NOTE TO READER:
The Joint Committee for Stroke Facilities was created through a contract with Regional Medical Programs Service. The project upon which this publication is based was performed pursuant to Contract HSM-110-69-436 between the American Neurological Association and Health Services and Mental Health Administration, Department of Health, Education, and Welfare to help fulfill the requirements of Section 907 of Public Law 89-239, which established the Regional Medical Programs in 1965.

The Committee hopes to review and update its guidelines periodically as new methods of diagnosis and treatment are developed. Comments, criticisms, and corrections are invited. They should be sent to:

General Chairman
Suite 1010, 1776 K Street, N. W.
Washington, D. C. 20006

The following subjects will appear in serial publications in STROKE, although not necessarily in the order listed:
Epidemiology for Stroke Facilities Planning
Clinical Prevention of Stroke
Clinical Management of Stroke
Strokes in Children
Nursing Care of Stroke Patients
Stroke Rehabilitation
Laboratory Evaluation of Stroke
Special Procedures and Equipment in the Diagnosis and Management of Stroke
Community Health Services for Stroke
Training, Education, Manpower, and Research

Cross-references will be indicated from time to time to material developed in other sections. Pages will be designated whenever possible, but the sequence of publications will not permit this in many instances. However, the Table of Contents included with each Section should aid in directing the reader to the appropriate pages.
REPORT OF THE JOINT COMMITTEE
FOR STROKE FACILITIES

III. The Laboratory Evaluation of Neurovascular Disease (Stroke)

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III. The Laboratory Evaluation of Neurovascular Disease (Stroke)

BY PATHOLOGY AND LABORATORY PROCEDURES STUDY GROUP
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Abstract: The Laboratory Evaluation of Neurovascular Disease (Stroke)

This report describes contributions the clinical laboratory of the 1970s can offer to physicians and their associates in diagnosing and managing patients with the several types of neurovascular disease (NVD). Specific chemical, serological, hematological, and microbiological tests, as well as procedures for macroscopical and microscopical evaluation of tissue obtained by biopsy or at autopsy, are tabulated and described under the headings of blood, urine, cerebrospinal fluid, and tissue. Interpretive comments and cautions as to limitations are provided for selected procedures.

Introduction

This study group was charged with preparing a report to guide as well as to inform those caring for patients with neurovascular disease (NVD). Individuals responsible for such patients include the physician and his associates as well as others ministering directly or indirectly to the patient. Since the physician has the greatest responsibility to ensure that laboratory methods are properly applied, this report is designed primarily for the clinician and his associates. Therefore, the document uses current medical terminology and bibliographical references. The major purpose is to achieve better clinicopathological correlation, in its broadest sense. If this objective can be achieved, more widespread knowledge of pathogenesis and rational therapy may follow.

Individuals other than the physician may find this presentation useful in understanding the breadth and complexity of modern laboratory methods available to the clinician. Nurses, technologists, physical therapists, social workers, and hospital administrators, to mention a few, may acquire some insight into the requirements in time and money which laboratory evaluation often entails. They may gain some appreciation of the fact that adjustments in schedules, personnel, and facilities may be necessary to carry out adequate laboratory evaluation.

Institutions, easily conceived as abstractions, but as different as the individuals clustered in them, may, through their various officers and governing boards, use the report as a comparative guide. It will allow them to construct a rough progress report of what American medicine in the 1970s can offer to patients with NVD in the realm of the laboratory. Some may find ways to develop their facilities, others may see the necessity for acquiring more personnel of special types, and still others may conclude that coordination, and sharing facilities and personnel are the best methods for their communities.

Laboratory procedures within the province of this study group include chemical, serological, hematological, and microbiological tests as well as the macroscopical and microscopical evaluation of tissue obtained by
biopsy or at necropsy.

The study group elected not to insert descriptive and categorical statements about personnel or facilities necessary to execute the tests listed herein. The qualifications of professional and technical personnel are best determined by the individuals and educational institutions training them, professional organizations, state and national licensing agencies, certifying boards for specialty training, and members of hospital staffs with whom they must work. Peers and superiors in a given professional or technical field are the most reliable judges in these matters.

The following laboratory procedures are described and discussed in the reports of other study groups: radiological studies (x-rays of any type, isotopic brain scans, isotopic cerebral blood flow studies), and electrophysiological studies (electroencephalography, electrocardiography, echoencephalography, electromyography, nerve conduction tests). This report begins with definitions and a clinicopathological classification of NVD, followed by a necessarily limited listing of tests pertinent to NVD diagnosis and management, and not to all diseases. Numerous diseases or secondary complications may be associated with NVD as will be evident from our comments about differential diagnosis; additional laboratory procedures not listed here may be required under certain circumstances.

Since each patient with NVD presents a distinctive problem, clinical judgment is mandatory in ordering laboratory procedures. Although some physicians may think in terms of “routine,” “major,” “most important,” or “battery of” laboratory procedures, it is obvious that the most important test or tests for a particular patient will depend on his age, mode and place of presentation, symptoms, signs, and numerous other variables. For example, the comatose adult with a stiff neck seen in the emergency room, the elderly man with a history of transient ischemic attacks, but devoid of neurological signs, who walks into the office, and the adolescent with focal seizures, presumably due to a vascular malformation, will all require certain tests—sometimes the same tests—but the urgency and order of the workups will differ appreciably. Lumbar puncture with a cerebrospinal fluid (CSF) survey early in the course is clearly “more important” for the first patient than for the elderly man with TIA. The “routine battery” of tests required for a black child with suspected neurovascular complications of sickle cell disease will be different in many respects from that obtained for an adult white male with a family history suggesting type II hyperlipidemia. Since formulas for ordering laboratory tests cannot reasonably take into account all of the pertinent variables, then clinical judgment augmented by a knowledge of the best current medical practice must be the determining factor. A tabulation of the frequency with which tests are ordered may contain interesting statistics showing some variation from institution to institution, but is irrelevant in the context of this report.

Under the headings of: Blood, Urine, Cerebrospinal fluid (CSF), and Tissue, specific procedures are tabulated. Whenever interpretive comment is necessary, a number in parenthesis follows the test name. This number may be consulted in Notes for Selected Items for a more detailed statement about the procedure in the context of NVD. The remarks in that section refer to the special indications for the use of a test in evaluating or managing patients. Some of the statements include cautions about the limitations of certain procedures; some refer to other tests necessary for optimal interpretation. When a test is listed without a number in parenthesis, the study group is of the opinion that its use is too obvious for the physician to require explanation or qualification.

Definitions and Clinicopathological Classification

Neurovascular disease is the term which will be used in place of stroke throughout this report, since the latter word may connote to some a wide variety of clinical states not necessarily of vascular origin, while others restrict its use to cerebrovascular disorders only.

Neurovascular diseases (NVD) are defined as disorders attributable to structural and functional alterations of the blood vessels (arteries, veins, capillaries and their subtypes) of the nervous system. NVD includes vascular disease not only of the brain (cerebrovascular disease) but of the spinal cord, the spinal roots, the peripheral and the autonomic nervous systems, and the membranous coverings of the nervous system.

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Listed below in outline form are the major clinicopathological entities considered as NVD.

CEREBRAL INFARCTION (ENCEPHALOMALACIA)
- With Arterial Thrombosis
  - With Atherosclerosis
  - Without Atherosclerosis (Other Causes Including Trauma)
- With Embolism (Cardiac, Atheromatous, Other Sources)
- With Venous Occlusion (Thrombosis or Embolism)
- Without Vascular Occlusion

INTRACRANIAL HEMORRHAGE (EPIDURAL, SUBDURAL, SUBARACHNOID, INTRAPARENCHYMAL)
- With Trauma
- Without Hypertension
- With Ruptured Arterial Aneurysm
- With Vascular Malformations
- With Blood Dyscrasias and Hemorrhagic Diatheses
- With Intracranial Neoplasms
- Other

SPINAL CORD INFARCTION (MYELOMALACIA)
- With Arterial Thrombosis
  - With Atherosclerosis
  - Without Atherosclerosis
- With Embolism
- With Venous Occlusion
- Without Vascular Occlusion

INTRASPINAL HEMORRHAGE
- With Trauma
- With Vascular Malformations
- Other

ANGIOPATHIC NEUROPATHIES AND RADICULOPATHIES
- With Trauma
- With Metabolic Diseases (Diabetes Mellitus, Other)
- With Angiitides (Collagen Diseases, Other)
- With Embolism
- Other

PATHOLOGICAL ALTERATIONS IN BLOOD VESSELS WITH OR WITHOUT INFARCTION OR HEMORRHAGE*

Arteries
- Congenital—Developmental Lesions
  - Atelesias, hypoplasias, persistent fetal anoma-
  - Unruptured aneurysm

Inflammatory Lesions (Arteritides)
- Traumatic Lesions and Effects of Physical Agents
- Lesions with Blood Dyscrasias
- Lesions with Metabolic Disease
- Lesions with Drugs
- Hemorrhage with anticoagulants
- Thrombosis with oral contraceptive agents
- Other (angitis, and related lesions, with nar-
  - cotic addiction)

Emboli with Cardiac Disease and Disease of the Extracranial Vessels
- Lesions with Neoplastic Disease
- Neoplastic emboli
- Marantic thrombi or emboli
- Compression with or without invasion

Lesions Due to Unknown Cause
- Atherosclerosis, uncomplicated
- Atherosclerosis, complicated
  - Ectasia
  - Ectasia and fusiform aneurysm
  - Stenosis
  - Thrombosis
  - Plaque hemorrhage
  - Plaque ulceration
  - With atheromatous embolization
  - Plaque calcification

Veins
- Congenital—Developmental Lesions
- Inflammatory Lesions (Phlebitides)
- Traumatic Lesions and Effects of Physical Agents
- Lesions with Blood Dyscrasias
- Lesions with Neoplastic Disease

Capillaries
- "Combined" Vessel Abnormalities
  - Vascular Malformations

ALTERATIONS IN BLOOD ELEMENTS AND COAGULATION STATUS WITH OR WITHOUT INFARCTION OR HEMORRHAGE*
- TRANSIENT ISCHEMIC ATTACKS (TIA)†
  - Emboli, Small (Atheromatous, Fibrinous, Calcific)
  - Thrombi, Small
- Hemorrhages, Small

Hemodynamic Changes, Local and Generalized (Cardiac Arrhythmias and Other Causes)

*These items are included in the classification as a reminder that laboratory evaluation, including the necropsy, often uncovers lesions which were unsuspected clinically or which produced no recorded symptoms or signs. Important contributions are made to the study of the natural history and therapy of disease (and often to the understanding of pathogenesis as well) by careful documentation of these lesions. The natural histories of intracranial arterial aneurysms and vascular malformations, for example, would be deceptively incomplete if necropsy studies had not disclosed how frequently these lesions may be clinically asymptomatic and discovered only incidentally.

†While definitions of TIA vary, the syndrome of reversible ischemia with complete functional restoration after a brief (seconds, minutes, hours, but usually not more than 24 hours) attack of neurological dysfunction is generally recognized. Information is lacking as to how many TIAs may be due to small infarcts of diverse pathogenesis, to hemodynamic and functional cardiac alterations (hypotension, cardiac arrhythmias), or to other factors as yet unsuspected, including combinations of all etiologies currently under suspicion. A consideration of the possible cause in a specific case should dictate the appropriate laboratory tests.
# Tabulation of Laboratory Studies

## BLOOD

- Hemoglobin (1)
- Hemoglobin Electrophoresis
- Hematocrit
- White Blood Count and Platelet Count
- Differential Blood Count (2)
- Erythrocyte Sedimentation Rate (3)
- Fasting and Two-Hour Postprandial Sugar (4)
- Urea Nitrogen
- Creatinine (5)
- Cholesterol (6)
- Triglycerides (7)
- Prothrombin Time (8)
- Partial Thromboplastin Time (9)
- Fibrinogen (10)
- Sodium, Potassium, Calcium, Phosphorus (12)
- Tests for Infectious Diseases (Febrile Agglutinins, Complement-Fixation, Viral Inhibition Tests, Blood Cultures) (13)
- Total Serum Protein and Serum Protein Electrophoresis (14)
- Thyroid Function Tests (15)
- Serological Tests for Syphilis (16)
- Bilirubin
- Blood and Serum Viscosity (17)
- Gases, pH (18)
- Platelet Adhesion and Aggregation Studies (19)
- Toxicological Studies (20)

## URINE

- Specific Gravity
- Glucose and Ketone Bodies
- Protein (21)
- Sediment Microscopy
- Twenty-Four Hour Vanilmandelic Acid (22)
- Porphobilinogen (23)
- Cyanide-Nitroprusside Test for Homocystinuria (24)

## CEREBROSPINAL FLUID (CSF)

- Color (25)
- Cells (26)
- Glucose (27)
- Protein (28)
- Enzymes (29)
- Serological Tests for Syphilis
- Cultures
- Gases and pH (30)

## TISSUE

- Biopsy
  - Arterial (31)
  - Muscle (32)
  - Nerve (33)
  - Brain (34)
  - Evacuated Hematoma (35)

## Autopsy

- Thoracic and Abdominal Viscera and Limbs (36)
- Intracranial and Extracranial, Intraspinal and Extraspinal Vessels (37)
- Brain and Spinal Cord (38)
- Peripheral Nerve and Muscle Samples

## Notes for Selected Items in Preceding Section

### BLOOD

1. **Whole Blood Hemoglobin Concentration:**
   - Accurate measurement of hemoglobin concentration in the acute NVD patient may be of special importance in several instances. When *elevated hemoglobin values* are obtained, the following conditions should be considered:
     1. Hemoconcentration secondary to dehydration;
     2. Polycythemia vera, a condition predisposing to thrombotic complications;
     3. Polycythemia associated with cerebellar hemangioblastomas and with certain other benign and malignant tumors (especially renal); and
     4. Polycythemia associated with hemoglobinopathies having increased oxygen affinity (and reduced oxygen delivery to tissues); phlebotomy would generally be contraindicated in such patients; *hemoglobin electrophoresis* may assist in detecting abnormalities such as hemoglobin Chesapeake and hemoglobin Rainer.

   When *low hemoglobin values* are found, consideration should be given to such serious underlying diseases as:
   1. Malignancy,
   2. Chronic or subacute blood loss,
   3. Uremia,
   4. Sickle cell anemia or sickle cell hemoglobinopathy—both detectable by the *metabisulfite screening test* for sickle hemoglobin or by *hemoglobin electrophoresis*;
   5. Paroxysmal nocturnal hemoglobinuria, in which thrombotic complications are common and which may be detected by the *sucrose hemolysin screening test* or the *Ham acid hemolysin test*;
   6. Myelofibrosis, in which thrombotic complications may occur and which may be diagnosed by characteristic changes on the blood smear, associated with hypoplastic bone marrow, splenomegaly, and hepatomegaly.
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(2) Differential Blood Count
The peripheral blood film prepared from freshly drawn venous or capillary blood can provide important information if properly stained and inspected. The laboratory should store the slide and have it available to the attending physician or his consultant. From the blood film the experienced observer can evaluate or estimate the following: size, shape, and hemoglobin content of erythrocytes; maturity, granulation, and numbers of leukocytes; and numbers and types of thrombocytes. The red blood cells also may be observed for the stippling of lead poisoning and presence of malarial parasites. Fragmented erythrocytes in the peripheral blood may be an indicator of consumptive coagulopathy. Rouleaux formation may indicate hyperviscosity.

(3) Erythrocyte Sedimentation Rate (ESR)
The ESR may be moderately elevated during the course either of cerebral infarction or of cerebral hemorrhage, though a normal value does not exclude either diagnosis. So many factors influence the ESR that the test should be regarded as nonspecific. In patients with cranial arteritis (temporal arteritis, giant cell arteritis), the erythrocyte sedimentation rate usually is greatly elevated.

(4) Fasting Blood Sugar (FBS) and Two-Hour Postprandial Blood Sugar (2-hr PPBS)
The FBS, or preferably the 2-hr PPBS, is an excellent screening test to detect diabetes mellitus. It is important that the patient be on a high carbohydrate diet for three days before performing a glucose tolerance test.

Hypoglycemia of diverse etiology with clinical manifestations ranging from weakness to coma may closely mimic NVD. It is also well recognized that fluctuations in the blood glucose level may occur in patients with acute NVD.

(5) Serum Creatinine
The serum creatinine level is a good screening test for renal disease, especially when used in conjunction with the urinalysis. When both are normal, significant renal disease generally is not present.

(6) Serum Cholesterol
Elevated serum cholesterol has been identified as a risk factor for NVD in persons under 50 years of age. Serum cholesterol, however, is only one risk factor; in the care of the individual patient it probably is of little value except as a part of overall evaluation. Agreement is fairly general that any level above 250 mg % may be considered elevated, though there are some who believe that the upper limit of normal should be placed at a lower concentration.

Fluctuations in serial serum cholesterol levels obtained over a long period of time may reflect laboratory error. In addition to these variations, individual fluctuations occur due to numerous physiological (age, sex, nutritional state, inheritance) and pathophysiological factors (thyroid, liver and pancreatic diseases, diabetes mellitus, nephrotic syndrome).

The relationship of cholesterol level to NVD remains a complicated and controversial problem, for which no easy or consistent formulation exists.

(7) Serum Triglycerides
Hypertriglyceridemia has been implicated as a risk factor in the development of coronary heart disease and thus may be a presumptive factor in the development of atherosclerosis in any vascular bed. At the present time no adequate studies evaluating hypertriglyceridemia as a risk factor for NVD have been published.

Agreement is general that the upper limit of normal fasting serum triglycerides is 150 mg %. The level of serum triglycerides can vary considerably with diet, especially in those persons with a carbohydrate-inducible hypertriglyceridemia. A “normal” individual who increases his carbohydrate intake abruptly may develop hypertriglyceridemia; however, this response usually lasts no longer than about six weeks.

Screening for hypertriglyceridemia is done by laboratory determination of serum triglyceride levels. The patient should fast for at least 12 hours before a triglyceride determination to avoid physiological triglyceridemia due to circulating chylomicrons. If serum triglyceride and cholesterol are normal, further lipoprotein studies are unnecessary. If the level of either is abnormal, the hyperlipemia can be classified further by electrophoresis using the method of Frederickson, Levy and Lees. As with serum cholesterol determinations, serum triglyceride levels may be subject to laboratory error when used serially over months or years.
Familial hyperlipidemias are much less common than those secondary to other diseases such as diabetes mellitus, pancreatitis, and alcoholism.

(8) One-Stage Prothrombin Time
This test is the original, and still by far the most widely used, procedure by which oral anticoagulant therapy is controlled. Though first introduced as a measure of plasma prothrombin, prolonged clotting times demonstrated with this assay may also reflect deficiency of one or more of three additional coagulation factors—factor VII, factor IX, and factor X. Prolonged one-stage times are also seen in disorders of fibrin polymerization. This fortuitous sensitivity of the one-stage time to deficiencies of blood coagulation factors other than prothrombin accounts for its widespread use to control anticoagulant therapy.

(9) Partial Thromboplastin Time (PTT)
Partial thromboplastin time (PTT) measures the intrinsic procoagulant activity of plasma in the presence of a "partial thromboplastin" (a platelet substitute). To reduce result variability due to contact activation, the test is generally performed using Celite, Kaolin or ellagic acid activation and is then described as the activated PTT. The original Langdell procedure and its modifications are all satisfactory. The assay is technically simple, is well standardized, and will detect most significant deficiencies (below 10% to 20% of normal values) of all procoagulant activities except platelet factor III (added during the test), factor XIII, and sometimes factor VII.

Abnormally prolonged times are found also in the presence of circulating anticoagulants and where coagulation disorders such as defective fibrin polymerization exist. A grossly shortened PTT is suggestive, but not diagnostic, of blood hypercoagulability.

(10) Plasma Fibrinogen
The concentration of plasma fibrinogen varies widely in healthy individuals, generally increasing with age. Also, many disease states may, directly or indirectly, influence the concentration. Consequently, the classification of a single fibrinogen value from an individual into the normal or abnormal category is frequently impossible unless the results of previous determinations are available. Nevertheless, plasma fibrinogen values, either obtained as part of a battery of coagulation assays or, preferably, as a series of sequential determinations, often provide information essential in patient management (for example, in making decisions concerning anticoagulant therapy).

Plasma fibrinogen is assayed preferably as thrombin-clottable protein using techniques such as those of Ratnoff and Menzie or radial immunodiffusion methods.

Recently the development of chromato-graphical methods for analyzing fibrinogen complexes, fibrinogen itself, and fibrinogen derivatives in plasma has shown this procedure to provide data of unique value in the diagnosis of thrombotic lesions, blood hypercoagulability, and fibrinolysis. Similarly, these procedures provide an objective guide for prescription and control of thrombolytic and anticoagulant therapy. Presently, technical difficulties are such that the methods are unsuited to routine use.

(11) Uric Acid
Hyperuricemia may be associated with atherosclerosis of the coronary, peripheral, and cerebral arteries, but the relationship of uric acid levels to the pathogenesis of cerebrovascular disease is controversial.

Hyperuricemia may be found in a number of conditions other than gout (hyperparathyroidism, myxedema, toxemia of pregnancy, starvation, high purine diet, diabetes mellitus, psoriasis, blood dyscrasias, multiple myeloma, renal disease, neoplasm). Chlorothiazide administration can cause high levels. The usual determination of uric acid may be subject to considerable laboratory error.

(12) Sodium, Potassium, Calcium, Phosphorus
These determinations may be critical in the management of severely ill patients, particularly when fluids are being given intravenously or lost in abnormal quantities, or when there are severe associated diseases (diabetes mellitus, for example).

Fluctuations in neurological signs with hyponatremia have been reported clinically and experimentally; deficits such as hemiparesis may worsen with low serum sodium and improve when this deficiency is corrected. Hyponatremia rather than hypo-osmolality has been considered the important factor in the "dialysis disequilibrium syndrome."
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Hypernatremia of diverse origins—from salt poisoning to hypernatremic dehydration—may be associated with brain lesions, especially in children.\textsuperscript{20-23}

Hypoparathyroidism and hyperparathyroidism may produce symptoms which mimic NVD.\textsuperscript{13}

Occasionally bacterial, viral, or protozoal invasion of the nervous system may mimic NVD and require the use of cultural or serological methods for differential diagnosis. Embolism, secondary to bacterial endocarditis, is an occasional cause of NVD and confirmation of this diagnosis may be obtained by blood culture.\textsuperscript{14}

Serum proteins may be determined either by chemical analysis of albumin and globulin concentrations, or by serum electrophoresis, a more valuable technique. Serum protein alterations may suggest the presence of the hyperviscosity syndrome and various systemic diseases including collagen vascular disorders, multiple myeloma, and Waldenström's macroglobulinemia.\textsuperscript{15}

The most common tests for thyroid function are: protein-bound iodine (PBI), thyroxine (T-4), triiodothyronine resin uptake (T-3), and radioiodine (I-131) uptake by the thyroid. PBI is still perhaps the most frequently used of these procedures. Under ideal conditions the PBI gives an adequate estimate of total thyroxine concentration, since most of the circulating protein-bound iodine is found in thyroxine. The PBI, however, is drastically affected and invalidated by ingestion or injection of materials containing iodine, such as radiopaque dyes. The T-4 test is not affected by exogenous iodides and is preferable to the PBI as a measure of total thyroxine. Thyroxine levels may be lowered by diphenylhydantoin.

Despite the fact that alterations in blood viscosity are probably of greater significance than changes in serum viscosity, the term "hyperviscosity syndrome" usually refers to alteration of the latter. This condition occurs secondary to dysglobulinemias, and diagnosis is usually made by paper or cellulose acetate electrophoresis or by immunoelectrophoresis.\textsuperscript{16}

The determination of Pa\textsubscript{O\textsubscript{2}}, Pa\textsubscript{CO\textsubscript{2}}, and pH may be extremely useful in the differential diagnosis of coma due to metabolic disease versus that due to NVD. Knowledge of blood gases and pH may also be important in the management of seriously ill patients with known NVD in whom renal, pulmonary, and neurological disease coexist.
cardiac complications occur. Details of collection, measurement and interpretation of results and the use of nomograms are discussed in several references.25-27

(19) Platelet Adhesion and Aggregation Studies

The concept that altered, usually enhanced, platelet functional activity may be of significance in certain thromboembolic diseases is currently one of importance.

Two main types of platelet assay are commonly used to investigate these problems. Those procedures primarily quantifying the ability of platelets to adhere to surfaces are termed platelet adhesion assays, while those quantifying the ability of platelets to adhere to each other are termed platelet aggregation assays. However, since assays for each separate platelet property do not always distinguish sharply between the two platelet characteristics, the assays are sometimes classed as the platelet adhesion-aggregation group.

Unfortunately, these tests present formidable standardization problems and their use in the clinical laboratory is correspondingly restricted. Therefore, these techniques must be classified at present as research methods, and specific recommendations for their performance are omitted. Excellent reviews are available.28-20

(20) Toxicological Studies

The appropriate evaluation of unconscious patients may require toxicological examination of body fluids. Samples must be collected as early as possible since the rate of serum clearance for many drugs and metabolites is extremely fast, a fact of particular importance when quantitative determinations of alcohols and other substances are desired. Whenever the cause of unconsciousness is obscure, blood and urine specimens should be obtained immediately and frozen for possible subsequent toxicological analysis. However, careful reconstruction of the circumstances prevailing immediately prior to and at the time the individual is examined has importance equal to that of prompt blood collection.

The history and physical examination should be used as guides in selecting the most reasonable suspects among the several toxic agents tabulated. At times, the history may be unobtainable, questionable, or even deceptive; whenever the cause of unconsciousness is presumed to be drug-induced, gas chromatography has been suggested as a means for rapid diagnosis of sedative intoxication.20

Drugs such as chlordiazepoxide hydrochloride (Librium) do not induce somnolence or unconsciousness unless ingested in large amounts or taken in combination with alcohol or with other nervous system depressants.

Table 1 lists some substances known to cause coma, with the type of specimen best suited for toxicology. References to be consulted for a quick screening test and for a quantitative assay method are provided in the appropriate columns.

URINE

(21) Urinary Protein

The urinary protein reported in routine urinalysis is primarily albumin. Minimal proteinuria can be found after exercise or long periods of standing. When the significance of proteinuria is in question, additional studies will be predicated on the patient's history, physical findings, and results of other laboratory procedures.

The absence of Bence Jones proteinuria does not exclude serum hyperviscosity (see: Blood and Serum Viscosity), but its presence raises the possibility of a hyperviscosity syndrome due to multiple myeloma.

(22) Vanilmandelic Acid (VMA)

Nearly all reported cases of NVD associated with a pheochromocytoma have occurred in patients with fixed rather than with paroxysmal hypertension. A few instances have been reported in which a cerebrovascular episode led to the discovery of pheochromocytoma in patients with previously unrecognized hypertension.

An important test for the diagnosis of pheochromocytoma is the demonstration of excessive catecholamines in blood or urine. Standard quantitative tests for measuring the urinary excretion of catecholamines and their metabolites, metanephrine, normetanephrine, and vanilmandelic acid (VMA) are available. These chemical determinations are very sensitive. Reliable methods are those described by Crout and Pisano and their collaborators.40-41

A single estimation of 24-hour VMA excretion is sufficient to establish the diagnosis of pheochromocytoma in the majority of patients. The test is cheaper, more reliable, and technically less difficult than determinations of
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TABLE 1

Some Pharmacological Substances Inducing Coma, With Bibliographical References to Methods for Determination

<table>
<thead>
<tr>
<th>Drug</th>
<th>Specimen</th>
<th>Screening test</th>
<th>Quantitative method</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alcohols (all)</strong></td>
<td>Blood</td>
<td>31, p 35*</td>
<td>34</td>
</tr>
<tr>
<td>Ethyl</td>
<td></td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Methyl</td>
<td></td>
<td>33*</td>
<td>34</td>
</tr>
<tr>
<td>Isopropyl</td>
<td></td>
<td>34</td>
<td></td>
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<tr>
<td>Carbon monoxide</td>
<td>Blood</td>
<td>31, p 42</td>
<td>31, p 182</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>Blood</td>
<td>31, p 30 or</td>
<td>36</td>
</tr>
<tr>
<td>Bromide</td>
<td>Plasma</td>
<td>32, p 10</td>
<td>31, p 172</td>
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<tr>
<td>Salicylates</td>
<td>Serum</td>
<td>31, p 46</td>
<td>31, p 46</td>
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<tr>
<td>Morphine</td>
<td>Urine</td>
<td>31, p 87</td>
<td>42</td>
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<tr>
<td>Phenothiazines</td>
<td>Urine</td>
<td>31, p 75</td>
<td>41</td>
</tr>
<tr>
<td>Glutethimide (Doriden)</td>
<td>Urine</td>
<td>43</td>
<td>43</td>
</tr>
<tr>
<td>Ethchlorvynol (Placidyl)</td>
<td>Urine</td>
<td>44, 45</td>
<td>44, 45</td>
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<td>Chloral hydrate</td>
<td>Blood</td>
<td>31, p 50</td>
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</tbody>
</table>

*Reference 31, p 35, refers to screening tests for alcohols. The presence of methyl alcohol may be ruled out through the use of a specific test; the presence of isopropyl alcohol may be ruled out by testing the urine for the presence of acetone.

†These substances, per se, are not known to induce unconsciousness. They are not subject to chemical assay in body fluids.

urinary catecholamines. Several screening tests for VMA detect other phenolic acids also; the patient should omit coffee, vanilla, and certain vegetables and fruits, especially bananas, from the diet before urinary VMA determinations are to be done.

Because blood catecholamines are difficult to measure, such determinations are done only in research laboratories. Urinary catecholamines usually are measured by fluorometry following extraction and purification; several methods exist, all of which pose technical problems. Another test, offering the advantage of measuring only physiologically active products, is the biological estimation of circulating or urinary catecholamines. However, it is less sensitive than the chemical methods and is used infrequently.

In summary, initial screening for pheochromocytoma should consist of at least one estimation of 24-hour urinary VMA excretion. Because a tumor may secrete intermittently, the test should be repeated in patients with normal VMA values in whom this diagnosis is still suspected.

(23) Urinary Porphobilinogen

The demonstration of porphobilinogen in urine during the acute phase of an illness is diagnostic of acute intermittent porphyria. A simple screening test for the presence of porphobilinogen is the first step in diagnosis. Quantitative porphobilinogen determinations are usually unnecessary since the screening test does not react to the small quantities present in normal urine. A screening test is always positive when the disease is active, and may revert to negative during the latent period. Excretion of delta-aminolevulinic acid is also increased in the acute illness phase but its presence is more difficult to determine than that of porphobilinogen.

(24) Cyanide–Nitroprusside Test for Homocystinuria

Homocystinuria is a genetically determined disease characterized by mental retardation,
dislocated lenses, connective tissue abnormalities, and thromboembolic lesions, including involvement of arteries supplying the brain. The procedure followed in performing the screening test commonly used is described below.

**CYANIDE-NITROPRUSSIDE TEST**

Cross Screening Test for Urine in Suspected Cases of Homocystinuria

Reagents:
1. Sodium cyanide 10% (fresh, no NaOH),
2. Sodium nitroprusside 1%.

Technique:
1. Place five drops of urine in a white spot plate,
2. Add one drop of 10% sodium cyanide,
3. Wait at least one minute,
4. Add one drop of 1% sodium nitroprusside.

Interpretation: An immediate red-pink color is a positive test, indicating the presence of either cystine or homocystine. A purple color is a negative test, and denotes the presence of ketone bodies.

**CEREBROSPINAL FLUID (CSF)**

Examinations for color and cellular elements are generally the most useful in diagnosing NVD, although once a spinal fluid specimen is obtained, it should be analyzed completely. Determinations of glucose, protein, chloride, enzymes, and other special procedures have less application in NVD, but are of importance in excluding conditions that must be considered in differential diagnoses. Occasionally these special tests aid in detecting disorders, often systemic, which secondarily cause cerebrovascular disease. Many standard works dealing with examination of the CSF are available.

(25) Color

If the CSF is not crystal clear and colorless, it can be subjected to spectrophotometric examination. The pigments commonly found in CSF are oxymoglobin, methemoglobin, bilirubin and proteins. CSF pigment analysis for diagnostic purposes is now uncommon because of the increasing utilization of angiography. While considerable information is provided by a single random specimen, much more data generally can be obtained from serial observations on the same patient. It is sometimes possible to distinguish pure subarachnoid hemorrhages from those in which bleeding has occurred within the neural parenchyma.

Spinal fluid may be colored in the absence of either icterus or intracranial or intraspinal bleeding, often in association with a high CSF protein content and usually due to a partial or complete blockage of the CSF pathway. The exact nature of the pigment in such cases is not clear.

Xanthochromia may be seen very early in traumatic lumbar punctures (see: Section on Special Procedures and Equipment in the Diagnosis and Management of Stroke), if blood contamination of the CSF is heavy. In general, there is relatively little lysis of red cells during the first two to four hours following a traumatic tap (see: CSF cells). Rarely, other substances may impart color to the spinal fluid. Among these are a pigmented chemical used in preparing the skin for lumbar puncture, carotene, and melanin in patients with cerebral and meningeal melanomatosis.

(26) CSF Cells

The cells to be identified in the CSF are erythrocytes, leukocytes, and those of neoplastic origin. Although erythrocyte crenation was formerly considered valuable for differentiating traumatic lumbar puncture from nontraumatic puncture and from other conditions giving rise to blood in the CSF, this finding is now considered of little value. In nontraumatic taps, the color intensity of serially collected specimens of the bloody CSF generally does not change, and no clot forms. As noted above, xanthochromia is absent in the blood from an acutely traumatic tap, but appears after several hours regardless of the bleeding source.

An abundance of leukocytes suggests either infection or meningeal leukemia. Appropriate cytological techniques may disclose neoplastic cells in many patients with metastatic malignancies (and a considerably smaller percentage of patients with primary malignancies) which may be confused with NVD syndromes.

(27) CSF Glucose

The CSF glucose level is rarely affected by NVD in the absence of massive subarachnoid hemorrhage. Its chief diagnostic value lies in detecting disorders which mimic NVD, particularly infections. CSF glucose may be lowered
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also in patients after significant subarachnoid hemorrhage without superimposed infection. Several days may elapse between the onset of hemorrhage and appearance of the hypoglycorrhachia. Blood and CSF glucose levels always should be determined simultaneously; the CSF glucose normally is approximately two-thirds the blood glucose value.

CSF lactate concentration and its relationship to CSF glucose and protein have been discussed recently; CSF lactate elevation has been reported in patients with NVD as well as in those with bacterial and viral meningitis, late-onset epilepsy, cervical spondylosis, and secondary carcinoma.

(28) CSF Protein
Slight elevations of spinal fluid proteins, to levels from 50 mg % to 100 mg %, are often encountered in patients with recent NVD. Substantially greater elevations may be found in a few patients with NVD, especially those with massive cerebral infarction and dural sinus thrombosis. Elevated proteins may impart color to the spinal fluid (see: CSF Color). Determination of CSF protein is of some value in excluding conditions resembling NVD, such as neoplasms and demyelinating disorders. Electrophoretic fractionation may assist in differential diagnosis.

(29) CSF Enzymes
Three enzymes have been studied in the CSF: glutamic oxalacetic transaminase (GOT), lactic dehydrogenase (LDH) and creatinine phosphokinase (CPK). These tests have been advocated as helpful in the differential diagnosis between NVD and brain neoplasms, but controversy still surrounds the significance of CSF enzymes in cerebrovascular disorders. Elevations in the levels of these enzymes are related in some way, not necessarily quantitatively, to the presence of a significant amount of necrotic neural parenchyma. Determinations of the serum enzymes must be made concurrently. Serum enzyme elevations occur less frequently in patients with NVD than in those with nonneural disorders (e.g., acute myocardial infarction and certain myopathies). When the CSF is bloody, a high spinal fluid CPK is the most useful indicator of neural tissue necrosis because concentration of this enzyme is low in red blood cells.

(30) CSF Gases (P_{O2} and P_{CO2}) and CSF pH
The interpretation of changes in CSF pH, P_{O2}, and P_{CO2} is uncertain, not only because factors controlling their regulation are not completely understood, but also because of difficulties in measuring them accurately. Alterations in CSF pH and gases in patients with systemic acidosis, trauma, and subarachnoid hemorrhage have been recorded. With subarachnoid hemorrhage, the CSF pH is generally increased and the P_{O2} decreased. While changes in CSF pH have been reported to affect cerebral blood flow, especially in experimental animals, the roles of CSF pH, P_{CO2}, and P_{O2}, measurements in the diagnosis and prognosis of human NVD are unclear. Hence their clinical value, at least on a routine basis, has not been established.

Tissue

(31) Arterial
The major indication for examining arteries by biopsy techniques is to diagnose cranial arteritis (giant-cell arteritis, temporal arteritis) and other arteritides, particularly when the temporal arteries are affected.

Atherosclerotic plaques and arterial segments should be submitted as surgical pathology specimens in the course of reconstructive vascular surgery, for example, carotid endarterectomy. Valuable correlative information can be obtained from such specimens if submitted intact and specially processed for the study of ulceration and thrombosis.

(32) Muscle
Muscle biopsy, although of limited use in the evaluation of patients with NVD, can be helpful in studying the vasculature. Small-vessel lesions are reported in a number of systemic conditions which may be associated with NVD, such as diabetes mellitus, systemic atheroembolism and the inflammatory arteritides.

For evaluating muscle biopsy, the proper technique of obtaining material is extremely important to avoid artifacts and to provide adequate amounts of tissue for study. These precautions include not only the careful selection of biopsy sites, but also technical matters including the use of isometric clamps and proper fixatives, such as Heidenhain's susa.
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Peripheral nerve biopsy for the differential diagnosis of NVD has little application except as it may detect angiitides (collagen diseases) of various types affecting the vasa nervorum.

Cerebral biopsy for diagnostic purposes has only limited application in the study of NVD. Occasionally vascular disease is encountered in biopsies performed for the diagnosis of obscure cerebral disorders. At present, cerebral biopsy for diagnosis alone is seldom recommended. The technique should be employed only in those centers prepared to utilize the material fully for investigative purposes. Additional details about the indications, techniques, complications, and interpretation of cerebral biopsies, as well as a review of the subject, are contained in recent publications.

Evacuated Hematoma

Hematomas from surgical or autopsy sources should be examined macroscopically and microscopically, particularly in the detection of some vascular malformations (cryptic angioma) and in the occasional occurrence of massive hemorrhage in a neoplasm. Details of a method sometimes helpful in evaluating evacuated hematomas are given in a recent publication.

Autopsy

The two essential elements contributing to an adequate examination of the thoracic, abdominal, and limb structures at autopsy are: (1) that a well-trained anatomical pathologist be available, and (2) that he be provided with complete clinical information so that he knows the specific questions to be raised and answered by his examination.

The necropsy always includes weights of the viscera and a description and often photographic documentation of all significant lesions. Depending on the case under investigation, certain pertinent negative findings should be included in the description. Tissue samples from all viscera should be fixed for possible histological study. In addition to preserving specimens from the major viscera, blocks should be taken at several sites from the lymph nodes, skeletal muscle, bone marrow, and peripheral nerves. Microscopic examination is performed to confirm impressions gained during the dissection or to detect lesions not evident on gross examination. Unfortunately, the number of histological slides prepared and examined is not necessarily indicative of the adequacy or thoroughness of an autopsy.

Assessment of the extent and severity of atherosclerosis is a major problem for the pathologist. Another problem related to atherosclerosis, as well as to other obstructive angiopathies, is that of determining the patency of vessels and their relationship to parenchymal lesions. Description of the vessels is valuable for clinicopathological correlation when it includes: (1) the precise location of lesions causing 75% or more luminal obstruction, (2) the location and approximate number of plaques causing lesser degrees of obstruction, and (3) the precise location of plaques showing thrombosis, ulceration, hemorrhage, and/or calcification.

Special modifications of dissection techniques pertinent to NVD are noted in the sections of this report devoted to the intracranial and extracranial and intraspinal and extraspinal vessels of the brain and spinal cord.

Another question that may be directed to the pathologist concerns the vascular disease case in which a discrepancy existed between the angiographic and clinical findings. Such patients sometimes have been diagnosed as having "small vessel disease," which is neither a single clinical nor a pathological entity. Methods for documenting this possible disorder at autopsy are not standardized.

"Small vessel disease" in the heart may refer either to inadequate collateral channels for the major extramural coronary arteries or to atrophic changes in the myocardium, particularly the posterior papillary muscle of the mitral valve, presumably caused by stenosing lesions of intramyocardial arteries. Although it is possible to visualize collateral channels with postmortem angiography, judgment of their adequacy is a subjective interpretation influenced by the clinical history. "Small vessel disease" involving the intramyocardial arteries probably is best detected by the presence of atrophic changes in the posterior papillary muscle. Whether the vascular changes observed in the atrophic muscle are the cause or the effect of the atrophy is not clear. Stenosing lesions in the arteries serving nodal tissue of the heart may or may not cause...
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clinical disease. A documented conduction disturbance is the only way of estimating whether such lesions were of clinical significance.

Marked basement membrane thickening about capillaries, especially the dermal, also has been referred to as "small vessel disease." It has been reported in cases of diabetes mellitus and of the prediabetic state. Capillary basement membranes vary in thickness in different anatomical sites and with age. These facts make it difficult in many instances to state whether the observed changes are pathological. Capillary basement membranes are best evaluated by electron microscopy, a technique unavailable in many laboratories.

(37) Intracranial-extracranial and Intraspinal-extra-
spinal Vessels
The central nervous system arterial supply extends from the endocardium of the left atrial and ventricular cavities to the parenchymatous capillaries in the brain and spinal cord.

A topographical subdivision of the arterial system follows:

Arteries of Brain:
1. Extracranial segment: left atrium, left cardiac ventricle, left cardiac valves, aortic arch, brachiocephalic (innominate) artery, subclavian, vertebral, common carotid, cervical internal carotid, and external carotid arteries;
2. Intracranial segments:
   a. Intracranial-extracerebral: vertebral arteries, basal artery, internal carotid, anterior and posterior communicating, anterior, middle and posterior cerebral, ophthalmic, and cerebellar arteries;
   b. Intracerebral (parenchymal): small perforating arteries, arterioles, and capillaries;
   c. Intraventricular: choroid plexus.

Arteries of Spinal Cord:
1. Extraspinal segment: thoracic aorta and intercostal arteries;
2. Intraspinal segment:
   a. Intraspinal-extraparenchymal (leptomeningeal): anterior median spinal artery and its branches, posterior spinal plexus;
   b. Intraspinal-parenchymal: arterioles and capillaries.

Veins of Central Nervous System:
The intracranial portion of the venous system consists of two major tributaries:
1. External cerebral venous system or superficial hemispheric veins that drain into the superior sagittal sinus and other dural venous sinuses,
2. Internal cerebral veins and their tributaries, Galenic vein, as well as infratentorial veins.

Details of the arterial and venous anatomy of the brain and spinal cord may be found in several publications.72"108-107

Interpretation of Vascular Pathology:
The evaluation of all vessels supplying the nervous system in the body of every patient dying with neurovascular disease is unrealistic and impossible. Again it is emphasized that specific questions must be posed before the autopsy, so that a correlative evaluation of the neural vasculature may be done. For this reason it is necessary that the pathologist be thoroughly familiar with the clinical, laboratory, and radiological data for each patient to be autopsied.

When occlusive vascular disease of the brain has been demonstrated or suspected clinically, evaluation of the extracranial vasculature, especially the arteries, is imperative. Decalcification of arterial segments is often necessary before they can be sectioned. For methods of dissecting the heart, aortic arch, and carotid-vertebral system en bloc, see pertinent references.108-109

Methods of evaluation include:
1. Perfusion of the extracranial arteries to demonstrate patency;
2. Postmortem angiography: vascular filling often is incomplete or excessive and interpretation difficult; postmortem angiography has been valuable in specific investigations, but not as a routine procedure;
3. Naked-eye inspection of the intimal surface of longitudinally opened extracranial arteries, with or without the use of dyes such as Sudan IV;109
4. Microscopic examination of vascular segments at different levels; this may include frozen sections and the application of fat soluble dyes (Oil Red O, Sudan IV) and, in paraffin-embedded material, the hematoxylin-eosin and elastic fiber stains;
5. Additional selected histochemical methods may be considered in some cases.

When hemorrhagic intracranial disease has been demonstrated clinically or at the time of brain removal, a careful search for arterial aneurysm or vascular malformation is necessary.110

The cause of epidural or subdural hemorrhage may be determined by careful removal of the dura mater and evaluation of the meningeal arteries and intracranial venous system.

Brain and Spinal Cord
Numerous books and monographs deal with autopsy technique and include special sections devoted to the brain and spinal cord. Publications specifically dealing with the nervous system, covering problems of technique in detail, and containing useful bibliographical reviews, are those of Earle111 and Romanul.112 Certain procedural points applicable to NVD require emphasis.

Removal of the brain in many pathology laboratories is considered a simple matter and is assigned to a nonmedical assistant. Many autopsy assistants who remove brains, although technically competent, lack sufficient skill to avoid damaging the specimen. Furthermore, certain lesions require special dissection techniques which should be performed only by the pathologist. Some deviation from the current ritualism of the autopsy is necessary in dealing with disease of the nervous system. In many cases with neurological lesions, particularly NVD, the pathologist, not his assistant, should remove the brain and spinal cord, attending particularly to the in situ relationships. The pathologist is responsible also for ensuring adequate fixation of the nervous system.

Dissection of the brain is covered adequately in references,111,112 but certain essential points should be stressed. No one method of dissection is applicable to all specimens. As in all other matters relating to the necropsy, a knowledge of the pertinent clinical findings is necessary to decide upon the best dissection technique. Generally, coronal sections through the cerebral hemispheres at one-centimeter intervals, and transverse sections through the brain stem and cerebellum at approximately five-millimeter intervals, will suffice. In special instances, horizontal or parasagittal sections of the cerebral hemispheres may be preferable.

The most precise dissection and preparation methods should be used at all times.

Good general rules for the selection of blocks for microscopy can be found in the monograph by Earle.111 In cases of NVD, special attention should be paid not only to the large vessels at the base of the brain, but also to the parenchymal and small leptomeningeal arteries and veins. Care should be taken in the course of removing sections for microscopy to avoid stripping away the leptomeninges and blood vessels.

Removal of the spinal cord is a problem in many laboratories, particularly since some pathologists seldom see or perform the various methods for removal of the spinal cord, which may be summarized as follows:

1. The least satisfactory method is by use of the Lindsay extractor which is passed through the foramen magnum; the spinal cord is removed intradurally after the roots on both sides have been severed by the extractor. Numerous artifacts are often produced in the spinal cord. In addition, the spinal cord may not be removable at all in cases of severe kyphoscoliosis or osteoarthritis. Also, when this method is used, visualization of the dura mater or the extradural tissues is impossible.

2. The second method is posterior removal of the cord. This is satisfactory particularly if one wishes to visualize the dorsal extradural tissues and the relationship of the spinal cord to the intervertebral disks, or if the high cervical spinal cord must be exposed and removed with great care, as in cases with high cervical tumors or those in which high cervical chordotomy has been done. Disadvantages include additional cutaneous incisions and difficulty in obtaining numerous dorsal root ganglia.

3. The third method is anterior removal, which has several advantages, among them the following:

   a. The spinal cord can be removed without making any additional incisions.

   b. Large numbers of dorsal root ganglia may be obtained.

   c. With proper removal of the cervical spine followed by extraction of the cervical spinal block, the intra-osseous portions of the vertebral arteries in the neck are easily exposed and removed. Recent discussions of removal of the spinal cord can be found in several publications.113,114
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Dissection of the spinal cord usually consists of cross sections at all major segmental levels. It is important to establish with great accuracy the segmental level from which one removes sections for microscopy. In rare instances, longitudinal sections may be indicated.

Brain and spinal cord sections may be used for teaching purposes, consultations, and photographic documentation. Storage of representative material is necessary for varying lengths of time.

Normal Values*

**Blood, plasma, or serum**

| Hemoglobin | Male: 13 to 16 gm/100 ml |
| Male: 13 to 16 gm/100 ml |
| Female: 12 to 15 gm/100 ml |

Hemoglobin studies:
- Electrophoresis for abnormal hemoglobin
  - Electrophoresis for A2 hemoglobin
  - Fetal hemoglobin (alkali-resistant)
  - Methemoglobin and sulhemoglobin
  - Serum hemoglobin
  - Thermolabile hemoglobin
- Hematocrit
  - 40% to 46%
- Leukocyte count
  - 4,800 to 10,800/cu mm
- Platelet count
  - 200,000 to 350,000/cu mm
- Erythrocyte sedimentation rate (ESR): Wintrobe method (screening)
  - Less than 20 mm in 1 hr
- Fasting sugar (FBS)
  - 0.15 to 0.35 gm/100 ml
- Two-hour postprandial sugar (PPBS)
  - 3.0 to 7.0 mg/100 ml
- Urea nitrogen (BUN)
  - 136 to 145 mEq/liter
- Creatinine
  - 3.5 to 5.0 mEq/liter
- Cholesterol
  - 4.5 to 5.5 mEq/liter
- Triglycerides
  - 3.0 to 4.5 mg/100 ml
- Prothrombin time
  - 0.7 to 1.5 mg/100 ml
- Partial thromboplastin time (activated)
  - 0.15 to 0.35 gm/100 ml
- Fibrinogen
  - 3.0 to 7.0 mg/100 ml
- Sodium
  - 136 to 145 mEq/liter
- Potassium
  - 3.5 to 5.0 mEq/liter
- Calcium
  - 4.5 to 5.5 mEq/liter
- Phosphorus (inorganic)
  - 3.0 to 4.5 mg/100 ml
- Total serum protein
  - 6.0 to 8.0 gm/100 ml
- Albumin
  - 4.0 to 5.0 gm/100 ml
- Globulin
  - 2.0 to 3.0 gm/100 ml
- Serum protein paper electrophoresis
  - Percent of total protein

*These values are presented for guidance only. They have been assembled from a variety of reference sources, plus the laboratory experience of study group members and their consultants. Opinions differ about certain values, and local conditions may introduce important variations. Therefore, whenever the symbol "t" appears after, or in place of, a value, the local laboratory and clinical pathologist should be consulted on matters of technique, range of values, and interpretation.
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Globulin:
- Alpha
- Alpha₂
- Beta
- Gamma

Thyroid function tests
- Thyroxine T-4
  - Total
  - Free

Bilirubin (van den Bergh test)

Serum viscosity

Gases
- Oxygen saturation (arterial)
- Pao₂
- Paco₂
- Pvo₂
- CO₂
- pH

Platelet adhesion and aggregation studies

Toxicological studies for the comatose patient
Alcohols:
- Methanol
- Isopropyl
- Ethanol

Carbon monoxide
Barbiturates

Glutethimide (Doriden)
Bromide
Salicylate
Therapeutic
Toxic

Morphine
Phenothiazines
Chloral hydrate

Urine
- Specific gravity
- Sugar:
  - Qualitative glucose
  - Quantitative glucose

4.2% to 7.2%
6.8% to 12.0%
9.3% to 15.0%
13.0% to 23.0%
4 to 11 μg/100 ml
0.8 to 2.4 ng/100 ml
1 min: 0.4 mg/100 ml
Direct: 0.4 mg/100 ml
Total: 0.7 mg/100 ml
Indirect is total minus direct
1.4 to 1.8 (expressed as the relative viscosity of serum compared to water)
†
96% to 100%
35 to 45 mm Hg
95 to 100 mm Hg
34 to 50 mm Hg
25 to 40 mm Hg
(40% to 70%)
21 to 31 millimol/liter
7.35 to 7.45
†

None
None
0.3% to 0.4%, marked intoxication; 0.4% to 0.5%, alcohol stupor; 0.5% or over, alcoholic coma
Symptoms with over 20% saturation
None
Coma level: phenobarbital, approximately 11 mg/100 ml; others, 2 to 4 mg/100 ml
None
None
Toxic level: 17 mEq/liter (150 mg/100 ml)
None
20 to 25 mg/100 ml; 35 to 40 mg/ml to age 10 yr
Over 30 mg/100 ml; over 20 mg/100 ml after age 60 yr
None
None
None

1.003 to 1.028
None
Less than 0.3 gm/24 hr
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Identification of reducing substances
- Fructose
- Pentose
- Ketone bodies
- Protein (qualitative)
- Protein (quantitative)
- Sediment microscopy
- 24 hour vanilmandelic acid (VMA)
- Porphobilinogen
- Cyanide-nitroprusside test for homocystinuria

Cerebrospinal fluid (CSF)
- Color
- Cell count
- Glucose
- Protein
  - Lumbar
  - Cisternal
  - Ventricular
- Electrophoresis
- Gamma globulin

Recommendations of the Study Group

1. Since laboratory examinations have assumed an increasingly complex and costly role in the diagnosis and management of neurovascular disease (stroke), it is necessary for the clinical physician to become familiar with the availability, potential, and limitations of laboratory procedures.

2. The physician should have access to laboratory facilities capable of providing the high-quality services required for total care of the patient, not merely those aspects of an illness related to neurovascular disease (stroke).

3. The physician should also have access to consultants in pathology and laboratory medicine for assistance in certain complicated cases.

4. It is also the responsibility of the practicing physician to make a judicious selection of laboratory tests, to ensure the proper collection of specimens and to secure autopsies on patients who die with neurovascular disease (stroke) and its complications, so that information of benefit to other patients may be obtained.

5. It is likewise the responsibility of pathologists to perform biopsy examinations and autopsies in the most skilful manner possible in cases of neurovascular disease (stroke). More enthusiasm, imagination, and flexibility, and less ritualism than now exist in most departments of pathology are necessary to revive superior autopsy studies of vascular disease of the nervous system.

6. Hospitals must provide adequate salaries, space, and equipment to maintain high-quality laboratories not only for clinical pathology, but for pathological anatomy (surgical pathology and the autopsy) as well.

7. Hospitals, medical schools, and departments of pathology should encourage teaching related to neurovascular disease and its laboratory assessment not only for medical students, but also for resident physicians and practitioners.

8. Many aspects of neurovascular disease require continued investigation or research including the standardization, range of values, applicability, and pitfalls of many laboratory tests. Research is also needed to assess accurately the value of automated laboratory procedures.

Special research activity should be directed toward:

None
None
None
None
Less than 0.1 gm/24 hr
1 to 2 rbc, wbc, epithelial cell per high-power field; occasional hyaline cast/hpf
Up to 9 mg/24 hr
None
Negative
Clear, colorless
0 to 5 mononuclear cells/cu mm
50 to 75 mg/100 ml
15 to 50 mg/100 ml
10 to 25 mg/100 ml
5 to 15 mg/100 ml
80% albumin
6% to 10% of total protein
a. Atherosclerosis and its complications,
b. Genetic and environmental factors in neurovascular disease,
c. Coagulation and bleeding mechanisms,
d. The role of fibrin-platelet and atheromatous emboli in TIA,
e. Reversible phases of neural ischemia,
f. Mechanisms of hemorrhage in intracranial arterial aneurysms and vascular malformations,
g. Mechanism of hypertensive intracerebral hemorrhage,
h. Cerebral edema and pathophysiology of the cerebrospinal fluid.

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Subjects

Vanilmandelic acid
Hemoglobin
Toxicology
Blood Gases and pH
Biochemistry
Lipid Chemistry
Hematology
Biopsy
Autopsy
Biochemistry
Lipid Chemistry
Thyroid Function
Cerebrospinal fluid
Neuropathology
Biopsy
Autopsy

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73. Tourtellotte WW: Cerebrospinal fluid examination in meningoencephalitis. Mod Treatm 4: 879-897, 1967


97. Anderson WR, Richards AM: Evaluation of lower extremity muscle biopsies in the...
111. Earle KM: Examination of the brain (Necropsy Technique). American Registry of Pathology, Armed Forces Institute of Pathology, Washington, D. C., 1966