APPROACHES TO THE PATIENTS WITH NEUROSURGICAL DISEASES

1. THE CLINICAL METHODS

Neurosurgery is considered to be one of the most difficult and exact medical sciences. Students and residents coming to the neurosurgical ward or clinic for the first time are nearly discouraged by what they see. Having had brief contact with neuroanatomy, neurophysiology, and neuropathology, they are already somewhat intimidated by the complicacy of the nervous system. The ritual they then witness of putting the patient through a series of actions directed to evoke certain mysterious signs the names of which are difficult to pronounce is hardly reassuring; in fact, the procedure often appears to conceal the very intellectual processes by which neurologic diagnosis is attained. Moreover, the students have had no experience in a number of special tests used in neurological diagnosis such as lumbar puncture, as well as electro encep halo graphic, angiographic, and imaging procedures they don't know how to interpret the results of such tests. Neurosurgery textbooks only confirm their fears as they read the myriad of details of rare diseases of the nervous system.

The importance of the clinical method stands out more clearly in the study of neurological diseases than in any other fields of medicine. In most cases, the clinical method consists of series of steps, as follows:

1. The symptoms and signs are secured by medical history and physical examination, respectively.
2. The symptoms and physical signs considered relevant to the current problem are interpreted in terms of physiology and anatomy, that is one identifies the disorder(s) of function and the anatomic structure(s) implicated by such disorder. Often one recognizes a characteristic clustering of symptoms and signs, constituting a *syndrome.* The formulation of symptoms and signs in syndromic terms is particularly helpful in ascertaining the locus and nature of the disease. This step may be called *syndromic diagnosis.*
3. These correlations permit the physician to localize the disease process, i.e., to name the part or parts of the nervous system in volved. This step is called the *an atomic,* or *topographic, diagnosis.*
4. From the anatomic diagno sis and other medical data, par ticularly the mode of onset, evo lution, and course of the illness, the involvement of nonneurological organ systems, the relevant past and family histories, and the laboratory findings, one deduces *pathologic diagnosis* and, when the mechanism and causation of the disease can be determined, *etiologic diagnosis.*
5. Finally, the physician should assess the degree of disability and determine whether it is temporary or permanent. This *functional diagnosis* is important in managing the patient's illness and judging the potential for restoration of function.

The foregoing steps in the clinical method are summarized in Fig. 1, which represents a kind of algorithm, by which the clinical problem is solved in a finite series of steps.

Taking the History

In neurosurgery more than in any other specialty, the physician is dependent upon the cooperation with the patient for a reliable medical history, especially for a description of symptoms that are unaccompanied by observable signs of disease. And if the symptoms are in a sensory sphere, only the patient can tell what he sees, hears, or feels. The first step in the clinical encounter is to enlist the patient's trust and cooperation and make him realize the importance of the examination procedure. The following points about history taking in neurosurgery deserve further comment:

1. Special care must be taken to avoid suggesting to the patient the symptoms that one seeks. The clinical interview is a bipersonal engagement, and the conduct of the examiner has a great influence

on the patient. Repetition of this truism may seem tedious, but it is evident that conflicting histories can often lead to the questions that either suggested symptoms to the patient or distorted the patient's story. Errors and inconsistency of the recorded history are as often the fault of both the physician and the patient. As a corollary, the patient should be discouraged from framing his symptom(s) in terms of a diagnosis that he may have heard, but should be urged to give a description of the symptom as accurate as possible, for example, to choose a single word that best describes his pain.

2. The practice of making bedside or office notes is particularly recommended. The patient who is given to highly circumstantial and rambling accounts can be kept on the subject of his illness by discreet questions that touch upon essential points. Immediate re cording of the history ensures maximal reliability. Of course, no matter how reliable the history may be, it is desirable to verify the patient's account by a knowledgeable and objective informant.

3. The mode of onset, evolution, and course of the illness are of paramount importance. One must attempt to learn how each symptom began and progressed. Often the nature of the disease process can be determined only out of these data. If such information can not be given by the patient or his family, it may be necessary to judge the course of the illness by what the patient was able to do at different times (e.g., how far he could walk, when it was no longer possible to go upstairs, carry on his usual work) or by changes in the clinical findings between successive examinations, provided that the physician has recorded the findings accurately and has quantitated them in some way.

4. Since neurological diseases often derange the mind, it is necessary, in every patient with cerebral disease, for the physician to decide, by an initial assessment of the mental status and the circumstances under which symptoms occurred, whether or not the patient is competent to give a history of the illness. If the patient's power of attention, memory, and coherence of thinking are inadequate, the history must be obtained from a relative, a friend, or employer. Also, illnesses that are characterised by seizures or other forms of episodic confusion impair the patient's memory of events occurring during these episodes. In general, students (and some physicians as well) tend to be careless in estimating the mental capacities of their patients. Attempts are sometimes made to take histories from patients who are feebleminded or so confused that they have no idea why they are at a doctor's office or at a hospital, or from patients who for other reasons could be aware of the details of their illness.

The Neurological Examination

The neurological examination always begins with an observation of the patient while the history is being obtained. The manner in which the patient tells the story of his illness may expose confusion or incoherence of thinking, impairment of memory or judgment, or difficulty in comprehending or expressing ideas. Observation of such matters is an integral part of the examination and provides information as to the adequacy of cerebral function. The physician should learn how to obtain this sort of information without embarrassment for the patient. A common error is to pass easily over inconsistencies in history and inaccuracies about dates and symptoms, only to discover later that these spotty memory defects were the essential features of the illness. Asking the patient to give his own interpretation of the possible meaning of symptoms may sometimes expose unnatural concern, anxiety, suspiciousness, or even delusive thinking.

The remainder of the neurological examination should be performed as the last part of the general physical examination, proceeding from an examination of the cranial nerves, neck, and trunk, to the testing of motor, reflex, and sensory functions of the upper and lower limbs. This is followed by assessment of sphincteral and autonomic nervous system functions and suppleness of the neck and spine (memngeal irritation). Gait and standing should be observed before or after the rest of the examination. The neurological examination is always performed and recorded in a consecutive and uniform manner in order to avoid omissions and to facilitate the subsequent anaysis of case records. In addition, it is often instructive to observe the patient in the course of his natural activities, such as walking, or dressing; this may disclose subtle abnormalities of gait and movement that are not evident in formal testing.

The type of clinical problem presented by the patient must of necessity govern the thoroughness of the neurological examination. It is pointless and uneconomical to spend a half an hour or more testing cerebral, cerebellar, cranial nerves, and motor-sensory function in the patient suffering from a simple compression palsy of an ulnar nerve. The examination must also be modified according to the patient's condition. Obviously many parts of the examination cannot be carried out in a comatose patient; also, infants and small children as well as psychotic patients need to be examined in special ways. The following comments apply to the examination procedure under these and other particular clinical circumstances.

Laboratory Diagnosis

From the foregoing description of the clinical method and its application, it is evident that the use of laboratory aids in the diagnosis of diseases of the nervous system is always preceded by rigorous clinical examination. Laboratory study can be planned only on the basis of clinical information. To reverse this process is the waste of medical resources. However, in neurosurgery the ultimate goal is the prevention of disease, because the brain changes induced by many neurological diseases are irreversible. In the prevention of neurological disease, the clinical method is inadequate, and necessarily one resorts to two other methods, namely, the use of genetic information and laboratory screening. Genetic information enables the neurologist to identify patients at risk of developing certain diseases, and it prompts the search for biologic markers before the symptoms or signs appear. Biochemical screening tests are applicable to the whole population and permit the identification of neurological disease in individuals who haven't shown their first symptom yet; in some such diseases, treatment can be administered before the nervous system has been damaged. In preventive neurosurgery, therefore, the laboratory methodology may take priority over the clinical methodology.

Shortcomings of the Clinical Method

If one adheres faithfully to the clinical method outlined here, neurological diagnosis is greatly simplified. In most cases, one can reach an anatomic diagnosis. The cause of the disease may prove to be more elusive and usually entails the intelligent and selective application of a number of the laboratory procedures described in the next chapter.

However, even after the most careful application of the clinical method and laboratory procedures, there are numerous patients who are not made a diagnosis. Under such circumstances we should follow the next rules of thumb: (1) Focus the clinical analysis on the principal sign or signs and avoid being distracted by minor signs and uncertain clinical data. As mentioned above, when the main sign has been mistakenly interpreted (e.g. a tremor has been taken for ataxia or fatigue for weakness) the clinical method is derailed from the start. (2) Avoid early closing of a diagnosis. Often this is the result of premature fixation on some item in the history or examination, which closes the mind to alternative diagnostic considerations. The first diagnostic formulation should be regarded as only a testable hypothesis, subject for modification when new items *of* information are secured. Should the disease be in a stage of transition, time will allow the full picture to emerge and the diagnosis to be clarified. (3) When several of the main features of a disease under consideration are lacking, an alternative diagnosis should always be implied. In general, however, it is more likely to encounter rare manifestations of common diseases than the typical manifestations of rare diseases (a paraphrase of the Bayes theorem). (4) It is preferable to base diagnosis on one's experience with the dominant symptoms and signs but not on the statistical analyses of the clinical phenomena. For the most part the methods of probability-based decision analysis have proved to be disappointing in neurosurgery because of the impossibility of weighing the importance of each clinical datum. (5) Whenever possible, obtain tissue for examination, for this adds the dimension of cellular pathology to the clinical study.

There is no doubt that some clinicians are more experienced in solving difficult clinical problems. Their talent is not intuitive, as it is sometimes presumed, but they pay close attention to the details of their experience in many diseases and catalogue them for future reference. The unusual case is fixed in memory and can be applied when another one like that is encountered. Great experience doesn't allow to accept an obvious explanation immediately.

The Purpose of the Clinical Method of Neurosurgery

We should say a few words about the purpose of the clinical method of neurosurgery. Accurate diagnosis has four main purposes: (1) it enables the physician to determine the proper treatment; (2) it is helpful in prognosis, i. el, in predicting the outcome of the disease; (3) if the

disease is hereditary, it allows for genetic counsel; and (4) it is the essential initial step in the scientific study of the clinical phenomena and the disease. The medical profession is primarily concerned with the prevention and the treatment of the illness, and all our knowledge is applied to this well-defined purpose. Therefore, the neurologist should not overlook the disease for which there is an effective treatment. Each of the curable causes of a given syndrome must be carefully considered and excluded by clinical and laboratory methods. For example, in the study of a patient with disease of the spinal cord, one must take special care to exclude the presence of a tumor, subacute combined degeneration, spinal syphilis, epidural abscess, herniated disc, and cervical spondylosis, for these are curable spinal cord diseases. In this respect, failure to recognize amyotrophic lateral sclerosis is a less serious error.

Therapeutics in Neurosurgery

Among medical specialties, neurosurgery traditionally occupies rather an unusual position, and it is considered to be something like an intellectual exercise concerned with making diagnoses of incurable diseases. This disdainful view at our profession is no longer valid. There are a growing number of diseases, both medical and surgical, for which specific therapy is available now and through advances in neuroscience, their number is steadily increasing. The therapy methods of these diseases are presented in relation to the description of individual diseases in later chapters.

In addition, there are many diseases in which the neurological function can be restored to a varying degree by appropriate stratagems, such as rehabilitation techniques, or by a proposed therapy that has not been fully validated. Claims for the effectiveness of a particular therapy, based on statistical analysis of large-scale clinical studies, must be treated appropriately. Was the study well conceived? Was there rigid adherence to the criteria for cases admission in the study? Were the randomisation and statistical methods standardised? Were the controls comparable? It has been our experience, based on the participation in a number of such multicenter trials, that the original claims must always be accepted with caution. Since newly proposed therapeutic agents are often risky and very expensive, it is usually prudent to wait until further studies confirm
the benefits that have been claimed for them or expose flaws in the design or fundamental assumptions of the original study.

Even when no therapy is possible, neurological diagnosis is more than an intellectual pastime. The first step in the scientific study of a disease process is its identification in the living patient. Until this is achieved, it is impossible to apply adequately the "master method of controlled experiment". Thus, the clinical method of neurosurgery serves both the physician, in the practical diagnosis and treatment of a patient's condition, and the clinical scientist, in the search for the mechanism and the cause of the disease.

SPECIAL TECHNIQUES FOR NEUROSURGICAL DIAGNOSIS

The analysis and interpretation of data elicited from a detailed history and examination may prove to be adequate for diagnosis. Special laboratory examinations then do no more than corroborate the clinical impression. However, it often used to be that the nature of the disease is not discerned only by "case study"; the diagnostic possibilities can be reduced to two or three, but the correct one is uncertain. Under these circumstances one resorts to the ancillary examinations outlined below. The aim of the neurologist is to arrive at a final diagnosis by artful analysis of the clinical data aided by the least number of laboratory procedures. Moreover, the strategy of laboratory study of disease should be based purely on therapeutic and prognostic considerations, not on the physician's curiosity or presumed medicolegal exigencies.

A few decades ago the only laboratory procedures available to the neurologist were lumbar puncture and examination of a sample of cerebrospinal fluid, radiology of the skull and spinal column, contrast myelography, pneumoencephalography, and electroencephalography. Now, through considerable advances in scientific technology, the physician's armamentarium has been expanded to a multitude of laboratory methods. Some of these new methods are so impressive that there i& a temptation to substitute them for a careful, detailed history and physical examination. Using the laboratory in this way should be avoided; it certainly does not guarantee a diagnosis. In fact, in a large, carefully examined series of neurological patients, laboratory

examinations failed to clarify the diagnosis in more than half (Chimowitz et al). The neurologist should always keep in mind the primacy of the clinical method and that he is the final judge of the relevancy and significance of each laboratory datum. Hence the neurologist must be familiar with all laboratory procedures relevant to neurological disease, their reliability, and their hazards.

Below is a description of laboratory procedures that have application to a diversity of neurological diseases. The procedures that are pertinent to a particular symptom complex or a disease category e.g., deafness audiogram; vertigo electronystagmograrn (ENG); neuromuscular disease electromyogram (EMG), are presented in the chapters devoted to these disorders.

Lumbar Puncture and Examination of Cerebrospinal Fluid

The information yielded by examination of the cerebrospinal fluid (CSF) is often crucial in the diagnosis of a neurological disease.

Indications for Lumbar Puncture

1. To obtain pressure measurements and to procure a sample of the CSF for cellular, cytological, chemical, and bacteriological examination.
2. To aid in therapy by the administration of spinal anesthetics and occasionally antibiotics or to antitumor agents or to reduce CSF pressure.
3. To inject a radiopaque substance, as in myelography, or a radioactive agent, as in scintigraphic cisternography.

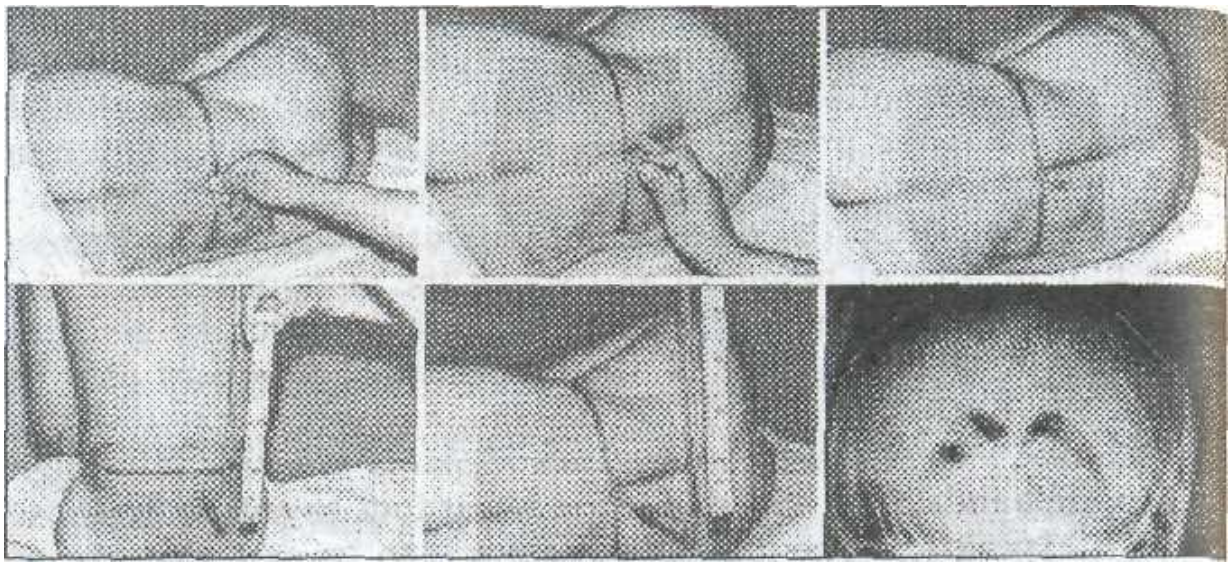
Lumbar puncture carries a certain risk if the CSF pressure is high (evidenced by headache and papilledema), for it increases the possibility of a fatal cerebellar or transtentorial herniation. The risk is considerable when papilledema is due to an intracranial mass, but it is much lower in patients with subarachnoid hemorrhage or pseudotumor cerebri, conditions under which repeated lumbar punctures is actually been employed as a therapeutic measure. In patients with purulent meningitis there is also a small risk of herniation, but this is far outweighed by the need for a definitive diagnosis and the administration of appropriate treatment at the earliest moment. With this exception, therefore, lumbar puncture should be preceded by computed tomography (CT) or magnetic resonance imaging (MRI) whenever an elevation of intracranial pressure is suspected. If the latter procedures do not disclose a mass lesion that causes displacement of tissue toward the tentorial opening or into the foramen magnum (the presence of a mass alone is of less concern) and it is considered essential to have the information yielded by CSF examination, the lumbar puncture should be performed with certain precautions. A fine-bore (no. 22 or 24) needle should be used, and if the pressure proves to be very high over 400 mm H2O one should obtain the necessary sample of fluid and then, according to the suspected disease and patient's condition, administer a unit of urea or mannitol and watch the manometer until the pressure falls. Dexamethasone (Decadron) should then be given in an initial intravenous dose of 10 mg, followed by doses of 4 to 6 mg every 6 h.

Cisternal puncture and *cervical subarachnoid puncture*, although safe in the hands of an expert, are too hazardous to entrust to those without experience. The lumbar puncture is to be preferred except in obvious instances of spinal block requiring a sample of cisternal fluid or myelography above the lesion.

Experience teaches the importance of meticulous technique. Lumbar puncture should always be done under sterile conditions. Lo-j cal anesthetic is injected in and beneath the skin, which makes the, procedure painless. Warming the analgesic by rolling the vial be- the palms should diminish the burning sensation that accompanies subcutaneous infiltration. The patient is positioned on his side, preferably on the left side for right-handed physicians, and asked to roll up with his head as close to his knees as comfort permits. The patient's back should be aligned near the edge of the bed and a small pillow placed under the ear. If the procedure has been performed in the decubitus position and the flow of CSF slows, the head can be elevated slowly. The trochar should be removed from the needle slowly in order to avoid sucking a nerve rootlet into the lumen and causing radicular pain. Otherwise, sciatic pain during the procedure indicates that the needle is placed too far laterally. When drops of CSF contact the edge of a collecting tube, capillary action also speeds up the collection. Occasionally, we resort to gentle aspiration with the small-bore syringe to overcome the resistance of proteinaceous and viscous CSF. The puncture is easiest to perform at the L3-L4 interspace, which corresponds to the axial plane of the iliac crests, or in the space above or below (Fig. 2)- In infants and young children, in whom

the spinal cord can extend to the level of the L3-L4 interspace, lower spaces should be used. Failure to enter the lumbar subarachnoid space after two or three trials can usually beovercome by doing the puncture with the patient in a sitting position and then assisting him to lie on one side for pressure measurements and fluid removal. The "dry tap" is more often due to an improperly placed needle than to obliteration of the subarachnoid space by a compressive lesion of the cauda equina or chronic adhesive arachnoiditis.

Beyond the risk of inducing brain herniation, there are few serious complications of the lumbar puncture. The most common is headache, the result of a reduction of CSF pressure and the tugging of cerebral and dural vessels as the patient takes an erect posture. Bleeding into the spinal meningeal spaces can occur in patients who are taking anticoagulants (prothrombin time 13.5 or an international normalized ratio INR 1.2), have low platelet counts (30,000 to 50,000/mm^3), or whose platelet function is impaired (alcoholism, uremia). Purulent meningitis and disc space infections have been known to complicate the lumbar puncture, the result of imperfect sterile techmque.The introduction of particulate matter (e.g., talc) can produce sterile meningitis.



Examination Procedures

Once the subarachnoid space has been entered, the pressure and in special cases "dynamics" of the CSF are determined (see below) and samples of fluid are obtained. The gross appearance of the fluid is noted, after which the CSF, in separate tubes, is subjected to some of the following determinations: (1) number and type of cells and presence of micro-organisms; (2) protein and glucose content; (3) exfoliative cytology, using a Millipore filter or similar apparatus; (4) protein electrophoresis and immunoelectrophoresis f_{or} determination of gamma globulin, other protein fractions, and $_o$ligoclonal bands; (5) biochemical and spectrophotometric tests for substances elaborated by tumors, pigments, lactate, NH_3, pH, CO_2, enzymes, etc.; and (6) bacteriological cultures, polymerase chain reaction for the detection of mycobacterial, herpesvirus and cytomegalovirus DNA, viral serology, and virus isolation (Table 1.)

Table 1.

Average values of constituents of normal CSF and serum

	Cerebrospinal fluid	**Serum**
Osmoiarity	295 mosmol/L	295 mosmol/L
Sodium	138.0 meq/L	138.0 meq/L
Potassium	2.8 meq/L	4.1 meq/L

Calcium	2.1 meq/L	4.8 meq/L
Magnesium	2.3 meq/L	1.9 meq/L
Chloride	119 meq/L	101.0 meq/L
Bicarbonate	23.0 meq/L	23.0 meq/L
Carbon dioxide tension	48 mmHg	38 mmHg (arterial)
pH	7.33	7.41 (arterial)
Nonprotein nitrogen	19.0 mg/dL	27.0 mg/dL
Ammonia	30.0 g/dL	70.0 g/dL
Uric acid	0.24 mg/dL	5.5 mg/dL
Urea	4.7 mmol/L	5.4 mmol/L
Creatinine	1.1 mg/dL	1.8 mg/dL
Phosphorus	1.6 mg/dL	4.0 mg/dL
Total Hpid	1.5 mg/dL	750.0 mg/dL
Total cholesterol	0.4 mg/dL	180.0 mg/dL
Cholesterol esters	0.3 mg/dL	126.0 mg/dL
Glucose	60 mg/dL	90.0 mg/dL
Lactate	1.6 meq/L	1.0 meq/L
Total protein	15-50 mg/dL	6.5-8.4 g/lOOdL
Prealbumin	1-7%	Trace
Albumin	49-73 %	56%
Alpha 1 globulin	3-7 %	4%
AIpha2 globulin	6-13%	10%
Beta globulin (betaj plus tau)	9-19%	12%
Gamma globulin	3-12%	14%

Pressure and Dynamics. In the patient being in the lateral decubitus position, the CSF pressure is measured by a manometer attached to the needle in either the lumbar subarachnoid space or the cisterna magna. In the normal adult, the opening pressure varies from 100 to 180 mm H_2O, or 8 to 14 mm Hg. In children, the pressure is in the range of 30 to 60 mm H_2O. A pressure above 200 mm H_2O in the patient relaxed and legs straightened reflects the presence of increased intracranial pressure. Pressures of 50 mm H_2O or below in an adult indicates intracranial hypotension. When measured with the needle in the lumbar sac in the patient in a sitting position, the fluid in the manometer rises to the level of the cisterna magna (pressure is approximately double that obtained in the recumbent position). It fails to reach the level of the ventricles because the latter are in a closed system under slight negative pressure, whereas the fluid in the manometer is influenced by atmospheric pressure. Normally, with the needle properly placed in the subarachnoid space, the fluid in the manometer oscillates through a few millimeters in response to the pulse and respiration and rises promptly with coughing, straining, or abdominal compression.

The presence of a spinal subarachnoid block can be confirmed by jugular compression. First one side of the neck is compressed, then the other one, and then both sides simultaneously, with enough pressure to compress the veins but not the carotid arteries (Queckenstedt test). In the absence of subarachnoid block, there is a rapid rise in pressure of 100 to 200 mm H_2O and a return to its original level within 10 s after release. Failure of the pressure to rise with the use of both maneuvers usually means that the needle is improperly placed. A rise in pressure with abdominal compression (coughing or straining) but not with jugular compression indicates a spinal subarachnoid block. Failure of the pressure to rise with compression of one jugular vein but not the other (Tobey-Ayer test) may indicate lateral sinus thrombosis. These tests are now rarely used, having been replaced by more precise and less hazardous imaging techniques, but they remain useful in appropriate circumstances. Jugular compression should never be performed when an intracranial disease is present or suspected.

Gross Appearance and Pigments. Normally the CSF is clear and colorless, like water. Minor degrees of color change are best detected by comparing tubes of CSF and water against a white background (by daylight rather than fluorescent illumination) or by looking down into the tubes from above. A pleocytosis imparts a hazy or ground-glass appearance; at least 200 red blood cells (RBC) per cubic millimeter (mm^3) must be present to detect this change. The presence of 1,000 to 6,000 RBC/mm^3 imparts a hazy pink to red color, depending on the

amount of blood; centrifugation of the fluid or allowing it to stand causes sedimentation of the RBC. A traumatic tap can seriously confuse the diagnosis if it is incorrectly interpreted to indicate a pre-existent subarachnoid hemorrhage. To distinguish between a traumatic and pre-existent subarachnoid hemorrhage type of "bloody tap," two or three samples of fluid should be taken during the lumbar puncture. With a traumatic tap, there is usually a decreasing number of RBC in the second and third tubes. Also with a traumatic tap, the CSF pressure is usually normal, and if a large amount of blood is mixed with the fluid, it will clot or form fibrinous webs. These are not seen with pre-existent hemorrhage because the blood has been greatly diluted with CSF and defibrinated. With subarachnoid hemorrhage, the RBC begin to hemolyze within a few hours, imparting a pink-red discoloration (erythrochromia) to the supernatant fluid; allowed to stand for a day or two, the fluid becomes yellow-brown (xanthocromia). Prompt centrifugation of bloody fluid from a traumatic tap will yield a colorless supernatant; only with large amounts of blood (RBC over 100,000/mm^3) will the supernatant fluid be faintly xanthochromic due to contamination with serum bilirubin and lipochromes.

The fluid from a traumatic tap should contain about one white blood cell (WBC) per 1,000 RBC assuming that the hematocrit is normal, but this ratio varies widely and unpr edict ably. With subarachnoid hemorrhage, the proportion of WBC rises as RBC hemolyze, sometimes reaching a level of several hundred per cubic millimeter; but because of the vagaries of this reaction it cannot be relied upon to distinguish the traumatic bleeding from the pre-existent one. The same can be said about crenation of RBC, which occurs in both types of bleeding.

The reason why red corpuscles undergo rapid hemolysis in the F is not clear. It is surely not due to osmotic differences, for osmolarity of plasma and CSF are essentially the same. Fish-roan suggests that the low protein content of CSF disequilibrates the red cell membrane in some way. The explanation for the rapid Phagocytosis of RBC in the CSF, which begins within 48 h, is also obscure. Histiocytes phagocytize the red cells, forming macrophages, and hemosiderin appears in their cytoplasm within 5 to 6 days. The pigments that discolor the CSF following subarachnoid hemorrhage are oxyhemoglobin, bilirubin, and methemoglobin; in pure form, these pigments are colored red (orange to orange-yellow with dilution), canary yellow, and brown, respectively. Mixtures of these pigments produce combinations of these colors. Oxy-hemoglobin appears first, within several hours of the hemorrhage, becomes maximal in about 36 h, and if no further bleeding occurs, diminishes over a 7- to 9-day period. Bilirubin begins to appear in 2 to 3 days and increases in amount as the oxyhemoglobin decreases. Bilirubin persists in the CSF for 2 to 3 weeks, the duration varying with the number of RBC that were present originally. Methemoglobin appears when hemorrhage is loculated or encysted and isolated from the flow of CSF. Spectrophotometric techniques can be used to distinguish the various hemoglobin breakdown products and thus determine the approximate time of bleeding, as well as detect a traumatic tap.

If blood is added to CSF in a test tube and allowed to stand for several days, oxyhemoglobin and then methemoglobin will form but not bilirubin, suggesting that the action of living cells is necessary for the formation of the latter pigment. Barrows and his colleagues have devised three simple biochemical tests that reliably indicate the presence or absence of these pigments as a benzidine reaction (for oxyhemoglobin), a modified Van den Bergh reaction (for bilirubin), and a potassium cyanide test (for methemoglobin). Not all xanthochromia of the CSF is due to hemolysis of RBC. With severe jaundice, bilirubin of both the direct- and indirect-reacting types will diffuse into the CSF. The quantity of bilirubin is from one-tenth to one-hundredth that in the serum. An elevation of CSF protein for some reason or other results in a faint opacity and xanthochromia, more or less in proportion to the albumin-bound fraction of bilirubin. Only at levels of more than 150 mg/100 mL the coloration appears due to protein become visible to the naked eye. Hypercarotenemia and hemoglobinemia (through its break-down products, particularly oxyhemoglobin) also impart a yellow tint to the CSF. Myoglobin does not enter the CSF, probably because a low renal threshold for this pigment permits rapid blood clearance.

Ceilularity. During the first month of life, the CSF may contain a small number of mononuclear cells. Beyond this period, the CSF normally contains no cells or mostly up to five lymphocytes or other mononuclear cells per a cubic millimeter. An elevation of WBC in the CSF always signifies a reactive process to bacteria or other infectious agents, blood, chemical substances, or a neoplasm or vasculitis. The WBC can be counted in an ordinary counting chamber, but their identification requires centrifugation of the fluid and a Wright stain of the sediment or the use of a Millipore filter, cell fixation, and staining. One can then recognize and count differentially neutrophilic and eosinophilic leukocytes (Hodgkin's disease, parasitic infection, cholesterol

emboli), lymphocytes, plasma cells, mononuclear cells, arachnoidal lining cells, macrophages, and tumor cells. Bacteria, fungi, and fragments of echinococci and cystjcerci can also be seen in cell-stained or Gram-stained preparations. An India-ink preparation is useful in distinguishing between lymphocytes and cryptococci or *Candida.* On occasion, acid-fast bacilli will be found in appropriately stained samples. The monographs of Dufresne and of den Hartog-Jager and the article of Bigner are excellent references on CSF cytology. Special immu-nostaining techniques applied to cells of the CSF permit the recognition of lymphoma cell markers glial fibrillary protein and car-cinoembryonic and other antigens. Electron microscopy permits more certain identification of tumor cells and may demonstrate such substances as phagocytosed fragments of myelin (e.g., in multiple sclerosis). These and other special methods for the examination of cells in the CSF are mentioned in the appropriate chapters.

Proteins. In contrast to the high protein content of blood (5,500 to 8,000 mg/dL), that of the lumbar spinal fluid is 45 mg/dL or less in the adult. The protein content of CSF from the basal cisterns is 10 to 25 mg/dL and that from the ventricles is 5 to 15 mg/dL, reflecting a ventricular-lumbar gradient in the permeability of capillary endothelial cells to protein (blood-CSF barrier) and a lesser degree of circulation in the lumbosacral region. In children, the protein concentration is somewhat lower at each level (less than 20 mg/dL in the lumbar subarachnoid space). Levels higher than normal indicate a pathologic process in or near the ependyma or meninges either in the brain, spinal cord, or nerve roots though the cause of modest elevations of the CSF protein frequently remains obscure.

As one would expect, bleeding into the ventricles or subarachnoid space results in spillage not only of RBC but of serum protems. If the serum protein concentrations are normal, the CSF protein should increase by about 1 mg per 1,000 RBC provided that the same tube of CSF is used in determining the cell count and protein content. Because of the irritating effect of hemolyzed RBC upon the leptomeninges, the CSF protein may be increased many times by this ratio.

The protein content of the CSF in bacterial meningitis, in which perfusion in choroidal and meningeal capillaries is increased, often reaches 500 mg/dL or more. Viral infections induce a less intense and mainly lymphocytic reaction and a lesser elevation of protein is usually 50 to 100 mg but sometimes it reaches 200 mg/dL; in some instances the protein content is normal. Para ventricular tumors, by reducing the blood-CSF barrier, often raise the total protein to over 100 mg/dL. Protein values as high as 500 mg/dL or even higher are found in exceptional cases of the Guillain-Barre syndrome and chronic demyelinating polyneuropathy. Values of 1,000 mg/dL or more usually indicate loculation of the lumbar CSF (CSF block); the fluid is then deeply yellow and clots readily because of the presence of fibrinogen. This combination of CSF changes is called the *Froin syndrome.* Low CSF protein values are sometimes found in meningismus (a febrile illness with signs of meningeal irritation but normal CSF), in the condition known as meningeal hydrops, in hyperthyroidism, or after a recent lumbar puncture.

The quantitative partition of CSF proteins by electrophoretic and immunochemical methods demonstrates the presence of most of the serum proteins with a molecular weight of less than 150,000 to 200,000. The protein fractions that have been identified electrophoretically are prealbumin and albumin as well as α1, α2, β1, β2, and gamma globulin. Immuno-electrophoretic methods have also demonstrated the presence of glycoproteins, haptoproteins, ceruloplasmin, transferrin, and hemopexin. Large molecules, such as fibrinogen, IgM, and lipoproteins, are mostly excluded from the CSF.

There are other notable differences between the protein fractions of CSF and plasma. The CSF always contains a prealbumin fraction and the plasma does not. Although derived from plasma, this fraction, for an unknown reason, concentrates in the CSF, and the level is greater in ventricular than in lumbar CSF (perhaps because of its concentration by choroidal cells). Also, the CSF β2 or tau fraction (transferrin) is proportionally larger than that in the plasma and again higher in the ventricular than in the spinal fluid. The gamma globulin fraction in CSF is about 70 percent of that in serum.

At present only a few of these proteins are known to be associated with specific diseases of the nervous system. The most important is IgG, which may exceed 12 percent of the total CSF protein in such diseases as multiple sclerosis, neurosyphilis, subacute sclerosing panencephalitis, and other chronic viral meningoencephalitides. The serum IgG is not correspondingly increased, which ns ₜhat this immune globulin must originate in the nervous system. However, an elevation of serum gamma globulin as occurs in irrhosis, sarcoidosis, myxedema, and multiple myeloma will be accompanied by a rise in the CSF gamma globulin. Therefore, in natients with an elevated CSF gamma globulin, it is also necessary to determine the electrophoretic patterns of the serum proteins. Certain qualitative changes in the CSF gamma globulin pattern, particularly

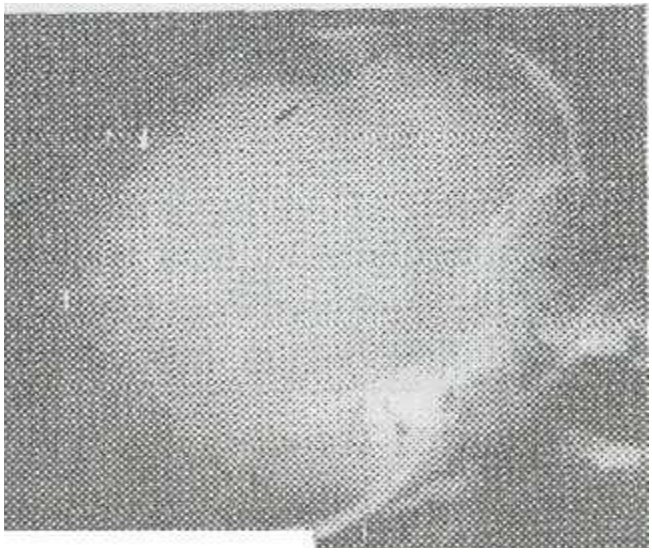
the demonstration of discrete (oligoclonal) bands, are of special diagnostic importance in multiple sclerosis and subacute sclerosing panencephalitis.

The albumin fraction of the CSF increases in a wide variety of central nervous system (CNS) and cranio-spinal nerve root diseases that increase the permeability of the blood-CSF barrier, but no specific clinical correlations can be drawn. Certain enzymes that originate in the brain, especially creatine kinase (CK-BB), are also found in the CSF after stroke or trauma and are used as markers of damage in experimental work.

RADIOGRAPHIC EXAMINATION OF SKULL AND SPINE

For a long time plain films of the cranium constituted a "routine" part of the study of the neurologic patient, but it is now evident that the yield of useful information from this procedure is relatively small. Even in patients with head injury, where radiography of the skull would seem to be an optimal method of examination, a fracture is found in only 1 out of 16 cases, at a cost of thousands of dollars per fracture and a small risk from radiation exposure. Nevertheless plain skull films are eminently useful in demonstrating fractures, changes in contour of the skull, bony erosions and hyperostoses, infection in paranasal sinuses and mastoids, and changes in the basal foramina (Fig.3.).

Fig.3. Radiography.Growingfracfilms of the child's skull.



Sequential refinements of technique such as pneumoencephalography, carotid and vertebral arteriography, and serial autotomography greatly increased the yield of valuable information in special cases, but without question the most important recent advances in neuroradiology, and indeed in neurosurgery, have come about with the development of computed tomography (CT) and magnetic resonance imaging (MRI) .

Computed Tomography

In this procedure the X-ray attenuation coefficients of the skull, CSF, cerebral gray and white matter, and blood vessels are measured with computer assistance. This major achievement in mathematical methodology, attributed to Hounsfield and others, permitted the astonishing technologic advance from plain radiographs of the skull to reconstructed images of

the cranium and its contents in any plane. More than thirty thousand 2- to 4-mm X-ray beams are directed successively at several horizontal leves of the cranium. The differing densities of bone, CSF, blood, and gray and white matter are distinguishable in the resulting picture. One can see haemorrhage, softened and edematous brain, abscess, and tumor tissue as well as the precise size and position of the ventricles and midline structures. The radiation exposure is not significantly greater than that from plain skull films.

The latest generation of CT scanners affords pictures of brain, spine, and orbit of great clarity. In the transverse section of the brain one actually sees displayed the caudal and lenticular nuclei, the internal capsules and thalami. The position and width of all main sulci can be measured, and the optic nerve and medial and lateral rectus muscles stand out clearly in the posterior parts of the orbit. The brain-stem, cerebellum, and spinal cord are easily visible in the scan at appropriate levels. The scans are also useful in imaging parts of the body that surround peripheral nerves and plexuses, thereby demonstrating tumours, inflammatory lesions, and haematomas that involve these nerves. In imaging of the head, CT has a number of advantages over MRI, the most important being safety when metal is present in the body and the clarity of imaging of blood from the moment it is shed. Other advantages are its lower cost, easy availability, shorter examination time, and superior visualization of calcium and fat. A novelty just 20 years ago, CT is now an integral part of diagnostic neurosurgery and within the reach of virtually every patient who needs it. CT images of many of the common lesions of the brain are included in the appropriate chapters of this book.

Magnetic Resonance Imaging

Magnetic resonance imaging, formerly referred to as nuclear magnetic resonance, also provides "slice" images of the brain in any plane, but it has the great advantages over CT of using non-ionizing energy and providing better resolution of different structures within the brain and other organs. For many neurological diseases, it has replaced CT.

MRI is accomplished by placing the patient within a powerful ptic field which causes the protons of the tissues and CSF to align themselves in the orientation of the magnetic field. Introduction a specific radio frequency (RF) pulse into the field causes Protons to resonate and to change their axis of alignment When *u* RF pulse is removed the protons return to their original ahgn*t* The RF energy that was absorbed and then emitted is deleted by electromagnetic devices and subjected to computer analysis, from which an image is constructed.

The images generated by the latest MRI machines are truly remarkable Because of the high degree of contrast between white fnd gray matter, one can identify all discrete nuclear structures and lesions within them. Deep lesions in the temporal lobe and structures in the posterior fossa and at the cervicomedullary junction are seen much better than with CT; the structures can be displayed in three planes and are unmarred by bony artifact. Demyehnative lesions stand out with greater clarity and infarcts can be seen at an earlier stage than with CT. Each of the products of disintegrated red blood corpuscles methemoglobin, hemosidenn, and terntm can be recognized, enabling one to date the age of hemorrhages and to follow their resolution. Similarly, CSF, fat, calcium, and iron have their own signal characteristics in different imaging sequences. Magnetic resonance imaging of the spine provides superbly clear images of the vertebral bodies, intervertebral discs, spinal cord and cauda equina, and of syringomyelia and other lesions (hermated discs, tumors, epidural or subdural hemorrhages and abscesses), it promises to replace contrast myelography.

The administration of gadolinium, a so-called paramagnetic agent that enhances the process of proton relaxation during MRI, permits even sharper definition of lesions.

The degree of cooperation required to perform MRI limits its use in young children as well as in the mentally confused and retarded. Studying a patient who requires a ventilator is difficult but manageable by using either hand ventilation or nonferromagnetic ventilators (Barnett et al). The main dangers in the use of MRI are torque or dislodgement of metal clips on blood vessels, of dental devices and other ferromagnetic objects, and of small metal fragments in the orbit, often acquired unnoticed ᵇУ operators of machine tools. For this reason it is wise, in appropriate patients, to obtain plain radiographs of the skull so ᵃˢ to detect metal in these regions. The presence of a cardiac pacemaker is an absolute contraindication to the use of *ЬI* since the magnetic field induces unwanted currents in the e vice and the wires exiting from it.

Because of the development of cataracts in fetuses of animals exposed to MRI, there has been hesitation in performing MRI in pregnant patients, especially in the first trimester.

However, cur. rent data indicate that it may be performed in such patients provided that the study is medically indicated. In a study of 1000 pregnant MRI technicians who entered the magnetic field frequently (the magnet remains on between procedures), no adverse effects upon the fetus could be discerned. Also it is considered safe to per-form cranial MRI in patients with hip prostheses, wire sutures, and some types of heart valves, as well as special cerebral aneurysm clips composed of titanium. MRI entails some risk unless there is direct knowledge of the type of prosthetic material. There have been several instances over the years in which physicians have rushed into the MRI room to assist an acutely ill patient, only to have their metal instruments drawn from their pockets and forcibly strike the patient or magnet.

Many types of MRI artifacts are known, most having to do with malfunctioning of the electronics of the magnetic field or of the mechanics involved in the imaging procedure. Among the most common and problematic are CSF flow artifacts in the thoracic spinal cord, giving the impression of an intradural mass; distortions of the appearance of structures at the base of the brain from ferromagnetic dental appliances; and lines across the entire image, induced by blood flow and patient movement. Also, at present, MR images often show alterations of periventricular and central white matter that have no clinical correlations and are uninterpretable.

The MRI device is costly and requires special housing and cooling to contain its powerful magnetic field. Nevertheless, as with CT earlier, MRI machines have proliferated and the technique has become indispensable for neurological diagnosis. In most clinical circumstances, as noted above, it is advantageous to proceed directly to MRI after the clinical analysis.

The technology of MRI is evolving constantly. The visualization of blood vessels in the CNS (MR angiography, see further on) and of developmental defects of the CNS are among the newer and more promising applications of MRI. Every few months there appears some refinement in the interpretation of signal characteristics and morphologic changes as well as new ways of using this technology in the study of brain metabolism and blood flow ("functional" or fMRI). The capacity of MRI to quantitate the volume f anatomic structures offers the prospect of demonstrating neuronal atrophies. Both physiologists and experimental psychologists - re adapting MRI techniques to study changes in blood flow during nervous and mental activity.

Angiography

This technique has evolved over the last 50 years to the point where it is relatively safe and an extremely valuable method for the diagnosis of aneurysms, vascular malformations, narrowed or occluded arteries and veins, arterial dissections, and angiitis. Since the advent of CT and MRI, the use of angiography has practically been limited to the diagnosis of these disorders.

Following local anesthesia, a needle is placed in the femoral or brachial artery; a cannula is threaded through the needle and then along the aorta and the arterial branches that are to be visualized. In this way, a contrast medium can be injected to visualize the arch of the aorta, the origins of the carotid and vertebral systems, and the extent of these systems through the neck into the cranial cavity. Highly experienced arteriographers can visualize the spinal cord arteries, cerebral arteries down to about 0.1 mm in lumen diameter (under optimal conditions), and small veins of comparable size.

Angiography is not altogether without risk. High concentrations of the injected medium may induce vascular spasm and occlusion, and clots may form on the catheter tip and embolize the artery. Overall morbidity from the procedure is about 2.5 percent, mainly in the form of worsening of a pre-existent vascular lesion or from complications at the site of artery puncture. Occasionally a frank ischemic lesion is produced, leaving the patient liemiplegic or quadriplegic; for these reasons the procedure should not be undertaken unless it is absolutely necessary. There may be an increased risk of stroke or transient ischemic attacks (TIAs) in migraineurs, particularly if there have been recent cerebral symptoms related to migraine. A cervical myelopathy is an infrequent but disastrous complication of vertebral artery dye injection; heralded by local pain in the dorsal neck mediately after injection. Progressive cord ischemia from an ill-defined vascular pathology ensues over the following hour The same complication may occur at other levels of the cord win visceral angiography.

A refinement of angiographic technique digital subtraction angiography uses digital computer processing of radiologic data to produce images of the major cervical and intracranial arteries The great advantages of this procedure are that the vessels can be visuahzed with relatively small amounts of dye it can be accomplished with smaller catheters than in standard angiography. The

arterial route is now used exclusively for dye injection. With modern computer techniques the resulting images often exceed the resolution of the standard "cut film" technique.

Magnetic Resonance Angiography. This is the newest noninvasive **technique** for visualizing the main intracranial arteries and can reliably detect extracranial carotid artery stenosis (Fig 8, 9). The technique approaches but has not yet reached the sensitivity of invasive angiography but is very useful in gauging the patency of the large cervical and basal vessels. The use of this and other methods for the investigation of carotid artery disease (Doppler flow and imaging techniques) is discussed further, on cerebral vascular disease.

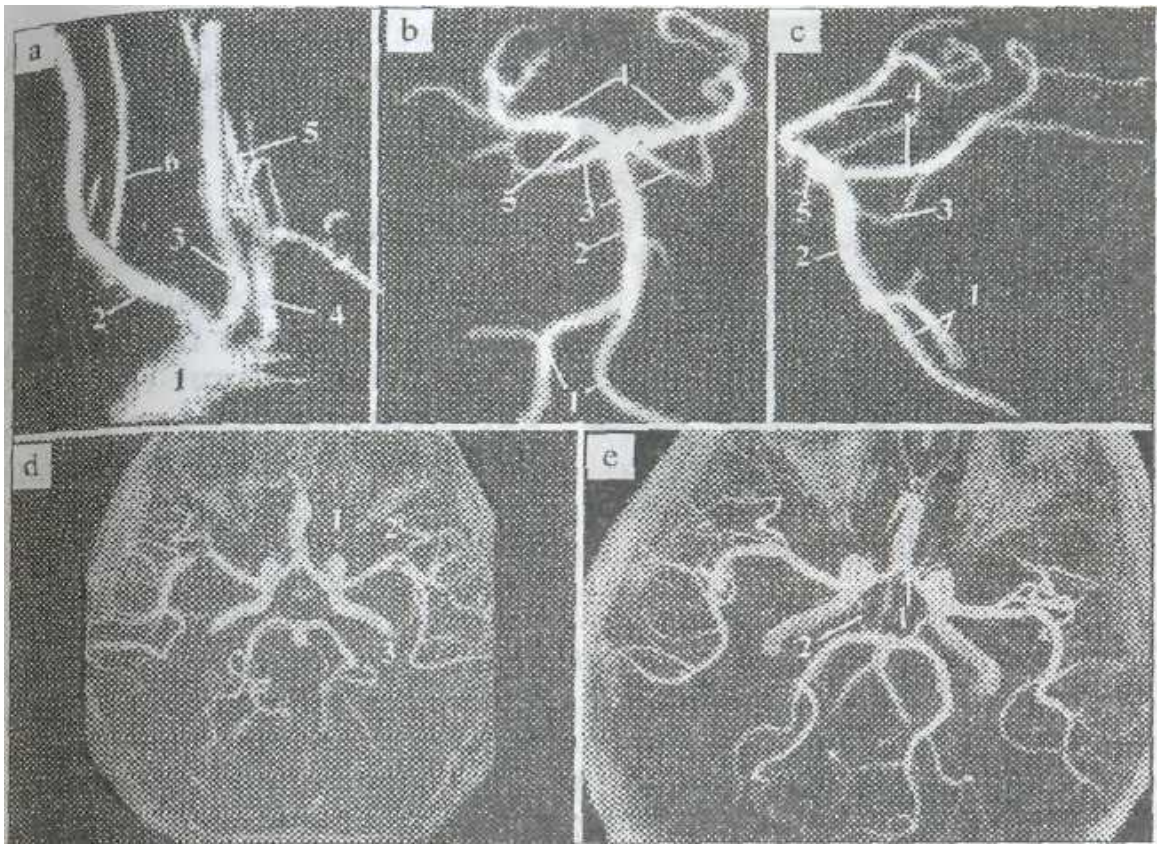


Fig. 8. MR-ANGIOGRAPHY. a) MR-angiogram of the arch of the aorta with departing main arteries (a direct projection). 1 —-the arch of an aorta, 2 — a brachycephalic trunk, 3 — the left carotid, 4 — the left subclaviaf artery, 5 — the left vertebral artery, 6 — the right vertebral artery.

MR-angiogram of vessels of vertebrobasilar system in a straight line (b) and oblique (c) projections. 1 — vertebral arteries, 2 — basilar artery, 3 — superior cerebeilar artery, 4 — posterior cerebral artery, 5 — posterior communicant artery.

MR-angiogram of vessels of the brain (d) 1 — anterior cerebral artery, 2— middle cerebral artery, 3 — posterior cerebral artery,

MR-angiogram of vessels of the brain (e) I — anterior communicant artery, 2 — posterior communicant artery

]Positron Emission Tomography

This technique, commonly known as PET, measures the cerebral concentration of systemically administered radioactive tracers. Positron-emitting isotopes (usually $^{i(}$C, ^{I8}F, ^{13}N, and ^{I5}O) are produced in a cyclotron or linear accelerator'and'incorpo-rated into biologically active compounds in the body. The concentration of the tracers in various parts of the brain is determined noninvasively, by detectors outside the body, and tomo-graphic images are constructed by techniques similar to those used in CT and MR I.

Cerebral blood flow, oxygen uptake, and glucose utilization can be measured by PET scanning, and the procedure has proved to be of value m grading primary brain tumors, distinguishing tumor tissue from radionecrosis, localizing epileptic foci, and differentiating types of dementing diseases. As yet, this technology is found in relat$_1$vely few medical centers and is not available for routine diagnosis (Fig. 10).

Single Photon Emission Computed Tomography

This technique (SPECT), which has evolved from PET, utilizes topes that do not require a cyclotron for their production. Here (so the isotopes (usually iodine-containing) are incorporated into biologically active compounds and their distribution is plotted. This procedure allows the study *of* cerebral blood flow, intense tissue metabolism (seizure discharge), neuroreceptors, and metabolism of glucose and amino acids, As with PET, the clinical potential of this technique has yet to be fully realized.

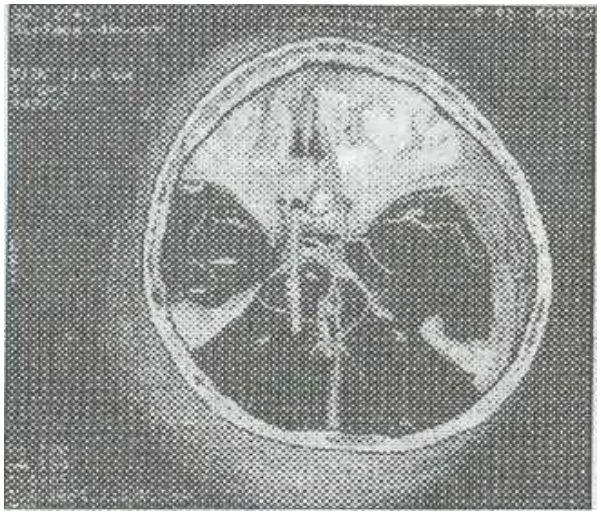


Fig. 9. 3D CT angiography

Ultrasound Scanning

In recent years this techniqu$_e$ has been refined to the *pouį* where it has become the principal methodology for clinical study of the fetal and neonatal brain. The instrument for this application consists of a transducer capable of converting
electrical energy to ultrasound waves of a frequency ranging from 5 to 20 kHz. These are transmitted through the intact skull into the brain. The different tissues have variable acoustical impedance and send echoes back to the transducer, which displays them as waves of variable height or as points of light of varying intensity. In this way one can obtain images of choroid plexuses, ventricles, and central nuclear masses. Usually several coronal and parasagittal
views are obtained. Intracerebral and subdural hemorrhages, s lesions, and congenitl defects can readily be visualized.

Similar instruments are used to insonate the basal vessels of the circle of Willis, and the cervical carotid and vertebral arteries for the study of cerebrovascular disease. Their greatest use is in providing accurate estimates of the degree of stenosis of the origin of the internal carotid artery.

This methodology has several advantages, notably that it is noninvasive, harmless (hence can be used repeatedly), convenient because of the portability of the instrument, and inexpensive.

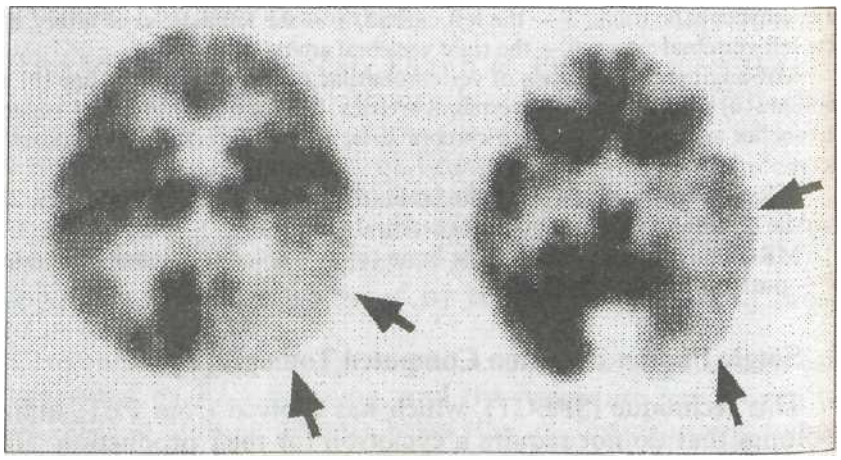


Fig. 10. PET. Typical parieto-occipito-temporal distribution (arrows) of hy-pometabolism seen with positron emission tomography using 18F-fluorodeoxy-glucose, in a patient with normal findings on magnetic resonance imaging. The darker areas represent higher metabolic rates

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Contrast Myelography

By injecting 5 to 25 mL of a radiopaque dye e.g., iopamidol (Isovue) through a lumbar puncture needle and then tipping the patient on a tilt table, the entire spinal subarachnoid space can be visualized. The procedure is almost as harmless as the lumbar puncture except for cases of complete spinal block, in which high concentrations of dye near the block can cause pain and regional myoclonus. Ruptured lumbar and cervical discs, cervical spondylotic bars and bony spurs encroaching on the spinal cord or roots, and spinal cord tumors can be diagnosed accurately. Iophendylate (Pantopaque), a formerly used fat-soluble dye, is still approved by the FDA but is now employed only in special circumstances (e.g., visualizing the upper level of a spinal canal lesion that completely obstructs the flow of dye from below). If iophendylate is left in the subarachnoid space, particularly in the presence of blood or inflammatory exudate, it may incite a severe arachnoiditis of the spinal cord and brain.

The CT body scan also provides excellent images of the spinal canal and intervertebral fo-ramina in three planes, making the combination of water-soluble dye and CT scanning a useful means of visualizing spinal and posterior fossa lesions. Contrast myelography is particularly useful in visualizing small areas within the spinal canal such as the lateral recesses and spinal nerve root sleeves. Magnetic resonance imaging provides even sharper visualization of the spinal canal and its contents as well as the vertebral and intervertebral discs. It has largely replaced contrast myelography because it does not require lumbar puncture and it images lesions (in three planes) within the spinal cord with greater clarity.

NEUROLOGICAL CONDITIONS WITH ABNORMAL ELECTROENCEPHALOGRAM

Epilepsy

All types of generalized epileptic seizures are associated with some abnormality in the EEG provided that it is being recorded at the time. Also, the EEG is usually abnormal during the more restricted types of seizure activity. Exceptions are seizure states that originate in deep temporal, mesial, or orbital frontal foci, from which the discharge fails to reach the scalp in sufficient amplitude to be seen against the normal background activity of the EEG, particularly if there is well-developed alpha rhythm. In these cases, extra scalp leads in the anterior frontal and temporal regions (which are the most free of alpha frequencies) or sphenoidal leads may pick up the discharge, especially during sleep. In some of such cases, the only way in which this deep activity can be sampled is by inserting an electrode into the substance of the brain, but this procedure is applicable only to the relatively few patients who are undergoing craniotomy. More often, a grid of subdural electrodes is used intraoperatively to localize the cortical region that is generating seizures. Occasionally one may fail to record an EEG abnormality in the course of one of the types of focal seizure (sensory, jacksonian, partial complex, epilepsia partialis continua) or in polymyoclonus. Presumably this means that the neuronal discharge is too deep, discrete, fast, or asynchronous to be transmitted by voiume conduction through the skull and recorded via the EEG electrode, which is about 2 cm from the cortex. More often, a corn-pletely normal EEG during a seizure indicates a "pseudoseizure" or hysteria. Also, some non-cortical myoclonic discharges are not seen in the EEG. The absence, myoclonic, and grand mal patterns correlate closely with the clinical seizure type and may be present in milder form in the interictal EEG.

A fact of importance is that between seizures a single EEG recording will show a normal pattern in as many as 20 percent of patients with absence seizures and 40 percent of those with grand mal epilepsy (this percentage is less with repeated recordings). Anticonvulsant therapy also tends to diminish the interictal EEG abnormalities. The records of another 30 to 40 percent of epileptics, though abnormal between seizures, are nonspecifically so; therefore the diagnosis of epilepsy can be made only by the correct interpretation of clinical data in relation to the G abnormality.

Brain Tumour, Abscess, Subdural Haematoma, and Encephalitis

Intracranial mass lesions are associated with characteristic abnormalities in the EEG, depending on their type and location, in some 90 percent of patients. In addition to diffuse changes, the classic abnormalities are focal or localized slow-wave activity or, occasionally, seizure activity and decreased amplitude and synchronization of normal rhythms. Although the EEG may be diagnostic tally helpful in cases of brain tumor or abscess, particularly when integrated with the other laboratory and clinical findings, reliance is now placed almost exclusively on CT and **MRI.**

However, EEG may be of considerable value in the diagnosis of herpes simplex encephalitis; periodic high-voltage sharp waves and slow-wave complexes at intervals of 2 to 3 per second in the temporal regions are characteristic. The other infectious encephalitides are often associated with sharp or spike activity, particularly if there have been seizures.

Cerebrovascular Disease

The EEG is now little used in the differential diagnosis of vascular hemiplegia. The main practical value of the EEG lies in its ability to distinguish an acute lesion in the distribution of the internal carotid or other major cerebral artery, which almost always Produces an area of slowing in the appropriate region. In contrast, with a lacunar infarction deep in the cerebrum or brainstem, the surface EEG is usually normal despite prominent clinical abnormalitits. After 3 to 6 months, roughly 50 percent of patients with infarction in the territory of the middle cerebral artery have a mal EEG. Perhaps half these patients will have had normal even in the week or two following the stroke. A persistent abnormality is associated with a poor prognosis for

further recovery Large lesions of the diencephalon or midbrain produce bilaterally synchronous slow waves, but those of the pons and medulla (i.e., below the mesencephalon) are usually associated with a normal or near-normal EEG pattern despite catastrophic clinical changes.

Cerebral Trauma

Cerebral concussion in animals is accompanied by a transitory disturbance in the EEG, but in humans this is usually no longer evident by the time a recording can be made. Large cerebral contusions produce EEG changes similar to those described for cerebrovascular disease. Diffuse changes often give way to focal ones, especially if the lesions are on the lateral or superior surface of the brain, and these, in turn, usually disappear over a period of weeks or months. Sharp waves or spikes sometimes emerge as the focal slow-wave abnormality resolves and may precede the occurrence of posttraumatic epilepsy; serial EEGs may be of prognostic value in this regard. They may also aid in evaluating patients for subdural hematoma.

Diseases that Cause Coma and States of Impaired Consciousness

The EEG is abnormal in almost all conditions in which there is impairment of consciousness. There is a fairly close correspondence between the severity of acute anoxic damage from cardiac arrest and the degree of EEG slowing. The mildest forms are associated with generalized delta activity, intermediate forms with widespread delta waves and the loss of normal background activity, and the most severe forms with "burst-suppression", in which the recording is almost isoelectric for several seconds, followed by high voltage sharp and irregular delta activity.

A unique pattern is that of "alpha coma," in which an apparent alpha rhythm in the 8- to 12-Hz range is distributed widely over the hemispheres rather than posteriorly; when analyzed by computer techniques, this apparent alpha is found not to be monorhythmic, like normal alpha, but instead varies in frequency in a narrow band. This is usually a transitional pattern after global anoxia; [c often alpha coma may be seen with acute large pontine lesions. Both burst suppression and alpha coma are usually transitional patterns leading to severe generalized slowing and voltage reduction or to electrocerebral silence.

With severe *hypothyroidism*, the brain waves are normal in configuration but usually of decreased frequency. In general, the more profound the depression of the state of consciousness, the more abnormal the EEG recording. In states of deep stupor or coma, the slow (delta) waves are bilateral and of high amplitude and tend to be more conspicuous over the frontal regions. This pertains to such differing conditions as acute meningitis or encephalitis; disorders that severely derange blood gases, glucose, electrolytes, and water balance; uremia; diabetic coma; and impairment of consciousness accompanying the large cerebral lesions discussed above. In *hepatic coma*, the degree of abnormality in the EEG corresponds with the degree of confusion, stupor, or coma. Characteristic of hepatic coma are paroxysms of bilaterally synchronous large, sharp "triphasic waves", although such wave forms may also be seen with encephalopathies related to renal or pulmonary failure and with acute hydrocephalus.

An EEG may also be of help in the diagnosis of coma when the pertinent history is unavailable. Perhaps its greatest value in this situation is the disclosure of status epilepticus in the absence of obvious convulsions. It may also point to an otherwise unexpected cause, such as hepatic encephalopathy, intoxication with barbiturates or other sedative-hypnotic drugs, the effects of diffuse anoxia-ischemia, or hysteria (when the EEG is normal).

Special Applications of the EEG

The EEG is useful in the operating room to monitor cerebral activity during the increasingly extensive procedures of modern cardiovascular surgery. The basic EEG apparatus has long been available for indicating the level of anesthesia, and such simple equipment can be used by the anesthetist to monitor both the cardiac and cerebral activity of patients undergoing open-heart or carotid artery surgery. Focal slowing or the loss of the fast beta rhythm that is induced by anesthesia are the most specific findings of inraoperative ischemia. A similar type of monitoring in the intensive care unit has disclosed a surprisingly high incidence of inapparent seizures in neurologic patients with diverse disease.

In the neurosurgical operating room, the EEG can be records from the exposed brain (electrocorticogram); seizure patterns can be localized more precisely than from the scalp, so that resectjon of such physiologically abnormal tissue may be undertaken.

The EEG remains useful in neonatal and infant neurosurgery The normal patterns from the seventh month of fetal life through infancy and childhood have been established. Full maturation namely, the time when the stable adult pattern is achieved varies considerably, making interpretation difficult. However, certain changes, as described by Stockard-Pope and colleagues, are clearlj indicative of a developmental disorder or disease.

A number of interesting topographic analyses ("brain mapping") of the EEG and of evoked potentials (described below) have been undertaken in recent years, especially in psychiatric medicine. Their technical validity has so far not been well established and certain correlations for example, with dyslexia are still tenuous. There is, however, ongoing investigation in this field.

Evoked Potentials

The stimulation of sense organs or peripheral nerves evokes a response in the appropriate cortical receptive areas and a number of subcortical relay stations as well. However, one cannot place a recording electrode near the relay stations, nor can one detect tiny potentials of only a few microvolts among the much larger background activity in the EEG or EMG. The use of averaging methods, introduced by Dawson in 1954, and the subsequent development of computer techniques have provided the means of overcoming these problems. Initially, emphasis was on the study of late waves (over 75 ms after the stimulus) be- £ cause they are of high amplitude and easy to obtain. However, there is more clinical utility in recording the much smaller, so-called short-latency waveforms, which are modified at each relay station and recorded by distant electrodes ("far-field recording"). These waveforms are maximized by the computer to a I point where their latency and voltage can easily be measured. One of the most remarkable properties of evoked potentials is their resistance to anesthesia, sedative drugs and, in comparison to EEG activity, even damage of the cerebral hemispheres. I

This permits their use for monitoring the integrity of cerebral always in situations that render the EEG useless. The details of these techniques have been reviewed by Chiappa and colleagues. The interpretation of afferent evoked potentials (visual "auditory, and somatosensory) is based on the latency of the appearance of waveforms after the stimulus, the interwave latencies, and asymmetries in timing. Norms have been established, but it is still advisable to confirm these in each laboratory Typically 2.5 or 3 standard deviations above the mean latency for any measurement are taken as the definition of abnormality. The amplitudes of the waves are less informative.

Visual Evoked Potentials

For many years it had been known that a light stimulus flashing on the retina often initiates a discernable waveform over the occipital lobes. In the EEG, such responses to fast rates of stimulation are referred to as the occipital driving response. In 1969, Regan and Heron observed that a visual evoked response could be produced by the sudden change of a viewed checkerboard pattern. The responses produced in this way by rapidly repeating the pattern reversal were easier to detect and measure than flash responses and more consistent in waveform from one individual to another. It became apparent that this type of stimulus, applied first to one eye and then to the other, could demonstrate conductional delays in the visual pathways of patients who had formerly suffered from the disease of the optic nerve even though in some instances there were no residual signs of reduced visual acuity, visual field abnormalities, alterations of the optic nerve head, or changes in pupillary reflexes.

This procedure, called pattern-shift visual evoked responses (PSVER) or pattern-reversal visual evoked potentials, has been widev adopted as one of the most delicate tests of lesions in the visual system. Usually, abnormalities in the amplitude and duration of PSVER accompany the abnormally prolonged latencies, but they are difficult to quantify. The expected latency for the positive polarity PSVER is near 100 ms (thus the term "P 100"); an absolute latency over approximately 118 ms or a difference in latencies of greater than 9 ms between the two eyes signifies involvement of one optic nerve. Bilateral prolongation of latencies, demonstrated separate stimulation of each eye, could be due to lesions in both optic nerves, in the optic chiasm, or in the visual pathways posterior to the chiasm.

As indicated above, PSVER is especially valuable in detecting an active or residual disease of the optic nerve. Examinations of a large number of patients who were known to have had

retrobuj. bar neuritis showed that among 51 such patients, only 4 had normal latencies (Shahrokhi and co-workers). These authors found similar abnormalities of PSVER in about one-third of multiple sclerosis patients who had no history or clinical evidence of optic nerve involvement. The finding of abnormal PSVER in a patient with a clinically apparent lesion elsewhere in the CNS may usually be taken as evidence of multiple sclerosis.

A compressive lesion of the optic nerve will have the same effect as a demyelinative one. Many other diseases of the optic nerves, including toxic and nutritional amblyopias, ischemic optic neuropathy, and the Leber type of hereditary optic neuropathy show abnormalities of the PSVER. Glaucoma and other diseases involving structures anterior to the retinal ganglion cells may also cause increased latencies. Impaired visual acuity has little effect on the latency but does correlate well with the amplitude of the PSVER. By presenting the pattern-shift stimulus to one hemifield, it is sometimes possible to isolate a lesion to an optic tract, radiation, or one occipital lobe, but with less precision than that provided by the usual monocular test.

Brainstem Auditory Evoked Potentials

The cortical effects of auditory stimuli can be studied in the same way as visual ones, by a procedure called *brainstem auditory evoked responses, ox potentials* (BAERs, or BAEPs). Between 1,000 and 2,000 clicks, delivered first to one ear and then to the other, are recorded through scalp electrodes and maximized by computer. A series of seven waves appears at the scalp within 10 ms after each stimulus. On the basis of depth recordings, the study of lesions produced in cats, and pathologic studies of the brainstem in humans, it has been determined that each of the first five waves is generated by the brainstem structures. The generators of waves VI and VII are uncertain. Clinical interpretations of BAERs are based mainly on latency measurements of waves I, III**,** and V. The most important are the interwave latencies 1-III and III-Y. The presence of wave I and its absolute latency are of particular value in testing the integrity of the auditory nerve.

A lesion that affects one of the relay stations or its immediate connections manifests itself by a delay in its appearance and an absence or reduction in amplitude of subsequent waves. These effects are more pronounced on the side of the stimulated ear than contralaterally. This is difficult to understand, since a majority of the cochlear-superior olivary-lateral lemniscal-medial geniculate fibers cross to the opposite side. It is also surprising that a severe lesion of one relay station would allow impulses, even though delayed, to continue their ascent and be recordable in the cerebral cortex.

As indicated above, BAEPs are a particularly sensitive means of detecting lesions of the eighth cranial nerve (acoustic neuroma and other tumors of the cerebellopontine angle) and of the auditory pathways of the brainstem. Almost one-half of patients with definite multiple sclerosis and a lesser number with a possible or probable diagnosis of this disease will show abnormalities of the BAEPs (usually a prolongation of interwave latencies **I-III** or **III-**V), even in the absence of clinical symptoms and signs of brainstem disease. The BAEPs are also useful in assessing hearing in infants who have been exposed to ototoxic drugs, in young children, and in hysterical patients who feign deafness.

Somatosensory Evoked Potentials

Somatosensory evoked potentials (SEPs) are now being used in most clinical neurophysiology laboratories to confirm lesions in the somatic sensory systems. The technique consists of applying 5-per-second painless electrical stimuli to the median, peroneal, and tibi-al nerves and recording the evoked potentials (for the upper limb) over Erb's point above the clavicle, over the C-2 spine and over the opposite parietal cortex, and (for the lower limb) over the lumbar and cervical spines and the opposite parietal cortex. The impulses generated in large touch fibers by 500 or more stimuli and averaged by computer can be traced through the peripheral nerves, Final roots, and posterior columns to the nuclei of Burdach and Goll in the lower medulla, through the medial lemniscus to the contralateral thalamus, and thence to the sensory cortex of the parietal lobes. Delay between the stimulus site and Erb's point or lumbal spine indicates peripheral nerve disease; delay from Erb's point (or lumbal spine) to C-2 implies an abnormality in the appropriate roots or in the posterior columns; the presence of lesions in the medial lemniscus and thalamoparietal pathway can be inferred from delays of subsequent waves recorded from the parietal cortex. The normal waveforms are designated by the symbol P (positive) or N (negative), with a number indicating the interval of time in milliseconds from stimulus to recording (e.g., N11, N13 P13, P22, etc.). As a shorthand for the polarity and approximate latency, the summated wave that is

recorded at the cervicomedullary junction is termed "N/P 13", and the cortical potential from median nerve stimulation is seen in two contiguous waves of opposite polarity, called "N 19-P 22". The corresponding cortical wave after tibial or peroneal nerve stimulation is called "N/P 37." For purposes of clinical interpretation, the SEPs are assumed to be linked in series, so that interwave abnormalities in latency indicate a conduction defect between the generators of the two peaks involved. Recordings with pathologically verified lesions at these levels are to be found in the review by Chiappa and Jayakar. This test has been most helpful in establishing the existence of lesions in spinal roots, posterior columns, and bramstem in such disorders as Guillain — Barre syndrome, ruptured lumbar and cervical discs, multiple sclerosis, and cervical spondylosis even when the clinical data are uncertain. The resistance of these waves to anesthesia and other types of suppression has already been mentioned. The obverse has also proved to be true namely, that obliteration of the cortical waves (assuming that all preceding waves are unaltered) reflects profound damage to the somatosensory pathways in the hemisphere or to the cortex itself. As a corollary, the bilateral absence of cortical somatosensory waves after cardiac arrest is a powerful predictor of a poor clinical outcome. Likewise, the persistent absence of a cortical potential after stroke usually indicates such profound damage that only a limited clinical recovery is to be expected.

BIOPSY OF MUSCLE, NERVE, SKIN, TEMPORAL ARTERY, BRAIN, AND OTHER TISSUES

The application of light, phase, and electron microscopy to the study of these tissues may be highly informative. Temporal artery biopsy is indicated when giant cell arteritis is suspected. Brain biopsy, aside from the direct sampling of a suspected neoplasm, is often diagnostic in cases of granulomatous angiitis, some forms of encephalitis, subacute spongiform encephalopathy (biopsy per-t-or01ed infrequently because of the risk of transmitting the infectious agent), and a number of rare diseases. An important advance in recent years has been the use of CT guided stereotactic biopsy, which is particularly valuable in tumor diagnosis and exposes the patient to less risk than a craniotomy and open biopsy do. In choosing to perform a biopsy in any of these clinical situations, the paramount issue is the likelihood of establishing a definitive diagnosis that would permit successful treatment or otherwise enhance the management of the disease.