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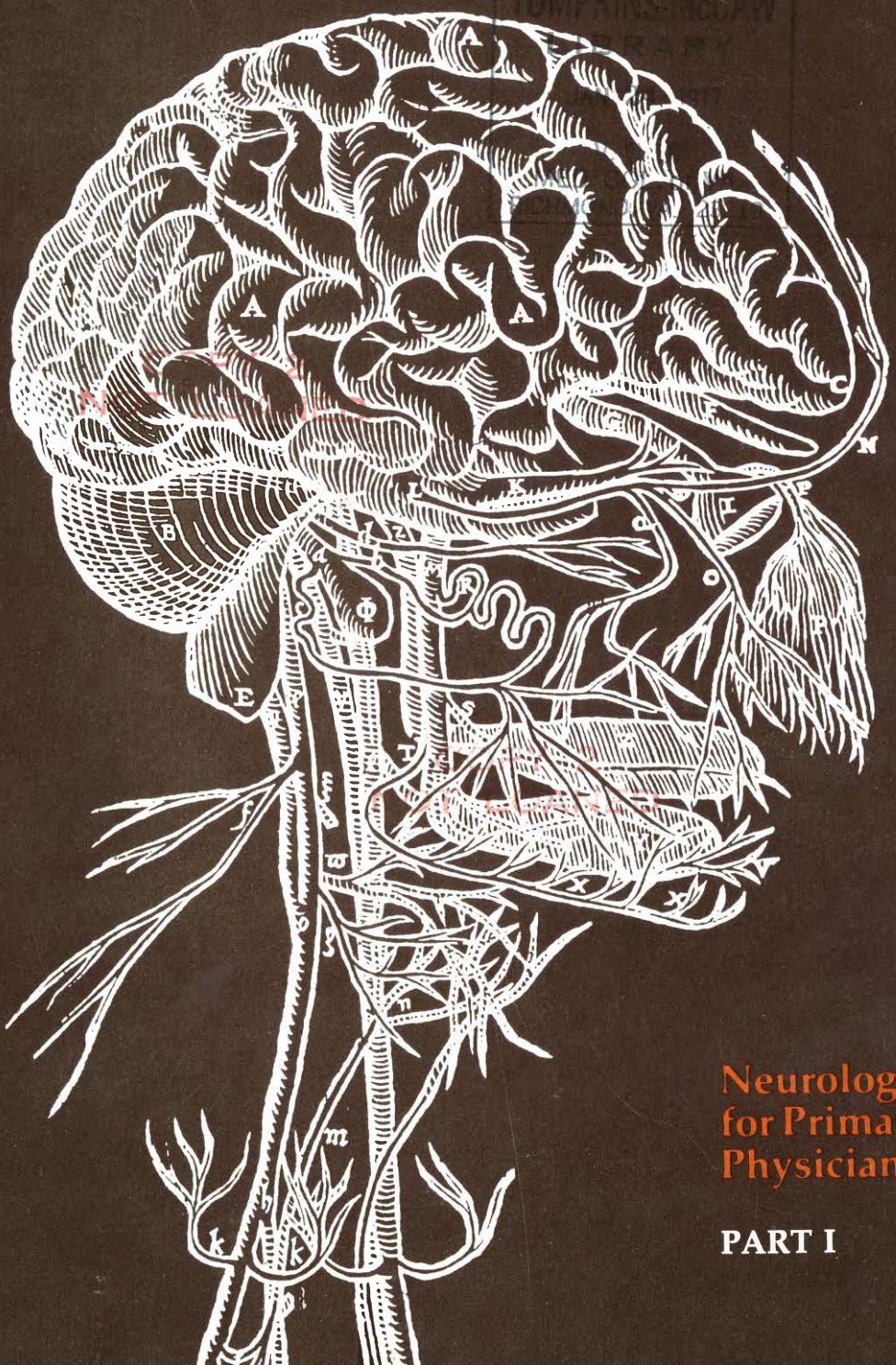

Neurology for Primary Care Physicians

PART I

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Neurology for Primary Care Physicians—PART I

A postgraduate course in Neurology sponsored by the Department of Neurology and the Department of Continuing Education, Medical College of Virginia, Health Sciences Division of Virginia Commonwealth University.

JOHN R. TAYLOR, M.D., *Guest Editor*

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INTRODUCTION

The 29th Annual Stoneburner Lecture Series was sponsored this year by the Department of Neurology because we sensed a need and a desire for a symposium approaching common neurologic problems encountered by primary care physicians. The attendance at the series was gratifying to the participating lecturers and confirmed our view.

Our approach to each topic has been to dwell on recognition and diagnosis, and to discuss new therapy and therapeutic dilemmas, omitting or touching only briefly on such areas as basic anatomy, physiology, chemistry, and pathology. In this first part of a two-part issue, I discuss some of the problems of treating Parkinson's disease that somehow have not been solved by the highly touted levodopa, Dr. Harbison provides us with an overview of sometimes vexing problems that present as episodic visual loss, and Dr. Grindal provides us with a rational approach to dizzy patients. Our Stoneburner Lecturer, Dr. Clark Millikan, offers an in-depth review of cerebrovascular insufficiency. Finally, Dr. Calabrese covers the value of the cerebrospinal fluid examination and certain measures that may be taken to improve interpretation.

In organizing this symposium, we have attempted to provide the primary care physician with some insight, perhaps new, into these complex and common areas, but it is necessary for primary care physicians themselves to continue providing us with information about their problem areas.

JOHN R. TAYLOR, M.D.

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Current Management of Parkinsonism

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James Parkinson, a London general practitioner and political activist,[1] delivered his essay on the shaking palsy in 1817 and encouraged others who "humanely employ anatomical examination" to study the cause and nature of "this malady." Even in his wildest fantasies I seriously doubt that he dreamed of the extent to which his advice would be followed. Today, in spite of a recognized incidence of only 20 cases per 100,000 persons per year,[2] articles concerning this disorder appear in nearly every issue of many neurology journals. The reason for this interest is explained by the significant work that took place in the 1960's. During that period a series of biochemical steps leading from tyrosine to biogenically active amines was elucidated,[3] and, further, the action of these amines at brain synapses was convincingly hypothesized.[4] Tyrosine is converted to levodopa and then to dopamine, a neurotransmitter. Since dopamine parenterally does not enter the brain, it was found that large doses of its precursor, levodopa, resulted in some levodopa entering the brain, driving the reaction in favor of more dopamine, and therefore enhancing neurotransmission. It is this concept that has excited neurologists out of all proportion to the frequency of Parkinson's disease in the general population. As is now known, the pathology of Parkinson's disease lies in the substantia nigra,[5] where neurons that ordinarily project to the striatum[6] and transmit via dopamine are degenerating; hence the rationale for the use of levodopa as a therapeutic tool. As attractive as this model is, I remain suspicious that the mechanisms are far more complex than as yet determined.

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In the management of Parkinson's disease, one must be reasonably certain of the diagnosis. In spite of the foregoing sophisticated biochemistry, there is really no laboratory test for the disease, so it becomes an entity that must be recognized on purely clinical grounds. While the differential diagnosis can be quite extensive and includes such rare entities as manganese poisoning, as well as such usually apparent causes as phenothiazine intoxication or carbon monoxide sequelae, several disorders and etiologies account for most of our diagnostic problems. Although we think of Parkinsonism as a triad of rest tremor, rigidity, and akinesia, the onset may be with any one of these, and if it is with tremor, the distinction from essential tremor may be difficult. Essential tremor, sometimes inherited as an autosomal dominant, is occasionally seen and resembles Parkinson's disease. The tremor is a little faster[7] and while many authors state that it begins in an arm, as does Parkinsonism, the head often begins to titubate soon after the tremor begins in the hand. The onset of essential (or familial) tremor is usually earlier than in Parkinson's disease, and may even be in childhood. Its progression is slow, and it often stabilizes so that the physician may encounter a patient who recounts years of tremor, often misdiagnosed as nervousness or Parkinsonism. The rigidity and akinesia of the latter are never present in essential tremor. Patients with essential tremor usually display more tremor on intention than at rest, and often find that a moderate amount of alcohol relieves their tremor for a time. The combination of family history, long-standing symptoms, head titubation, and absence of either rigidity or akinesia will almost always establish the diagnosis of essential tremor. Levodopa is of no value.

Cerebellar tremor associated with cerebellar degeneration or other cerebellar diseases is an occa-

sional problem. Usually the absence of rest tremor, akinesia, and rigidity, plus other signs, for example, truncal ataxia, will allow an easy distinction.

A variety of degenerative diseases may present with poverty of motion and a degree of rigidity. Most of the presenile dementias can present in this fashion, but the predominance of the dementing element usually permits an easy differential diagnosis to be made. Certain rare entities have been a problem, however, one of which is progressive supranuclear palsy.[8] Patients with this disease display many Parkinsonian features, including, occasionally, involuntary movements; however, early loss of voluntary vertical gaze, especially down gaze (with spared reflex gaze mechanisms, for example, oculovestibular reflexes) associated with conspicuous rigidity, along with a fairly rapid course, are usually enough to permit most clinicians to arrive at the diagnosis. Levodopa is of limited, if any, benefit.

Shy-Drager syndrome (idiopathic orthostatic hypotension)[9] is another rare syndrome that has led to some diagnostic difficulty, though usually easily resolved. This disease reflects, to some extent, a continuum of Parkinsonism; however, the Shy-Drager syndrome evinces a much more profound involvement of autonomic nuclei, with consequent severe orthostatic hypotension, anhidrosis, and incontinence, to the degree that the usually present bradykinesia, rigidity, and occasional tremor are overshadowed. Nevertheless, since orthostatic hypotension is occasionally a feature of Parkinsonism, the distinction is sometimes a problem. Patients with Shy-Drager syndrome respond poorly to levodopa.

Apart from these syndromes, the differential diagnosis of Parkinson's disease revolves mainly around its etiology. Though some reputable investigators appear to feel that the encephalitis epidemic in the second and third decades of this century accounts for most of the Parkinsonism we see, I believe that there are multiple etiologies for the disease just as there are for hemiplegia, and that the duty of physicians encountering patients with Parkinsonism is to attempt to elucidate the etiology.

Another area of interest that should be mentioned is genetic Parkinson's disease.[10] There is abundant evidence that familial clustering occurs in Parkinsonism, and the finding that individuals predisposed to developing Parkinsonian symptoms, after treatment with phenothiazines, have a higher incidence of family members with spontaneous Parkinson's disease[11] adds further weight to the idea that some Parkinsonism is hereditary, perhaps an inherited tyrosine hydroxylase deficiency. Nevertheless, this is not sufficiently established to require genetic counseling, nor is hereditary Parkinsonism sufficiently different from other forms to necessitate differences in therapy. Furthermore, familial clustering alone is insufficient evidence to rule out an infectious etiology.

Therapeutic avenues open to the physician managing patients with Parkinson's disease can best be summarized by considering the past, present, and future. That the treatment of this complex disease should change over the years is not surprising; however, that the treatment should take such profound swings over a period of fifteen years is surprising.

The Past. Charcot is said to have noted the value of atropine over 100 years ago.[12] Since then, and until levodopa appeared on the scene, atropine and about seven or eight similar drugs were the medications of choice in Parkinson's disease. The differences in these drugs are not great,[13] and all share, to a variable degree, anticholinergic side effects. The peripheral side effects of these drugs are well known; however, centrally, drug intoxication may lead to ataxia, dysarthria, hyperthermia, and frank psychosis. The drugs must be introduced in low dosages and increased slowly until improvement occurs or side effects force a halt to further increment of dosage. A modest improvement in rigidity and tremor can be expected in 70% of patients; however, akinesia does not respond to this treatment.[14] These drugs remain valuable in the treatment of mild Parkinsonism and as adjuncts to levodopa. Diphenhydramine (Benadryl®), an antihistamine, also possesses an atropine-like action, inhibiting striatal dopamine uptake, and is only mildly less potent than benztropine (Cogentin®).

Amphetamines enjoyed some popularity in the past. These drugs are chemically similar to dopamine and seem to be beneficial. Their benefits, however, are not great enough to override their side effects, and they are no longer used to any extent. Surgery, involving destructive lesions in several areas of the brain, but mostly in the thalamus, enjoyed a brief popularity in the fifties and early sixties. Useful mainly for tremor and least valuable in akinesia, thalamotomy procedures were often impermanent in their benefits and had occasional failures as well as complications, such as hemiplegia. As a result, the

use of thalamotomy waned rapidly after the development of levodopa, and the operation is now rarely performed for Parkinson's disease.

The Present. Long in preparation, levodopa has been in widespread experimental use for over seven years, and in general use for over five years.[15] First evaluations, particularly with patients early in the course of their disease, indicated that 70% of patients experienced at least a 50% improvement in their symptoms, especially akinesia and rigidity. This is a remarkable improvement for most patients. To achieve this goal, the daily dosage must be slowly worked up to levels of 5 to 9 gm, initiated at levels of 125 to 250 mg daily, with food. Single doses should not exceed 1.5 to 2.0 gm[13]; hence the need for multiple doses. The frequency of side effects is extensive. In one series of 100 patients,[16] 49 developed abnormal involuntary movements, 45 had gastrointestinal problems, 30 had psychiatric manifestations, and 11 had symptomatic hypotension. Other side effects occurred less frequently. As a result of these side effects, especially nausea, many patients never reach maximum dose levels, and treatment is discontinued because they cannot tolerate useful levels of the drug. Part of this problem has been solved by combining levodopa with carbidopa which is a chemical "look-alike" of levodopa that inhibits dopa-decarboxylase extracerebrally. Thus, since 95% of levodopa is decarboxylated before it reaches the brain[17] (and is therefore therapeutically ineffective), a combination drug allows levodopa to reach the brain in greater amounts respective to the oral dose. The only combination currently available commercially is Sinemet 25/250® (Merck, Sharp, and Dohme). This product provides a carbidopa:levodopa ratio of 1:10, and since carbidopa blocks at least 75% to 80% of peripheral decarboxylation of levodopa, it follows that a Sinemet 25/250® is roughly equivalent to 1.0 gm of oral levodopa, and in practice this seems to be the case. In switching from levodopa to Sinemet 25/250®, stop levodopa for 8 hours, then resume Sinemet 25/250® at one-fourth the dose for levodopa. The only real advantage to the combination is the avoidance of nausea, though a reduction in cardiac arrhythmias and in hypotension has been reported.[17] According to an oral communication from B. A. Huffman, in February 1976, the price of this combination drug is 15% to 20% above levodopa alone and since its chief value is in preventing nausea, the increased expense is hardly justified for those who tolerate, one way or the other, this side effect. Nonetheless, this combination drug offers a considerable advantage to those patients who seem unable to overcome nausea at even low doses. In addition, and of minor importance with out-patients, one can advance the dosage faster with combination therapy since nausea is a minimal problem. Finally, carbidopa inhibits the action of pyridoxine in reversing levodopa action; hence ordinary multivitamins may be used when indicated.

Other side effects that deserve special mention are the involuntary movements and the psychologic problems. Both can take almost any form, both are quite common complications, and, as a rule, the development of either problem is best managed by a reduction in dose. Both are central effects of levodopa; hence they readily occur with either levodopa alone or in combination with carbidopa.

A final note on side effects relates to orthostatic hypotension. This is a well-recognized side effect, and patients on levodopa should have periodic *standing* blood pressure determinations. A reduction in levodopa dose is usually required if this side effect occurs.

Other drugs may also be used to advantage with levodopa or levodopa/carbidopa. Atropine-like agents have already been mentioned, and while they were never shown to provide more than a 20% improvement in symptoms, this margin may occasionally be useful along with levodopa. Amantadine, originally an antiviral drug, has more merit as an adjunct as well as acting alone. In one study[18] involving 48 patients, benefits of 21% to 39% occurred in major Parkinsonian disabilities. Side effects, consisting mainly of gastrointestinal disturbances, sleep disturbances, and hallucinations occurred with amantadine, but the frequency of these is low. The dose used in this study was amantadine 200 mg daily in divided doses. There is a tendency for benefits to decline after several months.

Propranolol, a beta adrenergic blocking agent, has also been used in a variety of states with tremor[19,20] and consequently we have tried it in combination with other drugs to relieve the tremor of Parkinson's disease. The results have not been measured, but on occasion this has seemed to be a useful drug. Other clinicians[21] have had similar experiences. A maximum dose of 180 to 200 mg/day must be approached cautiously.

One may wonder why several drugs other than levodopa have been mentioned. Several facets of the nature of levodopa therapy account for this. First, a

fairly large group of patients do not respond well to it. Second, certain patients are unable to achieve adequate levels due to side effects. And, finally, there appears to be developing a "resistance" to levodopa benefit.[15] This resistance takes several forms, but occurs in one way or another in the majority of patients. In Barbeau's series, the percentage of patients with excellent or good results initially was 79% and dropped to 29% at 6 years, and 25% had stopped levodopa. The predicted survival of severely akinetic patients is 9.7 years,[22] thus it is suggested that levodopa probably will not stop the progression of Parkinsonism. Some investigators feel that there may be a finite period of time in which levodopa is effective and therefore withold the drug until disability is beginning to become clearly evident.

The resistance to treatment takes many forms, but three mechanisms stand out:

1. End-of-dose akinesia. Parkinsonian symptoms recur progressively earlier following a dose. Levodopa levels are low, and more frequent spacing of the drug is beneficial.

2. On/Off phenomenon. Patients note periods in which there is a sudden return of Parkinsonian symptoms, the "Off" period. The "On" period, unfortunately, is nearly always complicated by dyskinesias, usually appendicular and fairly distressing. In one report,[23] 29 such patients were encountered in a population of 300 Parkinson patients. Nineteen had been on medication more than 24 months, suggesting that the duration of the disease or of levodopa therapy is of significance. The "Off" period is characterized by low levodopa levels. This phenomenon is poorly understood and its management a subject of debate. Nevertheless, two views are worth mentioning. The first[24] embraces the concept that a hypersensitivity of the receptor occurs and suggests gradual reduction in levodopa dose to levels of about one-fifth the previous maintenance dose. The second[25] involves a reduction in presumably competing amino acids in the diet by reducing protein intake from the normal 1.0 to 2.0 gm/kg to .5 gm/kg, along with the usual dosages of levodopa and an inhibitor. Both methods, as well as a variety of other drug manipulations, have some merit; however, this problem remains quite serious.

3. Akinesia paradoxica. Sudden "blocking" seems to occur, often triggered by a sudden change in afferent sensory input (as unexpected stress), and the patient "freezes," often falling. Blood levels of levodopa are usually high,[21] and the theory is that there is a sudden, unanswered demand on the noradrenalin "drive" mechanism, now depleted by involvement of the locus ceruleus.[21] Fortunately, this complication is quite uncommon, since its management and pathogenesis remain uncertain.

In numerous other ways, and in spite of many drugs, Parkinsonian patients seem to gradually lose the benefit of medication and deteriorate after a number of years.

Several other facets of the treatment of Parkinsonism deserve special mention. A certain number of patients develop a mild-to-moderate dementia.[26] This part of the picture does not seem to be wholly reversible with levodopa and thus becomes part of the overall management. Discussion of this is beyond the scope of this paper. Another important part of present management is physical therapy. The motivation and assistance provided by this modality is of inestimable value, and no experienced clinician doubts the value of maintaining mobility in the patient with Parkinsonism. Seriously affected patients are best cared for by facilities offering this form of treatment.

Evaluation of the physician's treatment is quite important, since the probability of eventual failure is high. With any given patient, the physician must establish methods of continuing patient evaluation that include such actions as rising from a chair, handwriting, drawing whorls, and activities of daily living.[17] Once clear regression occurs, efforts at combating this, while often futile, must be instituted, and a periodic semi-quantitative evaluation of the patient is useful.

The Future. A number of pharmacologic attempts to alter Parkinson's disease are in progress, but most show little potential. Two that show the greatest possibility of success presently are bromocriptine[27,28] and apomorphine.

Bromocriptine, an ergot alkaloid containing a lysergic-acid residue, activates dopaminergic receptors. The evidence cited is but a single study in which 19 patients received an optimum dose of 20 to 75 mg daily; the original study consisted of 28 patients, but 1 failed to follow directions and 8 had intolerable side effects. Side effects, usually dose dependent, were in every way similar to levodopa, except for four new reactions: erythema, edema, and tenderness of the ankles; burning discomfort of the eyes; diplopia; and frequent extrasystoles. Of the 19 who continued bromocriptine, all but 4 were able to omit their levodopa or levodopa/carbidopa. All noted improvement

of Parkinsonian symptoms while on bromocriptine as compared to a placebo, but the authors were unable to draw any conclusion comparing bromocriptine and levodopa. The drug appears to have some promise, particularly since it obviates the necessity of having endogenous dopa decarboxylase, which is also depleted in the striatum of Parkinsonian patients as the disease progresses.

A second drug offering some promise is N-propylnoraporphine, an analog of apomorphine having a nephrotoxic dose far in excess of its therapeutic dose.[29] In the series by Cotzias et al,[29] all 24 patients improved, and the "On-Off" phenomenon of 6 patients, still present on N-propylnoraporphine alone, was abolished by co-administration of alpha-methyl dopahydrazine. Side effects, including drug-related renal toxicity in two patients, were not uncommon, and further evaluation is necessary.

Summary. While an exhaustive review of available management has not been attempted, the frequently missed differential diagnoses and important therapeutic modalities have been discussed. No treatment seems to stay the inexorable progression of this disease, but several avenues offer the patient a better quality of life as the disease proceeds.

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Episodic Disorders of Vision

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Introduction.

Of all our senses, vision is most commonly associated with patient distress, if not overt alarm, when abruptly compromised.

Despite patient concern, a rare, or rarely recognizable, clinical entity is perhaps of less significance to the physician than to the patient. When the broad spectrum of episodic disturbance of vision is closely examined, it becomes apparent that these visual symptoms are indeed of common occurrence in the population at large.

Surprisingly, despite their ultimate effect on the eye, a majority of the clinical entities that produce episodic disturbance of vision are neurologic (Fig 1).

Episodic is defined as being ". . . made up of separate, loosely connected episodes."* In turn, an episode is ". . . a usually brief unit of action . . . an occurrence or connected series of occurrences and developments which may be viewed as distinctive and apart, although part of a larger or more comprehensive series."*

In binocular man, episodic visual change has two essential parameters of basic diagnostic significance: Time and laterality.

In terms of time, an episode has both duration and frequency. Although both characteristics are of diagnostic value, duration is the one most frequently used in discussing disorders of vision. Episodes may vary in duration from seconds to as long as months (Fig 1).

A no less important element is the laterality of the visual event. Laterality is obviously restricted to right or left, a fact, however, which does not detract from its localizing value. Apart from laterality, yet closely related, is a further obvious fact: The eyes may be episodically involved independently or simultaneously. This too has great localizing value.

The entities that produce episodic visual disturbance will be considered in sequence of timing, beginning with those of brief duration and progressing to those of prolonged duration. Within each specific time unit the importance of laterality will be considered.

Visual Disturbances Lasting Seconds.

Obscurations. An obscuration is a brief alteration of vision. It may occur monocularly, but generally it is binocular. It usually lasts from 5 to 10 seconds, but it may continue for up to 30 seconds (Fig 2). Obscurations are usually frequent, occurring numerous times weekly if not daily. They may con-

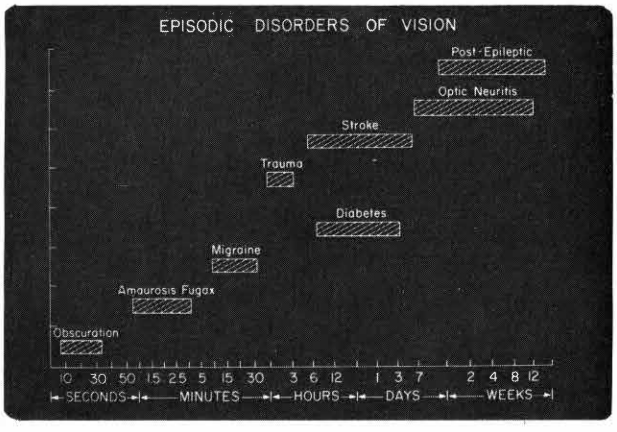

Fig 1—Graphic display of the time durations of all episodic disorders of vision.

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* Webster's *Third New International Dictionary*. Springfield, G & C Merriam Co, 1971.

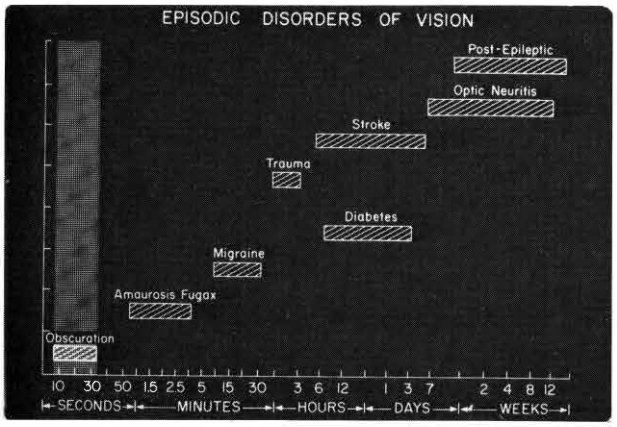


Fig 2—Graphic display of the time duration range of obscurations.

tinue over extended periods, their ultimate duration depending upon the course of the inciting illness. They seem to be infrequently brought on by posture or activity and are classically unpredictable.

A variety of terms are used in patient descriptions of obscurations. A popular description is that of ". . . a graying out of vision."[1] They are also called blackouts, fade outs, and simply blurring. They have been compared to fog, mist, and opaque curtains.

Obscurations are usually isolated events, unassociated with other neurologic or visual symptoms. Because of their very brief durations, they are less alarming than other episodic disturbances of vision.

Two causes of obscurations are presently recognized: Papilledema and vertebro-basilar insufficiency.[1,2] The differentiation of these two sources is simple and rests almost entirely upon the presence or absence of papilledema.

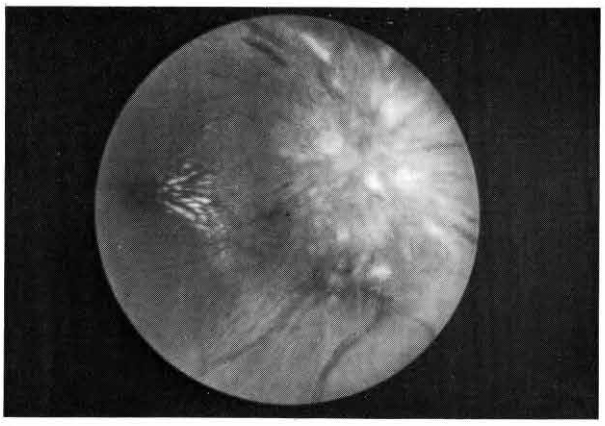


Fig 3—Example of severe papilledema resulting in obscurations.

When obscurations result from papilledema, the optic disc changes are nearly always severe (Fig 3). The obscurations of papilledema may be monocular or binocular. Their origin is presumed to be ischemia of the optic disc, secondary to the increased intracranial pressure. It is common to find additional signs and symptoms of increased intracranial pressure in patients presenting with obscurations of papilledema. These include headache, nausea and vomiting, and often diplopia. The incidence of focal neurologic signs is much less common and when present ominously suggests a mass lesion. Most patients in this group are young, reflecting the possibly single most frequent etiology of the increased intracranial pressure—pseudotumor cerebri.

Patients presenting with obscurations as a manifestation of vertebro-basilar insufficiency are, not surprisingly, much older. Here, obscurations are always bilateral and imply bilateral ischemia of the occipital cortex. Obscurations may be the only manifestation of transient ischemia in the vertebro-basilar arterial distribution, or they may be one of many. Other manifestations include dizziness, diplopia, facial paresthesias, dysarthria, weakness, and ataxia. These symptoms most commonly occur independently. Although they may presage a stroke in the vertebro-basilar arterial distribution, this relationship is unpredictable. Patients with obscurations of vertebro-basilar origin never have papilledema.

Obscurations per se are merely of diagnostic value and do not require treatment. Although papilledema may progress to blindness and optic atrophy the obscurations themselves do not reflect what the ultimate visual status will be.

Treatment should be directed at the etiology of the obscurations. In those associated with papilledema, a mass lesion must be ruled out or pseudotumor cerebri confirmed. Appropriate and specific therapy may then be initiated. If the obscuration is of vertebro-basilar origin, one must frequently evaluate the propriety of anticoagulation. In both circumstances appropriate therapy usually results in symptomatic resolution.

Visual Disturbances Lasting Minutes.

In differentiating the causes of episodic disturbances of vision lasting for minutes, discrete duration and laterality are of paramount importance.

Amaurosis Fugax. When the transient loss of vision occurs monocularly it is popularly referred to as amaurosis fugax—fleeting blindness.[3-8] This clini-

cal event is characteristically of abrupt onset; it seldom evolves in a progressive fashion. Its duration may be variable, lasting from one to several minutes, but the mode seems to be from one to three minutes (Fig 4). It is often difficult to establish the time sequence as concretely as one would like, since patients frequently lose the perspective and scale of time. The degree of visual loss varies from complete to only moderate blurring, and altitudinal visual loss is not infrequent. A sensation of color may accompany the visual loss, but photopsia or scintillations are rare. The resolution of the visual disturbance is generally as abrupt as its onset and usually complete without residual loss of acuity or field.

The episodes may recur many times per day or be separated by days, weeks, or months. They typically occur in isolation without associated neurologic symptoms, although additional transient signs of internal carotid ischemia such as hemiparesis, sensory change, and aphasia may occur independently.

The overwhelming majority of patients presenting with amaurosis fugax will harbor extracranial internal carotid artery disease of atherosclerotic origin with precise localization to the common carotid bifurcation (Fig 5). Although amaurosis fugax may be "the hallmark of carotid insufficiency," a wide variety of other sources exists. These include increased intraocular pressure; that is, glaucoma, arteritis of the branches of the ophthalmic artery; giant cell or temporal arteritis, alteration of numerous elements of the blood, red cells and proteins particularly, and thromboembolic events of cardiac origin such as mural thrombi, valvular vegetation of infectious or noninfectious origin, and tumor emboli.

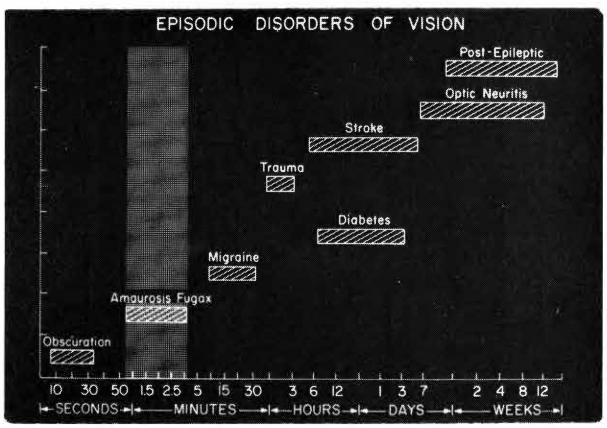


Fig 4—Graphic display of the time duration range of amaurosis fugax.

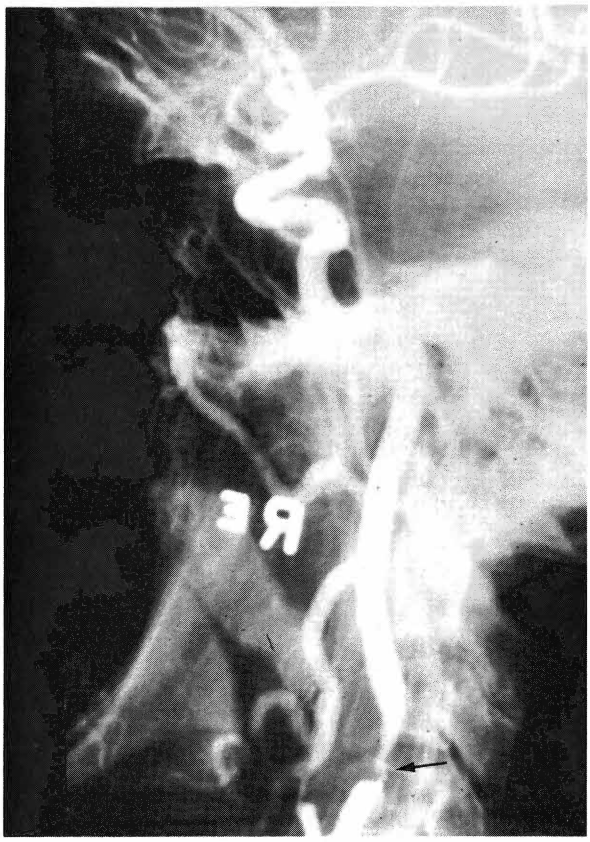


Fig 5—Lateral angiographic demonstration of extracranial internal carotid atherosclerotic disease (*arrow*) productive of amaurosis fugax.

As by far the most common etiology of amaurosis fugax is atherosclerotic disease of the carotid bifurcation, it is appropriate to direct diagnostic consideration to this focus.

The presence of a focal bruit over the carotid bifurcation at the angle of the jaw has been found to be strong evidence of disease. A bruit, however, may not be present even with significant disease and occasionally it may be falsely localizing with the significant changes occurring in the contralateral carotid. Asymptomatic bruits, although evidence of some degree of disease, should rarely be pursued diagnostically.

Changes in the carotid pulsation in the neck are seldom helpful. Often the external carotid overlies the internal carotid and masks changes in the latter vessel's pulsation.

Single or multiple bright refractile cholesterol emboli found in the ipsilateral retinal arterioles are

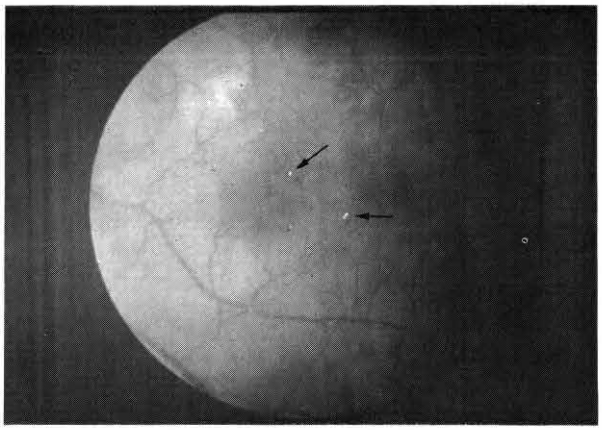


Fig 6—Fundus photograph of cholesterol emboli (*arrows*).

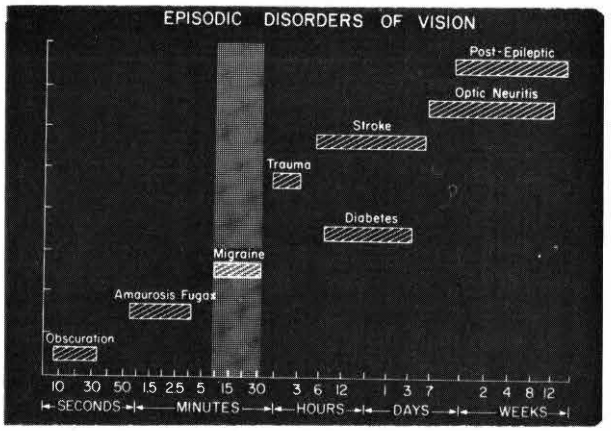


Fig 8—Graphic display of the time duration range of migraine.

strongly indicative of a carotid origin for amaurosis fugax.[9,10] Less apparent whitish platelet plugs may also be seen. These emboli often lodge in bifurcations of vessels distal from the optic disc, thus requiring pupillary dilatation and careful funduscopic examination for identification (Fig 6).

The use of ophthalmodynamometry, Doppler flow studies, and thermography provide additional pieces of incriminating evidence. It remains, however, for carotid angiography to confirm the presence, extent, and significance of bifurcation atherosclerotic changes (See Fig 5).

The identification of the other less common causes of amaurosis fugax is seldom difficult if their possibility is recognized.

Treatment should be directed at the cause of the amaurosis fugax. A significant incidence of stroke in the internal carotid artery distribution including the retina follows premonitory amaurosis fugax (Fig 7). In carotid bifurcation atherosclerotic disease we at the Medical College of Virginia have favored endarterectomy when appropriate. The primary obstacle to endarterectomy has been significant symptomatic cardiac disease. In this situation, anticoagulation may be advisable.

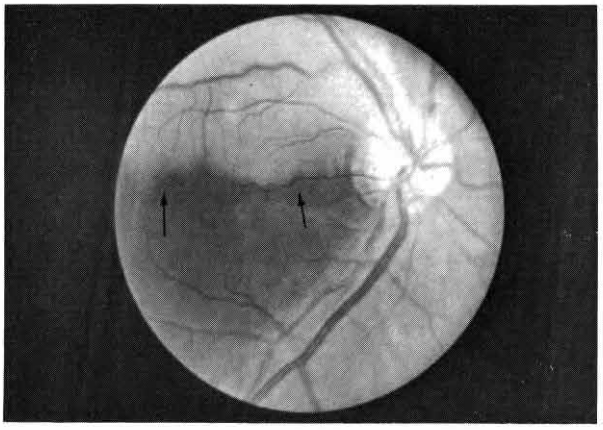


Fig 7—Fundus photograph of cloudy retinal edema (*arrow*) secondary to a central retinal artery branch occlusion with infarction.

Migraine. Typical amaurosis fugax which consistently lasts from 10 to 30 minutes should suggest the likelihood of a migrainous origin (Fig 8).

The recognition of visual phenomena as the forerunner of migraine dates to antiquity[11]; the variety of these visual hallucinations is remarkable.[12,13] It is also clear that the visual aura may constitute the sole manifestation of a migraine attack.[14] If indeed the visual aura is never followed by the hemicranial, vascular headache, nausea, and diffuse autonomic disturbance, one may have difficulty in recognizing its migrainous character. That this specific circumstance mimics amaurosis fugax seems well established.[14] Certain features of the clinical presentation are useful in identifying these admittedly uncommon cases of migraine.

Typically, the event recurs in an identical fashion over many years. It commonly begins under the age of 20. The expected hereditary aspect of migraine is frequently absent and the relationship of the visual event to the headache may become so inconstant as to appear to have no connection—so-called dissociated migraine. In some cases, headache may never occur. The most important feature, however, remains the duration. Amaurosis fugax as a manifestation of complicated migraine almost always lasts

between 10 and 30 minutes. It is comn presentation to resolve as the patient ac the 20's and 30's and be replaced by r migraine.

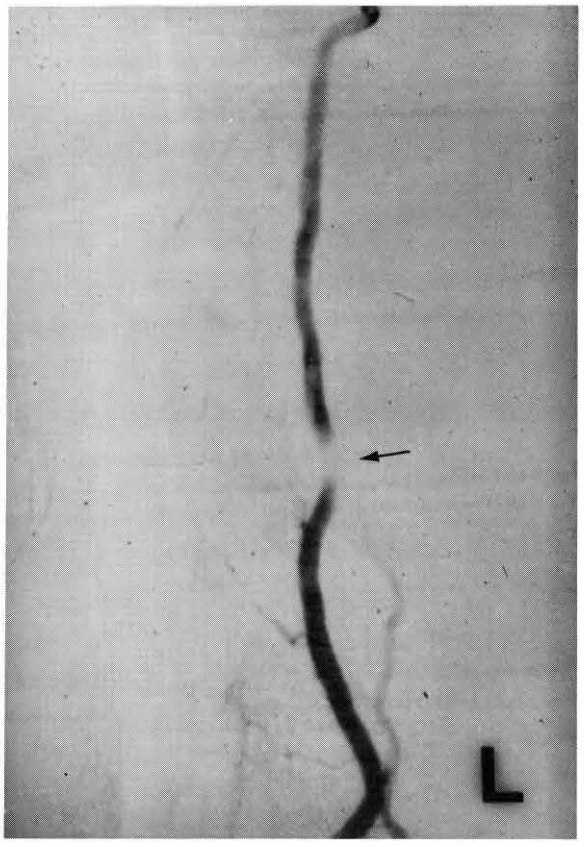
Vertebro-basilar Insufficiency. Whe loss of vision of minutes in duration occu the source most commonly is in the vert arterial distribution.[2] Although amauro internal carotid origin conceivably might erally and synchronously, this must ind Obscurations, the momentary visual loss onds due to vertebro-basilar insufficienc discussed above. More commonly, ho sient visual loss secondary to ischemia tebro-basilar distribution lasts one to fi With the increase in duration of the vi ment, patient concern is, understanda cantly increased. This in itself may acc greater frequency with which these visu reach the physician's attention. The e visual loss is variable from a simple per of central vision to total blackout.

In common with patients presenting rations of vertebro-basilar origin, this p tends to be elderly. The association o symptoms of brain stem origin occurring pendently or synchronously is to be antic would again expect historical evidence dizziness, vertigo, diplopia, dysarthria, a and bilateral extremities paresthesias as w ness.

The implied risk of stroke in the vert arterial distribution in this patient group those manifested simply by obscuratio eration of anticoagulation is appropriat few highly selected patients presenting a history of symptom precipitation by nec or position and confirmed by angiogr surgery directed at decompression of c vertebral arteries in the cervical spine ma ered (Fig 9). This patient population is t nificantly younger than the average patie tebro-basilar insufficiency, and frequently trauma is clearly evident.

Basilar Artery Migraine. In a mann amaurosis fugax, when transient bilater pairment occurs with a duration of fr minutes, a migrainous etiology becomes (See Fig 8).

Basilar artery migraine has been wel and adequately described for some tim



ig 9—Subtracted lateral view of a vertebral angiogram demonrating arterial compromise (*arrow*) by osteoarthritis in the cercal spine, which resulted in visual loss.

arked tendency to occur in a recognizable pattern. t is most common in adolescent girls. Visual symp-oms are the most common initial event with the isual disturbance varying from total loss of vision to lurring of central vision. Positive visual manifesta-ons characteristic of migraine may be totally absent. ssociated vertigo, ataxia, dysarthria, and sensory aresthesias are common. Characteristically, a severe robbing occipital headache often accompanied by ausea and vomiting follows. As with the migrainous maurosis fugax, however, headache may not occur.

Generally the clinical pattern is such that doubts f its migrainous origin do not arise. Once again here is a tendency for these attacks to be replaced by ore classic migraine as the years pass.

Visual Disturbance Lasting Hours.

Episodic disturbance of vision lasting hours eems to be less often recognized if not actually less

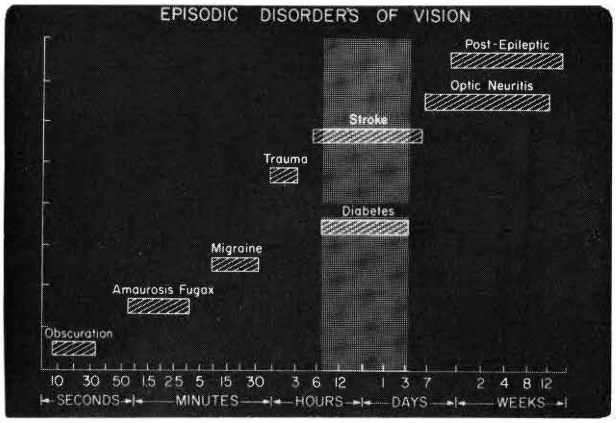


Fig 10—Graphic display of the time duration range of episodic visual loss secondary to uncontrolled diabetes mellitus.

common. Some of the sources of visual symptoms measured in hours are extensions of previously discussed entities. Some, however, are entirely new and distinct.

Diabetes Mellitus. The incidence of episodic visual disturbance lasting hours in diabetes mellitus is unclear (Fig 10). It is quite likely that early diagnosis and improved drug control has significantly reduced the magnitude of these visual symptoms if not their incidence.

Sudden bilateral blurring of vision is well known to occur in patients with diabetes mellitus.[16,17] It has on occasion been the initial symptom leading directly to the diagnosis in a previously unrecognized case. More commonly it occurs in established diabetic patients; its basis is known to be abrupt refractive changes in the eye of either myopic or hypermetropic nature. The refractive change seems rather clearly related to blood sugar levels; myopia occurring in the presence of hyperglycemia and hypermetropia with hypoglycemia. It may, in fact, be useful in alerting the physician to ineffective diabetic control.

The visual disturbance is described by the patient as blurring with impairment of central vision. In all circumstances it can be corrected by appropriate refraction. At the bedside the use of a pinhole may prove the refractive nature of the visual change to the satisfaction of the physician.

The precise mechanism by which the blood sugar level effects the abrupt refractive change is not entirely clear. It is postulated, however, to be the result of secondary changes of lens hydration.

The course of visual blurring in poorly controlled diabetics is transitory, lasting variable periods, usually measured in hours to a few days. It is almost invariably reversible. Occasionally cataracts may develop abruptly in this group of patients.[17]

Therapy of this episodic visual disturbance should be directed at more effective diabetic control rather than refractive correction by virtue of its transitory nature.

Post-traumatic Blindness. A second transient visual disturbance typically lasting hours which although probably uncommon is often unrecognized is post-traumatic or concussion blindness (Fig 11).

This transient bilateral visual loss seems clearly of occipital cortical origin. It is also quite certainly causally related to preceding head trauma. Children appear to be much more susceptible to post-traumatic blindness than adults.[18,19(pp2384–2385)] The degree of trauma necessary for the manifestation of this syndrome is markedly less in children where relatively minor head injury, usually occipital in nature, and unassociated with unconsciousness or skull fracture, has resulted in post-traumatic blindness. In adults the injury is frequently much more severe with unconsciousness and skull fracture the rule.

The visual disturbance is commonly severe with early total loss not unusual. The course of recovery is similar in both children and adults; there is generally progressive return of vision to normal over a period of from one to three hours. Permanent residual disturbance may or may not occur and generally reflects the magnitude of the occipital injury. The currently accepted mechanism of visual loss is felt to be occi-

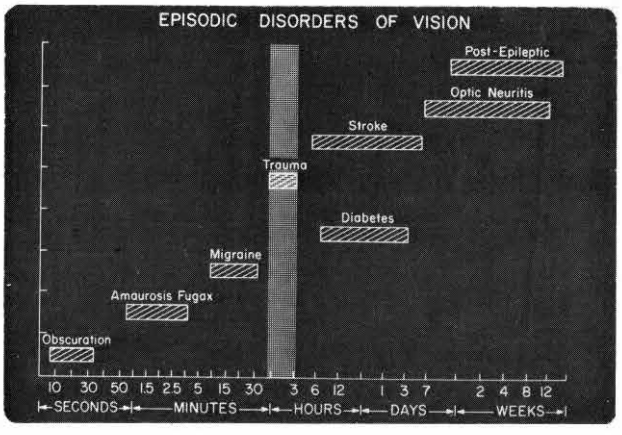


Fig 11—Graphic display of the time duration range of post-traumatic visual loss.

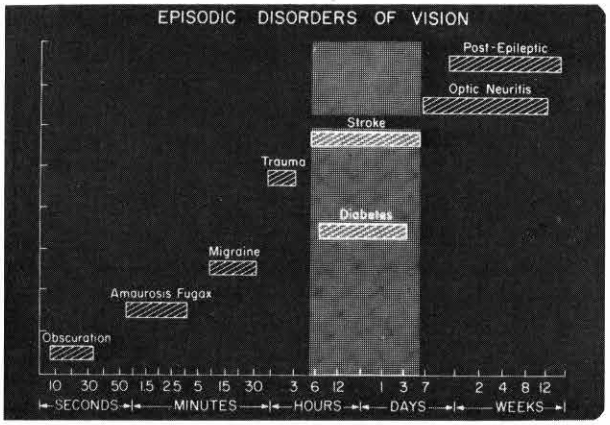


Fig 12—Graphic display of the time duration range of episodic visual loss secondary to stroke.

pital lobe-visual cortex concussion. Treatment is usually expectant requiring only observation.

Stroke. Final consideration in visual disturbances lasting hours should be given to those episodic disorders of vision previously discussed where the transient ischemia, whether localized to retinal vessels, internal carotid artery, or vertebro-basilar system, whether of atherosclerotic, systemic, or migrainous origin, ceases to be transient and results in more prolonged visual deficit (Fig 12).

An arbitrary point has been established at 24 hours which is used to separate transient ischemic attacks from strokes. As with most other artificial guidelines, much variation occurs in clinical practice. We therefore regularly classify as strokes events which last from 12 to 24 hours to three and more days.

Common to the majority of these events is a history of preceding episodes of transient visual disorder. These include obscurations,[2] amaurosis fugax,[8] and transient cortical visual loss,[3] as well as classical migrainous events of either monocular or binocular character.[12] Not infrequently, although resolution may be nearly complete, residual loss of visual acuity or field may remain, emphasizing that a stroke has occurred.

Retinal strokes basically consist of central retinal artery and central retinal artery branch occlusion.[9] The latter is obviously the most frequent retinal stroke to resolve.

The onset is classically abrupt with complete monocular visual loss. Characteristic of these events is funduscopic evidence of retinal ischemia. This usually is greyish retinal edema stopping short of the classic cherry-red spot of irreversible central retinal artery occlusion (See Fig 7). Recovery often begins within an hour or so and evolves over several hours. Residual visual acuity changes may vary from slight to severe and visual field changes are characterized most commonly by altitudinal or sector field loss.

Treatment should be directed toward the usually neglected internal carotid bifurcation disease (See Fig 5). Prompt therapy may avoid a tragic repetition resulting in permanent blindness.

Total occlusion of the cervical internal carotid artery at its bifurcation with the external carotid may result in a wide variety of clinical manifestations. On the one hand, a devastating hemisphere infarct with hemiplegia and aphasia may occur; on the other, the patient may note only the transfer of his odd, neck bruit from one side to the other and cessation of the bothersome episodes of transient monocular blindness. Between these two extremes, an episode of prolonged visual impairment of hours' to days' duration may occur. The clinical picture may so resemble that described for retinal strokes as to defy separation.

Of significant value in placing the inciting event in the internal carotid artery is the reversed bruit and an ipsilateral Horner's syndrome (Fig 13).

It is quite common for the focal bruit of internal carotid bifurcation disease to cease with occlusion of the artery. It is likewise frequent for a focal "increased flow bruit" to be either accentuated or become initially manifest over the contralateral internal carotid bifurcation. At the same time, in about 15% of internal carotid occlusions, edema of the arterial

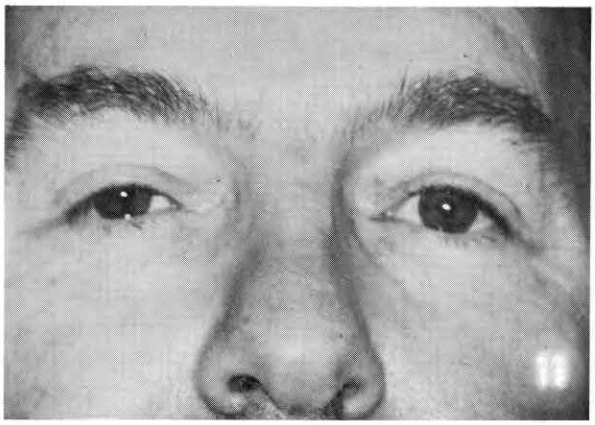


Fig 13—Right-sided miosis and ptosis of Horner's syndrome secondary to internal carotid artery occlusion.

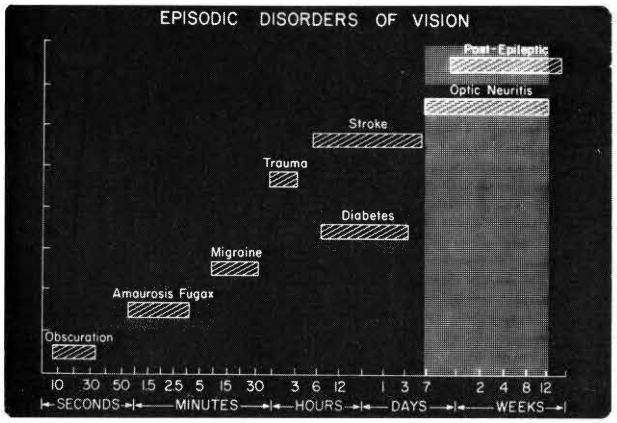


Fig 14—Graphic display of the time duration range of optic neuritis.

wall involves the vasa vasorum of the carotid sympathetic plexus resulting in an ipsilateral Horner's syndrome characterized by miosis and ptosis without anhidrosis (See Fig 13). The other clinical hallmarks, as with retinal stroke, may consist of funduscopically visible retinal edema, variable visual acuity loss, and field defects of altitudinal or sector character.

Diagnostic confirmation is angiographic. Unfortunately, therapy is ineffective, emphasizing the need of early clinical recognition of internal carotid arterial disease.

Strokes in the vertebro-basilar arterial distribution regularly result in prolonged visual loss lasting hours to days. Restitution of some visual function, however, is the rule. The association of additional neurologic deficit of brain stem and cerebellar origin is highly variable.

The onset of the bilateral visual loss is similar to a transient ischemic attack, which commonly has preceded the stroke by days to months. On this occasion, however, the vision does not improve promptly and blindness remains. Characteristically, vision begins to return in hours to a few days. In this time period the patient may experience a variety of visual phenomena including either crude or complex visual hallucinations and visual distortion.

Visual acuity not infrequently achieves remarkable recovery. Residual visual field defects of homonymous character, either hemianopic or quadrantinopic are frequent. It is not unusual for the patient to experience enduring visual agnosias of diverse nature including color-naming defects, and agnosias for faces, places, and even food.

Treatment again should be directed at prevention of repetitive strokes with anticoagulation, the most popular if not the most effective therapy.

The occurrence of permanent residual defects of vision following typical complicated migraine involving retinal, carotid, or basilar arterial distributions is well established, although rare.[12] The clinical circumstance is readily recognized by the presence of a long history of preceding typical repetitive episodes of visual disturbance suggesting a migrainous basis. The mechanism whereby a benign migrainous event is transformed into a permanent stroke is unclear. Therapy has been ineffective.

Visual Disturbance Lasting Days to Weeks.

A discussion of episodic visual disturbance lasting days to weeks becomes essentially a discussion of optic neuritis (Fig 14). There are unusual exceptions to this dictum which will be discussed subsequently.

Optic Neuritis. Optic neuritis is a misleading term. Its implication of an infectious or inflammatory basis of optic nerve disease is rarely accurate. Although bacterial and viral disease of the central nervous system and orbital contents occasionally results in optic nerve dysfunction, the clinical picture does not correspond in most circumstances with the general definition of optic neuritis. The systemic symptomatology, clear evidence of inflammatory orbital or central nervous system (CNS) disease as well as a more fulminant, frequently irreversible optic nerve injury, generally serve to distinguish this truly infectious optic neuritis from the more common clinical picture.

The clinical definition commonly used for optic neuritis is that of rapidly developing blurring of vision with or without pain about the eye or on movement of the eye.[20,21] It may occur either monocularly or binocularly. There is a tendency for binocular involvement to be most frequent in children.[22] The degree of visual loss is variable; however, loss of central acuity greater than 20/200 is the rule. The eye is normal on examination. Visual field evaluation should demonstrate field loss, most commonly in the form of a central scotoma. The funduscopic examination may be normal or reveal disc swelling and elevation with or without hemorrhages and exudates. Disc pallor is rare and if present should suggest previous bouts of optic neuritis whether or not a confirmatory history is available. Optic neuritis most commonly occurs in isolation without associated neurologic symptoms or signs.

The episode of optic nerve dysfunction tends to last from a few weeks to a few months. Total resolution is not uncommon, particularly from an acuity standpoint, but mild residual defects are not infrequent. Further episodes occur in a minority of cases, but may do so on multiple occasions.

The age of onset of optic neuritis varies tremendously from the pre-teens to the 70's and, rarely, 80's.[23] The median age in most studies has been about 30.

Optic neuritis has been characteristically classified as either typical or atypical. The typical patient is a young patient generally in the 20's, fulfilling rather closely the criteria already presented, with monocular involvement. The atypical patient generally falls outside the 20- to 40-year age group, and develops visual loss in either an abrupt fashion or progressively at a slower pace. Visual acuity is either insignificantly involved or severly impaired. Commonly, the episode of visual disturbance fails to remit or does so very incompletely in the expected period of days to weeks. Associated symptoms and signs of neurologic or medical disease are distinctly more frequent.

Within that group of patients with optic neuritis characterized as typical is a second subdivision. This is based upon the presence or absence funduscopically of disc edema and elevation. In the absence of disc changes, the optic neuritis is termed retrobulbar neuritis. In its presence, the optic neuritis becomes papillitis. This designation has little if any implication with regard to etiology or prognosis.[20]

If a specific etiology is not identified, it is common to assume that the optic neuritis is a harbinger of multiple sclerosis. Sufficient long-term studies are available to place the association of optic neuritis and multiple sclerosis in true perspective. It is now relatively clear that only one in six patients with optic neuritis can be expected to develop typical multiple sclerosis in the future.[20,21] This incidence of about 15% is significantly lower than prior incidence rates frequently placed nearer 50%.[24,25] Armed with this reduced statistical probability the physician can refrain from a discussion of multiple sclerosis and the psychological impact it carries with a much clearer conscience.

The potential etiology of remaining cases of optic neuritis is legion and virtually reads as an index of medical and neurologic disease.[23] Not surprisingly, however, a very substantial number of cases of typical optic neuritis remain of so-called idiopathic origin.

The identification of those cases of optic neuritis for which a firm etiology can be achieved is frequently linked to a more atypical presentation: binocular instead of monocular involvement; a young or elderly patient; and, perhaps most importantly, the association of additional medical or neurologic signs or symptoms.

The treatment of optic neuritis, typical or atypical, has been, and remains, an area of controversy. Obviously if a specific inciting etiology can be identified, therapy should be based on the diagnosis. In those cases classified as idiopathic, as well as those suspected to be premonitory of multiple sclerosis, it has been common to use adrenal corticosteroids; their efficacy remains controversial and many competent physicians do not use them. When adrenal corticosteroids are used, it is common to begin with a high dose, from 60 to 100 mg daily, and follow a rapidly tapering course over two to three weeks. Little if any difference in efficacy has been detected with the preparation used or the mode of administration. Prednisone, an inexpensive preparation taken orally, a simple painless mode of administration, is not an unreasonable approach if one wishes to treat a given patient.

A diagnostic pitfall occurs in a group of the atypical optic neuritis cases based upon their occasional response to adrenal corticosteroid therapy. Cases of optic neuritis ultimately found to be caused by sarcoidosis, meningioma, pituitary adenoma, and carcinomatous leptomeningitis may occasionally improve dramatically with steroids. This has led to diagnostic errors. In nearly every instance the optic neuritis has been atypical. Thus atypical features in optic neuritis should suggest diagnostic caution.

The typical course of optic neuritis has been one of resolution with or without a residual defect of variable nature and degree in from a few days to many weeks. Treatment with adrenal corticosteroids has been believed capable of hastening resolution but probably incapable of improving final function.

Post-epileptic Blindness. One final cause of episodic visual disturbance lasting from days to weeks is postictal amaurosis (Fig 15). Although this particular clinical entity occurs rarely, its occurrence can cause extreme consternation if the etiologic mechanism or association is unrecognized.

Postictal amaurosis of cortical origin has been repeatedly observed in young children and infants.[19(pp127–129),26] The convulsive episode has typically been violent. The blindness may be associated

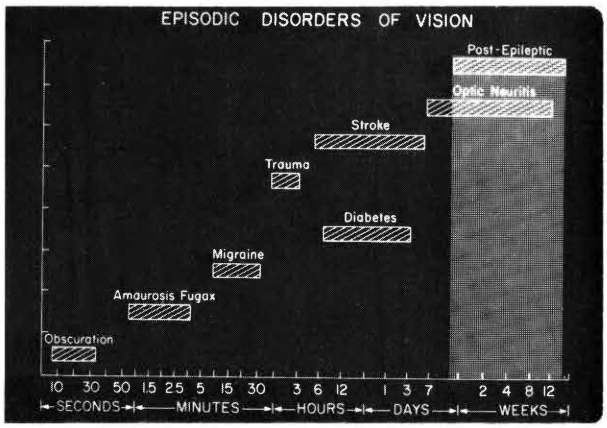


Fig 15—Graphic display of the time duration range of post-epileptic blindness.

with aphasia, deafness, or hemiplegia. Visual loss has typically lasted from days to weeks with slow, progressive recovery. The mechanism of its production remains unclear. No satisfactory therapy has been identified.

Summary.

A diverse and seemingly unrelated group of diseases has been integrated on the basis of their episodic disturbance of vision. The parameters of laterality, but more importantly the duration of individual episodes, have been used to direct diagnostic consideration. Many of these clinical entities are commonly encountered in practice. Their recognition and care are dependent upon prompt diagnosis based upon characteristic clinical signs and symptoms.

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An Approach to Dizziness

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Dizziness is a vague and ubiquitous symptom which frequently frustrates and perplexes the clinician. Dizziness in the broad sense implies any unpleasant sensation of disturbed relationship to surrounding objects. A number of synonyms such as faintness, light-headedness, giddiness, and swaying, although descriptive, are often no more specific. Problems in diagnosis, therefore, are due not only to the ambiguity of the term but also to the wide spectrum of disorders in which dizziness may be a prominent symptom. Although disorders of the vestibular system usually receive primary attention, it should be kept in mind that many neurologic, cardiovascular, psychiatric, and other disorders are not infrequently associated with dizziness.

The term vertigo, on the other hand, is specific and may be distinguished from other forms of dizziness in that it implies a definite rotational sensation or illusion of motion. Although it is often impossible to make a differentiation between vertigo and other types of dizziness in the individual patient, the distinction is important as vertigo specifically reflects dysfunction in the vestibular system.

The purpose of this paper is to review the anatomy and physiology of the vestibular system, to discuss the most common clinically significant causes of dizziness, and finally, to consider the practical office evaluation of the dizzy patient.

The Vestibular System. A basic understanding of the anatomy and physiology of the vestibular system is necessary in order to understand the procedures employed to test its integrity as well as the clinical manifestation of its dysfunction. The vestibular system includes the end organ (semicircular canals and otolith system), a portion of the eighth cranial nerve, and the vestibular nuclei in the brain stem.[1] Fibers from the vestibular nuclei project to the cerebellum, skeletal musculature, extraocular muscles, and undoubtedly to the cerebrum. The precise connections to the cortex are unknown, although vestibular representation in the posterior temporal lobes is suspected. The vestibular apparatus serves as the primary organ of equilibrium combining with visual and other sensory stimuli to provide sensation of motion and spatial orientation. The vestibular system also functions in the control of skeletal muscle tonus and in stabilizing the eyes during head movements. In the steady state, there is equal tonic neural input from the two end organs. With rotational movement, the semicircular canal in the plane of movement is stimulated, leading to a change of neural activity in the brain stem, which is projected to the cortex to produce the appropriate conscious sense of rotation. A disease state which changes the firing frequency of the end organ, or the neural input from the brain stem, causes vertigo. In such cases the cerebral cortex is seemingly deceived by the brain stem input and interprets it as rotational movement.[2]

Vestibular dysfunction may be classified as peripheral or central, the dividing line being where the eighth nerve enters the brain stem. Peripheral disease is generally felt to be most common and is not infrequently associated with a hearing disturbance due to the close anatomical relationship between cochlear and vestibular portions of the inner ear. A patient with unidirectional jerk nystagmus, vertigo in the direction of the first component, past pointing, and falling in the direction of the slow component is probably suffering from acute dysfunction of the end

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organ on the side of the slow phase. Bidirectional nystagmus varying with direction of gaze, vertical spontaneous nystagmus, past pointing, and falling toward the fast phase points to brain stem disease.[2] Vertigo is usually more intense with peripheral disorders and is commonly associated with nausea and vomiting.

Positional vertigo refers to the vertigo and accompanying nystagmus which occurs after the head is placed in a particular plane. Peripheral and central forms of positional vertigo have also been described, based on the characteristics of the nystagmus induced.[2] In the peripheral type, a latency of 3 to 40 seconds is observed between attaining the precipitating head position and the onset of nystagmus. If the head remains in this position, the nystagmus will decrease or fatigue after 30 to 60 seconds. Gradual habituation of the nystagmus occurs with repetition of the aggravating position and reproducibility is poor at any given examination. With central pathology, the onset of nystagmus is immediate and fatigue and habituation do not occur. Again, vertigo is generally more severe with peripheral disorders.

Otolaryngologic Causes of Dizziness. A variety of otologic disorders ranging from impacted cerumen, and otitis media to otosclerosis and trauma to the labyrinths may produce dizziness. This discussion will be limited to the more common and clinically significant disorders.

Meniere's disease or endolymphatic hydrops is predominantly a disease of middle-age or older, and is unilateral in 90% of cases. The onset is usually insidious, frequently beginning with tinnitus, fullness in the ears, and fluctuating hearing loss. The hallmark of the disease is episodic vertiginous spells usually lasting between 2 and 24 hours. During the attack, pain or numbness may be noted in the affected ear as well as diminution of auditory acuity. Spells recur at irregular intervals varying from days to years.[3]

The majority of patients with positional vertigo suffer from *benign positional vertigo.*[4] In this type, hearing and caloric responses are normal and transient symptoms occur only with assumption of a certain head position. The greatest incidence is between 40 and 60 years of age and symptoms often clear spontaneously within one year. The etiology is unknown.

Acute labyrinthitis may occur as a result of acute or chronic otitis media and is manifested by vertigo, nystagmus, severe hearing loss, nausea, and vomiting. *Toxic labyrinthitis* is usually secondary to ototoxic antibiotics such as streptomycin. Typical vertigo may not occur since both labyrinths are equally depressed. The primary manifestation may be difficulty walking with staggering and inability to stay on course. Hearing loss and high-pitched tinnitus may or may not occur.

Vestibular neuronitis or viral labyrinthitis is primarily a disease of young adults which frequently exists in epidemic form. This disease may be defined as a sudden vestibular crisis lasting days or weeks with partial or total loss of vestibular function in one ear without auditory involvement, and without recurrence.[3] The prolonged period of the attack and the absence of hearing loss and recurrence distinguish vestibular neuronitis from Meniere's disease.

Neurologic Causes of Dizziness. *Acoustic neuromas* are the most common of the cerebellopontine angle tumors comprising approximately 5% of all intracranial tumors. Early symptoms are usually vestibular and cochlear, but the latter usually appear first. The onset of unilateral high-frequency hearing loss and high-pitched tinnitus is often insidious. Vertigo is usually not a prominent symptom and most patients complain of transitory, but progressive, vague dizziness and unsteadiness which is aggravated by movement.[5] This may be explained by the slow expansion of the tumor which allows time for the vestibular nuclei to compensate for the disturbance.[6] Associated signs of involvement of the seventh, sixth, and fifth cranial nerves and cerebellum are usually late, although such signs should be sought and are diagnostic when present.

Although the sudden onset of dizziness is a frequent symptom of *vertebro-basilar cerebrovascular disease,* it rarely occurs in isolation without other symptoms of neurologic dysfunction such as diplopia, dysarthria, facial numbness, or hemiparesis. C. M. Fisher points out that dizzy spells that continue more than six weeks without accompanying symptoms are almost never cerebrovascular in nature.[7] There seems to be an unwarranted tendency to attribute mild giddy spells in elderly persons to "hardening of the arteries."

Dizziness is a frequent and often early symptom in *multiple sclerosis.* Like cerebrovascular disease, however, other signs and symptoms such as visual blurring, diplopia, ataxia, paresis, and paresthesias are almost always present. According to some authors, multiple sclerosis is the most common cause of the central type of positional nystagmus.[6] A unique

feature in this disease is the frequent dissociation of vertigo and nystagmus.

Vertiginous symptoms may occur as ictal phenomena in patients with *seizures of temporal lobe origin.* In such cases consciousness is usually impaired, momentary amnesia is often noted, and nystagmus does not occur. Some patients complain of being hurled into space as if in a tornado.

Cardiovascular Causes of Dizziness. The cardiovascular causes of dizziness have in common the production of symptoms by arrest or diminution of cerebral perfusion. With *orthostatic hypotension,* the patient experiences light-headedness, unsteadiness, and occasionally syncope upon suddenly assuming an erect position. This syndrome may be idiopathic, however, it is often secondary to prolonged bed confinement, anti-hypertensive agents, or impairment of sympathetic vasomotor reflex activity. Such attacks are usually accompanied by pallor, tachycardia, and sweating as well as the obvious drop in blood pressure. *Cardiac disorders* ranging from mechanical obstruction to alterations in cardiac rate or rhythm can impair cerebral blood flow and may produce vertigo and dizziness. In aortic stenosis, the onset of symptoms is usually related to sudden position change. In addition, almost any arrhythmia may produce vertigo and dizziness. The patient may state in such cases that his dizzy episode is associated with a detectable change in cardiac rhythm. *Overactive autonomic reflexes* may also result in dizziness followed by syncope. Hypotension and bradycardia may be triggered by an emotional or painful stimulus as in vasovagal syncope or be precipitated by micturition, paroxysmal coughing, or compression of the carotid sinus in the neck. An impending feeling of syncope characterizes dizziness of cardiovascular etiology.

Anemia and *hypoglycemia* should also be considered among the systemic causes of dizziness.

Other Causes of Dizziness. Dizziness is a common symptom in psychiatric disorders. These patients usually complain of a vague sensation of light-headedness, which tends to be continuous rather than episodic and is associated with symptoms of anxiety, depression, or other hypochondriacal complaints. *Hyperventilation syndrome* is a very common cause of dizziness, and the majority of these patients suffer from emotional problems. Acute attacks of hyperventilation produce relatively circumscribed episodes of light-headedness, frequently with circumoral and digital paresthesias and tightness in the chest. Positional vertigo occurring only after hyperventilation has also been reported.[8] The hypocapnia produced by hyperventilation leads to cerebral vasoconstriction and a reduction in cerebral blood flow.

Drachman and Hart described the occurrence of dizziness among patients with *multiple sensory deficits.*[8] The abnormalities comprising this syndrome consisted of two or more of the following: visual impairment (usually cataracts), peripheral neuropathy, vestibular deficits, cervical spondylosis, and orthopedic abnormalities interfering with ambulation. Typically, patients were elderly diabetics, who only complained of light-headedness when walking and particularly when executing a turn. Dizziness in this group was most closely reproduced by walking and turning the head when standing. Drachman and Hart postulate that the deprivation of accurate sensory information produces disorientation which is referred to as dizziness by its sufferers.[8]

There is considerable disparity between studies regarding the frequency of various causes of dizziness.[6] Most reports deal with a selected and limited segment of the dizzy population. The data compiled by the Northwestern University Dizziness Clinic perhaps best reflect the incidence of various types of dizziness in the general population.[8] This study consisted of 125 patients with the complaint of dizziness of any type without any selection. A reasonably certain diagnosis was claimed in 91% of cases (Table). Disorders of the peripheral vestibular system proved to be the most common cause of dizziness in this study. These patients complained of rotational vertigo, frequently associated with nausea and vomiting, occurring in the absence of evidence of neighboring brain stem deficits. Among the 38% of patients with peripheral vestibular disorders, benign positional vertigo occurred twice as frequently as any other ves-

Table
Major Causes of Dizziness*

Peripheral Vestibular Disorders	38%
Hyperventilation Syndrome	23%
Multiple Sensory Deficit	13%
Psychiatric Disorders	9%
Uncertain Diagnosis	9%
Brain stem Cerebrovascular	5%
Cardiovascular	4%
Neurologic Disorders (others)	4%

* Total is greater than 100% because several patients had more than one diagnosis.

tibular disorder. Meniere's disease and vestibular neuronitis each made up 4% of this total. Hyperventilation and multiple sensory deficits together accounted for over one third of the patients. The relative infrequency of cerebrovascular disease presenting with symptoms of dizziness is pointed out in the 5% figure. These patients, in keeping with C. Miller Fisher's statement,[7] all had evidence of additional neurologic involvement. The absence of cases of seizure and acoustic neuroma indicates that these are rare but nonetheless important causes of dizziness.

Evaluation. On the basis of the preceding discussion of the pathophysiology and causes of dizziness, we will now consider the clinical evaluation of the dizzy patient. Many sophisticated and expensive neurologic and otologic procedures are available. We shall concentrate, however, on practical office techniques and on indications for specialist referral.

The single most important aspect in the evaluation of a patient with dizziness is a good history, properly interpreted. Drachman and Hart[8] have noted that the patient's subjective experience of dizziness can often be separated into one of four types: 1) a definite rotational sensation, 2) a sensation of impending faint, 3) dysequilibrium or loss of balance with little or no head sensation, and 4) vague lightheadedness other than vertigo, syncope, or dysequilibrium.[8] Inquiries need to be made regarding precipitating factors such as relation to posture and motion, the intermittency or constancy of symptoms, and associated symptoms such as hearing loss, tinnitus, nausea or vomiting, and loss of balance.[9] The occurrence of other otologic symptoms (discharge, fullness, or pain in ears) and neurologic symptoms such as disturbances of vision, speech, motor, and sensory function should be sought. Past medical history including significant medical illnesses and use of medications must be obtained.

In view of the wide variety of disorders in which dizziness may be present, a complete physical examination is necessary. In addition, special attention should be directed to certain aspects of the otologic and neurologic examination. The external auditory canal should be checked for impacted cerumen or other abnormalities, and the eardrum carefully examined for evidence of fluid level, hyperemia, bulging, or perforation. Disturbances of hearing may become evident during conversation with the patient. Attention should be paid to the level of voice required for communication, the need for repetition, and the degree to which lip reading is depended upon. Although not as sensitive as standard audiometry, the classic Weber and Rinne tests using an audiometric tuning fork in the 500 Hz range are most informative. Certain aspects of the neurologic examination should be emphasized. The patient should be observed for past pointing. In this test the patient stands, extends both arms, points with both index fingers at the examiner's index fingers held at shoulder height, and then closes his eyes. Drift of the hands consistently in either direction is abnormal.[6] With peripheral disease, the arms will deviate in the direction of the slow phase of the nystagmus. Peripheral disturbances will be aggravated by testing the patient with his head inclined over one or the other shoulder. Past pointing in the direction of the fast phase or in the absence of nystagmus indicates central vestibular pathology.

Disturbances in gait and posture may be seen in patients with proprioceptive, cerebellar, and vestibular disorders. The Romberg test is classically positive in patients with proprioceptive defects; the direction of falling is usually variable. With peripheral vestibular disease, the Romberg test is also positive; however, the direction of fall is consistently to one side and is influenced by changing the position of the head. In cerebellar disease, station and gait are not remarkably influenced by closing the eyes, and ataxia is generally in evidence.

Because of the ever-present concern of the insidious cerebellopontine angle tumor, careful examination of the fifth and seventh cranial nerves should be carried out. The symmetry and strength of the facial musculature and muscles of mastication need to be evaluated. The corneal reflex is simple to test and is most informative. While the patient is looking upward and to one side, the physician touches the cornea on the opposite side with a piece of cotton. If blinking is absent in both eyes, this indicates a loss of sensation in the cornea tested; if blinking is absent only in the eye tested, the homolateral facial nerve may be impaired. Impairment of the homolateral corneal reflex is frequently noted in cerebellopontine angle tumors.

One of the most important components of the evaluation is the dizziness simulation battery. This battery exposes the patient to a number of situations that commonly trigger dizziness in an attempt to simulate the patient's own symptom. These maneuvers include: blood pressure determinations lying and standing, a standard Valsalva maneuver for 15 seconds, head turning with eyes open or closed, a sudden

turn when walking, hyperventilation for three minutes, and the Nylen-Bárány test.[8] The latter maneuver is a test for positional vertigo. The patient is abruptly moved from a seated to a supine position with the head hanging 45° backwards, and turned to one side and then the other. The patient is observed for vertigo and nystagmus, noting the onset, duration, and direction of nystagmus.

Another simple technique which can be performed in the office setting is the caloric test. Not only can vestibular function be assessed by this procedure but also the patient can compare the sensation produced with his own symptoms. One must first make certain that the ear canals are free of debris and that the drums are intact. If available, the use of 15–20(+) lenses or Frenzel glasses will inhibit visual fixation and magnify the eyes for better observation. With the patient recumbent and the head elevated 30°, 3 to 5 cc of ice water are slowly poured into the ear. The eyes should then be observed for nystagmus which should be horizontal with the quick component to the opposite side. How well the two sides agree is most important. A unilateral absent or hypoactive response may be the product of Meniere's disease, vestibular neuronitis or acoustic neuroma. Perversion of nystagmus, such as absence of the quick component, horizontal nystagmus, or a prolonged hyperactive response point to brain stem involvement. It should be emphasized, however, that one should not try to read too much into the findings obtained by the caloric testing.

Routine laboratory studies in the dizzy patient should include: a complete blood count, sedimentation rate, Fasting Blood Sugar (FBS), blood urea nitrogen (BUN), thyroid function studies, electrocardiogram, and skull x-rays with views of the internal auditory canals.[8,9]

A more extensive evaluation is often needed. Patients with objective otologic abnormalities including hearing loss should receive prompt referral to an otologist for audiologic testing and further diagnostic studies. The presence of abnormalities on neurologic examination or the history of ataxia, headaches, disturbance of consciousness, or visual disturbance would necessitate neurologic consultation. Even in those patients with transient symptoms or in whom a benign etiology has been demonstrated, careful follow-up is advisable.

Treatment. The treatment of the dizzy patient obviously depends on the underlying cause. Since a benign condition underlies the majority of dizziness cases, an important aspect of therapy in these patients is reassurance. Patients with peripheral vertigo should be informed about vestibular habituation. In other words, the nervous system will ordinarily adapt to an imbalance between the two end organs and vertigo will ultimately cease. In addition, since visual fixation has an inhibitory effect upon vestibular symptoms, vertiginous patients should resist the tendency to close their eyes and should fix a nearby object.[2] The prophylactic use of drugs for symptoms of dizziness has not been very gratifying. Most of the information on treatment is largely anecdotal. Vasodilators such as nicotinic acid and betahistine are often recommended; however, I am unaware of any data that clearly support their efficacy. Valium® may be beneficial since it apparently exerts some selective sedative effect on the vestibular nuclei.[10]

Meclizine in doses of 25 mg three times a day is perhaps the most popular and effective medication in the treatment of recurrent or continuous vertiginous symptoms. Cohen and DeJong[11] demonstrated in a double-blind crossover study that meclizine was significantly more effective than a placebo in the treatment of vertigo. There was, in addition, no difference in the response of patients with disease of the peripheral or central vestibular systems.

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Management of Transient Brain Ischemia

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Cerebrovascular disease is an exciting subject, so complex that we could devote 30 minutes to a discussion of aspirin, dipyridamole, and sulfinpyrazone and their potential actions in the prevention of thromboembolic events. A Classification and Outline of Cerebrovascular Disease II, published in the September–October 1975 issue of *Stroke*, depicts this complexity. The portion labeled "outline" describes some of the things summarized in this paper.

The first part of the Classification is labeled "Clinical Stage"; it is where we make contact with most patients, including even those with asymptomatic bruit. The "Clinical Stage" is subdivided into "Transient Ischemic Attacks," "Progressing Stroke," and "Completed Stroke." TIA is the abbreviation for transient *focal* cerebral ischemic attacks. It has become popular in the United Kingdom to refer to syncope as a TIA; elsewhere in the world, however, the word "focal" must be included in the term transient cerebral ischemic attack; thus syncope is not listed under "Transient Ischemic Attacks." TIAs are important because they are warnings of a serious or progressing or devastating stroke to come. They have certain significant characteristics: the onset is rapid (defined as no symptoms to maximal symptoms in less than two minutes); the duration commonly is 2 to 30 minutes. In an attempt to establish a standard, we state in the *Stroke* classification that a TIA can last as long as 24 hours. Seldom, however, does a TIA last 24 hours; most of us believe that someone who has a focal cerebrovascular event which lasts 20 hours probably has a small infarct. An attack which lasts two to five or ten minutes, as in amaurosis fugax, has not in that instance produced retinal ischemia to the point of retinal infarction. The same theory applies to the brain; an attack of short duration does not produce cerebral infarction. The resolution or disappearance of each episode is swift; the frequency of attacks is variable. Significantly, the diagnosis is almost always made on the basis of the history, particularly in office practice. Over 25 years I have witnessed only a few attacks. Frequently I am asked, "Did you really complete the study and prove the diagnosis by doing an arteriogram?" An arteriogram will not reveal whether a patient has had a TIA or not; it will only display detail concerning the morphology of the vessels. Anatomically, TIAs are subdivided into two categories; carotid and vertebrobasilar. With the development of surgical reconstruction for lesions in the carotid system, there is every reason for making the clinical distinction between these two symptoms.

> The typical history for a TIA in the carotid [arterial] system is . . . :
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> 1. Motor defect (weakness, paralysis, poor use, or clumsiness of one extremity or of both extremities on the same side).
> 2. Sensory defect (numbness including loss of sensation or paresthesias involving one or both exremities on the same side).
> 3. Aphasia (speech and/or language disturbance which may be only a minor defect or may be global and may or may not include difficulty in reading, writing, or performing calculations).
> 4. Loss of vision in one eye or in part of one eye when vision in both eyes was intact (amaurosis fugax).
> 5. Homonymous hemianopia.
> 6. Combinations of the above.
>
> These clinical phenomena generally represent a decrease or absence of function. When there is a sensory

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event, it is commonly described as coming on all at once, that is, without a march.

The typical history for a TIA in the vertebrobasilar arterial system is . . . .

1. Motor defect (weakness, clumsiness, or paralysis of any combination of extremities up to quadriplegia, sometimes changing from one side to another in different attacks).

2. Sensory defect (numbness, including loss of sensation or paresthesias in any combination of extremities including all four or involving both sides of the face or mouth. This is frequently bilateral trouble or the distribution may change from side to side in different attacks).

3. Loss of vision, complete or partial in both homonymous fields (bilateral homonymous hemianopia).

4. Homonymous hemianopia.

5. Ataxia, imbalance, unsteadiness, or dysequilibrium not associated with vertigo.

6. Either **vertigo** (with or without nausea and vomiting), diplopia, dysphagia, or dysarthria is not to be considered as a TIA when any of these symptoms occurs alone, but in combination with one another or with any of the above (numbers 1, 2, 3 and 4) the attacks should be considered a TIA.

7. Combinations of the above.

These clinical phenomena generally represent a decrease or absence of function. At times, the motor, sensory, or visual defect constituting the content of a vertebrobasilar attack will be unilateral. It becomes difficult in such instances to make a distinction between whether the locus of ischemia is in the carotid arterial system or in the vertebrobasilar arterial system. In the list above, "drop attacks" is omitted. Fainting (syncope) is frequently confused with a "drop attack," so the latter should be included in the vertebrobasilar profile only when the patient's description of the "drop attack" is absolutely clear. The variety of manifestations included in the vertebrobasilar profile makes the potential pattern of symptoms considerably more variable and complex than that in the carotid system.

The diagnosis of TIA rests on the history of the attacks; the skill with which the history is taken and the interpretation of the history, except for those relatively few instances where the physician is with the patient at the time of the attack. The criteria for making the diagnosis will vary depending on whether an individual physician is working with an individual patient or whether the purpose is the screening of a population for TIAs. A problem is created, as in much of medical diagnosis, because of the relative weight or significance of some historical phenomena compared to other phenomena. The symptom "numbness" (mentioned above) is an example. If the question is, "Have you ever had a numb hand?," the answer from most adults will be "yes." This question is almost completely non-selective (non-diagnostic) and must be followed by a series of questions to establish the meaning and significance of the "numbness." In contrast, another phenomenon, when present, is simple and relatively much more significant than "numbness;" i.e., "Have you ever had painless blindness in one eye which came on very quickly (seconds) and lasted only a few minutes (5 to 20)?" is a question which, if answered "yes," is reasonably specific. Another similar but less specific question is "Have you ever had the sudden onset of a 5 to 20-minute duration attack of severe weakness of one side of the body (arm and leg)?" Another is "Have you ever suddenly lost the ability to speak (5 to 20 minutes' duration) or to understand the speech of others?" These questions illustrate the importance of understanding that different questions may have relatively different complexity and importance.

The matter of relative significance of different symptoms is important in the vertebrobasilar system as it is in the carotid system. For instance, if one asks the question, "Have you ever had any dizziness?," almost all adults will answer "yes." This question is almost completely non-selective (non-diagnostic) and if answered affirmatively must be followed by a series of direct and branching questions to establish the meaning and significance of the original phenomenon—"dizziness." A diagnosis of a TIA in the vertebrobasilar system should **not** be made on the basis of a history of a few minutes of vertigo as the only symptom. This is emphasized since vertigo is the most common symptom in the vertebrobasilar system; however, a diagnosis of vertebrobasilar TIA is made **only** when there is concurrently with vertigo (dizziness) an additional symptom or symptoms.

In some instances, patients with carotid system TIAs may have physical signs of appropriate arterial disease. These include diminished pulsation in the carotid artery, a bruit over the carotid artery or eye, emboli in the retinal vessels, or other signs of ischemic retinopathy and relative hypotension in the retinal artery as measured with the ophthalmodynamometer. These are only signs of arterial disease and may be present in the absence of a history of TIAs. In certain instances, bruits signifying compromise of flow in the innominate artery, either subclavian artery, or at the origin of either vertebral artery may be present; however, the absence or presence of such sounds does not weigh heavily in the diagnosis of vertebrobasilar TIA since it is again emphasized that the diagnosis is dependent upon the history of the attack, not upon morphological evidence of change in patterns of blood flow.

Certain symptoms may appear in a TIA in either arterial system. The most important of these are:

1. Dysarthria, if it occurs alone, and
2. Homonymous hemianopia, if it occurs alone.

The occurrence of certain symptoms in solitary fashion constitutes an attack which is an "uncertain TIA." An attack which consists solely of each of the following symptoms should be categorized as an uncertain TIA:

1. **Vertigo** alone
2. Dysarthria alone
3. Dysphagia alone
4. Diplopia alone

For the sake of clarity, the following symptoms, transient or prolonged, are not to be included as TIA:

1. Unconsciousness including syncope
2. Tonic and/or clonic activity
3. March of a sensory defect

4. Vertigo alone
5. Dysphagia alone
6. Dysarthria alone
7. Incontinence of bowel or bladder
8. Dizziness or wooziness alone
9. Loss of vision associated with alteration of consciousness
10. Focal symptoms associated with migraine
11. Scintillating scotomata
12. Confusion alone
13. Amnesia alone

The differential diagnosis of TIAs includes "hemiplegic" migraine, focal convulsive events (often due to neoplasm and producing either sensory or motor phenomena), Meniere's disorder, sensory phenomena associated with hyperventilation, and finally some unknown mechanism. The differentiation of "hemiplegic" migraine is a semantic and practical problem. In those instances where the aura of migraine is associated with a definitely focal neurological event, the latter may well be the result of transient focal cerebral ischemia but the implications are different than the usual TIA. To establish a diagnosis of the migraine association, there is ordinarily a positive family history, characteristic unilateral headache with nausea and sometimes vomiting, and onset of the attacks several decades ahead of the age at which TIAs commonly begin. Very careful history-taking ordinarily delineates the transient focal events associated with brain neoplasm from TIAs and this is also true of the other items in the differential diagnosis.[1]

It is necessary to understand the pathogenesis of the attacks to treat them properly. Strokes occur in people who have atherosclerosis; common sites are in the cervical arteries and in the circle of Willis and its main branches. Strokes do not occur in patients free of atherosclerosis unless there is a distal occlusion by an embolus from the heart or other site. Cerebral infarcts are statistically associated with atherosclerosis. How does a static atherosclerotic lesion in the neck produce the sudden onset, in a matter of seconds, of a hemiparesis which lasts for five minutes and disappears leaving the person normal? How often does cerebral atherosclerosis occur without causing symptoms? In 100 consecutive autopsies of patients 50 years of age or older, the arch of the aorta, all cervical vessels, vessels at the base of the brain, and the brain were studied. Under the term "stenosis," only a lumen narrowed 50% or more was counted. There were 77 cervical stenoses in 28 patients. Of these 28 people, 18 had never had any symptoms of nervous system trouble of any kind. There were 15 cervical occlusions in 12 people. Six of these 12 had never had any symptoms of nervous system trouble. There were 40 people (40%) of the 100 who had cervical atherosclerosis, not counting intracranial lesions. Sixty percent of these patients were without any symptoms of nervous system trouble. This same observation has been made concerning coronary atherosclerosis. Many people with coronary atherosclerosis have neither angina nor a myocardial infarction. It is apparent that some factor, in addition to atherosclerosis, has to be present to produce the sudden onset and short duration of the attacks. In 1955, I postulated that atherosclerosis plus one or more of the following could cause an attack: transient systemic hypotension, polycythemia, kinking or external compression, shunting, transient hypoglycemia, vasospasm, severe anemia, thrombosis or embolism or both. The transient systemic hypotension theory was in vogue over a decade ago. The notion was that if there were distal stenosis of an artery and the perfusion pressure dropped, there would be a disproportionate decrease in perfusion distal to the stenosis, thereby causing ischemia for the duration of that decreased perfusion pressure, and ischemia in the territory supplied by that vessel. The physician should search for cardiac causes of transient systemic hypotension even though this is an uncommon cause of TIA. At the Mayo Clinic, only 1.4% of 290 consecutive patients being implanted with cardiac pacemakers had had focal transient neurological phenomena. In most instances there were episodes of diffuse cerebral ischemia (syncope). Polycythemia is found in 1% or 2% of our TIA patients, whether vertebro-basilar or carotid. Polycythemia should be appropriately studied and treated. Reversal of flow in a vertebral artery because of occlusion or stenosis of a subclavian artery has been called "subclavian steal." It can be diagnosed in the office as there is a decrease in brachial blood pressure on the side involved, a radial pulse lag, and a decrease in the palpable pulse pressure on that side. The symptom complex associated with this, certainly in our institution, has never been defined and operations for this defect are seldom performed.

The items of greatest importance in the pathogenesis of TIA appear to be thrombosis and embolism. Cholesterol and fibrin-platelet emboli have been observed in the retina; streamlining of flow explains the similarities between the neurological content of a patient's attacks while fragmentation of emboli or lysis of thrombosis is a plausible explanation for the short duration of episodes. The appearance of cholesterol emboli in the retina means that there is an ulcerated carotid lesion on that side.

The natural history of TIA has received consid-

erable study. Are TIAs warning events? Twelve reports are summarized in the following table (Table 1).

The one study with a result different from the others is Marshall's.[9] A few months later, Marshall[13] published an entirely different result; 43% of TIA patients had cerebral infarction when followed for 60 months. In Marshall's first report it appears that many of the patients had a complaint of occasional dizziness and were not having focal cerebral transient ischemic attacks. In the study by Pearce et al,[5] the duration of follow-up was only 10.6 months which is too short a time to discover the true natural history of TIA.

One is often asked about the indications for cranial arteriography. These are:

1. Differential diagnosis of the brain pathology. Even with careful attention to all the items listed under history, general examination, neurological examination, neurovascular examination, and additional tests, there still remain about 5% of patients whose diagnosis is uncertain. Computerized tomography (EMI, ACTA, DELTA scanners, and others) is revolutionizing the differential diagnosis of intracranial lesions. In a few instances, cervical-cerebral angiography is the best method for distinguishing between vascular occlusive disease, an intracerebral expanding mass such as hemorrhage, abscess or brain tumor, cerebral infarction, and subdural hematoma, as well as demonstrating aneurysms and arteriovenous malformations.

2. Transient focal ischemic attacks, particularly in the carotid system. Cervical-cerebral angiography should be performed if one or more of these conditions is evident: amaurosis fugax, bruit over the beginning of the internal carotid artery, retinal emboli, unilateral decrease in retinal artery pressure, or ischemic retinopathy. If none of these is present, the likelihood of finding a lesion accessible to the surgeon is small.

3. Selected instances of vertebro-basilar TIAs. It may be difficult to make a clinical distinction between the carotid and the vertebro-basilar system. If the TIAs are characteristic of those coming from the vertebro-basilar system, there is little need for extensive angiography.

4. Early progressing stroke or frequent TIAs in the carotid system with evidence of amaurosis, an appropriate bruit, retinal emboli, or other conditions.

5. Many patients with subarachnoid hemorrhage and some patients with intracerebral hemorrhage.

A less certain indication for cranial arteriography is a loud, long systolic or systolic-diastolic internal carotid artery bruit in patients scheduled for major general surgery. If there is prolonged hypotension or very severe blood loss, the carotid stenosis may decrease blood supply to a focal region of the brain to a critical level of ischemia. Recent observations suggest that such patients do not have an increased risk of stroke; therefore, arteriography is not necessary.

Table 1
Twelve Reports Summarizing Natural History of TIAs as Warning Events

Study	Number of Patients	Follow-up (Mos.)	Normal	Cerebral Infarct Total	Cerebral Infarct Lethal	Cerebral Hemorrhage
Siekert et al[2]	160	60	83 (52%)	51 (32%)	18 (11%)	7 (4%)
Cooperative[3]	20	20	?	5 (25%)	1 (5%)	0
Fisher[4]	23	?	?	8 (34%)	0	0
Pearce et al[5]	20	10.6	11 (55%)	2 (10%)	?	?
Baker et al[6]	30	40.6	?	7 (23%)	?	?
Baker et al[7]	79	41	?	17 (22%)		
Friedman et al[8]	23	27.4	?	8 (35%)	0	1 (2%) SAH
Marshall[9]	61	45	54 (89%)	1 (2%)	1 (2%)	
Ziegler and Hassanein[10]	135	36	?	22 (16%)	5 (3.7%)	?
Goldner* et al[11]	140	180 av ?	?	?	?	
	111	av ?		43 (38%)	27 (24%)	?
Whisnant et al[12]	198	60	?	62 (32%)	?	?
Marshall[13]	158	60	?	68 (43%)	?	?

* Goldner, Whisnant and Taylor reported concerning 140 TIA patients followed for 15 years. The table gives occurrence of stroke in 111 patients.

Recalling the thrombosis-embolism mechanism, it is apparent that there are several ways to treat TIAs; one of these is the administration of an oral anticoagulant. Table 2 shows the data in six reports in which a direct attempt has been made to compare untreated patients suffering from transient ischemic attacks with those receiving anticoagulant drugs.

Anticoagulants should not be used if: 1) the physician is unfamiliar with the drugs, 2) the patient is not fully cooperative, or 3) laboratory results are of uncertain quality. The actual number of patients in five of the studies in Table 2 is so small as to make comparison between the treated and untreated groups invalid. Nevertheless, the percentage of individuals with cerebral infarction was similar in all of the treated groups of each study. The effectiveness of concurrent treatment of arterial hypertension, in decreasing the frequency of intracerebral hemorrhage, cannot be assessed in these studies; it seems reasonable that the danger may be less now that antihypertensive therapy is better developed. It is apparent that anticoagulant therapy decreases the risk of cerebral infarction in patients with transient ischemic attacks. However, other types of treatment should be considered including thromboendarterectomy and the administration of antiplatelet agglutinating agents.

Although thousands of operations on the carotid artery have been performed since the report by Eastcott, Pickering and Rob[14] in 1954, knowledge concerning the effects of surgery to prevent subsequent cerebral infarction in patients with TIA is still limited. In the Joint Study of Extracranial Arterial Occlusion V,[15] the collaborating investigators reported that 316 patients had transient ischemic attacks; 169 received surgical treatment and 147 received medical treatment. The follow-up period averaged 42 months. In the surgically treated group, 15% of the patients suffered cerebral infarction (including postoperative complications) while 14% of the medically treated subjects had cerebral infarction. The best results were noted in a subgroup of 94 patients having transient ischemic attacks and unilateral carotid stenosis; 45 underwent surgery and 49 were treated medically. Six percent of the surgically treated patients had cerebral infarction during the total course of the study compared with 12% of the medically treated group. Bauer et al,[16] also reporting for the Joint Study of Extracranial Arterial Occlusion, noticed statistically significant differences in the cumulative survival rates at 42 months and reported that:

> (1) surgical treatment appeared more beneficial for unilateral carotid stenosis in patients with transient ischemic attacks or a mild to moderate neurological

TABLE 2
Six Studies Comparing Untreated TIA Patients with Those Receiving Anticoagulant Therapy

Study	Number of Patients	Follow-up (Mos.)	Normal	Cerebral Infarct Total	Cerebral Infarct Lethal	Cerebral Hemorrhage
Siekert el al[2]						
Control	160	60	83 (52%)	51 (32%)	18 (11%)	7 (4%)
Treated	175	60	131 (75%)	7 (4%)	3 (2%)	13 (7%)
Cooperative Study[3]						
Control	20	20	?	5 (25%)	1 (5%)	0
Treated	24	18	?	1 (4%)	0	2 (8%)
Fisher[4]						
Control	23	?	?	8 (34%)	0	0
Treated	29	30	?	1 (3%)	0	0
Pearce et al[5]						
Control	20	10.6	11 (55%)	2 (10%)	?	?
Treated	17	11.1	7 (41%)	1 (5%)	?	?
Baker et al[6]						
Control	30	40.6	?	7* (23%)	?	?
Treated	30	37.9	?	2	?	0†
Friedman et al[8]						
Control	23	27.4		8‡	0	1 (4%) SAH
Treated	21	27.4		0	0	0

* Three treated patients randomly chosen had CVA after A/C stopped.
† One cerebral hemorrhage in treated group but while *off* anticoagulant.
‡ One patient had been on A/C, but A/C was discontinued before the cerebral infarction.

deficit, (2) nonsurgical treatment produced better results for unilateral carotid stenosis in patients with a moderate to severe neurological deficit, (3) nonsurgical treatment appeared more beneficial for combined unilateral carotid artery stenosis and contralateral carotid artery occlusion of patients who had a moderate to severe neurological deficit, and (4) nonsurgical treatment appeared more beneficial for patients with completed strokes who had a marked and persistent neurological deficit.

It is apparent from the many reports in the literature that physicians clinically active in the cerebrovascular field are moderately to greatly enthusiastic about surgical treatment for carotid system TIA when an appropriate carotid lesion is discovered. Unfortunately, no long-term follow-up of a precisely studied group of surgically treated carotid TIA patients is available, but it seems likely that results have improved since the report by the Joint Study of Extracranial Arterial Occlusion.

In the last decade, aspirin, dipyridamole (Persantine®) and sulfinpyrazone (Anturane®) have been investigated in the laboratory and in some human clinical settings because of their effect on blood platelet aggregability or adhesiveness or both. A direct relationship between these characteristics of platelets and the pathogenesis of transient ischemic attacks has not yet been firmly established. Dyken et al[17] described 26 patients, in a retrospective study, of whom 15 were treated with aspirin (300 mg b.i.d.) and 11 were not. No difference was noted in the incidence of cerebral infarction or death in the two groups, but only two (13%) of those receiving aspirin had an additional TIA while nine (82%) of those receiving no aspirin had subsequent TIA. The author stressed that this study did not prove the effectiveness of aspirin, but that it pointed to the need for a prospective investigation of the subject.

Two cooperative studies of platelet aggregating agents' effect on transient ischemic attacks are underway, one in Canada and one in the United States. Formal comprehensive reports from these studies are not yet available. At the Tenth Princeton Conference on Cerebral Vascular Disease in 1976, Fields[18] gave a brief overview of some of the experience in the United States Cooperative Study of aspirin for the treatment of transient focal cerebral ischemic attacks. He reported that in patients having one attack, there was no difference between treated and untreated patients, but that in patients having multiple TIAs, those receiving aspirin appeared to have a better "result." This Cooperative Study has been discontinued. Barnett[19] (Canadian Cooperative Study) was asked about the results of his investigation which involved comparisons between several treatments (aspirin, sulfinpyrazone, and other drugs). He commented that the statistics to date had been carefully reviewed and that the results appeared to be inconclusive. There was no reason to stop the investigation and every reason to continue it. At this time, the pressing questions concerning the effectiveness of these agents remain unanswered.

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Recent Techniques in Cerebrospinal Fluid Examination

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The existence of the cerebrospinal fluid (CSF) has been known since ancient times, but it was Cotugno who first described it in some detail in 1764.[1] Quoting from his treatise, "In these experiments which I made on the bodies of nearly twenty adults, and which I repeated at different times, I could draw off freely from the hollow of the spine, four, or even sometimes five ounces of water: I commonly found it very clear in such subjects, though it sometimes inclined a little to a yellow color: but in fetus' strangled in difficult labor, little as it was, I observed it to be always red and opaque."[2] He also felt that the CSF was secreted by the arterial system, circulated in the subarachnoid space and was reabsorbed by the venous system.[2] Matters remained in that state until 1891 when Quincke described a refinement in lumbar puncture using a needle with a pointed stilette in it.[3] The first extensive treatise on CSF composition was written by Mestrezat in 1912.[1] Since then there has been very slow progress in the evaluation and interpretation of CSF even though there have been tremendous strides in the evaluation of other body fluids, particularly blood.

One of the reasons for this is a fear of lumbar puncture, a fear which is usually unwarranted. Unfortunately, this attitude permeates the medical profession almost as much as it does the lay public.

Tests such as cell counts, glucose, protein, and semiquantitative tests for globulins such as the colloidal gold test were products of the first part of this century. As new developments occurred in blood analysis these were applied to the CSF. These studies did not lead to any advances in the clinical chemistry of CSF, though they certainly had their place in furthering our understanding of brain chemistry and function.

The biggest advance in clinical CSF chemistry in the past decade has been the emergence of an abbreviated CSF immunology. This followed the development and refinement of agar electrophoresis and immunoprecipitation techniques.

The scope of this paper will include discussion of these advances and some promising studies of CSF enzymes in differential diagnosis as well as comment on a recurrent problem, that of the interpretation of bloody or xanthochromic CSF.

Blood in the CSF. Probably one of the most frequently encountered problems is the bloody CSF. Is it a subarachnoid hemorrhage or is it a traumatic tap?

One of the best tests and the one most commonly used is to do a cell count in the first tube and another in a subsequent tube, usually the third. This should be done even if the fluid looks grossly clear since about 500 cells must be present before the fluid becomes hazy.[4,5] A significant change in the red blood cell (RBC) count of the fluid indicates a traumatic tap since the blood from a subarachnoid hemorrhage should be homogeneous by the time it reaches the lumbar sac. I say a "change" in the RBC, not just a decrease, since a marked increase would also indicate a traumatic tap. One should also closely observe the fluid as it comes out of the needle. Gross blood can sometimes be seen streaming in the fluid. One may

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also see nonhomogeneous mixing in the fluid as it drops into the tube. In addition, a very bloody traumatic tap (greater than 200,000 RBC/mm^3) will clot on standing; this will not occur with subarachnoid bleeding. Microscopic examination of the red cells is of little value since crenation may occur with both subarachnoid bleeding and a traumatic tap.

The next step if the fluid is bloody or colored should be to centrifuge the fluid and determine the color of the supernatant. One often hears the remark that the fluid was xanthochromic, yet the fluid was not centrifuged. Xanthochromia should refer to a yellow color of the supernatant and should never be used in reference to unspun CSF. This coloration is usually due to either oxyhemoglobin, methemoglobin, or bilirubin. Very rarely it may be due to other pigments such as carotene.[6]

The sequence of events appears to be: hemoglobin is released from the red cells in the subarachnoid space. This appears as oxyhemoglobin which in low concentrations has an orange-red appearance. Depending on the amount of bleeding, one begins to see a change in the coloration of the fluid to yellow within a few hours to a day. This is due to the heme being metabolized to bilirubin. In the case of a subdural or an intercerebral hematoma the fluid may take on a brownish-yellow appearance due to the presence of methemoglobin.

The supernatant fluid in a traumatic tap can give one of two results. It is usually clear and colorless since the red cells have not had time to break down. If the RBC count is high, however, (>12,000/mm^3), some of the hemoglobin leaking out may be visible immediately.[5]

True subarachnoid bleeding will give different results depending on the time elapsed following the bleed. One should keep in mind that it may take a half hour for blood to reach the lumbar sac from the cortex. The CSF may be indistinguishable from a traumatic tap very shortly after the hemorrhage. In his classic text on subarachnoid hemorrhage, Walton observed xanthochromia in 7% of patients within 2 to 4 hours, but by 4 to 6 hours, 64% had it, and by 12 to 24 hours, 100% had it.[7]

There have been periodic attempts at using spectrophotometry as an aid in evaluating CSF pigments. The three major pigments have rather characteristic absorption patterns. Kronholm and Lintrup did a study on 1,250 CSF samples and were able to develop a set of formulae for determining the concentrations of hemoglobin, methemoglobin, and bilirubin. Their results showed that they could distinguish between intercerebral hematomas, subdural hematomas, and subarachnoid hemorrhage (Table 1; Fig 1).[8]

More recently, Kjellin and his group have expanded on this theme of CSF spectroscopy.[9,10] Besides the disorders noted above, they have been able to correlate various CSF patterns with hemorrhagic infarctions, nonhemorrhagic infarctions, and emboli, as well as hematomas and subarachnoid hemorrhage. In the past they have had to rely on clinical and occasional autopsy conformation. When this was available there was good correlation (Table 2).

I do not advocate that these procedures be used in place of others for evaluation of bloody CSF, but as adjuncts which may be invaluable in deciding if a lumbar puncture was traumatic or not.

CSF Proteins and Immunoglobulins. There is considerable evidence that under normal circumstances the proteins of the CSF are derived from the serum.[11] The most notable exception is the so-called (tau) protein seen in electrophoresis which is probably serum transferrin which has lost two sialic acid residues (Fig 2). Normally, the CSF proteins are made up of albumin, β globulin and γ globulin in the fractions 0.58, 0.20, and 0.10 respectively. These get into the CSF by secretion from brain tissue as well as from the choroid plexus. Efflux of protein is presumably through bulk flow through the arachnoid granules. Increases in protein, especially albumin, can come from: 1) hemorrhage into the CSF, 2) breakdown in the blood-brain barrier, 3) elevated serum protein, 4) lesions of the choroid plexus or 5) blockage of CSF flow, for example, spinal block, and 6) an efflux of soluble proteins into the CSF with damage to brain tissue.

CSF γ globulin or IgG also comes from the serum in normal persons. In conditions where there is

Table 1
CSF Pigments in Xanthochromic CSF

Intercerebral hematoma	Bilirubin > Hemoglobin Methemoglobin > 25% total Hb
Subdural	Same as above, but metheme may be very high
Subarachnoid	Hemoglobin > Bilirubin Methemoglobin < 25%
Traumatic	Same as subarachnoid though Bilirubin should be negligible

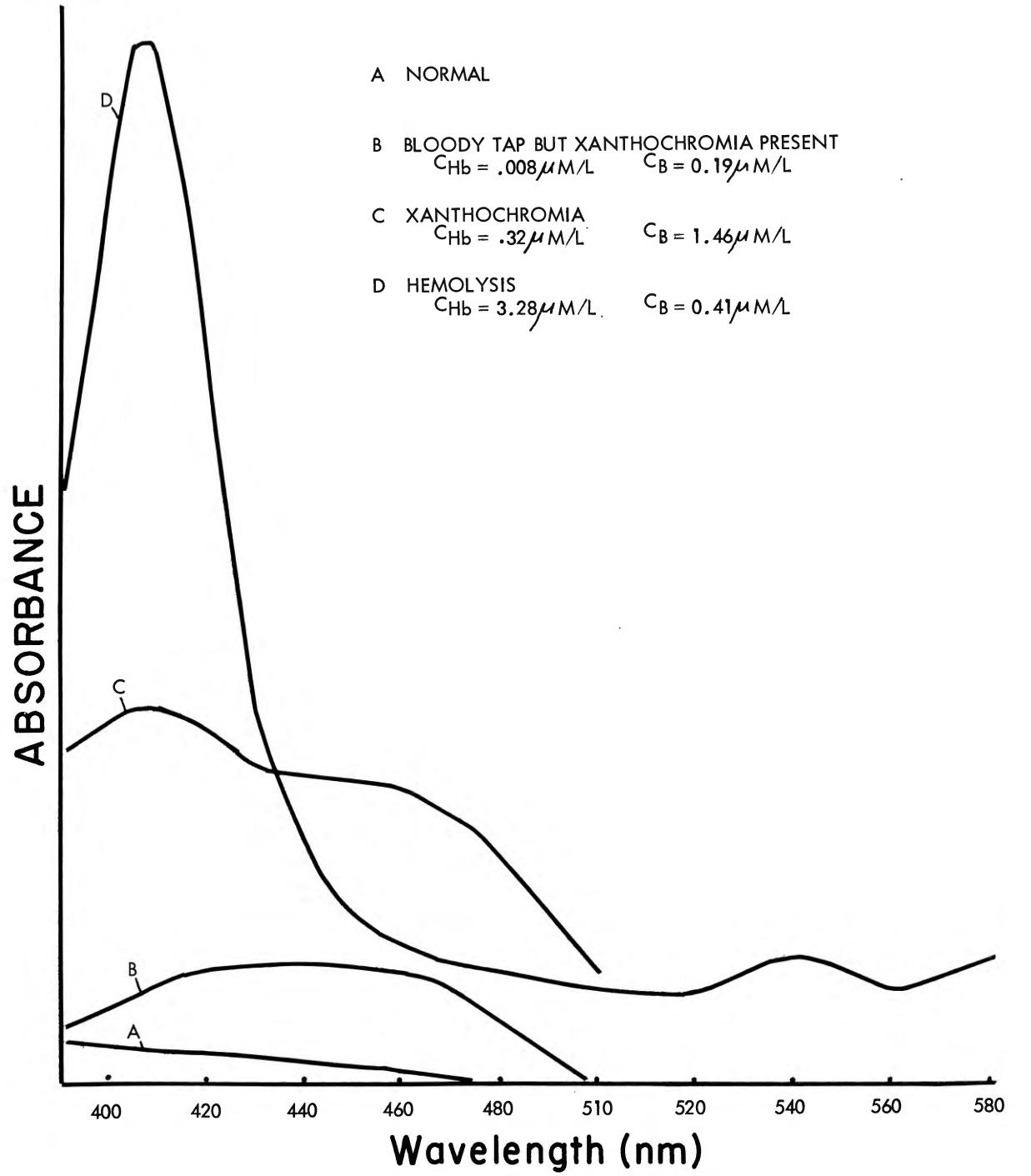

Fig 1—Absorption pattern of CSF. *A* is from a patient who did not have active CNS disease. *B* is from a patient who presented with a history of confusion and a bloody CSF. The absence of a hemoglobin peak indicates blood was from a traumatic tap, but bilirubin indicates an older subarachnoid hemorrhage. *C* is from a patient three weeks after an intercerebral hemorrhage. The hemoglobin peak is over 50% metheme. *D* is hemolyzed blood.

Table 2
Spectrophotometric Evaluation of CSF in Vascular Disease

Verified Disease	Pattern (% of cases)*			
	Infarction	Hemorrhagic infarction or Hematoma	Mixed	Hemorrhage
Infarction	71	24	—	—
Cerebral Hemorrhage	9	46	8	27
Aneurysm	—	8	8	83
Trauma (not subdural)	—	—	18	82

* A small number could not be interpreted, so figures do not add up to 100%.

an increased serum γ globulin or IgG, this will be reflected in the globulin composition of the CSF. In addition, if there is a breakdown in the blood-brain barrier, one may see an increase in the γ or IgG fraction simply because it makes up a higher proportion of the total protein in serum than it does in CSF.

There are times, though, when it appears that the increased immune globulins are coming from the brain itself. This was shown some years ago by Frick and Scheid-Seydel who used tagged IgG.[11] In multiple sclerosis (MS) patients they showed that a large portion of the IgG was coming from somewhere other than serum. At present it is thought that it is coming from immune competent cells situated in the periphery of MS plaques.[12] Other conditions which are felt to reflect central nervous system (CNS) IgG production with a raised CSF IgG are neurosyphilis and subacute sclerosing panencephalitis. Disorders such as meningitis or encephalitis may show increased IgG either from a breakdown in the blood-brain barrier or CNS production.

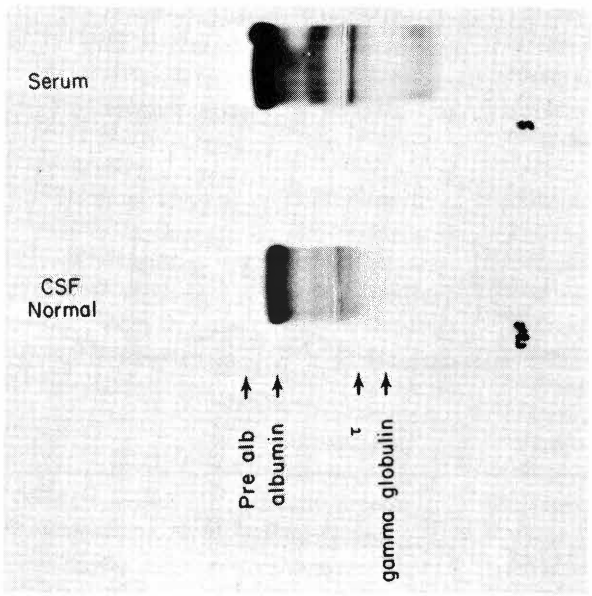

Fig 2—Agar gel electrophoresis of concentrated CSF and unconcentrated serum. Note presence of a prealbumin and a tau band in CSF which is not present in serum. Also note very broad gamma band.

In 1964, Lowenthal applied agar electrophoresis to CSF and was able to confirm this increase in immune globulins (See Fig 2; Fig 3).[13] Interestingly, conditions which have CNS immune globulin production usually show discrete banding of the γ fraction while those conditions in which the immune globulins originate in serum show a diffuse γ band. The next advance after agar electrophoresis was the development of immunoprecipitation methods, either electroimmunodiffusion or radial immunodiffusion where antibody to the immune globulins is added to the agar. The distance of the resultant precipitate from the origin is proportional to the immune globulin concentration. The advantage over electrophoresis is that only a few microliters of CSF are needed, and the subfractions of the immunoglobulins can be measured. The disadvantage is that only one protein fraction can be measured at a time.

Interestingly, the results by the different methods are remarkably similar.[13–20] In MS some 75% to 85% of the patients show an abnormal γ or IgG level at some time in their disease. There is no relationship, however, to the stage of the disease or to the prognosis. Its value is therefore purely diagnostic. Inflammatory diseases such as meningitis and encephalitis show an increased level in some 35% to 40%, the lowest level being in viral meningitis. Guillain-Barré syndrome shows an increase in 30% to

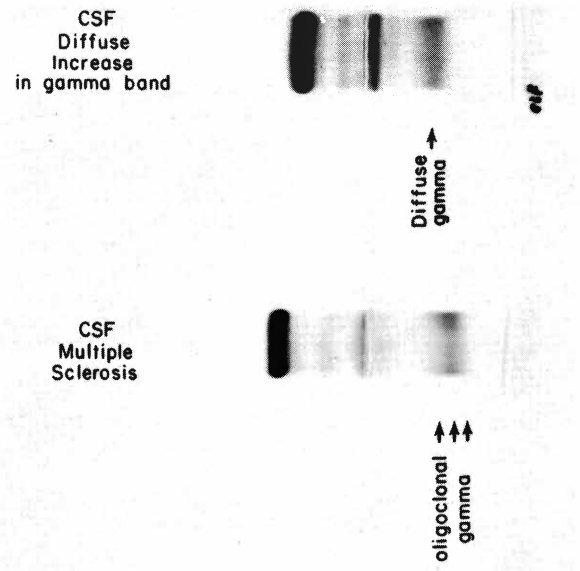

Fig 3—Agar gel electrophoresis of CSF from two patients with elevated gamma fraction. The first is a patient with acute lead encephalopathy. The diffuse gamma band is indicative of a serum source while the multiple bands from the multiple sclerosis patient indicate a CNS source.

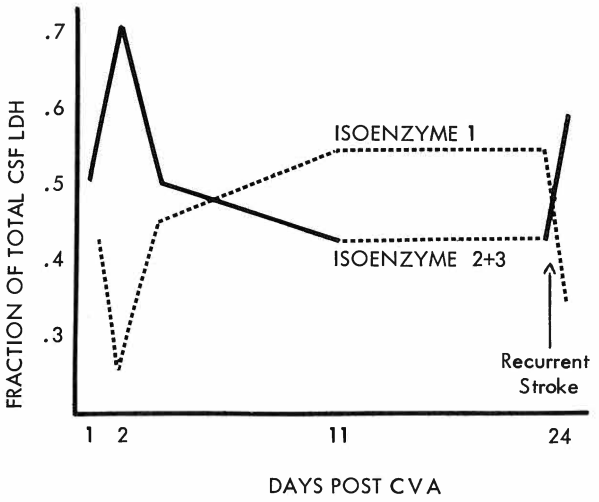

Fig 4—CSF LDH isoenzymes measured by agar gel electrophoresis. Normal LDH 2+3 = 0.40 and LDH 1 = 0.55. The LDH 2+3 curve follows the total LDH pattern while the LDH 1 actually showed a slight increase at two days when the absolute amount was calculated.

50%. Agar electrophoresis shows that this is a serum pattern. In other diseases such as degenerative disease, tumors, and vascular disease, the percentage with increased γ or IgG levels is quite low, though in these conditions the literature does vary a great deal and probably reflects variations in the integrity of the blood-brain barrier (Table 3).

CSF Enzymes. The measurement of CSF enzyme levels has not yielded the kind of information which was hoped for. The ones measured most commonly, lactic dehydrogenase (LDH) and glutamic-oxalacetic transaminase (GOT), appear to be elevated whenever there is significant disruption of brain tissues and do not seem to be specific for a given disease. The LDH is also increased when there is an increase in CSF polymorphonuclear cells. This relation to tissue destruction is shown by the results from a patient with recurrent strokes. Using LDH isoenzymes, it is of interest to note the transient shift to the more anaerobic forms of LDH during the acute phase (Fig 4).

Table 3
Conditions Giving Elevated CSF Gamma Globulin

Systemic Conditions with Increased CSF Immune Globulins	Conditions with 1° Increase in CSF Immune Globulins
Cirrhosis with ↑ γ globulin	Multiple Sclerosis
Myeloma	CNS Lues
Diseases with breakdown BBB	SSPE
Vasculitis ←?→	Vasculitis*
Infection ←?→	Infection*
Sarcoidosis ←?→	Sarcoidosis*

* In these three it is uncertain if the origin of the gamma globulin is serum or CNS or both.

CSF LDH has been noted to be elevated in meningitis of bacterial origin, but rarely in viral.[21–23] This elevation has been used to try and differentiate partially treated bacterial from viral meningitis.[24] For technical reasons the results were not really conclusive, but it did indicate a differentiation could be made by an elevated level in bacterial disease.

More impressive was a study on CSF lactate before, during, and after treatment.[25] Bacterial disease showed an elevated lactate level until after full treatment while aseptic meningitis was the same as the controls. CSF pH showed the inverse pattern as would be expected.

While further studies will be necessary to confirm these results, the outlook for a test to distinguish partially treated bacterial disease from a viral meningitis looks promising.

Table 1 is adapted from Kronholm and Lintrup, *Acta Psychiat Neurol Scand* (35:314–329, 1960).

Table 2 is adapted from Kjellin and Söderström, *J Neurol Sci* (23: 359–369, 1974).

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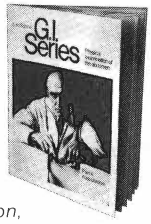

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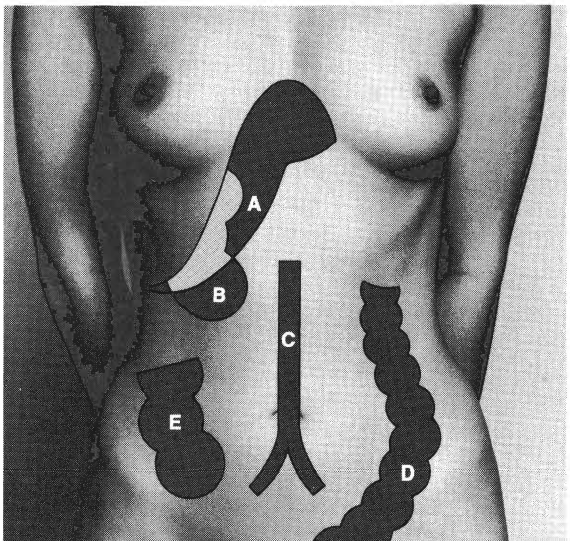
Impossible to outline, unless diseased, distended or enlarged: the gallbladder, pancreas, stomach, small intestine, transverse colon and spleen.



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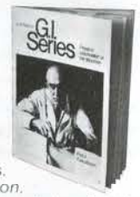

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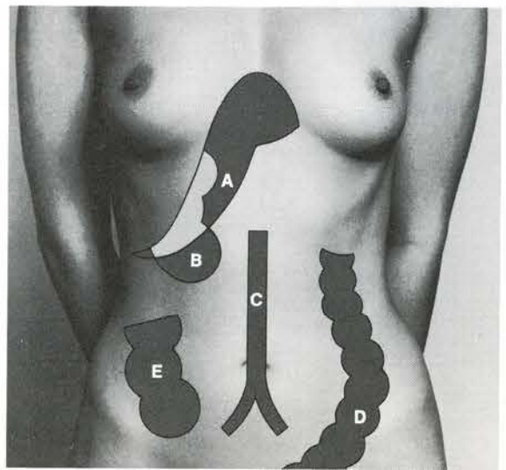

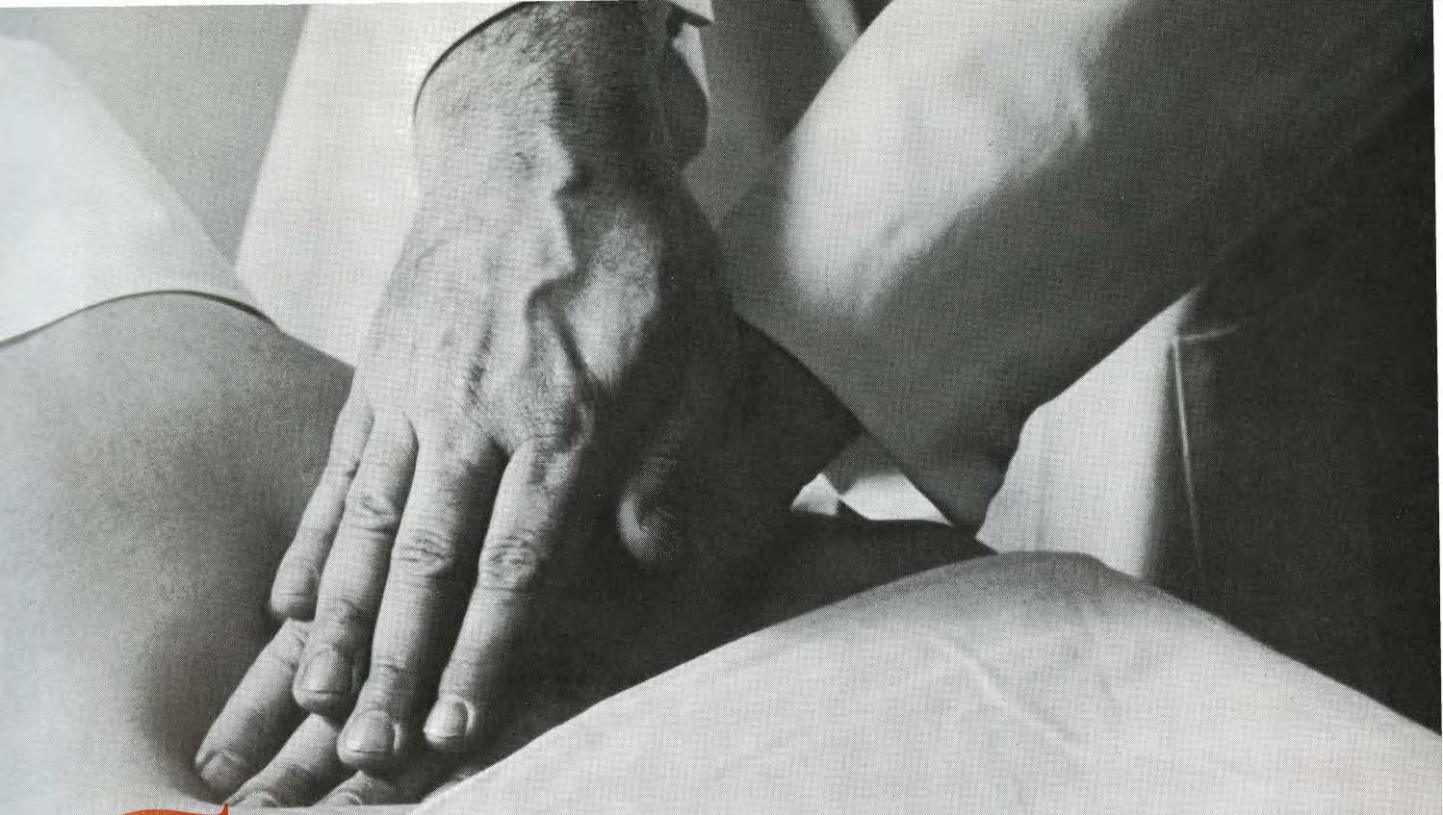

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