time	Pass-Fail	Score (Circle the appropriate score for each design.)
1. 60"	1		2
	2		0 1
2. 60"	1		2
	2		0 1
3. 60"			0 — 10-60: 4; 11-15: 5; 1-10: 6
4. 60"			0 — 10-60: 4; 11-15: 5; 1-10: 6
5. 60"			0 — 21-60: 4; 16-20: 5; 11-15: 6; 1-10: 7
6. 120"			0 — 30-120: 4; 26-30: 5; 21-25: 6; 1-20: 7
7. 120"			0 — 61-120: 4; 46-60: 5; 31-45: 6; 1-30: 7
8. 120"			0 — 76-120: 4; 56-75: 5; 41-55: 6; 1-40: 7
9. 120"			0 — 76-120: 4; 56-75: 5; 41-55: 6; 1-40: 7
			Total — Max=51

Digit Span	0-2	3-5	6	7	8	9-10	11	12-13	14	15-16	17	18-19	20-21	22-23	24	25	26	27	28
Scaled Score	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Block Design	0	1	2	3-7	8-13	14-19	20-22	23-26	27-30	31-34	35-37	38-41	42-43	44-46	47-48	49	50	—	51

WAIS-R Digit Span and Block Design Subtests

11. SIMILARITIES Discontinue after 4 consecutive failures.	Score 2, 1, or 0
1. Orange—banana	
2. Dog—lion	
3. Coat—suit	
4. Boat—automobile	
5. Eye—ear	
6. Button—zipper	
7. North—west	
8. Egg—seed	
9. Table—chair	
10. Air—water	
11. Poem—statue	
12. Work—play	
13. Fly—tree	
14. Praise—punishment	

—	0-7	8-15	16-22	23-29	30-36	37-43	44-47	48-52	53-56	57-61	62-65	66-69	70-74	75-78	79-82	84-86	89-90	91-92	93	—
—	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	—
—	0	1	2-4	5-6	7-10	11-13	14-15	16-17	18-19	20-21	22	23	24	25	26	27	—	28	—	—

Digit Symbol — Scaled Score

Similarities

Total

Max = 28

WAIS-R Digit Symbol and Similarities Subtests

TACTUAL PERFORMANCE TEST

Name _____ Date _____ Examiner _____

Indicate form used:

_____ 10-figure board - Ages 15 years & older
_____ 6-figure board - vertical position - Ages 9 through 14 years
_____ 6-figure board - horizontal position - Ages 5 through 8 years

Trial	Hand	Circle	Time	
1	Dominant Hand	R L	' "	= _____
2	Non-dominant Hand	R L	' "	= _____
3	Both Hands		' "	= _____

Total Time: _____

Memory: _____

Localization: _____

Comments:

USE REVERSE SIDE FOR DRAWING

LIST OF REFERENCES

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