MCV/Q

MEDICAL COLLEGE OF VIRGINIA QUARTERLY
VOLUME THIRTEEN • NUMBER THREE • 1977

Acute Problems in Neurology

MCV/Q

MEDICAL COLLEGE OF VIRGINIA QUARTERLY

MEDICAL COLLEGE OF VIRGINIA QUARTERLY Published quarterly (Spring, Summer, Fall, Winter) by the Medical College of Virginia, Health Sciences Division of Virginia Commonwealth University. The QUARTERLY publishes articles of original research and review in basic and clinical sciences. Contributions from outside the Medical College of Virginia faculty are invited. Manuscripts should be prepared according to recommendations in the Stylebook/Editorial Manual, of the American Medical Association, Publishing Sciences Group, Inc., Sixth Edition, Littleton, (Mass), 1976.

Correspondence: MEDICAL COLLEGE OF VIRGINIA QUARTERLY, Box 26, Medical College of Virginia, Richmond, Virginia 23298. Phone (804) 770-4027.

Subscription rates (per year): U.S.A., Canada, and Mexico $10.00 (Individuals); $14.00 (Libraries and Institutions). All other countries $12.00 (Individuals); $15.00 (Libraries and Institutions). Interns, residents and students $4.00. Single copy $3.00.

Third class postage paid at Richmond, Virginia.

Editorial Advisory Board
GREGG L. HALLORAN
HUNTER H. MCGUIRE
J. CRAIG MCLEAN
KINLOCH NELSON
JOHN R. TAYLOR

Editorial Consultants
LARRY F. CAVAZOS *Boston*
FAIRFIELD GOODALE, JR. *Augusta*
RICHARD G. LESTER *Houston*
SAMI I. SAID *Dallas*
MALCOLM E. TURNER, JR. *Birmingham*

Editor
FREDERICK J. SPENCER

Managing Editor
MARY-PARKE JOHNSON

Cover Designer
RAYMOND A. GEARY

MCV/Q

MEDICAL COLLEGE OF VIRGINIA QUARTERLY

A Scientific Publication of the School of Medicine
Health Sciences Division of Virginia Commonwealth University

1977 • Volume Thirteen • Number Three

CONTENTS

Acute Problems in Neurology
JOHN R. TAYLOR, M.D., *Guest Editor*

Presented by the Departments of Neurology and Continuing Medical Education, School of Medicine, Medical College of Virginia, Health Sciences Division of Virginia Commonwealth University.

Introduction 82
JOHN R. TAYLOR, M.D.

Brain Death 83
CARY SUTER, M.D.

Acute Bilateral Ophthalmoplegias 88
JOHN B. SELHORST, M.D.

Coma in Infancy and Childhood 93
EDWIN C. MYER, M.D.

The Search for Optimal Management of Head Injury 97
J. DOUGLAS MILLER, M.D., PH.D.

A Diagnostic Approach to Acute Headache 107

ALAN B. GRINDAL, M.D.

Differential Diagnosis of Progressive Generalized or Symmetrical Flaccid Paralysis 112

EDWARD R. ISAACS, M.D.

Acute Seizure Problems 116

CARY SUTER, M.D.

Bacterial Meningitis: Some Epidemiologic and Clinical Factors in Diagnosis 123

VINCENT P. CALABRESE, M.D.

COVER: Engraving by H. Weydmans, Dutch, c. 1620. Operation for Stones in the Head. Translation of caption from the Dutch reads: "Come, come with great rejoicing; here the stones can be cut out of your wife." Reproduced from *Medicine and the Artist (Ars Medica)* by permission of the Philadelphia Museum of Art.

© 1977 by the Medical College of Virginia, Health Sciences Division of Virginia Commonwealth University
Printed by the Byrd Press, Richmond, Virginia

INTRODUCTION

This issue of the *MCV Quarterly* is devoted to a review of some of the problems in clinical neurology that present soon after onset and often require urgent evaluation and care. Problems such as seizures and headache are regular features of many types of practice. Others such as acute ophthalmoplegias are infrequently seen outside the field of neurology. Still others, for instance, head injury, are commonly seen but often require the attention of physicians with specialized training, such as Dr. Miller of the MCV Division of Neurosurgery. While every acute neurologic problem cannot be reviewed in a single issue, the selection here is designed to provide readers with information useful not only in their own practices but also valuable for all physicians to know.

With the exception of Dr. Miller, our contributors are from the MCV Department of Neurology. All of the papers were presented at the Neurology postgraduate conference at The Tides Inn, Irvington, Virginia, September, 1977.

JOHN R. TAYLOR, M.D.
Associate Professor
Department of Neurology

Brain Death*

CARY SUTER, M.D.

Professor and Chairman, Department of Neurology, Medical College of Virginia, Health Sciences Division of Virginia Commonwealth University, Richmond, Virginia

Until recently determination of death was simple. The heart stopped. There was no pulse, no recordable blood pressure, and no heart sounds. There was no breathing. Now, methods of cardiopulmonary resuscitation are common knowledge, both to the layman and to the physician.[1] Hospitals have special "Code Blue" teams; emergency rooms and intensive care units are superbly equipped for life support; hearts that stop are started again.[2] Machines do an excellent job of respiration. Nevertheless, the patient's brain may be dead and damaged beyond recovery, either in whole or in part. When the whole brain is seriously damaged, including the cerebral cortex and brain stem, there is no possibility of return to an independent existence and even machines cannot keep the person alive longer than a week or two. When the brain is partially damaged, particularly with destruction of portions or layers of the cortex, or connections to the cerebral cortex, the patient may indeed survive with brain stem function alone in a so-called "vegetative state."[3] In this condition spontaneous respiration will occur and if the patient is fed and carefully nursed he may survive for months or years.

In addition to the common occurrence of cardiopulmonary resuscitation, the practice of transplantation of human organs has added another dimension to the necessity for determination of "brain death." Organs such as kidneys can be maintained for a while outside the body, but for best results they should be removed from the body while still in a healthy state. As a result, extensive studies have been carried out in an attempt to devise proper and foolproof criteria for the determination of brain death.

*This work was supported in part by NIH Contract 71-2315.

Correspondence and reprint requests to Dr. Cary Suter, Department of Neurology, Box 698, Medical College of Virginia, Richmond, Virginia 23298.

Though the requests for determination of brain death are greater in the larger medical centers, the matter must often be faced in smaller hospitals. For this reason, knowledge of the possible outcome of the patient in deep coma is useful to the primary attending physician in advising the family as to the value of transfer to a larger medical center, or that brain death has occurred and donation of organs for transplantation would be reasonable.

The first widely accepted criteria for determination of brain death were prepared by a committee at the Massachusetts General Hospital and the Harvard Medical School.[4] Following the publication of this article in 1968, the so-called "Harvard criteria" were widely used in determination of brain death. Essential elements of these criteria include a complete lack of response on the part of the patient to painful or other stimuli; the complete absence of both cranial and spinal reflexes; the complete absence of spontaneous respiration; and the recording of an electroencephalogram (EEG) showing no evidence of brain activity (a so-called isoelectric EEG or EEG showing electrocerebral silence). The criteria further stated that these conditions should be met over a twenty-four-hour period, or that the findings exist on two examinations at least twenty-four hours apart. In addition, there should be no history of drug overdose and no severe hypothermia.

Since the use of the electroencephalogram to measure brain activity was a part of the Harvard criteria, it rapidly became evident that the electroencephalographic records must be made with the most exacting techniques. Cases were reported that showed isoelectric EEGs on two occasions, twenty-four hours apart, and the patient still survived. Studies of these cases carried out by a committee of the American Electroencephalographic Society showed that in most instances there were technical problems in the EEG

recording. A lack of use of proper distance between electrode placement and lack of use of the highest possible amplification were the most common errors. In addition, a number of cases occurred where the patients were reported to show brain activity in the EEG recording, but a review of the EEG records demonstrated this to be an artifact. The criteria for EEG recording in cerebral death have recently been published by the American EEG Society[5] and include:

1. A minimum of eight scalp electrodes and ear lobe reference electrodes.
2. Interelectrode impedances under 10,000 ohm but over 100 ohm.
3. Testing the integrity of the entire recording system.
4. Interelectrode distances of at least 10 centimeters.
5. Sensitivity increase from 7 (7.5) μV/mm to 2 μV/mm during most of the recording with inclusion of appropriate calibrations.
6. Use of time constants of 0.3 to 0.4 seconds during part of the recording.
7. Use of monitoring techniques.
8. Tests of EEG reactivity to intense stimuli such as pain (for example, pinch), loud sound, and (optionally) strong light (stroboscopic if available).
9. Recording time of at least 30 minutes.
10. Recordings to be made only by a qualified technologist.
11. Repeating EEG if there is doubt about electrocerebral silence.
12. Telephone transmission of EEG not to be used for determination of electrocerebral silence.

In addition, as a result of the National Institutes of Health (NIH) study on cerebral survival, an atlas of the EEG in coma and death has been published,[6] setting forth the proper criteria for recording and also demonstrating the great variety of artifacts which may hamper the demonstration of electrocerebral silence.

Over a period of time it became evident to a number of physicians in the neurosciences that the Harvard criteria were perhaps over-demanding. In an attempt to establish a wider experience and a broader-based study the National Institute of Neurological Diseases and Stroke supported a study on cerebral survival from 1970 to 1973. This was carried out in eight centers throughout the country, one of which was the Medical College of Virginia. A total of 503 patients were included in the major portion of this study, of which 87 came from MCV. Actually, many other patients were studied before, and an even larger number of patients have been studied since, at MCV.

This experience has led to criteria for brain death somewhat different from those of the Harvard criteria. It was quickly demonstrated that the presence of spinal reflexes such as deep tendon or muscle stretch reflexes was not a criterion for brain death. It was further demonstrated that the absence of cranial or cephalic reflexes was of major importance. This included, particularly, dilated fixed pupils, absence of oculocephalic reflexes, and the absence of spontaneous respiration. If these clinical findings existed and the patient's coma was not the result of an overdose of medication, or in rare cases due to hypothermia, then the electroencephalogram was almost invariably isoelectric and the outcome was always death. These criteria applied in patients examined six hours or more after the onset of their coma and lack of respiration. Studies at MCV, particularly, also demonstrated the usefulness of succinylcholine chloride injections or some similar muscle relaxant, such as pancuronium bromide (Pavulon), to remove muscle artifact in the EEG records, thereby making a more exact determination of electrocerebral silence.[7]

If any additional proofs of brain death might be needed, it had previously been demonstrated, especially in Europe,[8,9] that the dead brain did not show evidence of cerebral circulation. Cerebral arteriograms carried out in some patients showed little or no evidence of contrast in the vessels in the brain. A radioisotope method of studying cerebral circulation by injection of a bolus of radioactive material also demonstrated that patients meeting the other criteria for brain death showed no evidence of cerebral blood flow.[10]

Partly because of the interest in organ transplantation at MCV, the State of Virginia was one of the first states to pass a law concerning "brain death." The Virginia statute is printed at the end of this article.

In view of the Virginia law, and in view of our experience at MCV, the following constitutes our present criteria for determination of brain death. This is a personal evaluation used in our practice in the Department of Neurology and not an official document, either of MCV or of any other body. It con-

forms essentially, however, to the conclusions recently published in the final report of the NIH study of cerebral death.[11]

Criteria for Establishment of Brain Death (Cary Suter, M.D., Medical College of Virginia, 1977)

Where, from the history and medical record, it is clear that the patient has suffered a sudden and definable episode of brain damage, either from cerebral anoxia, severe head trauma or wounds, or sudden stoppage of respiratory function in the course of illness such as brain tumor, or cerebral hemorrhage, then the following conditions, if they are found six hours or more following such an insult and exist for a period of thirty minutes, shall be considered sufficient criteria for declaring brain death. These criteria shall include the absence of severe hypothermia and the absence of drug overdose; the presence for thirty minutes or more of electrocerebral silence recorded according to the standards set forth by the ad hoc committee of the American EEG Society and interpreted by a duly licensed physician who regularly functions as a specialist in electroencephalography; the absence for a period of thirty minutes of any evidence of cerebral responsivity to any stimuli; the absence of all cranial nerve reflexes; the presence of dilated fixed pupils; evidence that there is no spontaneous respiration. These findings must be confirmed by a consultant in Neurology or Neurosurgery and be reviewed and concurred in by the attending physician.

In the absence of a clear time of onset of the cerebral insult, then the above conditions must be met for a period of thirty minutes and recorded again six hours later for another period of thirty minutes. If, at this point, the attending physician, the consulting Neurologist or Neurosurgeon or the Electroencephalographer have any doubts that brain death has occurred then other tests (such as tests of cerebral blood flow) should be done and an additional period of time shall be allowed to elapse until the consultants and the attending physician agree that the criteria for brain death have been completely met.

It should be clearly understood by the physicians, nurses, and other paramedical personnel as well as by the patient's family that in the presence of brain death, regular cardiac function may remain quite a long time and also that spinal reflexes resulting in the reflex movements of the body below the neck may occur. It should also be understood that these criteria have not yet been established for infants or newborns.

It is easy to see that the conclusions quoted from the cerebral death study are very much like the above.[11] That study concluded that:

> Based on the findings in a collaborative study of 503 comatose and apneic patients, the establishment of cerebral death requires (1) that all appropriate examinations and the therapeutic procedures have been performed, (2) that cerebral unresponsivity, apnea, dilated pupils, absent cephalic reflexes, and electrocerebral silence be present for 30 minutes at least six hours after the ictus, and (3) that if one of these standards is met imprecisely or cannot be tested, a confirmatory test be made to demonstrate the absence of cerebral blood flow. This would allow the diagnosis of a dead brain to be made in patients with small amounts of sedative drugs in the blood, in patients undergoing therapeutic procedures that make examination of one or more of the cranial nerves impossible, and in patients otherwise meeting the criteria whose pupils are small.

Recently there have been published criteria of brain death, which do not include the electroencephalogram.[12] It is certainly true that those patients meeting the criteria of complete absence of cranial reflexes, absence of spontaneous respirations, absence of hypothermia and no overdose of drugs, and who maintain this condition for six hours, almost always have EEGs showing electrocerebral silence. Such persons, of course, also have lack of cerebral blood flow. In making a decision about a matter as serious as brain death it would seem that both a clinical and laboratory evaluation would be reasonable. Since the electroencephalographic examination can be made at the bedside and in general entails less difficulties than a test for cerebral blood flow, it would appear that the combination of the clinical examination and the electroencephalogram are adequate and useful methods for making the determination of brain death. For the physician in the hospital without EEG services, or with questionable portable EEG services, the establishment of brain death on the basis of clinical criteria alone can certainly be used as a preliminary base for a decision about transfer to another center or about the possibility of the use of organs for transplantation.

In the study of patients with possible brain death one of the most bothersome and practical problems is that of drug overdose or of medication with sedative or anticonvulsant drugs. Certainly routine laboratory screening for toxic substances should be carried out on each patient before brain death is determined. When specific drugs have been given, particularly anticonvulsant drugs, serum levels of these drugs should be measured so that it is clear that they are not at toxic levels. In the patient whose coma is originally due to drug overdose this fact alone should prohibit the diagnosis of brain death. It is true that many patients with overdose suffer secondary anoxic brain damage which is irreversible, but it is clear that patients with drug overdose may meet all the criteria for

brain death for a period exceeding twenty-four hours and still recover.

In determination of brain death, evaluation of the presence or absence of spontaneous respiration is essential. This becomes a difficult problem since removing the patient from the respirator for long periods might suggest that additional hypoxic damage might occur. If, however, intratracheal oxygen is administered, no hypoxia occurs and $Paco_2$ levels rise to a level sufficient to trigger spontaneous respiration if it can occur.[13]

As a practical matter, the test of time is sufficient for determination of brain death. In the NIH collaborative study no patient meeting the criteria of brain death survived longer than seven days. In our personal experience at the Medical College of Virginia this has also been true. Patients who meet the criteria even with attempts at support by drugs to maintain blood pressure and by respirators for breathing eventually show a drop in their blood pressure, and irreversible cardiac arrhythmias and cardiac standstill develop.

There are indeed patients who are in deep coma who survive in a vegetative state, but these patients are not ones who have met the criteria of brain death. We have seen a few patients with electrocerebral silence on EEG recording who still had cranial reflexes. Some of these patients eventually regained spontaneous respiration and continued to exist in a vegetative state. This has not happened to any of our patients who met both the clinical and electroencephalographic criteria for brain death.

Another factor that modifies decisions about brain death has to do with the underlying illness. Obviously, a patient with a clearly severe gunshot wound to the head or with an excessively large intracerebral hematoma demonstrated by computerized tomography (CT) scan or with a known rapidly progressive brain tumor has a dismal prognosis from the underlying illness regardless of any specific criteria of brain death. On the other hand, patients with cerebral anoxic damage from cardiac or pulmonary arrest may have severe or moderate brain damage and their condition may change rapidly with marked improvement over a matter of hours and days.[14] This is also true of patients with metabolic coma and, in fact, with coma of any type of unknown cause. In such patients criteria for establishment of brain death must be adhered to completely and without any question. The possibility of drug overdose must always be kept in mind. In all considerations of the literature on brain death it should be recognized that the criteria established have been for adults and that there is not a good enough or large enough series of cases to allow these criteria to be absolutely imposed on infants or young children. In general, experience has demonstrated that the same criteria are applicable to children from three to four years upward.

The many cases of deep coma which are publicized in newspapers and periodicals, some of which eventually recover, have at no time met the criteria of brain death. It is in these patients with severe but not complete brain damage that the most difficult problems of continued nursing care, life support, and the treatment of complications must be faced. No simple answers are available in this set of patients, including the great number of patients in the so-called vegetative state. Studies related to determination of brain death, including electroencephalograms,[15] and cerebral-evoked potentials[16] as well as clinical examination continue to give us more information about prognosis. The CT scan also allows improved assessment of possible structural intracranial lesions.

From this discussion, it should be recognized that the matter of determination of brain death has been extensively studied and the criteria as set forth can be applied routinely and with confidence so long as exacting clinical neurological examination is performed and a technically adequate electroencephalogram is performed. Since patients meeting these criteria almost never survive more than seven days, patients who survive longer almost certainly do not have brain death unless some additional insult to the brain occurs.

The Commonwealth of Virginia Statute concerning brain death:

§32-364.3:1. **When person deemed medically and legally dead.**—A person shall be medically and legally dead if, (a) in the opinion of a physician duly authorized to practice medicine in this State, based on the ordinary standards of medical practice, there is the absence of spontaneous respiratory and spontaneous cardiac functions and, because of the disease or condition which directly or indirectly caused these functions to cease, or because of the passage of time since these functions ceased, attempts at resuscitation would not, in the opinion of such physician, be successful in restoring spontaneous life-sustaining functions, and, in such event, death shall be deemed to have occurred at the time these functions ceased; or (b) in the opinion of a consulting physician, who shall be duly licensed and a specialist in the field of neurology, neurosurgery, or electroencephalography, when based on the ordinary standards of medical practice, there is the absence of spontaneous brain functions and spontaneous respiratory functions and, in the opinion of the attending physician and such consulting physician, based on the ordinary standards of medical practice and consid-

ering the absence of the aforesaid spontaneous brain functions and spontaneous respiratory functions and the patient's medical record, further attempts at resuscitation or continued supportive maintenance would not be successful in restoring such spontaneous functions, and, in such event, death shall be deemed to have occurred at the time when these conditions first coincide. Death, as defined in subsection (b) hereof, shall be pronounced by the attending physician and recorded in the patient's medical record and attested by the aforesaid consulting physician.

Nothwithstanding any statutory or common law to the contrary, either of these alternative definitions of death may be utilized for all purposes in the Commonwealth, including the trial of civil and criminal cases.

REFERENCES

1. KOUWENHOVEN WB: Cardiopulmonary resuscitation. An account of forty-five years of research *JAMA* 226:877–881, 1973.

2. ZOLL PM: Development of electric control of cardiac rhythm. *JAMA* 226:881, 1973.

3. JENNETT WB, PLUM F: Persistent vegetative state after brain damage: a syndrome in search of a name. *Lancet* 1:734–737, 1972.

4. BEECHER HK: A definition of irreversible coma: report of the ad hoc committee of the harvard medical school to examine the definition of brain death. *JAMA* 205:337–340, 1968.

5. *American Electroencephalographic Society: Guidelines in EEG–1976,* American Electroencephalographic Society, 1976.

6. BETTETT DR, HUGHES JR, KOREIN J, ET AL: *Atlas of Electroencephalography in Coma and Cerebral Death.* New York, Raven Press, 1976.

7. SUTER C: The use of succinylcholine in the determination of electrocerebral silence. *Electroencephalogr Clin Neurophysiol,* 38:553, 1975.

8. GROS D, VLAHOVITCH B, FREREBEAU P, ET AL: Critères arteriographiques des comas dépassés en neuro-chirurgie. *Neurochirurgie* 15:477–486, 1969.

9. BUCHELER E, KAUFER C, DUX A: Zerebrale Angiographie zur Bestimmung des Hirntodes. *Fortschr Roentgenstr* 113:278–296, 1970.

10. BRAUNSTEIN P, KOREIN J, KRICHEFF I, ET AL: A simple bedside evaluation for cerebral blood flow in the study of cerebral death: a prospective study on 34 deeply comatose patients. *Am J Roentgenol* 118:757, 1973.

11. An appraisal of the criteria of cerebral death: a summary statement. *JAMA* 237:982–986, 1977.

12. Diagnosis of brain death. *Lancet* II: 1069–1070, 1976.

13. SCHAEFER J, CARONNA JJ: Duration of apnea needed to confirm brain death. *Neurology (Minneap)* 27:367, 1977.

14. GRINDAL AB, SUTER C, MARTINEZ AJ: Alpha-pattern coma: 24 cases with 9 survivors. *Annals of Neurology* 1:371–377, 1977.

15. SUTER C: Clinical advances in evaluation of deep coma. *Medical College of Virginia Quarterly* 10:152–162, 1974.

16. STOCKARD JJ, ROSSITER VS: Clinical and pathologic correlates of brain stem auditory response abnormalities. *Neurology (Minneap)* 27:316–325, 1977.

Acute Bilateral Ophthalmoplegias

JOHN B. SELHORST, M.D.

Assistant Professor, Department of Neurology, Medical College of Virginia, Health Sciences Division of Virginia Commonwealth University, Richmond, Virginia

Introduction

Bilateral ophthalmoplegia is that condition of weakness or paralysis involving one or more ocular muscles in each eye. Its sudden appearance due to an acute ocular myopathy is indeed unusual. Swash reported a single patient with acute necrotizing orbital myositis and carcinomatosis neuromyopathy.[1] The more common bilateral ocular muscle diseases, such as dysthyroid exophthalmopathy, orbital myositis, and progressive external ophthalmoplegia, develop insidiously and are restricted to the orbit.

In general, acute bilateral ophthalmoplegias afford a unique differential diagnosis of disorders affecting infranuclear and supranuclear pathways for the control of eye movements (Table). They present more abruptly than the myopathies and seriously jeopardize respiratory and/or neurologic function. Among these acute bilateral ophthalmoplegias are disorders which diffusely affect neuromuscular junctions or the nerves to ocular muscles (Table, Parts I and II). Occasionally these diseases are troublesome to diagnose because additional neurologic signs are sparse. In these instances progressive bulbar and respiratory weakness may develop unexpectedly. Familiarity with their differential diagnosis allows for timely therapeutic intervention. This discussion focuses on recognition of this group of acute bilateral ophthalmoplegias and their treatment.

Those disorders (Table, Parts III and IV) which involve only the intracranial portions of the nerves to ocular muscles or their brain stem origins have either distinctive patterns of ophthalmoplegia or are attended by telltale neurologic findings. These disorders are more easily identified and require less deliberation.

I. Disorders Affecting Neuromuscular Junctions

Botulism is the linchpin to the differential diagnosis of acute bilateral ophthalmoplegia because this disease primarily affects ocular and bulbar muscles. Furthermore it is both an individual and public health emergency, making its detection doubly necessary.

Although its epidemic occurrence is well known to physicians, several facets of the disease are less well recognized. Sporadic outbreaks frequently occur. Onset of symptoms appears up to eight days after ingestion of spoiled food.[2] Wound botulism which presents in the same manner as food-borne botulism was once thought rare, but is now more frequently diagnosed.[3,4] Available neurophysiologic techniques assist in its recognition; however, the presence of botulin is only confirmed by a biologic assay. Therefore diagnosis rests heavily upon clinical suspicion.

The following patient presentation typifies the disease.

A 42-year-old fish meal plant employee vomited and complained of pain in his throat while eating homemade vegetable soup. Shortly thereafter his vision was blurred. The following day he came to the Medical College of Virginia Hospitals because of dysphagia, diplopia, and hoarseness. He was not in any distress. Vital signs were normal. There was mild ptosis of each eyelid. His pupils were dilated to 8 mm and did not react to light or accommodation (Figure). Near card assessment of visual acuity was 20/100 in each eye. Moderate abduction and mild

Correspondence and reprint requests to Dr. John B. Selhorst, Department of Neurology, Box 698, Medical College of Virginia, Richmond, Virginia 23298.

downgaze paresis of external ocular muscles was present. Schirmer's I test showed deficient tear formation in each eye. Facial muscles were mildly weak bilaterally, the mouth was dry, and the gag reflex was slightly impaired. Motor, sensory, and reflex examinations of the limbs were normal.

Diagnostic studies began in the emergency room with a Tensilon test which was twice negative. A lumbar puncture yielded cerebrospinal fluid (CSF) under normal pressure which contained sugar of 71 mg%, protein of 28 mg%, and three RBC's. Routine laboratory data were normal. A clinical diagnosis of botulism was made, and serum was sent to the Center for Disease Control (CDC) in Atlanta, Ga. Bivalent (A,B) and trivalent (A,B,E) antitoxin prepared from horse serum was administered. Following a mild urticarial reaction, antitoxin therapy was discontinued. Weakness soon progressed to involve respiratory more than extremity muscles. Vital capacity dropped to 1100 cc. Tracheostomy was performed. Neurophysiologic tests were consistent with a diagnosis of mild botulism. Muscle potentials in the face were low in amplitude and short in duration, and rapid repetitive nerve stimulation (30 Hz) produced an incremental increase in muscle potentials recorded over the thenar eminence. Mouse-toxin neutralization tests performed by the CDC were positive for type B *Clostridium botulinum* toxin. Injection of the patient's serum killed all the mice not protected with antitoxin B. Although the most frequent cause of sporadic botulism occurs with home-processed foods, the source of this patient's exposure was not located. His family had eaten the same vegetable soup with him on two occasions and cultures of the soup did not grow *C botulinum*.

The patient's course was marked by a moderately severe aspiration pneumonia. He responded within one week to antibiotics and frequent suctioning. Four weeks after admission, he was discharged with mild hoarseness. Recovery was, otherwise, complete.

A pattern of weakness descending from bulbar regions to respiratory and extremity muscles characterizes botulism. Ideally the diagnosis is made before this descending paralysis occurs so that the option to use mechanical ventilation and antitoxin therapy is available. In the early stage of diagnosis several additional findings are helpful. A history of ingestion of putrid or home-processed food, exposure to epidemic botulism, or a recent outdoor wound or extremity surgery is important. To be kept in mind is that botulin is the most potent toxin known to man and that ingestion of one spoiled bean is reported to have led to death.[5]

Acute Bilateral Ophthalmoplegias

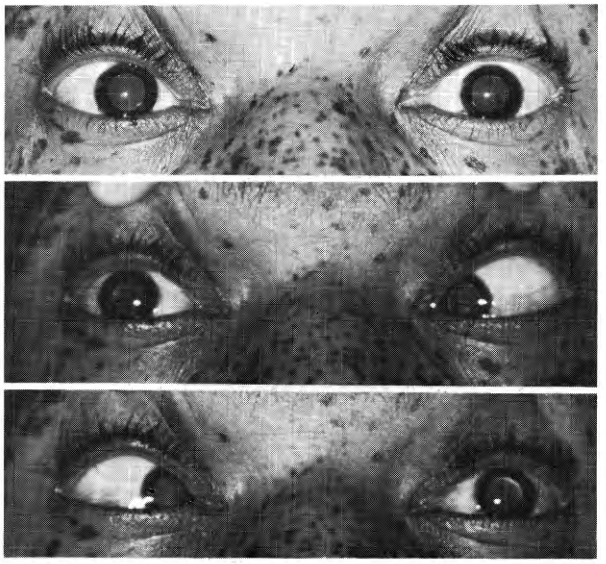
I. Disorders affecting neuromuscular junctions
   1. Botulism
   2. Myasthenia gravis

II. Disorders of ocular nerves
   1. Acute idiopathic polyneuropathy
   2. Diphtheria

III. Disorders within the meninges
   1. Infection
   2. Aneurysm
   3. Trauma

IV. Disorders of the brain stem
   1. Wernicke encephalopathy
   2. Multiple sclerosis
   3. Poliomyelitis
   4. Infarction
   5. Hemorrhage
   6. Trauma

Since botulin interferes with the release of acetylcholine from the distal nerve terminals of skeletal and smooth muscles, signs and symptoms referable to parasympathetic blockade are helpful. Dry eyes and dry mouth occur due to secretomotor inhibition of lacrimal and salivary glands. Blurred vision results from accommodation failure of a weakened ciliary



Fig—Botulism is suggested by the presence of dilated pupils (*top*) which are fixed to light, and accommodation and bilateral abduction paresis (*middle* and *bottom*). Ptotic lids are manually retracted.

muscle. Nonreactive pupillary light responses are caused by paralysis of the pupillary sphincter muscle. The involvement of the pupil coupled with acute bulbar and extraocular muscle weakness makes a diagnosis of botulism almost certain. However, pupillary paralysis occurs infrequently and is not to be depended upon for the diagnosis.

Once the diagnosis of botulism is suspected, specimens from serum and gastric contents are obtained for analysis and typing by mouse-toxin neutralization tests. Six pathogenic toxins have been identified (A, B, C, D, E, F).[6] Food suspected of contamination and stools from the patient are cultured for *C botulinum*. Recent use of stool cultures have shown botulism poisoning to cause a floppy infant syndrome.[7] An indication of botulism is obtained by standard neurophysiologic techniques. In severe cases size and duration of motor units are reduced and low-rate repetitive nerve stimulation (3 Hz) causes decremental muscle potentials, but at high rates of stimulation (50 Hz) an incremental response occurs. Mild cases show only the incremental response of muscle potentials at high rates of stimulation.[8] In botulism these phenomena are more likely to be found in the weakened muscles, and in some instances are not present in the early course of the disease.[9] Careful screening by the electromyographer is required for incremental responses caused by artifacts.

Therapy begins with gastric lavage, cathartics, and enemas. Purgation of the gastrointestinal track is now recommended since stool cultures of *C botulinum* have preceded detection of botulin in the serum. Administration of antitoxin involves risk of adverse reaction, particularly serum sickness, which is comparable to that for tetanus antitoxin.[6] Therefore, use of antitoxin is weighed against the rapidity of development and degree of respiratory failure. Moreover, antitoxin therapy has not resulted in a major decline in mortality rates. Guanidine hydrochloride enhances the release of acetylcholine from the nerve terminal and is used to reverse the neuromuscular blockade of botulism. It is helpful in reducing extraocular and limb weakness but unfortunately is least effective in reversing paralysis of respiratory muscles.[9] It also tends to depress the bone marrow.

In myasthenia gravis 40% of the patients have diplopia and ptosis either alone or accompanied by bulbar or extremity weakness.[10] The pattern of ocular muscle involvement is variable. Diagnosis of myasthenia gravis is often suggested by the observation of fatigue in extraocular muscles upon requesting the patient to maintain upgaze. In this position palpebral and elevator muscles of the eye gradually weaken. Another distinctive ocular sign in myasthenia gravis is the lid twitch phenomenon described by Cogan.[11] Rapid shift of the eyes from a downward position to quick upgaze results in a brief contraction or twitch of the levator palpebral muscle before it weakens and returns to its ptotic position. Claims of pupillary involvement in myasthenia gravis are poorly documented and unexpected since this is a disease of striated muscle.

Ordinarily the urgency of a diagnosis in myasthenia gravis does not occur because of its typically insidious onset. However, an acute fulminating form of ocular and bulbar weakness with early respiratory muscle involvement has been described.[10] In either instance the diagnosis of myasthenia gravis is usually made by intravenous injection of edrophonium chloride (Tensilon). Caution in the interpretation of this test in relation to the differential diagnosis of acute ophthalmoplegias is warranted by the report of Cherington,[12] who described improved muscle strength and resolution of ptosis following intravenous Tensilon in two patients with proven botulism. Clinically these patients also demonstrated fatigability, but neither responded to sustained amounts of anticholinesterase medication. In those unusual instances in which diagnosis of myasthenia gravis is not clearly established by intravenous Tensilon, repetitive nerve stimulation is recommended. A decremental response of muscle potentials is found with slow and rapid sequential stimulation of the nerve. Control of acute muscle weakness is usually gained by anticholinesterase medication. Steroids and possibly thymectomy are useful in later stages.

II. Disorders of Ocular Nerves

In patients with acute idiopathic polyneuropathy (Landry-Guillain-Barré syndrome), involvement of ocular nerves occurs in less than one quarter of the cases while bulbar and facial weakness are found in over one half the patients in large series.[13,14] Pupils are usually but not invariably spared. Ordinarily, ocular muscle weakness follows extremity weakness. This ascending paralysis in acute idiopathic polyneuropathy constitutes a major distinction with the descending paralysis that occurs in botulism. Acute idiopathic polyneuropathy is also suggested by the presence of sensory loss and early disappearance

of deep tendon reflexes. Laboratory evidence favoring acute idiopathic polyneuropathy is obtained by finding elevated protein in the CSF with no more than a mild pleocytosis and detection of slowed motor nerve conduction velocities. These tests are not always abnormal in the early course of this disease.

Recognition of an ophthalmoplegia due to acute idiopathic polyneuropathy is not always simple. Although others before him had described such a condition, Fisher in 1956 drew attention to a more restricted form of acute idiopathic polyneuropathy.[15] He described an acute polycranial neuritis manifested by an ophthalmoplegia with only generalized areflexia and ataxia. CSF protein was elevated. Others have since described this acute bilateral ophthalmoplegia and pointed out that subsequent weakness of the extremities does occur.[16] Pupils are usually spared, which has led to disputes regarding the central vs peripheral nature of acute polycranial neuritis. Success with prednisone therapy has not been shown, but its use is worthy of consideration early in the course of the disease.

Mention of diphtheria today as a cause of ophthalmoplegia is nearly a historical matter. Weakened ocular muscles occur in diphtheria due to a toxic motor neuropathy. Cases are reported in which a mild nasopharyngitis went undetected before the paralytic stage appeared. Recognition is further complicated by the tendency of the exudative membrane of diphtheria to clear off the larynx before paralysis develops. Usually the palate and ciliary muscles are the first to be affected.[17] Paralysis of ocular motor muscles generally follows dysphagia and loss of accommodation within several days to several weeks. Paralysis of respiratory and extremity muscles also follows palate or ciliary muscle weakness. Respiratory failure leads to death if the systemic polyneuropathy is severe. If the patient survives the toxic phase, all involved nerves usually recover in several months.

III. Disorders Within the Meninges

Infection of the leptomeninges, especially tuberculous meningitis, is known to disrupt nerves to ocular muscles bilaterally. Onset is sometimes sudden and the course fulminant. Fever, stiff neck, and typical CSF findings lead directly to the diagnosis. Neurosyphilis with CSF pleocytosis, elevated protein, and positive serology is another frequent cause of meningeal ocular palsies. Abrupt expansion or rupture of a posterior fossa aneurysm is reported to cause bilateral sixth nerve palsies.[18] Bilateral third and fourth nerve palsies[19] are described in closed head injuries and are thought to occur through injury of the nonfixed portion of the nerve in its meningeal compartment. Bilateral sixth nerve palsies due to trauma are usually associated with basilar skull fractures. Delayed onset of ocular muscle palsies is described with fractures of the clivus,[20] presumably from hemorrhage beneath the dura.

IV. Disorders of the Brain Stem

Structural alterations in infranuclear and/or supranuclear regions of the brain stem, which control eye movements, cause acute ophthalmoplegias. Supranuclear deficits include gaze palsies and internuclear ophthalmoplegia (INO) or combinations of both, which are recognized by their distinct pattern of involvement of ocular muscles. Paralysis of conjugate horizontal gaze with consequential contralateral deviation of the eyes occurs with a lesion in the ipsilateral pontine paramedian reticular formation.[21] Paralysis of adduction with abduction nystagmus is an INO and indicates a lesion in the medial longitudinal fasciculus (MLF).[22] Distinction of an INO from an infranuclear medial rectus palsy is evident by the preservation of adduction during convergence. Ipsilateral gaze and adduction paralysis was termed by Fisher the "one and a half" syndrome because of the coexistence of a unilateral pontine gaze center and MLF lesion.[23]

Bilateral involvement of the fasciculi or nuclei of oculomotor nerves is uncommon and is usually attended by additional neurologic findings. Altered consciousness and ataxia with ocular palsies are caused by thiamine deficiency in alcoholic patients with Wernicke encephalopathy. Neuronal degeneration, capillary proliferation, and hemorrhages are diffusely found in periventricular regions of the brain stem including nuclear and fascicular portions of ocular nerves. Similiar infranuclear lesions with long tract deficits occur in white matter regions involved with the demyelinating plaques of multiple sclerosis. Both Wernicke encephalopathy and multiple sclerosis also cause supranuclear oculomotor palsies. Murray and Walsh described infranuclear ocular muscle palsies in several patients with poliomyelitis.[24] Isolated bilateral nuclear or fascicular lesions are described only with infarction of third nerve fasciculi and are indeed rare.

Acute supranuclear gaze palsies in this discussion include unilateral or bilateral horizontal gaze palsy, the "one and a half" syndrome, and bilateral

INO. Contralateral pyramidal tract signs and facial paresis due to a lesion within the pons often accompany an ipsilateral horizontal gaze palsy. Acute upgaze palsy due to a lesion in the pretectal region[25] or sudden downgaze palsy[26] from disruption of the paramedian prerubral field occur rarely. In both horizontal and vertical gaze palsies of abrupt onset, additional neurologic deficits are the rule. They are most frequently caused by infarction, hemorrhage, and trauma. The one supranuclear disorder frequently not associated with contiguous neurologic signs is bilateral INO. In such instances bilateral INO strongly suggests multiple sclerosis.[21]

REFERENCES

1. SWASH M: Acute fatal carcinomatous neuromyopathy. *Arch Neurol* 30:324–326, 1974.

2. *Botulism in the United States, 1899–1973,* handbook for epidemiologists, clinicians, and laboratory workers. Atlanta, Center for Disease Control, 1974.

3. CHERINGTON M, GINSBURG S: Wound botulism. *Arch Surg* 110:436–438, 1975.

4. MERSON MH, DOWELL JR: Epidemiologic, clinical and laboratory aspects of wound botulism. *N Engl J Med* 289:1005–1010, 1973.

5. DONADIO JA, GANGAROSA EJ, FAICH GA: Diagnosis and treatment of botulism. *J Infect Dis* 124:108–112, 1971.

6. MERSON MH, HUGHES JM, DOWELL VR, ET AL: Current trends in botulism in the United States. *JAMA* 229:1305–1308, 1974.

7. PICKETT J, BERG B, CHAPLIN E, ET AL: Syndrome of botulism in infancy: clinical and electrophysiologic study. *N Engl J Med* 294:770–772, 1976.

8. OH SJ: Botulism: electrophysiological studies. *Annals of Neurology* 1:482–485, 1977.

9. CHERINGTON M, RYAN DW: Treatment of botulism with guanidine. Early neurophysiologic studies. *N Engl J Med* 282:195–197, 1970.

10. OSSERMAN KE, GENKINS G: Studies in myasthenia gravis: review of a twenty-year experience in over 1200 patients. *Mt Sinai J Med NY* 38:497–537, 1971.

11. COGAN DG: Myasthenia gravis: a review of the disease and a description of lid twitch as a characteristic sign. *Arch Ophthalmol* 74:217–221, 1965.

12. CHERINGTON M: Botulism. Ten-year experience. *Arch Neurol* 30:432–437, 1974.

13. PLEASURE DE, LOVELACE RE, DUVOISIN RC: The prognosis of acute polyradiculoneuritis. *Neurology (Minneap)* 18:1143–1148, 1968.

14. MCFARLAND HR, HELLER G: Guillain-Barré disease complex. *Arch Neurol* 14:196–201, 1966.

15. FISHER M: An unusual variant of acute idiopathic polyneuritis (syndrome of ophthalmoplegia, ataxia and areflexia). *N Engl J Med* 255:57–65, 1956.

16. MUNSAT TL, BARNES JE: Relation of multiple cranial nerve dysfunction to the Guillain-Barré syndrome. *J Neurol Neurosurg Psychiatry* 28:115–120, 1965.

17. GOODALL EW: On diphtheritic paralysis. *Brain* 18:282–309, 1895.

18. HOOK O, NORLEN G, GUZMAN J: Saccular aneurysms of the vertebral-basilar arterial system. A report of 28 cases. *Acta Neurol Scand* 39:271–304, 1963.

19. SAUNDERS BB, VANDERARK GD: Transverse fracture of the clivus. *J Neurosurg* 39:610–614, 1973.

20. CHAPMAN LI, URIST MJ, FOLK ER, ET AL: Acquired bilateral superior oblique muscle palsy. *Arch Ophthalmol* 84:137–142, 1970.

21. GOEBEL HH, KOMATSUZAKI A, BENDER MB, ET AL: Lesions of the pontine tegmentum and conjugate gaze paralysis. *Arch Neurol* 24:431–440, 1971.

22. COGAN DG: Internuclear ophthalmoplegia, typical and atypical. *Arch Ophthalmol* 84:583–589, 1970.

23. FISHER CM: Some neuro-ophthalmological observations. *J Neurol Neurosurg Psychiatry* 30:383–392, 1967.

24. MURRAY RG, WALSH FB: Ocular abnormalities in poliomyelitis and their pathogenesis. *Can Med Assoc J* 70:141–147, 1954.

25. SULLIVAN HG, HARBISON JW, BECKER DP: Parinaud's syndrome: cerebrovascular disease as a common etiology: analysis of 16 cases. *Surg Neurol* 6:301–305, 1976.

26. JACOBS L, ANDERSON PJ, BENDER MB: The lesions producing paralysis of downward but not upward gaze. *Arch Neurol* 28:319–323, 1973.

Coma in Infancy and Childhood

EDWIN C. MYER, M.D.

Assistant Professor, Pediatric Neurology, Medical College of Virginia, Health Sciences Division of Virginia Commonwealth University, Richmond, Virginia

Coma is defined as an altered state of consciousness from which arousal due to appropriate stimuli is not adequately achieved. Such a definition of the state of coma is plagued with semantic problems, and terminology describing various comatose states is vast and even more ambiguous when applied to the infant. Rather than using such terms as coma, semicoma, stupor, or obtundation, it is better to describe the physical state of the unresponsive patient. The description should include the patient's appearance, movements either spontaneous or elicited from stimuli, the patient's response to the stimulus, and the nature of the stimulus, whether voice, pressure, or pain. A detailed neurological description is not warranted when describing the comatose state, but it is appropriate to include whether or not respirations are spontaneous or supported, and the patient's cardiovascular state. Pupillary size and activity should be included in the description of the stuporous patient. The comatose state of an infant may be much more difficult to recognize and is often confused with physiological sleep states. An infant is considered to be in a coma when there is no appropriate response to shaking, pinching, visual, or auditory stimuli. As with the older child, a detailed description of the state is necessary. More difficult to recognize in infants and children are the less severe forms of coma, especially since fluctuating metabolic situations with rapid changes can occur and the state of consciousness may change equally rapidly. Notwithstanding these difficulties of definitions and recognition, a classification of coma (Table) in an infant and child is essential.

Correspondence and reprint requests to Dr. Edwin C. Myer, Box 211, Medical College of Virginia, Richmond, Virginia 23298.

Pathophysiology of Coma

From animal studies it appears that the ascending reticular activating system is chiefly responsible for the state of consciousness. When this system is damaged or destroyed, a slow synchronized electroencephalogram (EEG) and coma ensue. The ascending reticular activating system appears to include the rostral pons, pons, hypothalamus, and midbrain, and has indistinct boundaries with a multitude of interconnections involving the brain stem and forebrain. Physiologically, there are ascending and descending systems with many feedback mechanisms. Anatomically, this polysynaptic system has not been adequately deciphered; however, the area rostral to the pons appears to be essential for the maintenance of consciousness.

In extrapolating data to man many inconsistencies occur, such as hypothalamic destruction with sparing of midbrain reticular formation, followed by sustained somnolence. Because of the quality of the cognitive functions of the human cerebral hemispheres, substantial lesions of either or both hemispheres will interfere with mental integrative functioning; the more diffuse the lesion the more it affects the state of consciousness, whether or not associated brain stem lesions exist.[1] Eventually, irrespective of the insult causing changes in consciousness, the ultimate common pathway is the blood supply of the cells with oxygen and glucose necessary to maintain mitochondrial activity and intracellular metabolism, as well as to maintain membrane stability with ionic fluctuations and neurotransmitter release. Recently it has been shown that in head trauma serontonin and homovanillic acid levels change, indicating that basic neurotransmitter dysfunction does occur; therefore,

A Classification of Coma in the Infant and Child

SEIZURES

INFECTIOUS CAUSES
- Meningitis
- Encephalitis: Viral, Protozoal, Rickettsial
- Severe systemic infection

TRAUMA
- Subdural
- Concussion
- Hemorrhage: Subdural, Extradural, Intracranial, Subarachnoid

MASS LESIONS
- Neoplasms
- Hematomas
- Infective
- Hydrocephalus

VASCULAR LESIONS
- Thrombosis
- Vasculitis
- Embolization

DEGENERATIVE DISEASES

METABOLIC CAUSES
- Oxygen deprivation (Hypoxia or Anoxia): Cardiac, Pulmonary, Ischemic
- Hypoglycemia
- Hepatic coma
- Uremia
- Electrolyte abnormalities: Sodium, Potassium, Calcium, Magnesium, Water
- Acid base abnormalities
- Hormonal dysfunction: Inappropriate ADH
- Encephalopathy: Reye's syndrome

POISONS
- Antihistamines
- Barbiturates
- Belladonna
- Drugs of abuse
- Lead and other heavy metals
- Organophosphates
- Phenothiazines
- Salicylates
- Tranquilizers (Benzodiazepines)
- Tricyclics

to meet the high-energy demands required, a functioning metabolism is essential.[2]

Under normal physiological conditions, glucose is the main substrate used by the brain, but in certain circumstances ketones may be metabolized. As the brain's glucose reserve is minimal, any alteration of the state of consciousness may be an early sign of hypoglycemia. Certain enzymatic cofactors such as thiamine and pyridoxine are required to utilize the glucose; absence of these in the diet may affect the status quo of the brain. A constant oxygen supply to the brain is vital and when this is deficient, lactic acidosis quickly occurs. The brain consumes 15% to 20% of the total body's oxygen needs and this oxygen consumption increases rapidly during seizures. Cerebral blood flow is equivalent to about 15% to 20% of cardiac output and can increase or decrease under particular physiological stimuli, for example, changes in P_{CO_2} or pH. Similar states with regard to the reticular activating system and cortical grey matter probably exist in the infant, but as yet, detailed clinical and anatomical correlation of stupor in coma is not available in the neonate.[3]

Signs, Symptoms and Diagnostic Approach

With the unconscious patient a rapid gross assessment is necessary to establish the brain's basic requirements in terms of blood volume, blood flow, oxygenation, and glucose. This initial management is essential to prevent permanent brain damage or death or both. Once the state of unconsciousness has been ascertained, cardiac output should be ascertained and adequate respiratory exchange maintained. In addition intravenous fluids containing glucose should be administered after blood has been drawn for laboratory tests. When the initial steps of establishing an airway and observing adequate cardiac output have been taken, the patient should be examined to establish the cause of the coma.[4] A general evaluation may give clues to the diagnosis; specific entities to be observed are cutaneous abnormalities including birthmarks, skin punctures and

bruises, and skull trauma, ecchymosis, and rashes. Respiratory patterns may help in the localization of the dysfunction. Of particular interest are the apneic spells seen in premature newborns which may be related to brain stem immaturity or dysfunction.[3] The ears should be examined for hemotympanum. Heart murmurs may indicate endocarditis or brain abscess. Pupillary size and reactions may help localize the lesion. These are especially important in the deeply comatose patient when no history is available as metabolic encephalopathies usually have reactive pupils. A full neurological evaluation in the usual manner will help determine the process causing the unconsciousness.[5]

In children trauma is not always obvious and shaking an infant excessively may result in subdural hematomas. We have seen an infant who had inhaled a foreign body and was swung around in an effort to dislodge the article develop bilateral frontal lobe intracranial contusions sufficiently severe to cause death.

Subdural effusions in the infant with an open fontanelle are an infrequent cause of changes in consciousness; it is more likely that the underlying cerebral damage associated with the subdural hematoma may be responsible. Seizures associated with cortical damage have also caused problems of consciousness. Subdural and extradural hematomas in the infant with fused sutures have been the sources of problems; however, considering the size of the infant and child and the number of relatively severe falls, trauma, excluding the battered baby, is a relatively infrequent cause of coma. (The battered syndrome must always be excluded when observing trauma-induced unconsciousness in the infant and child.)[6]

Infection may cause serious changes of consciousness in the infant and child. Any neonatal infant who shows a non-physiological depression of its conscious state should be evaluated for meningitis. In the neonate and young infant this change of consciousness may be the first sign of an impending infection. Changes of consciousness associated with purpuric or ecchymotic rashes require urgent evaluation to exclude a meningococcal meningitis or Rocky Mountain spotted fever. All these infectious states in the young infant occur without any other typical signs of meningism. Thus, as part of the diagnostic work-up, immediate lumbar puncture is required. Supratentorial mass lesions or hydrocephalus are to be considered and spinal fluid may have to be obtained from other routes.

Infants and children with a history of seizures may frequently present with status epilepticus or in postictal states especially associated with noncompliance with drug therapy. Seizures may be due to any of a variety of causes and require an immediate evaluation for exclusion of treatable causes, such as metabolic dysfunction, noncompliance in medication, and certain poisons and toxins. Poisons and toxins causing coma require specific antidotes. It is essential that every comatose patient, infant and child, undergo immediate toxic screening of the urine and, if necessary, of serum, even when there is no history of ingestion; any delay may result in death. In our experience toxic screening revealed the presence of imipramine in the urine of a child who was admitted unconscious to our institution and whose parents had denied the existence of any drugs in their house. Unfortunately, the delay in performing the test resulted in the death of the child two hours later from what is a treatable condition. Poisons are listed in the coma classification and each one requires its own treatment.

Metabolic dysfunctions are probably the commonest causes of altered states of consciousness in the infant and child. They are not easily recognized and the signs and symptoms may be similar to those of an unconscious child who may or may not have reflexes present with or without brain stem signs but who usually shows intact pupillary reflexes and no neurological localizing signs. It has been our practice to evaluate the blood immediately with Dextrostix to rule out hypoglycemia. If indicated, calcium is given empirically, especially if the child is having a seizure. Routine laboratory tests to evaluate electrolyte status are obtained as soon as possible; arterial blood gases are monitored and the appropriate corrections made.

Reyes syndrome, with the associated encephalopathy, can result in profound metabolic coma, and the diagnosis needs to be considered in all comatose children where etiologies are in doubt. Depending on the type of metabolic dysfunction, specific treatment may be indicated, but in general the treatment is primarily supportive.

Evaluation

After acute treatment and assessment of a patient in a coma, an immediate EEG is done which frequently helps to establish the metabolic cause. The EEG is usually diffusely slow, and in the infant and neonate the slowness is difficult to correlate; however, suppression or diffusely slow, low-voltage EEGs may

be helpful. The advent of the computerized axial tomography (CT) scan has helped tremendously in the diagnosis of contusions and space-occupying lesions as well as acute hydrocephalus. In our institution this test is performed as an emergency procedure. X-rays of the skull are helpful in non-obvious trauma, and skeletal surveys are done if a battered baby is suspected.

Treatment

Once acute treatment has been established together with specific therapies, EEG, antibiotics, anticonvulsants, correction of electrolytes and acid base abnormalities, indicated surgery, and specific antidotes for poisons, the remainder of the treatment is supportive. The unconscious patient is nursed in an intensive care unit; if any problems are related to breathing, the patient is intubated and if necessary, respiratory therapy is instituted. After particular cerebral insults, cerebral edema may occur and specific precautions are taken for decreasing cerebral blood flow by hypoventilation while insuring that adequate oxygenation to the brain is maintained. Of particular importance is the onset of the inappropriate antidiuretic hormone (ADH) syndrome, and our practice has been to maintain these children on two thirds fluid maintenance in anticipation of the development of inappropriate ADH. This latter treatment has been a problem in sickle cell disease where acute crises have caused multiple vascular occlusions resulting in unconsciousness; in these circumstances we monitor serum and urine osmolalities regularly to anticipate inappropriate ADH.

Because of the association of cerebral edema with many metabolic unconscious states, we have routinely used two forms of intracranial pressure monitoring in conjunction with our neurosurgical colleagues: 1) a dural screw and 2) intraventricular pressure monitors. The latter form is especially helpful since intraventricular cerebral spinal fluid can be removed to relieve the increases of intracranial pressure. Although hyperosmolar agents have been used with this type of monitoring, we only use them with intracranial pressure monitoring unless a surgically correctable lesion is present such as acute hydrocephalus. Using this monitoring system we have successfully managed and treated the unconscious state in Reye's syndrome.

The management of consciousness changes in the neonate and infant is essentially the same as that of the child. In this group such changes have most frequently been caused by metabolic dysfunction, hypoxia, and intracranial hemorrhage. Correction of the metabolic state is essential in the treatment of the coma and seizures which are frequently associated with these metabolic changes. We have not used intracranial pressure monitoring with infants.

Conclusion

Coma in the infant and child requires that the physician always adhere to a specific plan, and that his actions be adequate to sustain brain function in order to prevent irreversible damage. The advent of intensive care units, advances in technology, and a better understanding of the pathophysiology of coma will help to decrease mortality and especially the morbidity associated with coma.

REFERENCES

1. PLUM F, POSNER J: *Diagnosis of Stupor and Coma*, ed 2. Philadelphia, FA Davis and Co, 1972.

2. VECHT CJ, WOERKOM T, TEELKEN AW, ET AL: The nature of brain stem disorders in severe head injured patients. *Acta Neurochirurgica* 34:11–21, 1976.

3. AVERY G (ED): *Neonatology*. Philadelphia, J Lippincott and Co, 1975, chap 32.

4. FROWEIN RA: The classification of coma. *Acta Neurochirurgica* 34:5–10, 1976.

5. SWAIMAN KF, WRIGHT FS (EDS): *The Practice of Pediatric Neurology*. St. Louis, CV Mosby Co, 1975, vol 1, chap 5.

6. CAFFEY J: The whiplash shaken infant. *Pediatrics* 396–403, 1974.

The Search for Optimal Management of Head Injury

J. DOUGLAS MILLER, M.D., Ph.D.

Lind Lawrence Professor of Neurosurgery, Medical College of Virginia, Health Sciences Division of Virginia Commonwealth University, Richmond, Virginia

Introduction

Head injuries of sufficient severity to bring the patient to a hospital occur in more than one per hundred of the population every year. The toll in death and disability is staggering; the majority of patients are young wage-earners with families so that the total socio-economic burden can hardly be guessed at. Much emphasis is laid on the concept that physical disruption of neurons in the brain is not a reversible process and that regeneration within the nervous system to the point of functional recovery does not occur; however, this rather dismal view of head injury is at variance with the facts. Most cases of head injury reaching the hospital are associated with relatively minor degrees of primary brain damage from which full functional recovery may be expected even though there are minor residual neurological signs. The major problem for the physician treating head injuries in hospitals is that secondary complications may supervene and change a relatively minor head injury case into a major disability problem or even a fatality. For the management of head injury considerable emphasis should be laid on the prevention of secondary complications; such an approach is outlined in this article.

The Rationale of Head Injury Care

Except with minor trauma, most head injuries result in some observable degree of sudden neurological deterioration followed by a trend towards recovery of neurological function. The limit of that recovery is set by the pretraumatic status of the brain (as affected by previous injury, by degenerative disease, or by congenital defects) and by the amount of structural damage to the brain caused by the primary impact. Immediately after injury, however, and continuing well into the recovery phase for days and even weeks the patient is at risk from a variety of secondary insults to the brain, any one or combination of which may further limit the chance of recovery or may, at worst, transform a trivial head injury into a fatal process.

Early secondary insults stem from possible hypoxic hypoxia due to poor airway care at the scene of the injury or during transport to the hospital, or to arterial hypotension as a result of blood loss, visible or occult. These insults superimpose cerebral hypoxia on an already damaged brain which, due to the injury, may lack the protective physiological mechanisms which normally maintain cerebral energy metabolism during physiologic stress. A further group of secondary insults relate to the formation of secondary intracranial mass lesions (hematoma, swollen contusion) which produce both brain shift with distortion and raised intracranial pressure.[1] Thus, the syndrome of brain compression may soon overshadow the effects of the original head injury. Another group of secondary cerebral insults are infective in origin and occur usually as a result of dural penetration by the injury process, producing meningitis or even an abscess of the brain in epidural, subdural, or intracerebral locations. While the patient remains unconscious he is at risk from chest and urinary tract infection, and from fluid and electrolyte imbalance, all of which may produce neurological deterioration.

The optimal care of patients with head trauma

Correspondence and reprint requests to Dr. J. Douglas Miller, Box 758, Medical College of Virginia, Richmond, Virginia 23298.

hinges on a comprehensive and rapid diagnostic assessment, and appropriate surgical and medical management which aims to anticipate rather than just treat secondary insults and complications of the primary head injury. The loss of any patient with head injury who arrived at the hospital able to talk has to be regarded as a failure of such a management regime. Although some such cases continue to occur even with the best care presently available, the goal of head injury management should be the maximum recovery possible consistent with the preexistent state of the brain and the degree of primary brain damage.

Diagnostic Assessment

The process of diagnostic assessment of patients with head injury may be regarded as a search for the answers to six questions, beginning as the patient reaches the hospital emergency room.

1. *What is the physiological status of the patient?*

During transport to the hospital and on arrival in the emergency room the primary consideration must be the patency of the airway, assessed ideally both by visual inspection and by measurement of arterial blood gases, with immediate relief of any obstructive problem. The next most urgent consideration is the arterial blood pressure. Systemic arterial hypotension is scarcely ever due to head injury, and a low blood pressure must prompt a thorough search for sources of visible or occult blood loss.[2] Correction of these problems may produce dramatic improvement in neurological status.

Thereafter, a rapid assessment must be made of the total extent of injuries which should be carefully noted in writing, preferably supplemented with drawings or diagrams. Special attention must be paid to the possibility of coexistent head and neck injuries. Cervical spine damage must be thought of in all patients with head injury but especially those who have no leg movement yet good facial movement in response to pain. Another pitfall in the assessment of the comatose patient is the soft tissue injury seen early before any substantial swelling has occurred. All major joints should be tested for abnormal mobility and no plans should be made to move the patient until spinal trauma has been excluded. Visual inspection will need to be supplemented by plain x-rays in the emergency room, and after recording the total burden of injuries suffered by the patient, a more accurate assessment can be made of blood and fluid transfusion requirements.

As a general principle, treatment of any injury should be definitive from the outset; there is nothing less impressive than the situation in which it takes four to five days to discover one by one all of the injuries suffered by a patient. In this respect the history of trauma is vitally important as multiple injuries can certainly be expected after a severe car wreck or a fall from a considerable height. The problem of multiple injuries is a common one; about one third of patients with serious head injuries have other injuries as well, and 80% of those patients in car accidents who have multiple injuries have serious head injury as part of the clinical picture. For this reason, patients with serious head injury should always be undressed completely in the emergency room in order to ascertain the full extent of injuries before any move is made to take the patient out of the room for x-ray or other maneuvers.

2. *What is the neurological status of the patient, and is it changing?*

The neurological evaluation of the comatose patient with a head injury is not difficult if two principles are followed. You can test only what can be tested and you must express your findings in objective terms, as your findings may have to be compared with those of others. The patient must be challenged verbally first of all to reply to questions or if there is no verbal response, to obey commands. Failing such a response a painful stimulus must be used and the response observed. Pain must be applied centrally, to the trunk, and to all four limbs, in turn, so that the best motor response can be determined. The motor response can be graded as obeying commands or localizing painful stimuli, both of these responses being regarded as purposeful. On the next level lower, the arm may flex as a withdrawal type of response to pain which can be classified as a semipurposeful response. Abnormal motor responses consist of those where there is an element of pronation combined with arm flexion, usually called a decorticate response, or arm extension combined with pronation (decerebrate response). Finally, at the extreme, motor responses to painful stimuli may be completely absent and the limbs flaccid.

The pupils should be examined for inequality in size under normal lighting conditions and the response tested both directly and consensually to light to distinguish between optic nerve and oculomotor nerve damage. Oculocephalic or oculovestibular responses should be tested only after ruling out cervical spine and tympanic membrane damage respectively.

Normal findings in awake patients will be suppressed eye movement in the case of the oculocephalic responses, or nystagmus in the case of the oculovestibular response. In patients who are unconscious the intact doll's eye response and the ipsidirectional tonic conjugate oculovestibular response (to irrigation of the ear with ice cold saline) both imply that brain stem structures responsible for eye movement are largely intact, while dysconjugate or absent responses to both forms of stimulus point to damage in the brain stem.

In this examination scheme there is no place for the use of terms such as obtunded, stuporous, or semicomatose nor is there any place for the recording of tendon reflexes or the plantar response. In the hours following head injury funduscopic examination is of value only to detect preexisting disease or possibly subhyaloid hemorrhage in the patient in whom there is doubt concerning the differential diagnosis between head injury and subarachnoid hemorrhage.

The value of serial, objectively expressed, neurological assessment can hardly be overemphasized. In this regard we have found very useful, and strongly recommend, a standardized form such as is illustrated in Figure 1. This form which is filled out by the nursing staff in the intensive care unit has been adapted from one which was developed by Dr. Graham Teasdale at the University of Glasgow, Scotland, after an extensive study to determine that terminology which was least ambiguous and most consistently recorded no matter whether by doctors, students, or nurses.

The neurological findings on admission or shortly after admission to the hospital must be compared with any evidence to suggest a different neurological status shortly after the injury. This is vital information which can be gleaned from witnesses and ambulance men. The patient's relatives must also be questioned to construct a picture of the pre-injury neurological status of the patient and reference to school records is very often of considerable help. Finally, two factors commonly contribute to errors in the clinical diagnostic assessment of patients with head injury. These are epileptic seizures and overuse of alcohol. Early epileptic seizures in the first few hours after injury are oftentimes a cause of dramatically sudden neurological deterioration followed by an equally rapid recovery of consciousness in many cases. Conversely, the cause of coma after head injury is more often attributed wrongly to the ingestion of alcohol. Blood alcohol levels are not usually available until the following day, but in a recent, very large series of head injury patients in whom blood alcohol levels were measured, the conclusion very clearly was that it was wiser at all times to proceed on the assumption that the patient's low conscious level was due to head trauma rather than alcohol consumption.[3]

3. *Does the patient have an intracranial mass lesion?*

Traditional teaching on head injury management has laid much emphasis on first looking for evidence of neurological deterioration to suggest that an intracranial hematoma or other mass lesion is developing, then pursuing the appropriate diagnostic measures to localize the mass lesion (Fig 2). With the advent of a new, noninvasive diagnostic technique, computerized axial tomography (CT), this view needs to be modified. The central question in many clinical cases has to be, If this patient deteriorates neurologically from this point, what will his neurological function be? Deterioration in a patient who is already decerebrate would render him flaccid and apneic and cannot be risked.

Some three and a half years ago Dr. Donald Becker instituted a uniform protocol for all patients with head injury who entered the Medical College of Virginia unable to obey simple commands. All such patients were studied immediately by twist drill ventriculography, by angiography, or more recently, by CT scan. In this way some 40% of patients were discovered to be harboring intracranial mass lesions and were taken immediately to surgery to have these removed. Patients who arrive at the hospital after head injury still able to obey commands still have some form of intracranial study within 24 hours of admission. By proceeding directly to these intracranial radiological studies, it is hoped to anticipate neurological deterioration due to expansion of an intracranial mass lesion.

Two criticisms of this approach may be made: first, lesions may be detected which might never have caused any trouble for the patient and second, lesions may develop later which would have been undetected by the early routine studies. Complete answers cannot be given to such questions at this stage as experience with CT scanning is still limited, but our viewpoint is that it is always better to know in advance that a patient has an intracranial mass lesion; whether or not it should always be operated on is another question. We know, however, that the presence of an intracranial mass lesion presents great

VIRGINIA COMMONWEALTH UNIVERSITY
MEDICAL COLLEGE OF VIRGINIA HOSPITALS
Richmond, Virginia 23298

NEURO SCIENCE GRAPH

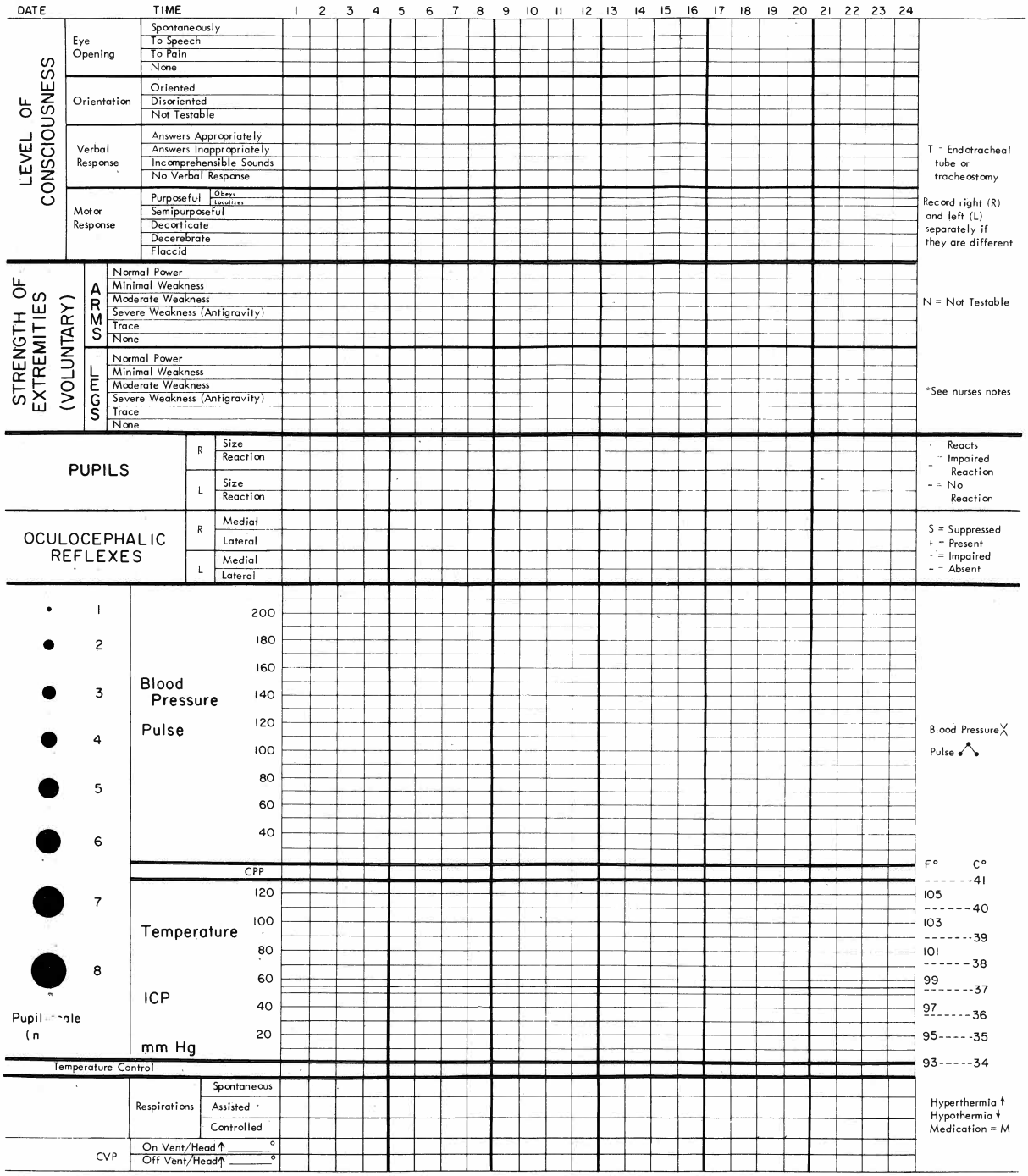


Fig 1—Neurological evaluation and progress sheet for intensive care unit. (Fluid balance chart on reverse).

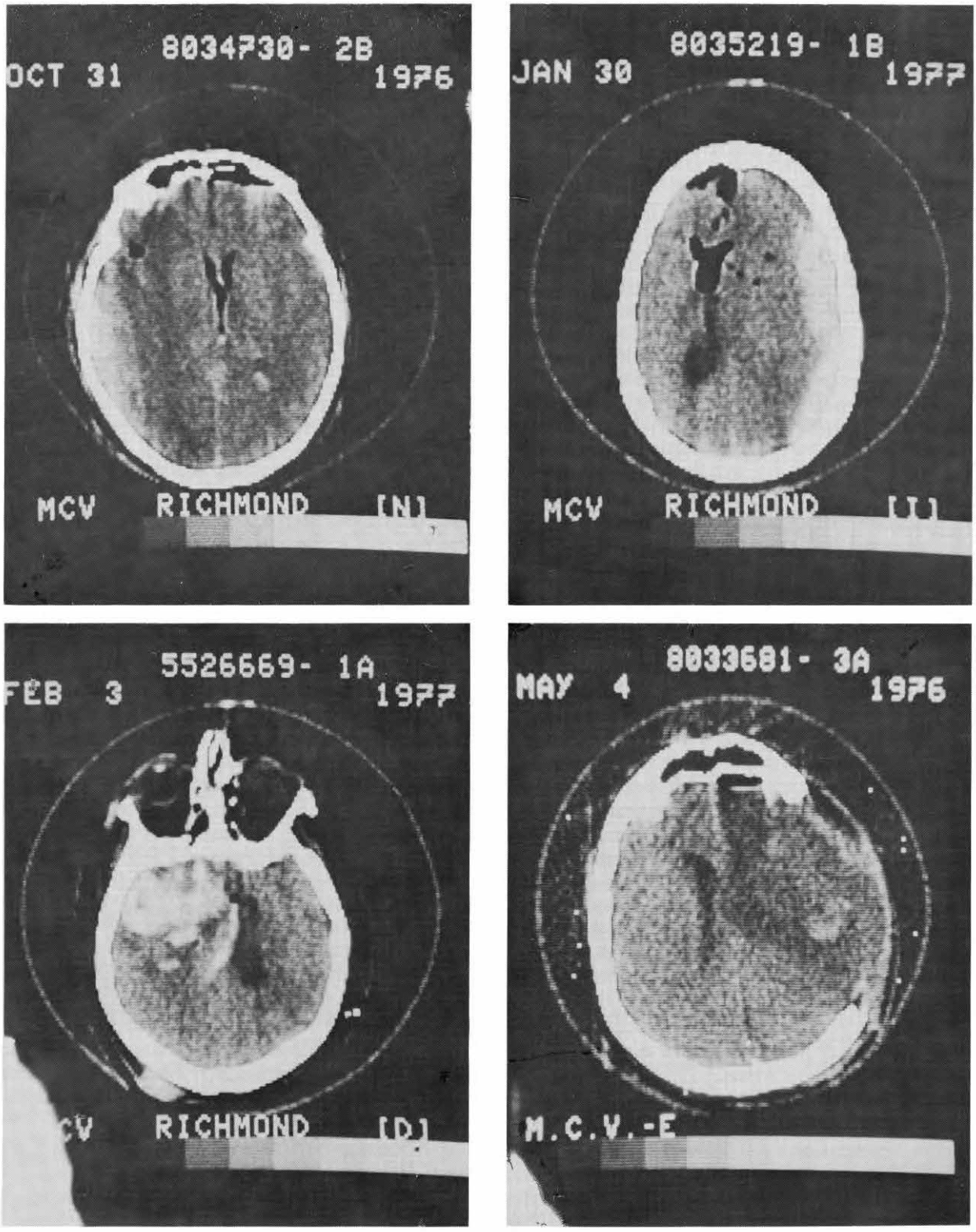


Fig 2—Computerized axial tomograms in patients with head injury. *Top left.* Extracerebral mass lesion; acute epidural hematoma, underlying edema. *Top right.* Extracerebral mass lesion; acute subdural hematoma. *Bottom left:* Dense intracerebral mass; intracerebral hematoma. *Bottom right.* Large, low density lesion in brain; cerebral edema formation.

danger to the patient during anesthesia, during sleep, or when there is any respiratory obstruction. Even if intracranial pressure is normal under resting conditions, any cerebral vasodilation causes severe intracranial hypertension.[4] Our experience to date is that intracranial hematomas following trauma are virtually always present when the patient is first admitted to the hospital, while brain swelling associated with cerebral contusion undoubtedly develops after admission during the first three to five days following injury. For that reason we believe that follow-up CT scans are also vitally important.

4. *Is the dura penetrated?*

The importance of this question relates mainly to the risk of infection following injury, but another common complication of penetrating head wounds is the formation of intracerebral hematomas.[5] Dural penetration may be linked to the exterior not only through scalp lacerations and fractures of the skull vault but also through the nose and ears, through fractures of the anterior and middle cranial fossa, and through small puncture wounds in the eye and cheeks with penetration of the base of the skull. These latter injuries are very important to remember as the small puncture wounds may soon become obscured, for example, by swelling of the eyelids.[6] For this reason the history of injury is very important when there is any suggestion that a sharp object has penetrated the head or face for any appreciable distance. In such injuries the patient frequently has never been unconscious so that there is always a real danger of dismissal from the hospital without recognition of the problem.

External examination may immediately reveal that there has been dural penetration; cerebrospinal fluid (CSF) or brain tissue may be seen issuing from a small scalp wound or CSF may be seen coming from the nose or ear. Indirect evidence occurring a few hours after injury is the formation of periorbital bruising (raccoon eyes) or bruising behind the ear (Battle sign) which indicate the presence of fractures of the anterior and middle cranial fossae respectively. These appearances are not in themselves indicators of dural penetration, however, and this may be extremely difficult to judge as CSF leakage may be only transient or may never occur.[7] Plain x-rays of the skull may yield further clues to the presence of dural tearing; the appearance of an aerocele or spontaneous ventriculogram is certain evidence of a dural fistula. When skull x-rays are carried out to detect intracranial air, the crucial film is a brow-up lateral view where the air will be found on the undersurface of the frontal bone or in the frontal horns.[8] Deeply imbedded bone fragments or foreign bodies in the head will also provide evidence of dural penetration, but it must be remembered that many materials such as wood do not appear on x-ray and, in some instances, exploration of the head wounds will have to be based only on a history of deep penetration of the head by some object. It is essential in any case to carry out toilet, debridement, and thorough exploration of compound fractures of the skull, though great care is needed for those fractures which overlie the great venous sinuses.[5]

5. *Is the intracranial pressure elevated?*

The only way in which this question can be answered is by direct measurement of intracranial pressure, preferably from the lateral ventricles or cerebral epidural or subarachnoid space. Lumbar puncture is not justified as a means of obtaining an answer to this question for two reasons. First, if the patient has a sizable mass lesion in the supratentorial compartment, performance of lumbar puncture may precipitate tentorial or tonsillar herniation. Second, under these same circumstances, the recorded spinal fluid pressure will not nearly approximate the true level of intracranial pressure so that this type of measurement from the lumbar subarachnoid space is not only misleading but dangerous.[9,10] There are no clinical neurological signs which will indicate a particular level of intracranial pressure. The so-called signs of raised intracranial pressure, pupillary dilation, extensor rigidity, bradycardia, and arterial hypertension are all manifestations of brain herniation, not indicators of any particular level of intracranial pressure. Papilledema which can truly be said to result from intracranial hypertension does not appear early after head injury and is not, in any case, identified with any particular level of intracranial pressure. If the answer to this question is important, therefore, the only solution is for supratentorial pressure to be directly measured. This has been done in a series of 160 patients seen at the Medical College of Virginia over a three-year period and the results from this large series can be reasonably confidently extrapolated to experience with head injuries as a whole.[11] On admission to the hospital, virtually all patients with surgically significant intracranial mass lesions will have some degree of elevated intracranial pressure, at least over 10 mm Hg but going up in some cases as high as 70 mm Hg, particularly in patients with acute subdural hematoma. Of patients with diffuse brain

injury without an intracranial mass lesion more than two thirds will have some degree of intracranial hypertension on admission, although in most cases the increased pressure will be moderate, in the range of 10 to 20 mm Hg. Even if surgical masses are evacuated promptly and patients are ventilated to avoid any hypoxia or hypercapnea and given steroids, raised intracranial pressure will still present a problem in many instances, in approximately half of those patients who have had mass lesions removed, and in approximately one third of those patients with diffuse brain injury. Of patients who die of severe head injury, nearly half do so because of fulminating intracranial hypertension and associated brain shift and ischemia. In the survivors, high intracranial pressure is associated with a poorer outcome.

It is our belief, therefore, that given adequate equipment and personnel, optimal assessment of patients with severe head injury who remain unconscious should include direct measurement of intracranial pressure on a continuous basis for two or more days as indicated. The technique is not without risks, however, and these risks, mainly of infection, must be weighed against the expected benefit of the technique which should be restricted to centers having an intensive care unit with full, round-the-clock, medical and nursing staff.

6. *What is the extent of damage to the brain?*

In determining the final outcome from head injury the extent of the injuries scattered throughout the brain may be of more importance than the severity of injury at any one place. The neurological examination in the early stages after injury may be more a reflection of the strategic location of the most severe cerebral injury and its capacity to depress the total nervous system than an accurate index of the total extent of areas of brain damage. Nevertheless, the length of time that a patient is unconscious and the length of time until recovery of full continuous memory (the period of posttraumatic amnesia) seem to reflect increasing extent of diffuse brain damage in contrast to persisting hemiplegia which is a manifestation of focal damage in a crucial location. The electroencephalogram (EEG) is of little or no value in this respect and the procedures of ventriculography, angiography, and ultrasonic studies all point only to the most severely involved hemisphere of the brain or to shift of the brain by an extra-axial mass lesion. With the advent of CT, it is possible for the first time to look in a morphological way at the extent of brain damage and it is to be hoped that a clearer prognosis will be possible by the early identification of those patients with, for example, significant bilateral brain lesions.

In the physiological study of the central nervous system (CNS) the use of multi-modality evoked potentials is looking extremely promising, with some capacity to determine the extent of brain damage located both in the brain stem and in the hemispheres. Good correlation has been obtained between persistent focal neurological deficit and local abnormalities in evoked potentials and between prolonged coma and poor outcome and particular combinations of abnormal evoked responses.[12] The main limitation of this technique is that there is no way as yet to perform specific evoked potential responses which will determine function in the frontal lobe of the brain; thus about 50% of the volume of each hemisphere is unavailable for this type of neurophysiological study. Measurements of cerebral blood flow in multiple regions of the brain are now possible and stress tests can be done to see how these areas respond to elevation or lowering of the arterial P_{CO_2} or blood pressure. When such studies are done, oftentimes areas of impaired blood flow regulation will be seen in the frontal and temporal parts of the brain, corresponding with those areas which are most frequently affected by cerebral contusions after blunt head injury.[13]

Surgical Management in Head Injury

Surgical procedures are required in only a minority of head-injured patients admitted to hospitals, but it is important that if they are going to be done, they should be done for clear indications as expeditiously as possible and should lean towards being radical rather than inadequate. Burr hole exploration in acute head injury is only an incomplete approach to diagnosis; it is virtually never an adequate therapeutic measure.

There are two main indications for surgical intervention in patients with head injury. The first is intracranial infection for which the debridement and repair of penetrating wounds of the skull is carried out with the aim of forestalling this condition. Thus, the principles in this form of surgical treatment are the same as those for compound wounds elsewhere. The second indication, which is more particular for CNS trauma, is intracranial mass lesions which require surgical evacuation. There is no question that these lesions must be removed immediately if associated with any neurological deterioration, but it is

also our belief that any sizable lesion associated with shift of the intracranial structures should be evacuated even if at that time there are no definite indications of neurological deterioration. In a seriously ill patient any degree of neurological deterioration may push the patient beyond the recoverable stage, and even if the mass itself does not immediately jeopardize the patient, the superimposition of any one of several types of secondary insults may suddenly precipitate the patient into fulminating brain compression. Examples of this are cerebral vasodilation due to hypoxia, hypercarbia, the administration of volatile anesthetic agents, and even a sharp increase in body temperature.[4]

The surgical approach to the penetrating wound is governed of necessity by the site of the damage, but adequate exposure of the wound must be obtained and enough bone removed to permit a clear view of all areas of possible contamination. If the dura is extensively torn, it should be repaired, if necessary, with a graft taken from temporal fascia or from the thigh. All imbedded bone fragments should be removed and x-rays on the operating table are useful to ensure that this end has been satisfactorily achieved. Deeply imbedded metallic fragments such as bullets need not be removed if they are difficult of access surgically as it is considered that the risk of infection from these metallic fragments is much less than from indriven bone. There is a particular risk of intracranial infection in penetrating wounds which involve the frontal sinuses.

In the surgical approach to decompression of intracranial mass lesions there is little place for the use of multiple burr holes once the location of the mass has been established by ventriculography, angiography, or CT scan. In these cases a very large bone flap should be turned which will expose the frontal and temporal lobes and go posteriorly beyond the limits of the frontal lobe (Fig 3). If there is in addition to extracerebral hematoma a pronounced degree of frontal or temporal tip contusion and necrosis, this should be removed. In some cases the swelling is entirely intracerebral and in these instances a frontal or temporal lobectomy of at least 5 cm should be carried out.

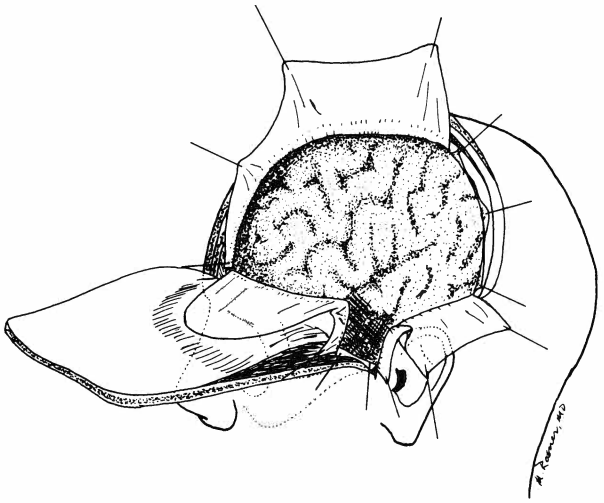


Fig 3— Extent of craniotomy required in patients with mass lesions (acute hematoma).

Medical Management of Head Injury

The medical management of the patient with head injury is an exercise in maintaining the physiological milieu of the patient as stable as possible. Since abnormal respiration is a common problem soon after injury we believe that all unconscious patients should be artificially ventilated on a volume respirator using a high tidal volume for several days at least after the injury or until they are clearly regaining consciousness. For patients who resist the ventilator small doses of morphine or chlorpromazine may be used or muscle relaxants may be required. In the latter event, however, the neurological evaluation can be done only in those periods of time when the effect of the muscle relaxant has worn off.

We prefer to adjust the minute volume to maintain an arterial P_{CO_2} level of 25 to 35 mm Hg and also adjust the fraction of inspired oxygen to keep arterial P_{O_2} well over 70 mm Hg. Although there is no hard evidence that steroids exert a favorable influence on severe acute brain injury, we currently give patients a standard dose of dexamethasone (4 mg every six hours). Recent reports from West Germany have suggested that higher doses of steroids may be efficacious in head injury.[14,15] This aspect of head injury care is currently being studied in several centers. It has been our policy to give prophylactic anticonvulsant therapy in the form of phenytoin 100 mg three times daily to all patients with serious head injury, to those patients with penetrating injuries who have dural tearing, and in particular where there has been an intracranial hematoma, infection, or missile wound.

Intracranial pressure is monitored continuously for at least two days and longer as required. In-

creased intracranial pressure is treated by increased hyperventilation, by controlled CSF drainage against a positive pressure, and by intravenous mannitol therapy alone or in combination. Present indications for treatment of intracranial hypertension are an intracranial pressure rise over 30 mm Hg or any increase in intracranial pressure associated with neurological deterioriation.

The Outcome of Severe Head Injury

Of the 160 patients with blunt head injury who have been treated with this policy of early diagnosis and evacuation of mass lesions followed by artificial ventilation and intracranial pressure monitoring, the results have been extremely gratifying.[16] Sixty percent of the patients have recovered to the extent of becoming independent and in more than half of these cases the patients have been able to return to their former occupational level. The mortality rate has been 30% with the remaining 10% of patients being either severely disabled and manageable at home (8%) or remaining in hospitals or nursing homes in a permanent vegetative state (2%). These results compare favorably with results reported in patients with similar degrees of head injury from other centers and of particular interest is that this policy of early and radical surgical decompression has not been associated with an increase in the number of permanent vegetative survivals.

In examining the factors which regulate the outcome from severe injury we find that age is important in that older patients are much more prone to die of infective or other systemic complications of the head injury. Signs which indicate brain stem dysfunction (absent pupillary light response and impaired or absent oculocephalic response) are strongly associated with a bad outcome. The presence of decerebrate or extensor rigidity or loss of the motor response signifies a bad outcome only in those patients without intracranial mass lesions. In the patients with mass lesions a good recovery is still possible despite a combination of all three adverse signs, this being in the small group of patients in whom such signs relate to brain compression rather than to the primary injury and in whom the brain compression is relieved early, before secondary brain dysfunction has become irreversible. Intracranial hypertension occurring on admission or, more important, during the intensive care unit management phase does carry adverse significance for the patient, and should be treated. Increased intracranial pressure is, we believe, related to the extent of brain damage rather than to any particular location.

In the evaluation of outcome of penetrating wounds emphasis must be placed on complete debridement of wounds; bad results are usually due to inadequate surgical debridement and this usually happens because the surgeon is unaware of the extent of the lesion at the time of surgery. For this reason, as complete a diagnostic work-up as possible is also needed in these patients.

Conclusions

Optimum management of head trauma consists largely of making plans to avoid as many of the secondary complications of head trauma as possible. This may be effected through a comprehensive and rapid diagnostic process, by early and adequate surgical decompression, by full debridement and dural repair in penetrating wounds, and by meticulous intensive care. The measure of the success of such a regime will be the small number of patients in whom neurological deterioration occurs after their admission to the hospital.

REFERENCES

1. MILLER D, ADAMS H: Physiopathology and management of increased intracranial pressure, in Critchley M, O'Leery JO, Jennett WB (eds): *Scientific Foundations of Neurology*. London, Heinemann, 1972, pp 308–324.

2. ILLINGWORTH G, JENNETT WB: The shocked head injury. *Lancet* 2:511–514, 1965.

3. GALBRAITH S, MURRAY WR, PATEL AR, ET AL: The relationship between alcohol and head injury and its effect on the conscious level. *Br J Surg* 63:128–130, 1976.

4. MILLER JD: Infection after head injury, in Vinken PJ, Bruyn CW (eds): *Handbook of Clinical Neurology*. Part 2: *Injuries of the Brain and Skull*, vol 24; R Braakman (ed). Amsterdam, Elsevier, 1976, pp 215–230.

5. MILLER JD, JENNETT WB: Complications of depressed skull fracture. *Lancet* 2:991–995, 1968.

6. GUTHKELCH AN: Apparently trivial wounds of the eyelids with intracranial damage. *Br Med J* 2:842–844, 1960.

7. LEECH PJ, PATERSON A: Conservative and operative management for cerebrospinal fluid leakage after closed injury. *Lancet* 1:1013–1015, 1973.

8. NORTH JB: On the importance in intracranial air. *Br J Surg* 58:826–829, 1971.

9. LANGFITT TW, WEINSTEIN JD, KASSELL NF, ET AL: Transmis-

sion of increased intracranial pressure. I. Within the craniospinal axis. *J Neurosurg* 21:989–997, 1964.

10. KAUFMANN GE, CLARK K: Continuous simultaneous monitoring of intraventricular and cervical subarachnoid cerebrospinal fluid pressure to indicate the development of cerebral or tonsillar herniation. *J Neurosurg* 33:145–150, 1970.

11. MILLER JD, BECKER DP, WARD JD, ET AL: Significance of intracranial hypertension in severe head injury. *J Neurosurg,* to be published.

12. GREENBERG RP, BECKER DP, MILLER JD, ET AL: Evaluation of brain function in severe human head trauma with multimodality evoked potentials. Part II. Localization of brain dysfunction and correlation with post-traumatic neurological conditions. *J Neurosurg* 47:163–177, 1977.

13. BRUCE DA, LANGFITT TW, MILLER JD, ET AL: Regional cerebral blood flow, intracranial pressure, and brain metabolism in comatose patients. *J Neurosurg* 38:131–144, 1973.

14. FAUPEL G, REULEN HJ, MÜLLER D, ET AL: Double-blind study on the effects of steroids on severe closed head injury, in Pappius HM, Feindel W (eds): *Dynamics of Brain Edema.* Berlin, Heidelberg, New York, Springer-Verlag, 1976, pp 337–343.

15. GOBIET W: The influence of various doses of dexamethasone on intracranial pressure in patients with severe head injury, in Pappius HM, Feindel W (eds): *Dynamics of Brain Edema.* Berlin, Heidelberg, New York, Springer-Verlag, 1976, pp 351–355.

16. BECKER DP, MILLER JD, WARD JD, ET AL: The outcome from severe head injury with intensive management. *J Neurosurg,* to be published.

A Diagnostic Approach to Acute Headache

ALAN B. GRINDAL, M.D.

Assistant Professor, Department of Neurology, Medical College of Virginia, Health Sciences Division of Virginia Commonwealth University, Richmond, Virginia

Headache is one of the most common symptomatic ailments encountered by the physician. According to one estimate, headache constitutes the major complaint in more than 50% of patients seen in office practice.[1] This figure refers to patients with chronic recurring headache, many of whom are seen electively when they are asymptomatic, and may not accurately reflect the frequency with which patients present, during the acute phase, complaining of head pain. The term acute headache refers to those episodes of cephalgia which lead the patient to seek immediate medical care.

Headache must of course be regarded as a symptom and not a disease. Almost everyone suffers an occasional headache, be it from psychologic stress or excessive indulgence. Fortunately the vast majority of head discomforts stem from minor and reversible conditions which do not pose a threat to health. On the other hand, headache secondary to a bacterial meningitis or subdural hematoma calls for prompt and often heroic measures. Referring to headache, Wolff states in the preface to his text, "Failure to separate the ominous from the trivial may cost life or create paralyzing fear."[2] Therefore, the evaluation of the patient with acute headache must avoid the extremes of passing the symptom off as a minor condition with only a haphazard evaluation, on the one hand, and of subjecting the patient to an unnecessarily expensive and extensive evaluation, on the other.

It is the purpose of this report to describe the evaluation of the patient who suffers from the onset of acute headache. The most important decision to be made in this setting is whether one is dealing with a benign or malignant illness. By malignant, I am referring to disorders in which early intervention is necessary to prevent death or disability. The symptoms and signs which may aid in this distinction will be presented as well as a sequential diagnostic approach which, one hopes, will insure as complete an evaluation as is necessary and at the same time cause no harm or undue discomfort.

Correspondence and reprint requests to Dr. Alan B. Grindal, Department of Neurology, Box 698, Medical College of Virginia, Richmond, Virginia 23298.

History

A detailed history is usually the clinician's most valuable tool in evaluating the patient with acute headache. The basic headache history should be concise and organized so that relevant facts are not overlooked. A simple outline of the important areas to be covered is in Table 1.

Onset. It is particularly helpful to establish the time and mode of onset. Headaches which begin in the second and third decades of life are commonly of vascular origin and migraine rarely makes its first appearance after the age of 50. On the other hand, temporal arteritis and glaucoma must be considered when headache has its onset in the fifth decade or later. Headaches secondary to cervical spondylosis or depression are also more likely to occur among older patients.

The time of day at which the headache begins may also be helpful. Pain due to space-occupying intracranial disease is notoriously worse on waking in the morning. Head pain, on the other hand, due to muscle tension or cervical osteoarthritis usually is worse in the late afternoon, and cluster headaches typically awaken the patient in the middle of the night.

Also under the heading of onset, one should establish the rapidity of onset. An abrupt severe

TABLE 1
Headache History Outline

1. Onset
2. Location
3. Severity
4. Temporal course (prodrome, duration, frequency)
5. Associated symptoms
6. Precipitating factors
7. Medical and family history

headache should make one suspicious of subarachnoid hemorrhage particularly if there is associated alteration of consciousness.

Location. The location of the headache may provide a diagnostic clue. In this regard, it is useful to have the patient point to the precise area of pain, and the region of radiation if one exists. Relying on the patient's anatomic knowledge may be dangerous, and indeed a "sinus heachache" may be located over the occiput.[3] The site of pathology may be clearly delineated in patients with dental and sinus disease. Pain localized to one eye should raise the suspicion of cluster headache or ocular pathology. Occipital and nuchal pain are often seen with chronic tension and with cervical osteoarthritis. Unilateral headaches typically occur in migraine but can also occur in more serious diseases such as temporal arteritis and subdural hematoma.

Severity. Pain itself cannot be measured by the observer and the headache may be equally intense whether its implications are benign or malignant. According to Wolff, "there are few instances in human experience where so much pain may mean so little in terms of tissue injury."[2] Severity of pain may, however, be estimated by asking such questions as, Did the pain awaken you from a sound sleep? Did it compel immediate rest and cessation of all activity? Severe pain is worrisome particularly if it comes on suddenly or if it represents the result of progressive increase in intensity.

Temporal Course. Prodromal, or premonitory, symptoms, such as scotomata and hemianopia, preceding the headache suggest migraine. Similar visual symptoms may uncommonly occur with angiomas and tumors.

Vascular headaches such as migraine and cluster are throbbing in character, usually last from minutes to hours, but tend to be episodic and recurrent. Tension headaches, on the other hand, are dull and nagging and characteristically are persistent, often lasting weeks and even months without a pain-free interval. Headache in the patient with a space-occupying lesion may be intermittent at first but generally becomes progressively more constant and severe.

Associated Symptoms. Nausea and vomiting are commonly associated with migraine. Vomiting, however, may also occur with increased intracranial pressure and frequently is unaccompanied by nausea. Patients with cluster often exhibit nasal congestion, unilateral redness of the eye, and lacrimation. Similar symptoms may be seen in the patient with upper respiratory infection (URI) or sinusitis, but these are generally more prolonged. Disturbance of vegetative functions such as sleep, bowel function, and appetite may suggest underlying depression. Associated convulsions or disturbance in consciousness should always raise concern of serious underlying disease. Focal neurologic symptoms and disturbances of vision, although commonly associated with migraine, should be carefully investigated.

Precipitating Factors. A variety of precipitants have been implicated in initiating a migraine attack. These include fatigue, menstruation, bright sunlight, alcohol, and tyramine-containing foods. Emotional factors, which so frequently precipitate headache, should be sought with careful questioning regarding recent marital, occupational, or financial difficulties. The exertional headache should always arouse suspicion of an intracranial lesion. This is a headache which comes on from complete comfort following activities such as running, coitus, and Valsalva maneuver. Although the pain is often quite severe, it usually is of brief duration. Also of concern are headaches which are precipitated by changes in posture or head position. Such headaches could represent a ball-valve effect produced by an intraventricular tumor.

Past Medical and Family History. A strong family history of migraine may be reassuring when evaluating the young adult with the sudden onset of unilateral headache; however, neither its presence nor absence is diagnostic. Since a variety of systemic illnesses such as chronic pulmonary and renal disease are associated with cephalgia, a complete medical history and review of systems should be performed. History of surgery on a melanoma or other primary tumor should alert the physician to the possibility of metastatic brain disease. A medication history should also be obtained. Previous relief from ergotamine or activation of headache with nitrates might suggest migraine. Recent use of reserpine in the predisposed

individual might provoke a depressive episode which is manifested by headache.

Examination

After obtaining the history the physician generally has a fairly good idea of the type of headache he is dealing with. A complete and careful physical and neurologic examination, however, provides an additional screen for underlying serious disease and helps in deciding what further diagnostic studies are necessary. Rather than reviewing the entire examination, this discussion will be limited to those aspects of the physical and neurologic examinations which are particularly relevant to the headache patient.

Observation. The appearance and activity of the patient during the initial interview often provides valuable information. Individuals with severe head pain have a characteristic facial expression and tend to move slowly and deliberately; the patient with psychogenic disease, on the other hand, often appears relaxed while complaining bitterly of severe discomfort.[4] Gait and station should also be observed; ataxic gait associated with the recent onset of headache is alarming and should be expeditiously pursued diagnostically.

Physical Examination. The vital signs, particularly temperature and blood pressure, should be routinely recorded. Fever and its resultant vasodilation may be responsible for headache; however, its presence should prompt a search for infection. A central nervous system infection such as meningitis or brain abcsess must be considered. It should be remembered that fever may also be present in some systemic illnesses such as temporal arteritis. Headache can be the earliest symptom in the patient with malignant hypertension. The headache associated with hypertension is usually generalized, throbbing, and often increased in the supine position.

A careful examination of the head and neck is essential in evaluating the patient with head pain. Inspection may reveal a tortuous and prominent superficial temporal artery in the patient with temporal arteritis, or facial erythema and lacrimation in the individual suffering an acute cluster attack. Fundoscopy is a 'must' in any patient presenting with acute headache. Visual fields should be checked by confrontation. Any patient with a disturbance of vision or visual field defect which is not transient, or clearly associated with a migraine attack, must be investigated further. One can also grossly evaluate intraocular pressure by palpating the eye through the closed lid. Glaucoma may present initially with headache, and careful tonometry needs to be performed if this diagnosis is suspected. Finally the nose, ears, and mouth should be examined for evidence of inflammation. Patients with URI and flu-like syndromes often list headache as their primary complaint.

Limitation of movement or spasm on examination of the neck would suggest cervical spondylosis or chronic tension. Stiffness, however, with limited neck flexion is usually noted in the presence of meningeal irritation, and meningitis or subarachnoid hemorrhage should be suspected.

Neurologic Examination. A complete neurologic examination of the headache patient is very important. Perhaps the most important part of this examination is the assessment of mental status. Altered consciousness in a patient presenting with headache should always be regarded with concern. An evaluation of the cranial nerves should also be carried out. The first cranial nerve is often neglected and may be easily tested by having the patient identify common odors, such as tobacco, through each nostril. Anosmia may be the only sign of olfactory groove meningioma.

Motor and sensory function as well as reflexes and coordination should be systematically tested. Any abnormality on neurologic examination which cannot be confidently explained on the basis of a previous illness or injury requires further diagnostic study.

Diagnostic Studies

The diagnostic evaluation of the headache patient should proceed in a logical sequential manner to insure a complete investigation when necessary and to prevent costly and potentially harmful studies when these are not indicated. To conceive of the acute headache evaluation occurring in stages is a useful approach[5]; however, certain circumstances may require a more expedient evaluation and therefore this approach is intended to be a guide rather than a cookbook to testing patients complaining of acute headache (Table 2).

The first and probably the most important stage consists of a detailed history and thorough examination as outlined earlier in this paper. All patients except those requiring urgent therapeutic procedures should pass through this phase. Unless there has been a recent evaluation or the diagnosis of a benign entity is certain, patients should undergo routine screening

TABLE 2
Approach to Diagnostic Evaluation

Stage 1	History and physical
Stage 2	Routine screening (eg. CBC, ESR, skull x-rays)
Stage 3	Extensive systemic and neurologic evaluation (eg. CT scan, EEG, lumbar puncture)
Stage 4	Invasive diagnostic studies (eg. angiography, ventriculography)

tests. The procedures which constitute Stage 2 not only provide information which cannot be obtained on examination but also serve to reassure the patient that a complete evaluation is being carried out.

Stage 2 at a minimum should include a complete blood count (CBC), erythrocyte sedimentation rate (ESR), and skull x-rays. Other studies such as urinalysis, chest x-ray, and blood sugar might also be included. An elevated ESR is a sign of chronic inflammation and primarily serves as a screen for cranial arteritis.

Although the skull x-ray is frequently normal in the headache patient, exceptions must not be forgotten. When least expected, the skull x-ray may reveal signs of raised intracranial pressure, deviation of the pineal, or metastatic lesions. Because of the widely held belief in the infallibility of x-rays, a normal skull series may take on prophylactic and therapeutic properties.[6] An acute tension headache may become chronic through the fear of an underlying tumor.

If, following the completion of Stage 2, one is convinced that the headache is secondary to tension, migraine, URI, or other benign entity, the initial evaluation should be completed. It is probably wise, however, in most cases to arrange for a follow-up visit within a couple of weeks.

TABLE 4
Examination Findings Suggesting Serious Underlying Disease

1. Disturbed level of consciousness
2. Difficulty walking or sitting
3. Disturbance of vision or visual field that is not clearly migrainous
4. Hypertension
5. Stiff neck
6. Any unexplained abnormality on neurologic examination

TABLE 3
Historical Features Suggesting Serious Underlying Disease

1. Abrupt onset
2. Persistent unilateral pain
3. Progressive course
4. Disturbance of consciousness
5. Convulsions
6. Focal neurologic symptoms
7. Headache precipitated by:
   a. exertion
   b. change in posture
8. History or symptoms suggestive of systemic illness

Patients should advance to the third stage of testing when disturbing information is obtained on history, abnormalities are found on examination, or routine screening studies are abnormal (Tables 3 and 4). Some but not all patients who reach this stage require hospitalization. Included at this level would be electroencephalogram (EEG), brain scan, computerized tomography (CT) scan, and lumbar puncture. Depending on suspicions, cervical spine x-rays, sinus films, or other special studies might be indicated.

Stage 4 consists of the use of invasive techniques such as angiography and ventriculography. On occasion it may be necessary to employ these studies after a brief history and examination. However, most often they should be performed after screening procedures have been completed and careful consideration has been given. The studies at this level require hospitalization.

The Acute Headache Problem

In an attempt to put the acute headache problem into some perspective, the emergency room admission records of patients seen in the Medical Emergency Room at the Medical College of Virginia during the month of March, 1977, were reviewed. Of the 1998 visits that month, 105 or 5% listed headache as one of the major complaints. Sixty-one percent of these 105 patients were under the age of 30 despite the fact that no patients under 15 are seen in the Medical Emergency Room. Better than two thirds of the patients were female.

According to the emergency room records, the majority of patients suffered either from tension, URI, or migraine, in that order. A complete breakdown of diagnosis is presented in Table 5.

Only eight patients were admitted to the hospital; three of these had meningitis and two were admit-

TABLE 5
Characteristics of 105 Acute Headache Patients Seen in MCV ER

AGE	15–20	21–30	31–40	41–50	>51
	22	42	19	10	12
SEX	Male	Female			
	34	71			
DIAGNOSIS:			Anxiety-Tension		30
			URI-Flu Syndrome		23
			Vascular-Migraine		17
			Posttraumatic		6
			Hypertension		6
			Depression		4
			Sinusitis		4
			Meningitis		3
			Alcohol intoxication		3
			Other		9
ADMITTED TO HOSPITAL			Meningitis		3
			Depression		2
			Cerebral hemorrhage		1
			Cerebral infarct		1
			Alcoholism		1

ted to the psychiatry service because of depression.

Based on this somewhat superficial review of a selected population, it would appear that the patient seeking acute care for headache is usually young, female, and suffers from a benign entity. However, one cannot be complacent. As is demonstrated, headache is a symptom of a wide variety of disorders, some of which are life-threatening. In order to arrive at a correct diagnosis, an organized approach based on a careful history, complete examination, and sequential testing is essential.

REFERENCES

1. FRIEDMAN AP, MERRITT HH: *Headache: Diagnosis and Treatment.* Philadelphia, F A Davis Co, 1959.

2. WOLFF H: *Headache and Other Head Pain.* New York, Oxford University Press, 1963.

3. YOUNG AK: The clinical approach to the evaluation of head pain. *Headache* 6:66–72, 1966.

4. KUNKEL RS: Examining the headache patient. *Postgrad Med* 56:81–85, 1974.

5. SHERRILL RG JR: Sequential testing for headache complaints. *Postgrad Med* 56:93–98, 1974.

6. HEYCK H: Examination and differential diagnosis of headaches, in Vinken PJ, Bruyn GW (eds): *Handbook of Clinical Neurology.* Amsterdam, North-Holland Publishing Co, 1968, vol 5, chap 3.

Differential Diagnosis of Progressive Generalized or Symmetrical Flaccid Paralysis

EDWARD R. ISAACS, M.D

Assistant Professor, Department of Neurology, Medical College of Virginia, Health Sciences Division of Virginia Commonwealth University, Richmond, Virginia

Progressive flaccid paralysis occurring over a period of hours or days is usually associated with the Landry-Guillain-Barré-Strohl syndrome.[1,2,3] This symptom complex is often accompanied by a history of a previous flu-like illness, antecedent myalgias, and subjective sensory complaints of tingling or simply a "tight" sensation in hands and feet. The paralysis that ensues either ascends from the feet and legs or descends from the facial muscles to involve all or most of the voluntary skeletal musculature. Along with paralysis of the intercostal and diaphragmatic musculature, severe cases may also involve other cranial nerves as well as the autonomic nervous system. In all cases the deep tendon reflexes are markedly diminished or absent early in the course of the disease. Sensory abnormalities are usually mild or absent. Confirmatory diagnostic studies include examination of the cerebral spinal fluid (CSF) which shows no or few mononuclear cells and an elevated protein. Nerve conduction studies may show prolonged distal latencies, slowing of nerve conduction velocities, and prolonged F responses which measure the radicular segments of the nerve. Overall prognosis is difficult to predict, with recovery taking weeks to months. Fatalities can occur despite optimal care in an intensive care unit. Electromyographic evidence of denervation suggests a more prolonged course with a greater chance of residual weakness. Atypical forms of this syndrome are more difficult to diagnose as can be illustrated by the following case history:

Correspondence and reprint requests to Dr. Edward R. Isaacs, Department of Neurology, Box 698, Medical College of Virginia, Richmond, Virginia 23298.

The patient was a 15-year-old boy with a progressive flaccid paralysis which began with leg pains and a gait disturbance; he required tracheostomy 72 hours later. Two weeks prior to this he suffered a flu-like illness and the day before he became weak he had been mowing a field freshly sprayed with insecticide. Initial examination showed a flaccid paraplegia and absent deep tendon reflexes, but the CSF was normal with no cells and a protein less than 50 mg/100 ml. Nerve conduction studies done on arrival at the hospital and the next day showed normal distal latencies, nerve conduction velocities, and F wave latencies. In some of the severely weakened distal muscles no compound action potential could be elicited and in others these potentials were of low amplitude and not augmented by 30 Hz trains of supramaximal stimulation. During the second week of total paralysis, distal latencies were slightly prolonged and conduction velocities had decreased. The spinal fluid remained normal. After the third week, the patient began to recover, initiating movements in arms and legs. Nerve conduction studies now showed definite prolongation of distal latencies and prolonged F wave latencies. The spinal fluid now had an elevated protein and no cells. By the fifth week strength had returned and the patient was weaned from the respirator.

Discussion

The absence of the early electromyographic and spinal fluid changes[1] usually associated with a post-infectious polyradiculopathy instigated a search for other disorders which may present in a similar fashion. In devising a systematic approach towards a differential diagnosis in this atypical case, it was help-

ful to consider the component parts of the motor unit, specifically the anterior horn cell, axon (peripheral nerve), neuromuscular junction, and the muscle fibers innervated by that anterior horn cell.

Anterior Horn Cell Disease

Most of the anterior horn cell diseases that are encountered today are chronic and progressive and are not likely to be confused with the clinical presentation under discussion.[4,5] However, there remains the possibility of the emergence of a new neurotrophic virus or the occurrence of acute poliomyelitis in the uninoculated. Poliomyelitis presents as a biphasic illness beginning as a flu-like syndrome which remits within 48 hours. Headache, severe myalgias and meningismus mark the next phase, with the spinal fluid showing a pleocytosis of 50 to 250 cells, an elevated protein (100 to 250 mg/100 ml), and a normal glucose. Some cases may then progress with muscle fasciculations and paralysis. If mild, the paralysis can be quite asymmetrical, but if severe, it may appear symmetrically and involve bulbar musculature. Deep tendon reflexes may be exaggerated early, but these are lost in the paralytic stage of the disease.

Peripheral Nerve

Acute polyneuropathies or polyradiculoneuropathies most often fall within the symptom complex of the Guillain-Barré syndrome.[1,2] A wide variety of infective agents are capable of producing a state likened to experimental allergic neuritis with monocytic infiltration, edema, and demyelination of the peripheral nerve as the common pathological reaction. Such agents appear to combine with cell membranes, triggering an aberrant immune response which is directed towards cell membrane and, consequently, myelin. Generalized inflammatory states as seen with systemic lupus erythematosus are capable of producing a syndrome indistinguishable from the postinfectious variety. Furthermore, this syndrome has also been caused by infiltrations of plasma cells in association with multiple myeloma.

In some patients there is a tendency to suffer from a chronic relapsing steroid-dependent form of a polyradiculoneuropathy.[6,7] In these patients the onset is usually more gradual, over one to two weeks, and usually does not involve cranial nerves or respiratory muscles. With the use of steroid medication, the patients become asymptomatic, although nerve conduction studies still remain abnormal. In the event of steroid withdrawal there is an exacerbation of all symptoms with a progressive paralysis.

Diphtheria toxin, although rapidly fixing to peripheral nerve, has a delayed effect as it appears to block myelin production.[8] Consequently, the turnover of new myelin is inhibited, resulting in progressive demyelinization of the peripheral nerve weeks to months later. Despite the characteristic clinical features of diptheria, long delays between the time of the initial infection and the subsequent neuropathic complications may make the association difficult. Paralysis begins and may be localized to cranial nerves involving, in particular, the palate and the pupil with a characteristic fatigue of accommodation. More rarely, facial and extraocular muscles are also involved. A certain number of patients then develop a generalized peripheral sensori-motor neuropathy with loss of reflexes, mild sensory loss, and peripheral weakness. A tachycardia is oftentimes associated with the peripheral neuropathy, as well as spinal fluid changes of elevated protein with or without pleocytosis. A similar onset and cause have also been described in the neuropathy associated with extra faucial diphtheria.

The hepatic porphyrias,[9] especially the acute intermittent and variegated forms, can cause paralysis following the abdominal and psychic manifestations. Oftentimes, pain precedes the weakness in affected muscles, which usually involves the upper limbs first and especially proximal muscles and wrist extensors. Progression may be stepwise over one to four weeks and involves limbs, trunk, cranial, and autonomic nerves. The spinal fluid protein is slightly increased and there are few monocytes. Nerve conduction studies are frequently normal since it is the axons which suffered a primary insult and not the myelin. Other abnormal metabolic states, such as hepatic and renal failure, as well as diabetes, are more likely to cause chronic neuropathies and do not present as acute paralytic states.

Exposure to toxic substances,[10] either during their manufacture or use, can be the cause of progressive, flaccid paralysis. Cases are usually sporadic and in some this reaction seems to be determined by individual susceptibility. Cases can appear so typical that without a history of exposure to endrin, aldrin, dichloro-diphenyl-trichloroethane (DDT), or dichloro-diphenyl-dichloroethane (DDD), a diagnosis of acute, infective polyneuritis may be made. The ingestion of thallium salts[11] found in rodenticides and insectides can cause an acute polyneuropathy in addition to gastrointestinal disturbances. The neuropathy is mostly sensory, affecting the lower extremities, and is associated with migratory arthralgias. In some pa-

tients paralysis may be generalized, involving respiration and associated with circulatory difficulty as the autonomic system is involved as well. Usually, with massive doses, central nervous system symptoms predominate with hallucinations, convulsions, and death. Several weeks after the ingestion of thallium, alopecia occurs and this is what implicates thallium poisoning.

It would be an oversimplification to state that there are a wide variety of agents capable of producing polyneuropathy—heavy metals, drugs, and toxic chemicals—but for the most part these do not present as acute neuropathic polyneuropathies. New substances are found capable of producing the syndrome and isolated case reports continue to appear in the literature. Examples of this are the ascending polyradiculopathies associated with the ingestion of the fruit from poisonous shrubs[12] as well as reports of this syndrome as a complication of hyperalimentation.[13]

Neuromuscular Junction

Neuromuscular blockade can occur either presynaptically or postsynaptically and cause a rapidly progressive, generalized, or selective paralysis. Presynaptic blockade is thought to be the mechanism of action in tick paralysis.[14] Five to six days after the attachment of certain female gravid ticks, usually located on the scalp, there is a rapid ascending paralysis which may begin with a gait disturbance and myalgia. If the tick is not removed, this may proceed to respiratory embarrassment. Spinal fluid is usually normal. The substance which the tick secretes must be quite potent, but it would also seem to have a rather short half-life since symptoms improve within hours of removing the tick.

Presynaptic neuromuscular blockade appears to be the mechanism of action of botulinus toxin.[15] Twenty-four to 48 hours after the ingestion of the toxin, ocular motor weakness, pupillary paralysis, and respiratory paralysis occur, usually preceded by a gastrointestinal disturbance. Progression to generalized paralysis can also occur. Nerve conduction studies are usually normal, neuromuscular blockade being demonstrated by high frequency stimulation with subsequent augmentation in the compound action potential.

Postsynaptic neuromuscular blockade can occur due to the inability of the postsynaptic membrane to respond to acetylcholine as it would in the myasthenic crisis.[4,16,17] Occasionally myasthenia gravis may begin with an acute, generalized severe form of muscular weakness which involves cranial nerves. Deep tendon reflexes are usually preserved and there is no sensory loss. Myasthenics may develop acute paralysis due to under-medication, or as a result of exposure to drugs which have mild presynaptic blocking properties and do not ordinarily affect nonsusceptible individuals.[18] Postsynaptic blockade can also occur as in cholinergic crises when acetylcholine is not degraded at the receptor site. Such blocks can occur in the myasthenic secondary to overmedication with antiacetylcholinesterase-type drugs[4,16,17] or in individuals who have been exposed to organophosphates such as tri-orthocresyl phosphate.[10] Organophosphate compounds are not only capable of producing an acute cholinergic crisis but also cause severe demyelinating types of polyneuropathies usually after a latent period of one to three weeks after exposure.

Muscle Fibers

Primary and secondary periodic paralyses are classified as hypokalemic, hyperkalemic, and normokalemic depending upon the serum potassium at the time of the paralysis.[4,19] The onset is rapid and progressive and usually follows exercise, exposure to cold, or the ingestion of a heavy meal. During a severe attack, deep tendon reflexes are depressed and there is an inability to initiate muscle contraction by electrical stimulation. Motor nerve conduction velocity may thereby be unobtainable. Spinal fluid is normal. The diagnosis may be suspected in the hereditary forms which are recurrent and by the potassium levels during the attack. The hyperkalemic[20] and normokalemic[19] forms may be associated with the onset of myotonia after exposure to cold between attacks. The secondary periodic paralyses are usually sporadic. Hypokalemic periodic paralysis may be seen as the presenting complaint or as a complication of thyrotoxicosis in certain individuals. Hypokalemic periodic paralysis is also seen in association with hyperaldosteronism as well as a complication of thiazides and sprinolactone.[4] Hyperkalemic forms occur in association with renal and adrenal failure. It would be extremely unusual for other myopathies to present as rapidly progressive paralysis. With fulminant forms of polymyositis or in rhabdomyolysis with associated myoglobinuria, patients are extremely ill, muscles are quite painful and the serum creatinine phosphokinase levels should be very high.[19]

As with many conditions involving the nervous system, the ability to localize the site of a particular

abnormality provides a logical means for considering a differential diagnosis in terms of what can happen at that particular site. In viewing the motor unit and its component parts a similar process is useful when considering progressive paralysis.

Acknowledgement: The author wishes to thank Walter J. O'Donohue, Jr., M.D. for his referral of the patient presented and his advice and encouragement in the preparation of this paper.

REFERENCES

1. ARANSON BGW: Inflammatory polyradiculoneuropathies, in Dyck PJ, Thomas PK, Lambert EH (eds): *Peripheral Neuropathy*. Philadelphia, WB Saunders Co, 1975, vol 2, pp 1110–1148.

2. BRADLEY WG: *Disorders of Peripheral Nerves*. Oxford, Blackwell Scientific Publications, 1974.

3. MCLEOD JG, WALSH JC, PRINEAS JW, ET AL: Acute idiopathic polyneuritis. *J Neurol Sci* 27:145–162, 1976.

4. ROWLAND LP, LAYZER RB: Muscular dystrophies, atrophies, and related diseases, in Baker AB, Baker LH (eds): *Clinical Neurology*. Hagerstown, Maryland, Harper and Row, 1975, vol 3, chap 37.

5. LIVERSEDGE LA, CAMPBELL MJ: Motor neurone diseases, in Walton JN (ed): *Disorders of Voluntary Muscle*. Edinburgh, Churchill Livingstone, 1974, pp 775–803.

6. PRINEAS JW, MCLEOD JG: Chronic relapsing polyneuritis. *J Neurol Sci* 27:427–458, 1976.

7. MATTHEWS WB, HOWELL DA, HUGHES RC: Relapsing corticosteroid-dependent polyneuritis. *J Neurol Neurosurg Pschiatry* 33:330–337, 1970.

8. MCDONALD WI, KOCEN RS: Diphtheritic neuropathy, in Dyck PJ, Thomas PK, Lambert EH (eds): *Peripheral Neuropathy*. Philadelphia, WB Saunders Co, 1975, vol 2, pp 1281–1300.

9. RIDLEY A: Porphyric neuropathy, in Dyck PJ, Thomas PK, Lambert EH (eds): *Peripheral Neuropathy*. Philadelphia, WB Saunders Co, 1975, vol 2, pp 942–955.

10. HOPKINS A: Toxic neuropathy due to industrial agents, in Dyck PJ, Thomas PK, Lambert, EH (eds): *Peripheral Neuropathy*. Philadelphia, WB Saunders Co, 1975, vol 2, pp 1207–1226.

11. GOLDSTEIN NP, MCCALL JT, DYCK PJ: Metal neuropathy, in Dyck PJ, Thomas PK, Lambert EH (eds): *Peripheral Neuropathy*. Philadelphia, WB Saunders Co, 1975, vol 2, pp 1227–1262.

12. CALDERON-GONZALEZ R, RIZZI-HERNANDEZ H: Buckthorn polyneuropathy. *N Engl J Med* 277:69–71, 1967.

13. WEINTRAUB MI: Hypophosphatemia mimicking acute Guillain-Barré-Strohl syndrome. *JAMA* 235:1040–1041, 1976.

14. SWIFT, TR, IGNACIO OJ: Tick paralysis: electrophysiologic studies. *Neurology (Minneap)* 25:1130–1133, 1975.

15. CHERINGTON M: Botulism. Ten-year experience. *Arch Neurol* 30:432–437, 1974.

16. OSSERMAN KE, KORNFELD P, COHEN E, ET AL: Studies in myasthenia gravis. *AMA Arch Int Med* 102:72–81, 1958.

17. ENGEL WK, FESTOFF BW, PATTEN BM, ET AL: Myasthenia gravis: NIH conference. *Ann Int Med* 81:225–246, 1974.

18. MCQUILLEN MP, CANTOR HE, O'ROURKE JR; Myasthenic syndrome associated with antibiotics. *Arch Neurol* 18:402–415, 1968.

19. MCARDLE B: Metabolic and endocrine myopathies, in Walton JN (ed): *Disorders of Voluntary Muscle*. Edinburgh, Churchill Livingstone, 1974, pp 726–759.

20. LAYZER RB, LOVELACE RE, ROWLAND LP: Hyperkalemic periodic paralysis. *Arch Neurol* 16:455–472, 1967.

Acute Seizure Problems

CARY SUTER, M.D.

Professor and Chairman, Department of Neurology, Medical College of Virginia, Health Sciences Division of Virginia Commonwealth University, Richmond, Virginia

Seizures are a symptom and not a disease. A seizure is the result of an abnormal electrical discharge of a collection or group of living but damaged or abnormal neurons. When the group of neurons is in the cerebral cortex, a focal or partial seizure occurs, producing abnormal activity related to that part of the brain. The victim may experience a focal jerking or focal numbness, or flashing lights if the lesion is in the occipital lobe; or he or she may be subject to peculiar automatic behavior if the lesion is in the temporal lobe. When the activity spreads to the central portions of the brain in the thalamus and upper brain stem, neurons in this area discharge, producing unconsciousness and a generalized convulsive or generalized nonconvulsive seizure. Abnormality of neurons in the central part of the brain (centrencephalic system) will, of course, produce generalized seizures without a focal beginning. Despite the fact that a seizure is only a symptom, many persons, including physicians, find seizures frightening and there is almost a reflex reaction to stop the seizure at all costs. For this reason, individual episodes of seizures are often over-treated with sedative and anticonvulsive drugs without due regard to the underlying disease, and without an orderly plan of drug therapy.

Acute seizure problems include a variety of conditions that demand immediate attention to obtain the most accurate diagnosis and treatment. These include:

I. Convulsive Status Epilepticus
   1. Focal or partial
      a. Motor status (Jacksonian status)
      b. Epilepsia partialis continua
   2. Generalized
      a. Primary generalized
         a. Tonic-clonic status (grand mal status)
         b. Status myoclonus
      b. Focal with secondary generalization
         a. Focal motor with secondary generalization
         b. Focal adversive with secondary generalization

II. Nonconvulsive or Stupor Status Epilepticus
   1. Absence status (petit mal status)
   2. Psychomotor status

III. Other Types of Seizures
   1. Seizures in the newborn
   2. Febrile seizures
   3. First or single seizure
      a. Childhood
      b. Teens
      c. Adults
      d. Elderly
   4. Withdrawal seizures
   5. Hysterical attacks

These conditions will be discussed with special emphasis on drug therapy and diagnosis of underlying disease in convulsive status epilepticus.

I. Convulsive Status Epilepticus

The most serious acute seizure problem is that of status epilepticus, particularly generalized convulsive status epilepticus.[1,2,3] This condition has been defined as the occurrence of repeated generalized convulsive seizures without the patient regaining consciousness between attacks and with the seizures and unconsciousness lasting longer than thirty minutes. Though such continued seizures may cause additional brain

Correspondence and reprint requests to Dr. Cary Suter, Box 698, Medical College of Virginia, Richmond, Virginia 23298.

damage, the major concern actually has to do with the primary cause of the unconsciousness. Acute disease states such as poisoning, encephalitis, drug withdrawal, hypoglycemia, or hypocalcemia may all produce repeated convulsive seizures without the patient regaining consciousness. When confronted with such a problem the physician should quickly observe the patient's attacks to see if there is any evidence for focal beginning or any indication that the attack might be hysterical. The physician should examine the patient quickly to see if there are any clear focal or lateralizing signs such as a dilated pupil or a unilateral Babinski sign; the presence of fever should be noted. Most important of all, the physician should not panic and should not immediately treat the patient with a large injection of medication.

First, blood should be drawn for chemical analysis. A tube of blood should be saved for toxicology study and also blood for serum determination of anticonvulsant drugs. Next, an intravenous infusion should be started and the patient should be given intravenous glucose up to 1 gm/kg of weight as a 25% or 50% solution; for infants, calcium gluconate is often given. The patient may become cyanotic during the tonic phase of the convulsion, but respiratory assistance is seldom necessary. An oral airway may be inserted and mechanical respirator support should be available if required, particularly after giving anticonvulsant medicine. Only after these measures are taken should drug therapy begin. Except in unusual cases, the drug therapy will be nonspecific and symptomatic and aimed solely at reducing the frequency and severity of the convulsive seizures as attempts are made to diagnose the underlying cause.

Drug Therapy.

At the present time in the United States there are three main drugs available for the treatment of status epilepticus. These are phenobarbital, diazepam (Valium), and phenytoin (Dilantin).

Phenobarbital: Phenobarbital is the oldest, safest, and most commonly used anticonvulsant for control of status epilepticus. It does produce some respiratory depression and also some sedation, but it has a relatively long-lasting anticonvulsant effect. Maximum concentration in the brain is not achieved until nearly one hour after administration. The most common mistake in giving phenobarbital for status epilepticus is to give it in doses that are too small and do not represent an adequate loading dose. The intravenous dose should be a total of 5 to 15 mg/kg; in an adult this should be given in single doses of at least 240 mg to 360 mg at a time, and repeated in 30 to 60 minutes. In infants it can be administered as a slow intravenous infusion until a total of 10 to 15 mg/kg has been given. In many respects phenobarbital remains the most universally useful, safest drug for status epilepticus and is usually the best drug for use in the neonate and infant. At any age, if phenobarbital in adequate doses is not effective, then it should be followed either with phenytoin, paraldehyde, or some short-acting anesthesia with respiratory support of the patient. An injection of diazepam after the patient has already been given phenobarbital carries considerable danger of respiratory arrest.

Diazepam (Valium): Since its introduction by Gastaut[4] in 1965, diazepam has become very popular as a treatment for status epilepticus.[5,6] It is a rapidly acting drug and the speed with which it stops the seizures has a reassuring effect upon the physician. Unfortunately, the fact that the seizure stops so quickly may lull the physician into an unrealistic sense of security and keep him from pursuing the underlying cause of the status epilepticus with sufficient diligence. Diazepam can be given in a total dose of 0.25 to 0.5 mg/kg. A starting dose of 10 mg given intravenously at the rate of 1 mg/min is often sufficient to stop the clinical seizures, at least temporarily. This dose may then be repeated if the seizures recur.

Respiratory arrest is often a side effect of diazepam injection, particularly if the patient has previously received barbiturates. Hypotension also occurs at times. For this reason diazepam should be given with respiratory assistance at hand. To maintain long-term control of the seizures, drugs such as phenytoin often have to be added.

Phenytoin (Dilantin): Until recently, phenytoin was not considered a first-line drug in the treatment of status epilepticus. Recently, however, a number of physicians have used phenytoin as the first and only drug in the treatment of status epilepticus and reported excellent results.[7] To be effective, phenytoin needs to be given intravenously in a so-called loading dose which is between 10 and 15 mg/kg. The danger of intravenous phenytoin injections is that of cardiac arrhythmia and occasional cardiac arrest. It is best to give phenytoin with a cardiac monitor and to stop the injection if any evidence of arrhythmia develops. There are reports of giving a single loading dose of 700 to 1,000 mg of phenytoin without complication, but we have had a personal experience with a fatal

cardiac arrest giving this amount as a single injection. It is probably safer to figure the total loading dose and give it in either two or three separate intravenous infusions, perhaps 30 to 60 minutes apart. In adults a total dose of 400 to 500 mg can be given at once (at 50 mg/min), and later an additional amount to bring the total up to the calculated loading dose.

The advantage of phenytoin is the fact that it has a relatively long duration of action when given in a loading dose and also that it does not produce the amount of sedation produced by a larger dose of either diazepam or phenobarbital.

Other Drugs Used in Status Epilepticus: Paraldehyde is a very effective anticonvulsant given rectally or intravenously. It can be given intravenously in a diluted solution in normal saline with the usual dose being 4 to 6 cc of paraldehyde. It should not be given to adults in the emergency room due to the possibility of giving the drug to a patient with alcohol still in the bloodstream and producing a breakdown to formaldehyde with consequent toxic effects. When paraldehyde is given it should be in fresh solution and should be in a tube or syringe specified as inert.

In alcohol withdrawal seizures which do not usually present as status epilepticus, chlordiazepoxide (Librium) is effective, though phenobarbital is also.

A number of other drugs have been used in status epilepticus, particularly sodium amytal, which have considerable danger of producing respiratory arrest. Drugs such as clonazepam are not commonly available for intravenous use,[8] though they may be effective in certain types of status epilepticus, particularly myoclonus. Sodium valproate has been reported effective in status epilepticus, but it is not available in the United States.[9]

It has been recently recognized that a severe status epilepticus may be produced by overdoses of tricyclic antidepressants[10]—amitriptyline (Elavil), imipramine (Tofranil), and others. In addition, it has been recognized that physostigmine represents a direct treatment for this type of convulsion and may be lifesaving.

Other treatments such as intravenous urea and intracarotid sodium amytal have been reported, but are not in common use.[11,12]

Diagnosis of Underlying Disease.

The symptomatic treatment of generalized convulsions should not retard investigation to determine the underlying cause of the seizures. A great variety of diagnostic aids are available. In addition to the blood chemistries mentioned previously, screening for toxic substances is available in most hospitals. In the absence of any evidence of increased intracranial pressure, a lumbar puncture and cerebrospinal fluid (CSF) examination is indicated; this is especially true in a neonate and also in children, particularly if they have fever or stiff neck. However, examination of spinal fluid is indicated at any age since it may give some clue to the underlying disease.

Strange as it may seem, the use of an electroencephalogram (EEG) in monitoring the treatment of status epilepticus has not been common. Only recently have 24-hour bedside or emergency room EEGs been available. The use of the EEG in both the diagnosis and monitoring of treatment of status epilepticus is ideal[13]; it is particularly useful in showing focal or asymmetrical abnormality, and in showing response to anticonvulsant drugs. In a few patients with repeated attacks which are thought to be convulsive seizures, an EEG is normal and the diagnosis of hysterical attacks can be made. The EEG is also of value in consideration of the problem of coma so that the type of EEG may give some indication as to the underlying cause of the unconsciousness in addition to showing the repeated seizure activity.[14]

The recent widespread use of computerized tomography (CT) scan makes the screening of patients for intracranial lesions much easier.[15] This is especially indicated if the seizures have a focal beginning or result in focal postictal findings. Obviously, the patient's actual convulsive seizures must be controlled before the tests can be adequately carried out.

The EEG is useful even if it cannot be obtained immediately during the convulsive seizure. During the postconvulsive state it may give information concerning postictal slowing, focal abnormality, or even continuous electrographic seizure activity, which will be useful in diagnosis. Since the seizure is a symptom of the brain and since it is manifested primarily by electrical abnormality, it is only reasonable that an EEG should be used to monitor its diagnosis and treatment whenever possible.

Other Types of Status Epilepticus.

Focal or partial status epilepticus of a motor variety occurs in both acute and chronic central nervous system diseases. Patients with old areas of damage in the central nervous system and with a history of repeated focal and secondary generalized convulsive seizures may present with primarily focal motor status epilepticus. Such patients will usually be

conscious. This condition may continue after the generalized status epilepticus has been controlled. In such patients control of the focal motor status epilepticus, though desirable, does not justify the use of massive doses of sedative drugs. Diazepam is often successful and when it is not, a loading dose of phenytoin is reasonable treatment.

So-called epilepsia partialis continua is more often an acute condition, secondary to a cerebral embolus, cerebral hemorrhage, or a brain tumor[16]; it may also occur in encephalitis. In this condition the patient may be confused or unconscious, secondary to the underlying disease, and the motor movements may be relatively weak, though repeating continuously in an irregular though somewhat rhythmic fashion. This condition is often associated with cerebrovascular lesions in patients with additional toxic or metabolic disease. The EEG in such cases often shows a pattern which has been described as periodic, lateralized epileptiform discharges (PLED).[17,18] Treatment of this type of focal status epilepticus with anticonvulsant drugs has been relatively unsuccessful. The condition usually runs a self-limited course, coming to an end in two to four days, often without recurrence. In this instance treatment to correct any underlying metabolic or toxic situation is as important as treatment with anticonvulsant drugs, and any treatment with anticonvulsant drugs should not be overdone.

A particular type of status epilepticus consisting of repeated myoclonic jerks is seen in patients who have suffered severe anoxic damage to the brain. These attacks often occur 12 to 24 hours after cardiorespiratory arrest and continue for one or two days; they are frequently associated with an otherwise isoelectric EEG and generally their occurrence suggests a very poor prognosis. Useful treatment for this condition has not been clearly defined. Large doses of phenobarbital or phenytoin may produce some decrease in the myoclonic jerks, but this may also happen spontaneously. When such patients are treated with large doses of drugs and then otherwise meet the criteria for brain death, problems arise due to the presence of such medications in their blood. In some patients with these myoclonic attacks drugs such as clonazepam and sodium valproate may be most effective.

II. Nonconvulsive or Stupor Status Epilepticus

A rare but interesting group of patients are those with nonconvulsive status epilepticus. These comprise a group of so-called petit mal status epilepticus or spike-and-wave status epilepticus.[19,20,21] Such patients may simply be confused yet able to walk around and carry on some kind of conversation but may be very forgetful; they often give the appearance of being severely toxic with medication and as a result may be withdrawn from medication and have a generalized convulsive seizure. In such patients observation of rhythmic twitching of the eyebrows or facial muscles is often a tip-off that this is actually a status epilepticus. In these patients the EEG is, of course, diagnostic. Treatment with diazepam or clonazepam intravenously or orally may be useful.

More rare is the small group of patients with so-called psychomotor status epilepticus. In these patients peculiar behavior may go on for hours or days, associated either with a temporal lobe discharge or with a diffused theta discharge in the EEG.[22,23] Here, again, the EEG is the essential diagnostic test.

III. Other Types of Seizures that Present an Acute Problem

1. Seizures in the newborn. These are common and represent an acute problem primarily in terms of diagnosis, and to some degree, of control of the attacks.[24] The neonate is particularly subject to seizures secondary to metabolic derangements, such as hypoglycemia, hypocalcemia, and hypomagnacemia. Of course seizures are frequently secondary to congenital abnormalities or birth injuries. The possibility of infection, particularly meningitis, is always present and as a result, unless the infant responds quickly and definitely to treatment for metabolic derangement, a CSF examination is always indicated. Certainly in seizures of the newborn a search for the underlying cause is most important. As far as drug treatment is concerned phenobarbital is the drug of choice, but phenytoin also may be used and must be given intravenously since oral medication is not absorbed. In the neonate, phenytoin has a long half-life (up to 100 hours), so a single loading dose (10 to 20 mg/kg) may be sufficient.[25] Since seizures in the newborn are often accompanied by changes in respiration and in cardiac function, the electroencephalographic recording really must be a polygraphic recording, including EKG, respiration, eye movement, and motor tone. Such polygraphic recording for diagnosis and during the treatment of continued seizures in the newborn should be used if available.[26]

2. Febrile seizures. The problem of seizures with fever in children, particularly between the ages of six

months and three years, occurs frequently in the practice of pediatricians and family physicians. There is extensive literature on this condition and considerable disagreement about the diagnosis and management. Misunderstanding arises from the fact that careful neurological examination and electroencephalographic recordings have not been used to make a differential diagnosis in the matter of febrile seizures. In any case, when a seizure occurs in an infant with fever, it is important to know that the child does indeed have a fever and if possible what the underlying cause of the fever might be. It is also important to observe the child as soon as possible for evidence of any central nervous system lesion or focal neurological abnormality. In this regard an EEG in the acute state can be useful but often shows only diffuse slowing while an EEG a week or ten days after the seizure, especially with a child on no medication, is a much more valuable test. If such an EEG is completely normal, it is very likely that the child falls into a classification of so-called "benign febrile seizures." The predisposition to such seizures seems at times to run in families, and the condition is almost always limited to a few seizures, with sudden rising fever, between the ages of six months and three years and is almost never followed by recurrent focal or generalized seizures in adulthood. If, however, the EEG is abnormal, it may indicate preexisting brain damage and thus a prognosis of possible future seizures without fever. Children with such EEGs often have retarded development and some neurological findings, either postictally or between the seizures. A few children with fever or seizures show a so-called centrencephalic type of EEG. In the families of such children adults often have a history of inherited epilepsy of typical petit mal and grand mal syndrome. When febrile seizures are separated in this fashion, those children with an abnormal EEG as well as those with focal seizures or focal neurological findings have a distinct likelihood of having epilepsy later in life. Those with no focal findings, no abnormal EEGs, and only brief generalized seizures, have an excellent chance of never having difficulty later in life.

Treatment of truly "benign febrile seizures" may only require aspirin and phenobarbital when the child has fever, or regular use of phenobarbital for one or two years. Children with abnormal EEG and neurological findings may need prolonged anticonvulsant treatment.

A particular syndrome of fever associated with repeated convulsions (often one-sided) and then with hemiplegia has been described as being associated with the occurrence of focal motor or psychomotor seizures later in life.[27] This has been called the hemiconvulsion, hemiplegia, epilepsy (HHE) syndrome and apparently represents an acute illness, either of a vascular or infective nature. In this situation CT studies as well as cerebral arteriograms are useful in making an etiological diagnosis.

3. The first or single seizure. The first or single seizure at any age represents an acute problem. In the past such attacks have often not been observed closely and persons having single seizures have not been studied sufficiently to arrive at a diagnosis. If the seizure is actually a generalized convulsive attack, patients are often started on anticonvulsant drugs without any type of neurological study other than a brief examination. Once on anticonvulsant drugs EEGs may be normal and the dilemma exists as to what the underlying diagnosis might be. As a rule the first or single seizure should not be treated with anticonvulsant drugs unless it represents a status epilepticus. One or two seizures occurring and then stopping should not be treated until the patient has been studied neurologically and with the EEG, and if indicated, with CT scans, CSF examination, and other tests. A firm diagnosis as to the cause of the seizure is very important in planning future management. Again, the immediate use of the EEG is often very helpful; in any case an EEG is advisable before putting the patient on treatment even if this takes two or three days.

In childhood the first or single seizure, though it may appear to be a generalized convulsive attack, is most commonly secondary to a focal or partial derangement in the brain. In addition to a great number of focal lesions remaining from birth and infancy a number of children have so-called benign central temporal epilepsy.[28] These children often have sharp waves in the central temporal region associated with focal and secondary generalized convulsive seizures. Their EEG abnormalities are often banished easily with anticonvulsive drugs and are usually seen only if a sleep-deprivation record is obtained. Petit mal seizures also usually begin in childhood but do not present as an acute problem.

It is well known that any prior existing condition such as cerebral palsy, birth injury, or the so-called HHE syndrome may first cause clinical seizures during the teens. There is some element related to growth and sexual development which seems to increase the tendency to seizures at this time. During the teens

persons who have only had petit mal type seizures in childhood often have their first generalized convulsive seizure. For this reason, the great number of seizures beginning in the teens are actually caused by hereditary conditions, or to damage to the brain before, during, or after birth. Obviously, a few seizures begin during the teens from acute causes, such as encephalitis, brain tumors, and toxic metabolic causes, but these are rare. Careful electroencephalographic recording, including a wake and sleep-deprivation record, are useful; depending on the findings other tests can be made. At times a careful history brings out the fact that the teen-ager actually had a seizure early in life.

Adult-onset seizures have characteristically been considered more likely to represent the occurrence of a new central nervous system disease, such as an infection, brain tumor, or vascular abnormality. This is indeed true, though a number of persons have their first seizure in early adulthood based on preexisting hereditary or other lesions. In any case, the occurrence, particularly of a focal and secondary generalized seizure in adulthood, demands a complete neurological study; in addition to the EEG and plain skull x-rays this must include, if possible, a CT scan and an isotope brain scan. If all of these tests are negative except for a focal EEG, then cerebral arteriography should be considered. Again, it is important to make a diagnosis, if at all possible, before committing the patient to anticonvulsant medication.

The occurrence of seizures in the elderly, though having all the implications of seizures in younger adults, are more likely to be related to metastatic brain tumor and to cerebrovascular disease. For this reason, again, CT scans, isotope brain scans, and cerebral arteriography are indicated. The diagnosis of the cause rather than simple symptomatic treatment of the seizure is of utmost importance.

4. Withdrawal seizures. Many patients who present at an emergency room with the occurrence of a recent generalized convulsive seizure, and occasionally a repeated generalized convulsive seizure in the emergency room, are suffering from withdrawal syndrome. The most common withdrawal syndrome is alcohol withdrawal,[29,30] but patients also have withdrawal seizures from barbiturates, diazepam, and a number of other medications.[31] Such patients are usually not in status epilepticus and do not have focal neurological findings. They may have some mental derangement or confusion and with alcoholism they may have true delerium tremens; in many of these patients the history of previous alcohol intake is clear. The patient presenting with the first withdrawal seizure deserves hospitalization and limited diagnostic study. Certainly a complete neurological examination should be made and an EEG should be obtained on the first or second day; CSF examination and a plain skull x-ray are also indicated. If these tests are normal and the history is clear, further studies may not be needed. If there is any doubt, a CT scan should be obtained. In the patient who presents repeatedly with withdrawal seizures such elaborate study may not be indicated, but care should be taken not to miss the occurrence of a recent subdural hematoma, or development of some other intracerebral lesion. Since withdrawal seizures are essentially self-limited, the drug treatment is not vitally important. Most withdrawal seizures respond well to diazepam, phenobarbital, or phenytoin. Alcohol withdrawal seizures can also be treated with chlordiazepoxide. If the attacks are clearly withdrawal seizures, continuous anticonvulsant medication is not indicated.

5. Hysterical attacks. Some of the most dramatic attacks, both in their severity and repeated frequency, are not cerebral seizures at all but are behavioral in origin and represent a variety of hysterical attacks. The patient often shakes violently, usually from side to side rather than in a true tonic or clonic fashion. Patients may begin with focal manifestations and may seem to have a typical postictal state; in addition to shaking from side to side they may stiffen or arch their backs without much movement. Such attacks are frequent, never occur while the patient is asleep, and are usually viewed with much concern by relatives and friends. The neurological examination is, of course, normal and the EEG, if it can be seen free of movement or artifact, is also normal. Repetition of such attacks can often be produced by suggestion during EEG monitoring. One such patient who presented at our emergency room, and others in our vicinity, imitates such a perfect focal and secondary generalized convulsive seizure that he has on at least one occasion experienced respiratory arrest due to an injection of 40 mg of diazepam. Other patients with hysterical attacks have been rushed or flown into the medical center, receiving large doses of phenobarbital or phenytoin. A considerable amount of skepticism about repeated severe attacks in the patient who is neurologically normal is indicated.

In summary, the EEG is the ideal instrument for monitoring seizure activity in acute seizure problems. Increased use of the EEG in the diagnosis and monitoring of treatment of the seizure is one of the major

changes that has come about in management of this condition. The availability of CT scanning is also changing our ability to diagnose underlying disease.

When presented with an acute seizure problem the physician must always remember that the seizure is a symptom and must not consider it any different from any other symptom, such as cough due to pulmonary disease or vomiting or diarrhea due to gastrointestinal disease. Just as with symptoms such as cough, vomiting or diarrhea, the physician should strive to diagnose the underlying illness.

REFERENCES

1. WHITTY CWM, TAYLOR M: Treatment of status epilepticus. *Lancet* 2:591–594, 1949.

2. HUNTER RA: Status epilepticus. History, incidence and problems. *Epilepsia* 1:162–188, 1960.

3. JANZ D: Conditions and causes of status epilepticus. *Epilepsia* 2:170–177, 1961.

4. GASTAUT H, NAQUET R, TASSINARI CA: Treatment of status epilepticus with diazepam (valium). *Epilepsia* 6:167–182, 1965.

5. BROWN TR, PENRY JK: Benzodiazepines in the treatment of epilepsy. A review. *Epilepsia* 14:277–310, 1973.

6. FERNGREN HG: Diazepam treatment of acute convulsions in children. A report of 41 patients, three with plasma levels. *Epilepsia* 15:27–37, 1974.

7. WILDER BJ, RAMSAY RE, WILLMORE LJ, ET AL: Efficacy of intravenous phenytoin in the treatment of status epilepticus. *Annals of Neurology* 1:511–518, 1977.

8. GASTAUT H, CAURJON J, POIRE R, ET AL: Treatment of status epilepticus with a new benzodiazepine more active than diazepam. *Epilepsia* 12:197–214, 1971.

9. BARNES SE, BLAND D, COLE AP, ET AL: The use of sodium valproate in a case of status epilepticus. *Develop Med Child Neurol* 18:236–238, 1976.

10. BURKS JS, WALKER JE, RUMACK BH, ET AL: Tricyclic antidepressant poisoning. Reversal of coma, choreoathetosis, and myoclonus by physostigmine. *JAMA* 230:1405–1407, 1974.

11. CARTER CH: Status epilepticus treated by intravenous urea. *Epilepsia* 3:198–200, 1962.

12. BLADIN PF: Intra-carotid treatment of status epilepticus. *Epilepsia* 4:151–166, 1963.

13. CELESIA GG: EEG monitoring in status epilepticus, in Janz D (ed): *Epileptology,* Stuttgart, Georg Thieme Publishers, 1976.

14. SUTER C: Clinical advances in the evaluation of deep coma. *Medical College of Virginia Quarterly* 10:152–162, 1974.

15. GASTAUT H, GASTAUT JL: Computerized transverse axial tomography in epilepsy. *Epilepsia* 17:325–336, 1976.

16. KRISTIANSEN K, KAADA BR, HENRIKSEN GF: Epilepsia partialis continua. *Epilepsia* 12:263–267, 1971.

17. CHATRIAN GE, SHAW CM, LEFFMAN H: The significance of periodic lateralized epileptiform discharges in EEG: an electrographic, clinical and pathological study. *Electroencephalog Clin Neurophysiol* 17:177–193, 1964.

18. SUTER C, CREVELING JG: A report of 20 cases with periodic lateralized epileptiform discharges (acute spikes) in the electroencephalogram, abstract. *Neurology (Minneap)* 16:304, 1966.

19. NEIDERMEYER E, KHALIFEH R: Petit mal status ("spike-wave stupor"). *Epilepsia* 6:250–262, 1965.

20. ANDERMANN F, ROBB JP: Absence status. A reappraisal following review of thirty-eight patients. *Epilepsia* 13:177–187, 1972.

21. LIPMAN J, ISAACS ER, SUTER C: Petit mal status. A variety of non-convulsive status epilepticus *Dis Nerv Sys* 32:342–345, 1971.

22. HENRIKSEN GF: Status epilepticus partialis with fear as clinical expression. *Epilepsia* 14:39–49, 1973.

23. DEPASQUET EG, GAUDIN ES, BIANCHI A, ET AL: Prolonged and monosymptomatic dysphasic status epilepticus. *Neurology (Minneap)* 26:244–247, 1976.

24. AICARDI J, CHEVRIE JJ: Convulsive status epilepticus in infants and children. A study of 239 cases. *Epilepsia* 11:187–197, 1970.

25. PAINTER MJ, PIPPINGER C, CARTER G, ET AL: Metabolism of phenobarbital and phenytoin by neonates with seizures. *Neurology (Minneap)* 27:370, 1977.

26. SMITH JB: EEG polygraph studies in evaluation of neonatal seizures and apnea. Read before the Hans Berger Day Symposium, Medical College of Virginia, Richmond, VA, May 16–17, 1977.

27. GASTAUT H, POIRIER F, PAYAN H: H.H.E. syndrome. Hemiconvulsions, hemiplegia, epilepsy. *Epilepsia* 1:418–447, 1960.

28. BEAUSSART M: Benign epilepsy of children with rolandic (centro-temporal) paroxysmal foci. A clinical entity. Study of 221 cases. *Epilepsia* 13:795–811, 1972.

29. ISBELL H, FRASER HF, WIKLER A, ET AL: An experimental study of the etiology of "rum fits" and delirium tremens. *Quart J Stud Alcohol* 16:1–33, 1955.

30. VICTOR M, BRAUSCH C: The role of abstinence in the genesis of alcoholic epilepsy. *Epilepsia* 8:1–20, 1967.

31. ESSIG CF: Clinical and experimental aspects of barbiturate withdrawal convulsions. *Epilepsia* 8:21–30, 1967.

Bacterial Meningitis: Some Epidemiologic and Clinical Factors in Diagnosis

VINCENT P. CALABRESE, M.D.

Assistant Professor, Department of Neurology, Medical College of Virginia, Health Sciences Division of Virginia Commonwealth University, Richmond, Virginia

In ancient times all acute delirium states were known as "phrenesis." It was not until the 17th century that inflammations of the meninges and cerebrum were differentiated from each other.[1] By the 19th century meningitis had been described to the extent that a number of epidemics were reported both in the United States and Europe,[2] but it was the development of the lumbar puncture by Quincke in 1893[3] which opened up a new diagnostic era for the disease.

Therapeutically, the history of bacterial meningitis can be divided into three phases (1) that of the pretreatment era (prior to 1906), (2) serological treatment and (3) the antibiotic treatment which began with Domagk in 1932 when sulfonamides were first used.

Etiology

During the latter part of the 19th century and the early years of the 20th century, the meningococcus was considered the only important cause of meningitis other than tuberculosis. Disease caused by *Diplococcus pneumoniae, Haemophilus influenzae* and the streptococcus were considered sporadic and listed along with colon bacilli, Salmonella, *Pasteurella pestis* (plague), and *Pseudomonas mallei* as unusual causes.[4] It soon became apparent that there were other common causes of meningitis besides *Neisseria meningitidis.* In a study by Ward and Fothergill,[5] 83% of their nontuberculous cases were caused by *D pneumoniae, N meningitidis*, or *H influenzae.* Indeed, other early authors, while usually not giving figures, stated these to be the most common agents, and it is extremely interesting that when one looks at recent series[6,7,8] in the antibiotic era, these organisms remain the most common agents of meningitis (Fig 1). Note also that these studies are from three diverse areas of the United States. Not all studies have agreed with them, however; two, one from the Mayo Clinic[9,10] and one from Boston City Hospital,[11] showed an alarmingly high percentage of cases due to *Staphylococcus aureus.* Part of this could be explained in the Mayo series by the large number of patients with neoplastic or congenital disorders. These data were not given in the Boston series, but with half their cases being caused by *S aureus* one wonders whether the meningitis was caused by these disorders or by hospital-acquired infections. In addition the Boston study revealed a number of patients with pneumococcal pleural empyema who developed meningitis yet had sterile cerebrospinal fluid (CSF). The authors did not include these cases in the pneumococcal group although they probably should have.

The importance of hospital-acquired infections is shown by the study of Hodges and Perkins.[12] If one excludes those cases of suspected bacterial meningitis where no organism was isolated, *D pneumoniae, N meningitidis*, and *H influenzae* accounted for 72% of the total cases of meningitis. However, among those infections acquired in the hospital, these organisms accounted for only 7% of cases whereas *S aureus* accounted for 21% and Staphylococcus (all species), Streptococcus, and gram-negative bacilli (especially pseudomonas) accounted for 93% of the cases!

A number of studies have shown that the causative agent depends upon the age of the patient; these

Correspondence and reprint requests to Dr. Vincent P. Calabrese, Box 698, Medical College of Virginia, Richmond, Virginia 23298.

Etiology	% of Cases		
	Boston (6)	Seattle (7)	Atlanta (8)
D pneumoniae *N meningitidis* *H influenzae*	71	73	77
Others	29	27	23

Fig 1—Percentage of cases of bacterial meningitis due to various etiologies. All studies fall within the era of antibiotic therapy.

studies are consistent in their findings and are summarized in Figures 2 and 3.

The reason for this age variation is not entirely clear. The neonate may be more susceptible to the organisms listed because it is deficient in the immunoglobulin IgM which neither crosses the placental barrier nor is produced by the newborn and which is thought to be the bactericidal immunoglobulin for gram-negative organisms. In addition the phagocytic and bactericidal activity of the leukocytes in newborns may be impaired; as debilitation also affects these functions, this may account for the occurrence of these organisms in the hospital patient and the elderly.

The high incidence of *H influenzae* in young children but not in neonates may be ascribed to the fact that neonates acquire antibodies to *H influenzae* from the mother then lose them within two months, not producing their own until 2 to 3 years of age.

Age-Related Etiology of Bacterial Meningitis

Age	Predominant Cause
0-2 mo	Gram-negative bacilli Streptococcus, groups B *S aureus*
2 mo-3 yrs	*H Influenzae* *D Pneumoniae* *N Meningitidis*
3 yrs-young adult	*D Pneumoniae* *N Meningitidis*
Elderly	*D Pneumoniae* Gram-negative bacilli Streptococcus, group B *S aureus*

Fig 2—Distribution of bacterial meningitis according to age.

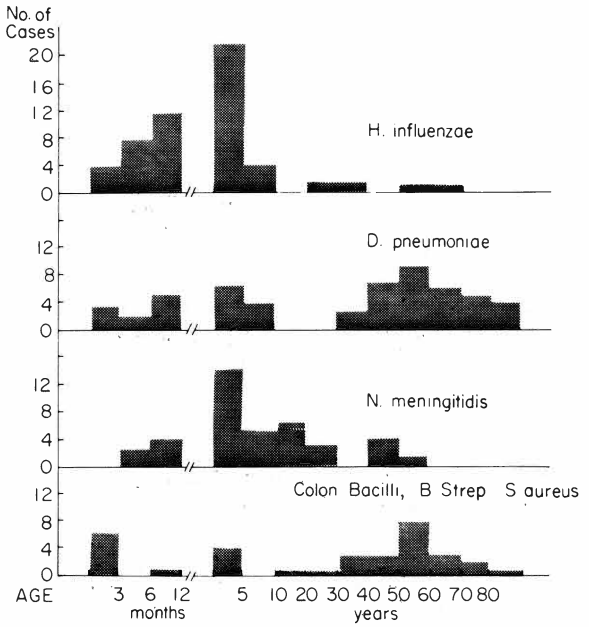


Fig 3—Distribution of bacterial meningitis by age, with number of cases to give relative frequencies.

Children are also born carrying maternal antibodies to the meningococcus which disappear after a few months; antibodies increase again from 2 to 12 years of age. Since the infection is thought to spread via the nasopharynx, this would explain its prevalence in school-age children, its disappearance as these groups develop immunity to the prevalent strain, and its reappearance when new social groups of people are formed as in military camps.

Incidence

There can be no doubt that although the relative frequencies of the different forms of bacterial meningitis have remained fairly constant, the absolute numbers have fallen dramatically since the advent of adequate chemotherapy. During the epidemic of 1904-1906, New York City registered 6,755 cases of meningitis.[4] The census of the city was 4,766,883 in 1910, giving an estimated attack rate of 142/100,000.

Although epidemics have sprung up periodically (Fig 4), with the advent of antibiotics the number of cases of meningococcal meningitis has steadily declined; in 1966, 3,381 cases were reported whereas in 1975 the figure had dropped to 1,478.[13] One must keep in mind that these are reported cases. Since meningococcal meningitis is the only reportable bacterial meningitis this figure is a gross miscalculation

of the total number of cases of bacterial meningitis which have been estimated to be between 10,000 and 20,000 in the United States.[14]

Certain factors are also important in attack rates. For the general population the frequency of the disease is 7/100,000; however, in neonates it jumps to 310/100,000.[15] Prematurity as well as dural defects, trauma, splenectomy, hypogammaglobulinemia, or sickle cell disease predisposes the newborn to meningitis.[6,7,14,16,17] Alcoholism in the adult has a high association with pneumococcal meningitis; it is of interest that this was noted in the preantibiotic era as well. Debilitating diseases, such as tumors (especially lymphoid), and surgery also increase susceptibility to meningitis. The spread of disease to the central nervous system (CNS) or recurrent meningitis can occur with chronic or acute mastoiditis, sinusitis or otitis media, CSF rhinorrhea, bacterial endocarditis, and pneumonia. One often finds that meningitis caused by one of the more unusual organisms is associated with one of these diseases.

Mortality

Prior to serum therapy or antibiotics the mortality from meningococcal meningitis was exceedingly high. In the pandemic of 1904-1909 the fatality rate ranged between 70% to 90% regardless of the city.[4] In a number of outbreaks in various European countries during this time the mortality rate was essentially the same though in some cases it dropped as low as 30% to 40%. Pneumococcal meningitis was thought to be even more lethal with death being the rule and survival being considered a reportable case.

Introduction of serum therapy brightened the outlook at least for meningococcal disease. In a study reported by Flexner,[18] the overall mortality dropped to 31%, certainly a triumph in medical therapy. In the era of antibiotics mortality has greatly changed though it seems to have leveled off at 2000 deaths per year.[13,19] It is very dependent upon the etiology as is seen in Figure 5. Clearly the neonatal group still has an extremely high mortality rate whereas the mortality in *H influenzae* is quite low. The percentage mortality for meningococcus has remained relatively stable for a number of years although pneumococcal deaths remain disturbingly high despite what would appear to be adequate antibiotic therapy. A number of factors come into play including the clinical state of the patient at the time of therapy and the toxins released by the bacteria. An additional noteworthy fact is that one study showed that 28% of fatal cases in children were not diagnosed during life.[20]

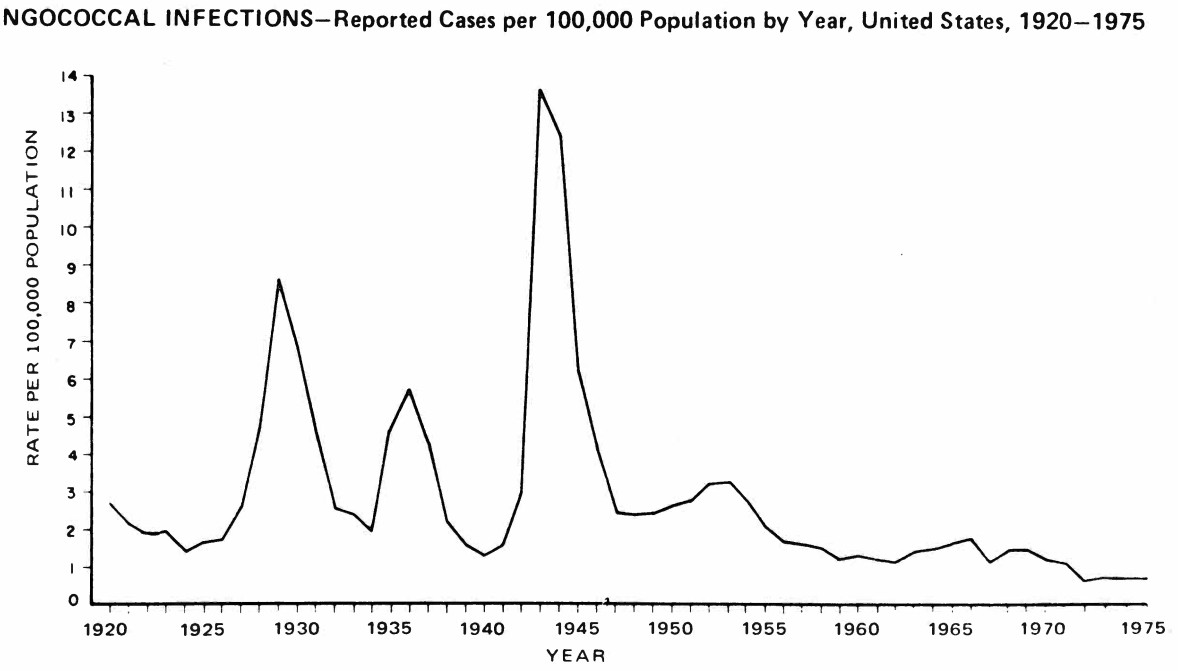


Fig 4—Reported rate of meningococcal infection over the past 55 years. Note the marked dampening of outbreaks following the introduction of penicillin.

Etiology	Percent Mortality for Meningitis					
	Seattle 1950-60 (7)	Boston 1956-62 (6)	Atlanta 1969-72 (8)	Oxford 1969-73 (20)	USA 1966 (19)	1974
D pneumoniae	59	29	39	16		
H influenzae	18	8	0	6		
N meningitidis	13	15	20	11	26	23
Neonatal Group	64	58	57	44		

Fig 5—Percent mortality for different forms of bacterial meningitis. Note that the series from Oxford included only children which may account for the low mortality with pneumococcus.

A discussion of some of the factors affecting mortality should be prefaced by some observations on the clinical picture in meningitis.

Clinical Aspects

Neonatal meningitis. Meningitis in the newborn not only has a different etiology from the other age groups but also different clinical signs.[6,14,21] The signs are often deceptive and may resemble those of other diseases; the best help in making the diagnosis comes simply from having a suspicion that the disease exists.

The usual signs of meningeal infection—neck stiffness and fever—are often absent. The neonate may even be hypothermic, especially if premature. The most consistent signs are those of irritability or listlessness, poor feeding, and vomiting. Bulging of the fontanelle is characteristic but may be a late sign; unexplained jaundice may also occur as may seizures. Examination of the peripheral blood smear is also often unrewarding though either a leukopenia or a leukocytosis should raise suspicion as should a thrombocytopenia. It should be kept in mind, however, that a leukocytosis may be normal in newborns. One clue may be a neutrophilic leukocytosis since lymphocytes predominate in the normal infant for the first three to four years. Blood cultures can be invaluable in identifying the causative agent since they are positive in 70% to 80% of cases; this also applies to the urine.[14] The CSF characteristically shows an elevated protein and cell count with predominant polymorphonuclear cells. The glucose level is reduced but is related to the systemic blood sugar levels so that a simultaneous blood sugar should be obtained. CSF cultures usually yield an organism but 13% of cases[22] in one series and 6% in another[21] did not do so. In the latter study those with negative cultures had positive smears, pointing up the importance of this examination.

Predisposing factors to meningeal infection include difficult deliveries (50% to 65% of cases), remote infections (gastrointestinal, respiratory, skin, omphalitis, catheterization of umbilical vessels), and congenital anomalies (meningomyelocele).[23-26]

Older age groups. In older children and in adults the clinical aspects are much clearer. There is usually a prodromal state with symptoms referable to an upper respiratory infection, ear infection, or nonspecific "flu" symptoms. Medical attention is sought early, usually within 72 hours.[21] In one series all adults and all children older than 2 years save one (who was age 2) had stiff necks,[21] although another series had only a 33% incidence of this phenomenon.[7] Kernig and Brudzinski signs were variable and could not be relied upon as much as the stiff neck. Fever over 38 C is commonly seen as are headache, vomiting, and lethargy—headache is especially frequent in patients over 5 years of age.

In *H influenzae* meningitis, fever was the only symptom present in more than 50% of cases in one series, and in fact Bell and McCormick point out that the symptoms with this agent are often more subtle and less fulminating than with others.[14]

Meningococcal infections are usually preceded by an abrupt onset of fever, chills, vomiting, and headache. Again a stiff neck need not be an early sign; on the other hand, the disease may be so fulminant that the patient goes from apparent health to death within a matter of hours. The skin rash is an indication of meningococcal disease but may be absent in 50% of cases.[6] The rash is usually petechial but may be erythematous or maculopapular; it usually begins over the lower limbs and should be distinguished from the rash of Rocky Mountain spotted fever and viral exanthema. If present, blood smears obtained from the skin lesions or skin scrapings often reveal the organism.[14] Sometimes associated with the meningitis are myocarditis, the Waterhouse-Friderichsen syndrome, and disseminated intravascular coagulation (DIC). Deaths from the Waterhouse-Friderichsen syndrome have been ascribed to adrenal insufficiency; however, this may not always be the case as there have been documented cases of clinical disease where the adrenals were only slightly affected[27] and in others where the serum corticosteroid levels were actually elevated.[28] It is probable that at least in some of the cases, the syndrome is caused by bacterial endotoxin.

About ten years ago another complication of meningococcal disease was noted, that of disseminated intravascular coagulation. In the study by McGehee and Rapaport[29] all patients on the communicable disease service were evaluated. Of 19 patients with meningococcus infection, 6 had evidence of coagulopathy using platelet count, prothrombin time, partial thromboplastin time, fibrinogen, and Factor V, VII and VIII studies. Of the six, all but one died. The survivor had only equivocal evidence of coagulopathy when treatment was instituted. The authors concluded that probably all patients with fulminant meningococcemia with shock have DIC, a fact which is reflected in the underdiagnosis of DIC in encephalopathy associated with widespread tumors.[30] The point illustrated by the latter study is that frequently only one of the many coagulation tests may be abnormal in proven cases.

In pneumococcal meningitis the onset of symptoms is also usually abrupt and the frequency of the initial symptoms is variable[6,7,14,31]; these usually consist of fever, headache, stiff neck, and vomiting. A significant number are alcoholics[7] and many have an associated pneumonia[7,31] or infection of the ears or sinuses.[6,7] In one study[31] fibrinogen degredation products were found in the CSF, again raising the question of DIC in this disorder.

Neurologic Signs

Other than the stiff neck and headache, neurologic signs usually consist of generalized dysfunction, the most common being altered states of consciousness which occur in 80% to 87% of cases.[6,7] Seizures are also surprisingly frequent, especially in infants, and are associated most commonly with *H influenzae* and least commonly with meningococcus.[6]

Focal signs are unusual in nontuberculous bacterial meningitis although they do occur. The most common are visual defects, particularly of the oculomotor variety.[6,7] Surprisingly hemiparesis also occurs[6,7] although this is probably a Todd's paralysis since in most cases it is very transient. One is probably talking about less than 10% to 15% of cases for these focal signs, however.

Laboratory Tests

Examination of the CSF is the most important laboratory test to be performed; the findings are summarized in Figure 6 and are compared with aseptic, tuberculous, and fungal meningitis. Both a Gram's stain smear and culture should be done. As noted for the neonatal group, the smear may be positive and yet the CSF not grow any organisms. Cultures are positive in about 90% of cases[6,7] and in Swartz and Dodge's series[6] this included meningococcus which probably reflects care in handling the sample. Blood cultures can also be helpful. In one series[6] *H influenzae* was grown from blood in 79% of cases, *D pneumoniae* in 56%, and meningococcus in 33%. Peripheral leukocyte counts are also usually elevated with polymorphonuclear cells predominating, a differentiating point from viral in-

Disease	Appearance[a]	Cell Count	Differential	Protein	Glucose[c]
bacterial meningitis	often opalescent	10-20,000 +	Predominantly Polymorphonuclear	Mildly to Markedly Elevated	Reduced
viral meningitis	clear	5-2000	Predominantly Mononuclear[b]	N1-Elevated (usually 150)	Normal[d]
tuberculous meningitis	often opalescent	5-2000	Predominantly Mononuclear	Mildly to Markedly Elevated	Reduced
cryptococcal meningitis	usually clear	5-2000	Predominantly Mononuclear	N1-Elevated	Reduced

Fig 6—CSF findings in different forms of meningitis: a) if the protein is very high, the fluid will become xanthochromic; b) early in the disease polymorphonuclear cells may predominate; c) in relation to blood sugar; d) can be reduced in meningitis due to *Herpes simplex* or mumps.

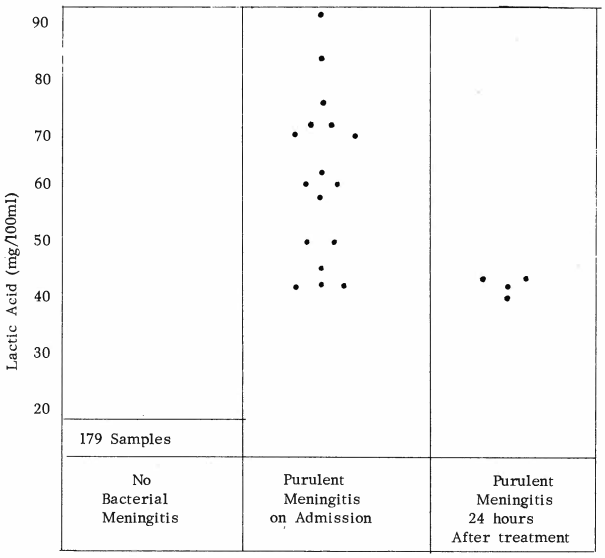


Fig 7—CSF lactate levels in noninfected patients and patients with bacterial meningitis. In other studies including viral meningitis their levels fall in with the control group.

fections. Nasopharyngneal, sputum, and urine cultures may also be valuable in establishing the etiology.

In the past few years some additional laboratory aids have been devised to help in the diagnosis of bacterial meningitis, some of which will be summarized here.

Nitroblue tetrazolium dye test (NBT). This test is based on the ability of phagocytizing leukocytes to reduce nitroblue tetrazolium to an insoluble purple particle which can be seen inside the leukocyte. Early reports were enthusiastic about the test in differentiating bacterial diseases from viral, tuberculous, and other conditions, but as more experience accumulated, the incidence of false-positives and false-negatives rose to such a level as to make the test almost useless, particularly as an occasional bedside test.[32,33]

Limulus test. This test is based on the property of gram-negative endotoxin to cause a gel to form in a lysate from the horseshoe crab *Limulus polyphemus.*[34] It is subject to some of the same problems as the NBT test, that is, operator technique and the fact that old material may become contaminated and give a false-positive test. In addition it is only useful for gram-negative meningitis which would make a negative test uninformative, particularly in adults.

Counter-immunoelectrophoresis. This is an immunologic test for the detection of bacterial antigens in either blood or CSF.[35,36] It is quite sensitive though in some series is no better than routine smear and culture even in partially treated meningitis.[37] In addition one would have to have antigens from all possible bacteria before a negative test could be considered certain.

CSF lactic acid. Elevations of CSF lactate in bacterial meningitis have been known since 1924[38] but have only been used recently to differentiate bacterial from viral meningitis. Bland et al found the CSF lactate to be elevated in bacterial meningitis until full treatment was completed, while the CSF in viral meningitis remained the same as normals.[39] In another study using a more sensitive gas chromatographic determination in 1.0 ml samples of CSF,[40] elevated CSF lactates were found in all 21 patients with bacterial meningitis from various agents (even in five who had already been started on therapy), while 0/179 controls showed an elevation (Fig 7). The disadvantage of this test is the need for special handling of the samples to avoid false elevation of the lactate.

CSF enzymes. A word should be said about the enzymes of the CSF in meningitis. Both lactic dehydrogenase and glutamic-oxaloacetic transaminase are elevated in bacterial meningitis but not in the viral form, a fact which some have attempted to use clinically.[41-44] For some reason, however, these tests have not become popular although they appear to be useful.

Factors Influencing Mortality

In a number of studies the prognostic value of various signs and tests has been evaluated.[6,7,41] In general, patients at the extremes of life, those with coexisting serious illnesses, those in whom therapy was delayed, and those who developed seizures—all had a poor prognosis. Mental state on admission also had a profound effect on outcome with one study showing a 52% mortality if the mental status was worse than simple lethargy and 35% if it was better,[7] while another series showed the difference to be 34% and 10% respectively.[40] Interestingly, the absence of nuchal rigidity was found to be a bad sign.[41] Changes in the CSF may also give some clues to outcome; the higher the protein, the worse the prognosis.[41] This might be expected since an elevated protein level reflects either blood-brain barrier breakdown or tissue destruction, that is, the severity of the infection. In a similar manner, an elevated bacterial antigen level was also a poor sign.

Summary

The advent of antibiotic therapy has decreased the number of patients with bacterial meningitis, yet it remains a significant problem. An attempt has been made to present some of the factors influencing etiology and prognosis as well as some of the clinical and laboratory findings.

Figure 2 is reproduced with permission from Bell and McCormick[14] and WB Saunders Company, Philadelphia.

Figure 3 is reprinted by permission from the *New England Journal of Medicine* (272:725–731, 1965).

Figure 4 is reproduced with permission from the Center for Disease Control, Atlanta, Georgia.

Figure 7 is reproduced with permission from Controni et al[40] and Plenum Publishing Corporation, New York.

REFERENCES

1. WILSON K, BRUCE AN: *Neurology.* Baltimore, William & Wilkins Co, 1940, p 2.

2. GRAY L: *A Treatise on Neurons and Mental Diseases.* Philadelphia, Lea Brothers and Company, 1893.

3. QUINCKE H: Die lumbalpunction des hydrocephalus. *Berlin klin Wochenschr* 28:929–933, 1891.

4. ROSENAU M: *Preventive Medicine and Hygiene.* New York, D Appleton and Co, 1913, p 176.

5. WARD HK, FOTHERGILL LD: Influenzal meningitis treated with specific antiserum and complement Report of five cases. *Amer J Dis Child* 43:873–881, 1932.

6. SWARTZ MN, DODGE P: Bacterial meningitis—A review of selected aspects. *N Engl J Med* 272:725–731, 779–787, 842–848, 898–902, 954–960, 1003–1010, 1965.

7. CARPENTER RR, PETERSDORF RG: The clinical spectrum of bacterial meningitis. *Am J Med* 33:262–275, 1962.

8. KARANDANIS D, SHULMAN JA: Recent survey of infectious meningitis in adults: review of laboratory findings in bacterial, tuberculous, and aseptic meningitis. *South Med J* 69:449–457, 1976.

9. EIGLER JO, WELLMAN WE, ROOKE, ED, ET AL: Bacterial meningitis. I. General review (294 cases). *Proc Staff Meet Mayo Clinic* 36:357–365, 1961.

10. GORMAN CA, WELLMAN WE, AND EIGLER JO: Bacterial meningitis. II. Infections caused by certain gram-negative enteric organisms. *Proc Staff Meet Mayo Clinic* 37:703–712, 1962.

11. FINLAND M, JONES WF JR, AND BARNES MW: Occurrence of serious bacterial infections since introduction of antibacterial agents, COUNCIL ON DRUGS. *JAMA* 170:2188–2197, 1959.

12. HODGES GR, PERKINS RL: Hospital-associated bacterial meningitis. *Am J Med Sci* 271:335–341, 1976.

13. Morbidity and Mortality Weekly Report Annual Supplement. CDC-USDHEW, Atlanta, GA, 1975.

14. BELL W, MCCORMICK W: *Neurologic Infection in Children.* Philadelphia, London, Toronto, WB Saunders Co, 1975.

15. FILICE G, FRASER D: Epidemiology of bacterial meningitis. A review of selected aspects, abstract. Conference on Neurological Epidemiology, Georgetown University and NINCDS, May 1977.

16. HAMBLETON G, DAVIES PA: Bacterial meningitis. Some aspects of diagnosis and treatment. *Arch Dis Child* 50:674–684, 1975.

17. CHAMBERS RA: The early diagnosis and investigation of the meningitides. *Practitioner* 217:82–90, 1976.

18. FLEXNER S: The results of the serum treatment in thirteen hundred cases of epidemic meningitis. *J Exp Med* 17:553–576, 1913.

19. Monthly Vital Statistics Report. Final Mortality Statistics, 1975. 25:14–15 (suppl), CSC-USDHEW, Atlanta, GA, 1977.

20. GOLDACRE MJ: Acute bacterial meningitis in childhood. *Lancet* 1:28–31, 1976.

21. HORENSTEIN S, SCHREIBER D: Clinical features of bacterial meningitis, in *Advances in Neurology. Infectious Diseases of the Central Nervous System*, vol 6; R Thompson, J Green (volume eds). New York, Raven Press, 1974, pp 141–159.

22. FOSSON AR, FINE RN: Neonatal meningitis: presentation and discussion of 21 cases. *Clin Ped* 7:404–410, 1968.

23. ABELLO V, RILEY HD: Meningitis during the first three months of life: a review of cases. *J Okla St Med Assoc* 69:503–508, 1976.

24. ZIAI M, HAGGETY RJ: Neonatal Meningitis. *N Engl J Med* 259:314–320, 1958.

25. GROOVER R, SUTHERLAND J, LANDING B: Purulent meningitis in newborn infants. *N Engl J Med* 264:1115–1121, 1961.

26. BERMAN PH, BANKER BQ: Neonatal meningitis. A clinical and pathological study of 29 cases. *Pediatrics* 38:6–24, 1966.

27. FERGUSON JH, CHAPMAN OD: Fulminating meningococcic infections and the so-called Waterhouse-Friderichsen syndrome. *Am J Pathol* 24:763–782, 1948.

28. MELBY JC, SPINK WW: Comparative studies on adrenal cor-

tical function and cortisol metabolism in healthy adults and in patients with shock due to infection. *J Clin Invest* 37:1791–1798, 1958.

29. McGehee WG, Rapaport SI, Ajort PF: Intravascular coagulation in fulminant meningococcemia. *Ann Int Med* 67:250–260, 1967.

30. Collins RC, Al-Mondhiry H, Chernik NL, et al: Neurologic manifestations of intravascular coagulation in patients with cancer. A clinicopathologic analysis of 12 cases. *Neurology (Minneap)* 25:795–806, 1975.

31. Tugwell P, Greenwood BM, Warrell DA: Pneumococcal meningitis: a clinical and laboratory study. *Quart J Med* 45:583–601, 1976.

32. Baehner RL: Use of the nitro blue tetrazolium test in clinical pediatrics. *Am J Dis Child.* 128:449–450, 1974.

33. Lace JK, Tan JS, Watanakunakorn C: An appraisal of the nitroblue tetrazolium reduction test. *Am J Med* 58:685–693, 1975.

34. Nachum R, Lipsey A, Siegal SE: Rapid detection of gram-negative bacterial meningitis by the limulus lysate test. *N Engl J Med* 289:931–934, 1973.

35. Edwards EA: Immunologic investigations of meningococcal disease. I. Group-specific *Neisseria meningitidis* antigens present in the serum of patients with fulminant meningococcemia. *J Immunol* 106:314–317, 1971.

36. Coonrod JD, Rytel MW: Determination of aetiology of bacterial meningitis by counter immunoelectrophoresis. *Lancet* 1:1154–1157, 1972.

37. Mandal B: The dilemma of partially treated bacterial meningitis. *Scand J Infect Dis* 8:185–188, 1976.

38. Nishimura K: The lactic acid content of blood and spinal fluid. *Proc Soc Exp Biol Med* 22:322–324, 1924.

39. Bland RD, Lister RC, Ries JP: Cerebrospinal fluid lactic acid level and pH in meningitis. *Am J Dis Child* 128:151–156, 1974.

40. Controni G, Rodriguez WJ, Deane CA, et al: Cerebrospinal fluid lactate determination: a new parameter for the diagnosis of acute and partially treated meningitis, in Williams JD, Geddes AM (eds): *Chemotherapy.* New York, Plenum Press, 1976, vol 1, pp 175–182.

41. Lending M, Slobody LB, Mestern J: Cerebrospinal fluid glutamic-oxalacetic transaminase and lactic dehydrogenase activities in children with neurologic disorders. *J Ped* 65:415–421, 1964.

42. Neches W, Platt M: Cerebrospinal fluid LDH in 287 children, including 53 cases of meningitis of bacterial and non-bacterial etiology. *Pediatrics* 41:1097–1103, 1968.

43. Beaty HN, Oppenheimer S: Cerebrospinal fluid lactic dehydrogenase and its isoenzymes in infections of the central nervous system. *N Engl J Med* 279:1197–1202, 1968.

44. Feldman WE: Cerebrospinal fluid lactic acid dehydrogenase activity. *Am J Dis Child* 129:77–80, 1975.

ANNOUNCING

MEDICAL COLLEGE OF VIRGINIA QUARTERLY

DECEMBER ISSUE

HUMAN GENETICS

PREPARED BY THE DEPARTMENT OF HUMAN GENETICS IN COLLABORATION WITH THE DEPARTMENTS OF PEDIATRICS, OBSTETRICS AND GYNECOLOGY, MEDICINE, RADIATION BIOLOGY, MICROBIOLOGY, AND RADIOLOGY

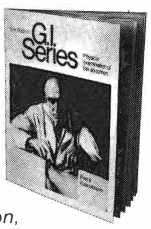
Single copy $3.00

A service to medical education from A. H. Robins:

Excerpted from Volume 2 of the

G.I. Series

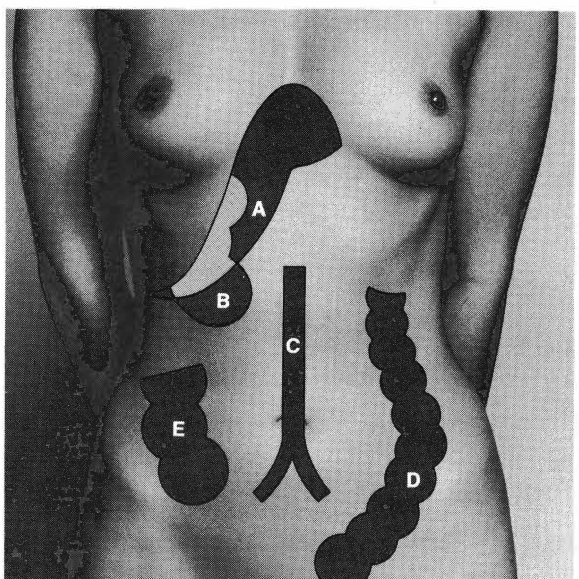
on physical examination of the abdomen:



The A. H. Robins G.I. Series consists of six booklets, designed to provide a quick, yet comprehensive review of basic procedures and practices in G.I. medicine—with particular emphasis on the physical examination as performed in the office or at bedside. If you have teaching responsibilities, limited quantities are available: Part 1—*Inspection*, Part 2—*Palpation*, Part 3—*Percussion*, Part 4—*Auscultation*, Part 5—*Abdominal Pain* and Part 6—*Differential Diagnosis of Abdominal Disorders*. Write to: The Medical Department, A. H. Robins Company, 1407 Cummings Drive, Richmond, Virginia 23220.

Normally palpable organs: the edge of the liver descending, on inspiration, below the costal margin (A); the lower pole of the right kidney (B); the abdominal aorta (C); the descending colon and the sigmoid (D); the ascending colon (E); and occasionally the bladder (though rising of this organ beyond the pubis does not necessarily indicate disease).

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



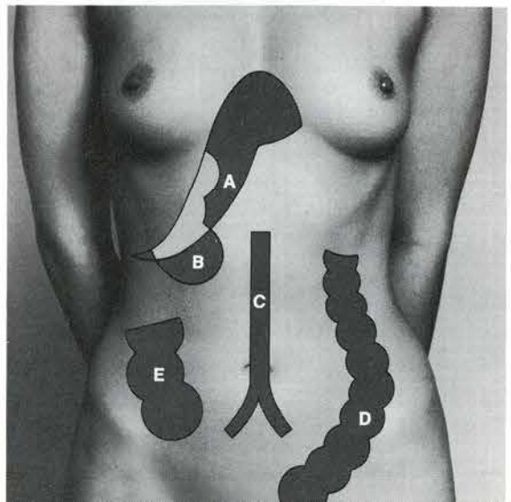
A service to medical education from A. H. Robins:

Excerpted from Volume 2 of the **G.I. Series** on physical examination of the abdomen:

The A. H. Robins G.I. Series consists of six booklets, designed to provide a quick, yet comprehensive review of basic procedures and practices in G.I. medicine—with particular emphasis on the physical examination as performed in the office or at bedside. If you have teaching responsibilities, limited quantities are available: Part 1—*Inspection*, Part 2—*Palpation*, Part 3—*Percussion*, Part 4—*Auscultation*, Part 5—*Abdominal Pain* and Part 6—*Differential Diagnosis of Abdominal Disorders*. Write to: The Medical Department, A. H. Robins Company, 1407 Cummings Drive, Richmond, Virginia 23220.

Normally palpable organs: the edge of the liver descending, on inspiration, below the costal margin (A); the lower pole of the right kidney (B); the abdominal aorta (C); the descending colon and the sigmoid (D); the ascending colon (E); and occasionally the bladder (though rising of this organ beyond the pubis does not necessarily indicate disease).

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



Spasm reactor? Donnatal®!

	each tablet, capsule or 5 ml (tsp.) of elixir (23% alcohol)	each Donnatal No. 2 Tablet
Phenobarbital (warning: may be habit forming)	(¼ gr) 16.2 mg	(½ gr) 32.4 mg
Hyoscyamine sulfate	0.1037 mg	0.1037 mg
Atropine sulfate	0.0194 mg	0.0194 mg
Hyoscine hydrobromide	0.0065 mg	0.0065 mg

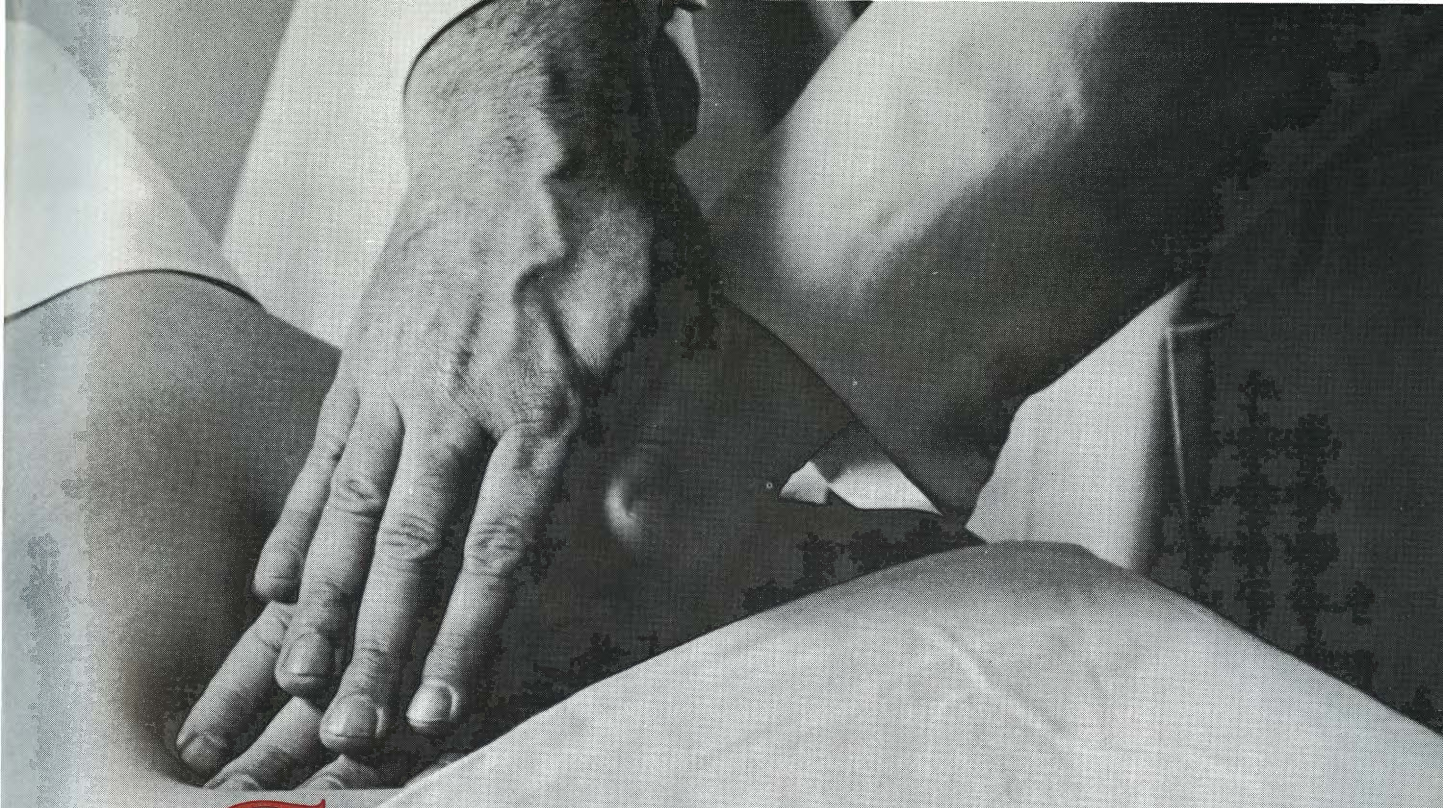
Indications: Based on a review of this drug by the NAS/NRC and/or other information, FDA has classified the following indications as possibly effective: adjunctive therapy in the treatment of peptic ulcer; the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.

Final classification of the less-than-effective indications requires further investigation.

Brief summary. Contraindicated in patients with glaucoma, renal or hepatic disease, obstructive uropathy (for example, bladder neck obstruction due to prostatic hypertrophy) or a hypersensitivity to any of the ingredients. Blurred vision, dry mouth, difficult urination, and flushing or dryness of the skin may occur at higher dosage levels, rarely at the usual dosage.

A·H·ROBINS

A. H. Robins Company, Richmond, Virginia 23220



Spasm reactor?

Donnatal®!

	each tablet, capsule or 5 ml (tsp.) of elixir (23% alcohol)	each Donnatal No. 2 Tablet
Phenobarbital (warning: may be habit forming)	(¼ gr) 16.2 mg	(½ gr) 32.4 mg
Hyoscyamine sulfate	0.1037 mg	0.1037 mg
Atropine sulfate	0.0194 mg	0.0194 mg
Hyoscine hydrobromide	0.0065 mg	0.0065 mg

Indications: Based on a review of this drug by the NAS/NRC and/or other information, FDA has classified the following indications as possibly effective: adjunctive therapy in the treatment of peptic ulcer; the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.

Final classification of the less-than-effective indications requires further investigation.

Brief summary. Contraindicated in patients with glaucoma, renal or hepatic disease, obstructive uropathy (for example, bladder neck obstruction due to prostatic hypertrophy) or a hypersensitivity to any of the ingredients. Blurred vision, dry mouth, difficult urination, and flushing or dryness of the skin may occur at higher dosage levels, rarely at the usual dosage.

A·H·ROBINS

A. H. Robins Company, Richmond, Virginia 23220