Manual of Neurologic Therapeutics

With Essentials of Diagnosis

Second Edition

Edited by
Martin A. Samuels, M.D., F.A.C.P.

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Dedication
First Edition

This manual is dedicated to **Raymond D. Adams, M.D.**, on the occasion of his retirement from the Bullard Professorship of Neuropathology, Harvard Medical School, and as Chief of the Neurology Service, Massachusetts General Hospital.

The contributing authors are among the last group of neurology residents fully trained by Dr. Adams. Throughout his 25-year tenure, Dr. Adams's extraordinary talents as a neuroscientist—and particularly as a neuropathologist—have been well known, placing him in the vanguard of the profession.

Those of us who have had the privilege of training under him know of another talent equally impressive but less generally known: his skill as a clinician. His incredible abilities, not only as a superb diagnostician but also as the classic bedside physician, have made him the role model for all of us concerned with the art of clinical medicine.

It seems appropriate, then, that a manual on the treatment of neurologic disease should be inspired by, and dedicated to, this premier neurologic therapist.

Dedication
Second Edition

This manual is dedicated to **C. Miller Fisher, M.D.**, on the occasion of his recent retirement as Professor of Neurology at the Massachusetts General Hospital, Harvard Medical School.

The contributing authors were a single group of neurology residents who finished training at the Massachusetts General Hospital in 1977. As such, we had the unique opportunity to come under the influence of the remarkable C. M. F. With a few years' perspective, it is now obvious to all of us what a major impact Dr. Fisher has had on everyone whom he has trained. The stamp of a C. M. F.-trained neurologist is unmistakable. Even his sense of humor, mannerisms, and gesticulations can be seen in fragmentary form among his numerous pupils now dispersed throughout the world.

Of greater importance are his qualities as a truly great clinical neurologist—healthy skepticism, critical observation, and creativity. He imparts his knowledge and philosophy not through pedantic pedagogy but by example as seen on the wards, in the emergency room, and at the brain-cutting table. Each of his papers is a true pearl. In an age when huge bibliographies are generated from only a tiny kernel of data, Dr. Fisher has remained loyal to his principles, publishing only that which he personally knows to be new and correct from his own critical observations. In this way, he has attained a level of credibility that is unmatched in the academic world.

With all this, Dr. Fisher's greatest asset is his humanity. He remains authentically interested in and loyal to all of his pupils, colleagues, and patients. He imparts a true sense of fraternity to all who have trained under him. We are happy to note that since his retirement C. M. F. continues to care for patients, write, and teach much as he has done in his entire career.

It is fitting that a book written by an entire "class" of his pupils be dedicated to this stellar clinical neurologist.

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Preface to the Second Edition

Major additions to the diagnostic and therapeutic armamentarium of the neurologist have occurred since the first edition of the **Manual of Neurologic Therapeutics** was published in 1978.

Treatment of increased intracranial pressure has become more sophisticated with widespread availability of intracranial pressure-monitoring devices. There has been a burgeoning of interest in the field of dementia with numerous new efforts at therapy aimed at manipulating cholinergic systems in the brain thought to be related to memory storage and retrieval. The legal, ethical, and medical aspects of brain death and persistent vegetative states have received a great deal of attention, with some further clarification of prognosis and management of patients with severely damaged nervous systems. Therapy for stroke and transient ischemic attacks has become oriented toward efforts at manipulating the prostaglandins that seem vital to the pathophysiologic processes of platelet adhesiveness and thrombosis. The treatment of primary and metastatic brain tumors has advanced considerably with the availability of new chemotherapeutic regimens. Plasmapheresis has become a popular technique for the treatment of disorders in which humorally mediated pathologic alterations may occur, such as myasthenia gravis, Guillain-Barré syndrome, and even multiple sclerosis.

As always, one must temper the enthusiasm of the moment with the test of time when evaluating new forms of therapy. The effort in the second edition of this manual is to provide the reader with a solid base of what are considered standard therapeutic techniques together with a reasonable evaluation of new therapies as well as can presently be assessed. In many cases, the present data are incomplete or subject to alternative interpretations. Thus, some of the recommendations must, by necessity, reflect the opinions and experience of the authors. In particularly controversial areas, selected readings are recommended so the reader may further evaluate the raw data independently.

In some areas the amount of pathophysiologic and diagnostic material has been increased. However, this book remains primarily a therapeutics manual and depends largely on the proper diagnosis having already been made. The reader should refer to the standard neurology textbooks for more extensive discussions of relevant anatomy, physiology, and diagnosis.

We wish to thank the many colleagues and friends whose criticisms and comments regarding the first edition were invaluable in the preparation of the second edition of this manual. Work on this volume was punctuated by the birth of my son, Charles, from whom I received incalculable inspiration. My sincere thanks again to my daughter, Marilyn, and my wife, Linda, who continue to provide me with untold amounts of patience, wisdom, and encouragement.

M. A. S.

Preface to the First Edition

Until very recently the neurologist's primary task was to categorize and organize the structure and pathologic alterations of the nervous system. In fact, neurology has long been known as a discipline with elegantly precise and specific diagnostic capabilities but little or no therapeutic potentiality. Further, many surgeons, pediatricians, and internists have traditionally thought of the neurologist as an impractical intellectual who spends countless hours painstakingly localizing lesions while ignoring pragmatic considerations of treatment. Perhaps this conception is largely attributable to the peculiar complexity of the nervous system and the consequent relative naivete of physicians in their understanding of its functions.

Many of the classic descriptions of disease states in other medical disciplines were completed in the last century; in neurology, these have only been described in the past generation, and only in the last ten years has neurology begun to be characterized by subcellular mechanistic concepts of disease. This maturity has meant that the neurologist is now as much involved in the therapeutic aspects of his specialty of medicine as any of his colleagues. Certain neurologic diseases, such as epilepsy, have been treatable for relatively long periods of time, but understanding of the subcellular mechanisms of other diseases has led to newer, more effective forms of therapy.

An example of this is the enlarged understanding we now have of the biochemical alterations in Parkinson's disease, and the resultant therapeutic implications. Now, much as the endocrinologist treats diabetes with insulin and the cardiologist treats congestive heart failure with digitalis, the neurologist treats Parkinson's disease with L-dopa. In all these situations, the underlying condition is not cured; rather, an attempt is made to alter the pathophysiologic processes by utilizing a scientific understanding of the function of the diseased system.

This manual embodies a practical, logical approach to the treatment of neurologic problems, based on accurate diagnosis, that should prove useful to both clinician and student. No attempt is made to reiterate the details of the neurologic examination; it is assumed that the reader is competent to examine the patient—although particularly important or difficult differential diagnostic points are mentioned when appropriate. In this regard, it should be emphasized that this manual is only a guide to diagnosis and therapy, and each patient must be treated individually. The manual is organized to best meet the needs of the clinician facing therapeutic problems. Thus, the first seven chapters are concerned with symptoms, such as dizziness and headache, while the last ten consider common diseases, such as stroke and neoplasms.

I thank the many colleagues and friends whose criticism and comments were useful in the preparation of this book, in particular Drs. G. Robert DeLong, C. Miller Fisher, George Kleinman, James B. Lehrich, Steven W. Parker, Henry C. Powell, E. P. Richardson, Jr., Maria Salam, Bagwan T. Shahani, Peter Weller, James G. Wepsic, and Robert R. Young. In addition, I am indebted to Sara Nugent and Helen Hyland for their assistance in the preparation of the many manuscripts, and to Diana Odell Potter, formerly of Little, Brown and Company, for her editorial skills. Jane Sandiford, formerly of Little, Brown and Co., and Kathleen O'Brien and Carmen Thomas of Little, Brown provided invaluable assistance in the final preparation of this material. Deep appreciation goes to Lin Richter, Editor in Chief of the

Medical Division, Little, Brown and Company for her support throughout this effort. I further thank Jon Paul Davidson, also formerly of Little, Brown, for his valuable encouragement and help early in the course of this project. Much support and encouragement was derived from my new colleagues in the Peter Bent Brigham Hospital Neurology Section, The Longwood Avenue Neurology Program, and the West Roxbury Veterans Administration Hospital. A great deal of inspiration came from the birth of my daughter Marilyn, and my deepest thanks go to my wife, Linda, who provided constant encouragement, editorial skill, and infinite patience.

M. A. S.

Contents

Neurologic Symptoms

Notice. The indications and dosages of all drugs in this manual have been recommended in the medical literature and conform to the practices of the general medical community. The medications described do not necessarily have specific approval by the Food and Drug Administration for use in the diseases and dosages for which they are recommended. The package insert for each drug should be consulted for use and dosage as approved by the FDA. Because standards for usage change, it is advisable to keep abreast of revised recommendations, particularly those concerning new drugs.

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Coma and Other Alterations in Consciousness

Telmo M. Aquino
and Martin A. Samuels

I. **General principles.** When confronted with a patient with impaired consciousness, the clinician proceeds in an orderly, systematic manner. He gathers information while he performs specific therapeutic maneuvers aimed at maintaining vital functions and avoiding further neurologic damage.

Impairment of consciousness may derive from a variety of causes. The first priority is to define and treat, as expeditiously as possible, those causes that are potentially reversible (see sec. **V**).

II. **Pathophysiology.** Consciousness consists of two components: **Awareness** and **arousal** (or wakefulness). **Awareness** refers to the higher-level integration of multiple sensory inputs that permit meaningful understanding of self and environment. The mechanisms of awareness reside diffusely in the cerebral cortex. **Arousal** (or wakefulness) refers to a more primitive set of responses that are located entirely within the brainstem and are synchronized by a diffuse network of nuclei and tracts; this network is located in the core of the brainstem and extends from the medulla to the thalamus. This ascending reticular activating system (ARAS) mediates such responses as eye opening to painful stimuli, which is one clinical expression of intact arousal mechanisms. Other testable aspects of ARAS functioning include corneal reflexes, pupillary reactions, and ocular motility, either spontaneous or reflex (e.g., oculocephalic and vestibuloocular reflexes). Via thalamic relay nuclei, the ARAS projects diffusely to the cerebral cortex, thus acting as an "on-off switch" for the cortical awareness system. In normal circumstances, it is the cycling of this system that accounts for the sleep-wake cycles and the corresponding electroencephalographic findings.

With these simple anatomic and physiologic points in mind, one can conceive of three mechanisms by which consciousness may be impaired.

A. **Bilateral diffuse cerebral cortex failure,** which leads to a state of impaired awareness with intact arousal mechanisms (the so-called vegetative state). This circumstance most commonly results from a diffuse anoxic and/or ischemic insult such as cardiac arrest.

B. **Brainstem failure,** which produces a state of impaired arousal. In such cases the cortical awareness mechanisms would be untestable since the ARAS "switch" would be shut off and would produce, in effect, a state of pathologic sleep. In clinical practice, a state of brainstem failure could be due to either:

1. **Primary brainstem pathology,** such as pontine hemorrhage or infarction, or
2. **Secondary brainstem injury** due to compression from masses that normally are situated in other compartments; examples of this are transtentorial (uncal) herniation due to a mass in the temporal lobe or cerebellar herniation due to a mass in the cerebellum. Such compressing masses can cause permanent brainstem lesions (e.g., Duret hemorrhages) by distorting the brainstem's vascular supply through the stretch or torque imposed by the mass.

C. **Combined bilateral cortical and brainstem failure** is seen most commonly in cases of metabolic encephalopathy and intoxications in which the relative

amount of brainstem, as opposed to cortical, dysfunction varies, depending on the toxin involved and the severity of the metabolic derangement.

III. Diagnosis

A. History. Frequently, the patient is brought to the emergency ward unresponsive, and no information at all is available. Whenever possible, family, friends, ambulance personnel, and physicians who have previously treated the patient should be contacted. **Important features** of the history are trauma, previous illnesses, medications, addiction to drugs or alcohol, and psychiatric disorders.

B. General physical examination should pay special attention to the following points:

1. **Vital signs:** patency of the airway, and circulatory and ventilatory status.
2. **Skin:** signs of trauma, stigmata of liver disease, needle marks, and infective or embolic phenomena.
3. **Head:** Battle's sign indicates mastoid fracture; "raccoon's eyes" suggest orbital fracture; and localized tenderness or crepitus and/or hemorrhage from ears or nostrils indicate basilar skull fracture.
4. **Neck stiffness** may be indicative of infection or subarachnoid bleeding. **(Do not manipulate the neck if there is suspicion of cervical spine fracture.)**
5. **Chest, abdomen, heart, and extremities** are examined, and **rectal** and **pelvic** examinations are done, all in the usual manner. A **stool guaiac test** also is done.
6. **Breath** may exhibit fetor hepaticus ("liver breath"), the fruity smell of ketoacidosis, the smell of liquor, or the urinous smell of uremia.

C. A neurologic examination is performed in all patients and recorded. With the goal of defining the presence, location, and nature of the process causing impaired consciousness, special emphasis is placed on the following:

1. **Observation of the patient**

   a. Observe whether the patient **lies in a natural, comfortable position,** as though in natural sleep. If so, unconsciousness is probably not very deep. Yawning and sneezing have the same significance, although other automatisms such as coughing, swallowing, or hiccuping do not necessarily reflect light coma.

   b. **Jaw and lid tone** are also indications of the severity of unconsciousness. Open lids and hanging jaw indicate severe unresponsiveness.

2. **Level of unconsciousness.** Abnormalities of consciousness comprise a continuum, ranging from full alertness to total unresponsiveness. It is useful in clinical practice to subcategorize patients with abnormal consciousness according to stages of progressive unresponsiveness. Because there is much confusion surrounding the meanings of terms describing levels of consciousness, it is good practice to describe in detail on the record the responses of the patients to various stimuli. Use of terms such as lethargy, somnolence, or obtundation should be avoided since they have no specific neurologic meaning.

   a. **Confusion** is defined as the inability to maintain a coherent stream of thought or action. The neurologic substrate for confusion is inattention. **Attention** is difficult to define, but it refers to the ability of the individual to sort out and stratify the many sensory inputs and potential motor outputs so that a particular thought or action may be completed in a coherent fashion. It is evident from this concept that the mechanisms for attention must involve both arousal and awareness. Thus, confusion may be seen in states of cortical and/or ARAS dysfunction. The most common

cause of confusion is metabolic or toxic encephalopathy, although it may be seen in patients with certain focal cortical lesions, particularly those occurring in the right parietal lobe. Confusion is evident clinically when the apparently awake patient fails tasks requiring persistent coherent thought, such as the serial 7s test. Such patients also have very disturbed writing but have no other specific abnormalities of cortical modalities.

b. **Drowsiness** is characterized by ready arousal, ability to respond verbally, and fending-off movements induced by painful stimuli in the absence of hemiparesis or aphasia.

c. **Stupor** is characterized by incomplete arousal to painful stimuli. Response to verbal commands is inconsistent and vague. No verbal response or moaning is elicited. The motor responses are still of the purposeful, fending-off type.

d. **Light coma** is characterized by primitive and disorganized motor responses to painful stimuli. There is no response to attempts at arousal.

e. **Deep coma** is characterized by absence of response to even the most painful stimuli.

f. When there is a question of **psychogenic unresponsiveness,** try to obtain a forced conscious response, for example, by letting the patient's hand fall toward his face. Do not apply noxious stimuli to eyes, testicles, breasts, or other sensitive areas.

3. **Respiration.** The respiratory pattern is helpful in localizing and, in certain instances, determining the nature of the process.

a. **Cheyne-Stokes respiration** is characterized by periods of hyperventilation that gradually diminish to apnea of variable duration; respirations then resume and gradually build up again to hyperventilation. Cheyne-Stokes breathing indicates bilateral deep hemispheric and basal ganglionic dysfunction. The upper brainstem also may be involved. (**Note:** Cheyne-Stokes respiration is most commonly observed in nonneurologic conditions, such as congestive heart failure.)

b. **Central neurogenic hyperventilation** (CNHV) refers to continuous rapid, regular, and deep respirations at a rate of about 25/min. It has no segmental localizing significance. Regularity is an unfavorable prognostic sign, since increasing regularity correlates with increasing depth of coma.

Systemic acidosis (e.g., diabetic ketoacidosis) and hypoxemia should be excluded (two PO_2 determinations over 70 mm Hg in 24 hr is considered adequate for this purpose) before it is concluded that hyperventilation is of neurogenic origin.

c. **Apneustic breathing** consists of a prolonged inspiratory phase followed by apnea (the inspiratory cramp). It may be followed by **cluster breathing,** which consists of closely grouped respirations followed by apnea. Either pattern implies lower pontine damage.

d. **Ataxic breathing** and **gasping breathing** (Biot's respirations) imply damage to the medullary respiratory centers. In ataxic breathing, respirations are chaotic. Gasping breathing is characterized by gasps followed by apnea of variable duration. Both are agonal events and usually precede respiratory arrest.

e. **Depressed breathing** consists of shallow, slow, and ineffective breathing caused by medullary depression, usually produced by drugs.

f. **Coma with hyperventilation** is seen frequently in metabolic disorders.

(1) **Metabolic acidosis** (e.g., diabetic ketoacidosis, uremia, ingestion of organic acids, lactic acidosis).

(2) **Respiratory alkalosis** (e.g., hepatic encephalopathy, salicylate poisoning).

4. **Position of the head and eyes.** The normal cerebral hemisphere tends to move both head and eyes conjugately toward the opposite side. In hemispheric lesions, the healthy hemisphere becomes unopposed, and, as a result, the head and eyes look toward the lesion and away from the hemiparesis. The reverse occurs in pontine lesions, in which the eyes deviate toward the hemiparesis and away from the lesion.

5. **Visual fields and funduscopy**

   a. In patients who are not completely unresponsive, visual fields should be tested with threatening movements, which should evoke a blink. Asymmetry of the blink response indicates hemianopia (in the absence of blindness or optic nerve damage). Air movement into the eyes can produce a false-positive response.

   b. Funduscopy may reveal papilledema suggestive of increased intracranial pressure. A **subhyaloid hemorrhage**—a rounded, well-defined clot on the surface of the retina—is commonly associated with ruptured aneurysms.

6. **Pupils.** Note size, roundness, and equality in reaction to light, tested both directly and consensually.

   a. **Midposition (3–5 mm) nonreactive pupils** are evidence of midbrain damage.

   b. **Reactive pupils** indicate midbrain intactness. In the presence of unresponsiveness and absent extraocular movements and corneal reflexes, reactive pupils are suggestive of metabolic abnormality (e.g., hypoglycemia) or drug ingestion (e.g., barbiturate).

   c. **A unilaterally dilated and unreactive pupil** in a comatose patient is a sign of third-nerve compression due to temporal lobe herniation. Other components of third-nerve dysfunction (e.g., drooping of the eyelid and abduction of the eye as the result of unopposed action of the lateral rectus muscle) may be concomitant with or follow pupillary dilatation. Less frequently, midbrain damage caused by compression or direct damage is expressed by a dilated, nonreactive pupil.

   d. **Small but reactive pupils.** These pupils signify pontine damage, as in infarction or hemorrhage. Opiates and pilocarpine also produce pinpoint reactive pupils. A magnifying glass may be helpful in the examination.

   e. **Dilatation** of the pupils in response to a painful stimulus in the neck (the normal ciliospinal reflex) indicates lower brainstem integrity.

7. **Extraocular movements** (EOMs). If the patient is responsive enough to follow commands, saccadic and pursuit eye movements should be tested. A large number of ocular and gaze palsies may be present. In addition, spontaneous abnormal displacements of the eyes may be observed. **The most useful tests** are:

   a. **Doll's-head maneuver** (DHM), or **oculocephalic reflex. (Do not perform this maneuver when there is a question of cervical spine injury.)** DHM is performed by turning the patient's head with quick lateral and vertical displacements. **The reflex is normal or preserved** if the eyes move in the orbits in the direction opposite to the rotating head, maintaining their position in relation to the environment. **Abnormal response** (no movement of the eyes in the orbits, or asymmetry of movements) is suggestive of a destructive lesion at the pontine-midbrain level. Barbiturate poisoning also may abolish the reflex.