

An Analysis of Diagnostic Reasoning

I. The Domains and Disorders of Clinical Macrobiology¹

ALVAN R. FEINSTEIN²

Eastern Research Support Center and the Department of Medicine, West Haven Veterans Administration Hospital, and the Department of Medicine and Epidemiology, Yale University School of Medicine, New Haven, Connecticut

Received November 28, 1972

Diagnostic reasoning in modern medicine is a process of converting observed evidence into the names of diseases. The *evidence* consists of data obtained from examining a patient and substances derived from the patient; the *diseases* are conceptual medical entities that identify or explain abnormalities in the observed evidence.

The procedures of diagnosis have not always been the same from one era of medicine to the next. The "input" evidence has been altered by changes in technology, and the "output" nomenclature has been changed by new intellectual concepts of disease. An example of change due to new types of technologic evidence is the identification of *pulmonary tuberculosis*. This diagnosis, which once depended exclusively on symptoms and physical signs, will today require suitable microbial and roentgenographic confirmation. An example of change due to new concepts of disease is the diagnostic designation of *dropsy*. This designation, which might formerly be applied to patients with peripheral edema, would now be replaced by some other diagnostic term, such as *congestive heart failure*.

During the past century both ends of the diagnostic process have received many alterations, but the internal rational pathway that connects input to output has retained the same general purpose and format. The purpose of the reasoning is to provide satisfactory explanations for the observed evidence; and the format consists of a branching series of logical decisions, each of which produces intermediate conclusions during the progressive transformation of input to output. This branch-

¹This investigation was supported by PHS Grant Number HS 00408 from the National Center for Health Services Research and Development.

²Professor of Medicine and Epidemiology, Yale University School of Medicine, New Haven, Connecticut; Chief, Clinical Biostatistics and Eastern Research Support Center, Veterans Administration Hospital, West Haven, Connecticut.

ing pattern of sequential logic is the rational activity that gives diagnostic reasoning its distinctively clinical character.

Amid diverse recent analyses of the "diagnostic process" (1-11), this distinctively clinical pattern of logic has not been delineated. Knowledgeable clinicians, although familiar with the pattern, seldom attempt to give it a precise description. They generally believe that the logic of the pattern is too complex to be stipulated, and that the rational distinctions are too intuitive or judgmental to be expressed scientifically.

Because this logic has not been articulated in a clinical "language," connoisseurs of statistics and computers have used their own concepts of logic to give diagnosis a new intellectual "syntax." Based on mathematical "grammar" rather than clinical "idioms," these new diagnostic approaches bear no resemblance to conventional forms of clinical reasoning. The new mathematical proposals for diagnostic decisions are often derived from a concept of probability called *Bayes Theorem* (3-4). In the Bayesian approach, the input depends on the patient's symptoms, signs, or other medical data, but there is no logical pathway of reasoning. Instead, a statistical formula is used to calculate, as output, the likelihood that a particular disease is present. The actual performance of a Bayesian calculation is difficult (8, 12, 13) because it depends on quantitative data that are seldom available: the rates with which certain symptoms, signs, and diseases occur in the pertinent population.

Regardless of practical merits, however, the Bayesian strategy provides only the computation of a diagnostic probability. In directly converting input evidence to output diagnoses, the Bayesian procedure ignores the internal path of diagnostic logic. What emerges is a diagnostic name, but not an explanation of clinical evidence. For example, a Bayesian calculation of diagnosis for a patient with dyspnea might provide quantitative probabilities for the likelihoods that the diagnosis is pulmonary emphysema, mitral regurgitation, or cancer of the rectum. But these calculated diagnoses would contain no explanatory indication that the dyspnea is caused, in the first instance, by defective ventilation; in the second instance, by cardiac decompensation; and in the third instance, by cardiac tamponade due to a pericardial effusion secondary to metastatic cancer.

The traditional principles of science require that natural phenomena be explained, not merely labelled. As stated by Claude Bernard, science "consists in finding the relations which connect any phenomenon with its immediate cause" (14). The scientific connections for the relations between symptoms and diseases can be demonstrated only when diagnosis is performed by sequential explanations, not when a single statistical calculation is used for instantaneously converting an "input" symptom to an "output" disease.

My purpose in this series of papers is to demonstrate that diagnosis is a rational activity of clinical medicine, rather than a computational exercise in numerical statistics; and I shall try to describe the branching logic of the diagnostic process. I believe the description will help statisticians, computer scientists, and other non-clinicians to discern intellectual subtleties with which they are not intimately familiar as they join with clinicians in developing the potential of new technology. To make this potential become actual requires adapting statistics and computers to the practical realities of clinical medicine rather than forcing clinical phenomena into Procrustean modifications to fit the theoretical concepts of statistics and computers.

One of the most prominent realities of clinical activities is that diagnostic reasoning may not be aimed at diagnosis alone, and seldom occurs in a direct, continuous sequence. With major clinical problems, the clinician may be interested not in finding a precise diagnostic identification, but in ruling out the possible presence of a disease that can be cured or ameliorated. In many clinical situations, the sequence of purely deductive thoughts may be interrupted by the performance of laboratory tests or by the administration of therapy. The therapy may sometimes be used as a type of diagnostic test or as an end in itself, so that the "diagnostic" process may be terminated without achieving a precise diagnosis if the patient's symptoms have disappeared after the treatment.

The concluding paper of this series will be concerned with some of the many important clinical variations in diagnostic sequences and targets. The first two papers will be devoted to the classical sequence of reasoning that serves as a basis for the diagnostic process. Because this process is performed somewhat differently by each clinician, no single account can be acceptable to all the people who engage in diagnostic activity, and no general formulation can possibly capture all the nuances of different situations and modes of reasoning. I hope that this series of papers will represent a primitive beginning on which to build future growth and improvement.

In this paper, I shall list some of the problems, and define some of the necessary terms and concepts. The definitions deal with the "input" evidence, with the "output" conclusions, and with a group of microbiologic entities, called *domains* and *disorders*, that are intermediate branching points in diagnostic reasoning.

THE "INPUT" AND "OUTPUT" OF DIAGNOSTIC REASONING

Observational Evidence

From direct examination of a patient, a clinician obtains two types of data: demographic and clinical. *Demographic data* describe the patient's environment (place of birth, place of residence, occupation, etc.) and such personal attributes as age, race, and sex. *Clinical data* comprise the patients' history of the symptomatic development of his illness, and the findings (called *signs*) that are noted during physical examination.

In addition to this evidence, a clinician can obtain paraclinical data by examining diverse substances, derived from the patient, with technologic tests that are not part of the ordinary clinical examination. The term *paraclinical data* thus includes the results of such procedures as urinalysis, blood counts, roentgenography, endoscopy, paracentesis, biopsy, cytology, catheterization of various structures, electrocardiography, and the diversity of other modern laboratory tests. Some or many of these paraclinical procedures may be performed "routinely," regardless of the findings obtained at clinical examination, whereas other procedures may be ordered only in response to appropriate "indications."

Diagnostic Terminology

Since the "end-points" of diagnosis are the names of diseases, a knowledge of available concepts and terminology of disease is a pre-requisite to diagnostic reasoning. The classification and nomenclature of disease is a branch of medicine, called *nosology*, that has undergone many changes since antiquity (15). The

changes can best be described by noting the entities that have been regarded as names of disease, as direct evidence of disease, and as causes of disease.

At the time of Hippocrates, disease was considered to be a purely clinical phenomenon. It was observed directly in the patient at the bedside, and was identified directly, according to the observed clinical evidence, with such names as *fever*, *cyanosis*, and *consumption*. In the medical practice of that era, the identification of disease was an act of observation, requiring no diagnostic reasoning. Instead, the process of "diagnosis" consisted of etiologic conjectures about such causes of disease as angry gods or deranged humors.

For many centuries thereafter, clinical phenomena retained their status as entities of disease. Most of the reasoning of the bedside was concerned with choices of treatment, and with diverse speculations about pathogenetic causes of the observed diseases. During the 17th century, Thomas Sydenham founded the discipline of nosology (15) by insisting that diseases were "specific" and not merely "the confused and irregular operations of disordered and debilitated nature." Before that time, the doctors who thought of disease as a clinical entity had regarded each sick person as having his own ailment. Sydenham offered the "ontologic" idea that a disease might have its own identity and a "natural history" that could be observed from its clinical course in patients. He proposed a nosologic classification of diseases into "certain definite species" in a manner similar to that "which we see exhibited by botanists in their description of plants" (15).

Sydenham's successors in the 18th century devised various nosologic schemas for classifying groups of symptoms and signs into "diseases" (16). These 18th century nosologies had no permanent value and have been forgotten today because the "diseases" were selected in a wholly arbitrary manner. Each nosologist created his own collection of "diseases," based on his own beliefs about grouping diverse clinical manifestations together into a clustered entity called a "disease." The names of the clusters were not related predictively to the clinical course and outcome of the "diseases" they identified (13), and morbid anatomy had not yet been investigated well enough to provide morphologic or other "causal" correlations. Having neither prognostic nor etiologic significance, the 18th century nosologies made no enduring contributions to "disease" or to clinical science.

The confusion created by these arbitrary acts of nomenclature prepared the scene for the nosologic revolution, during the 19th century, that completely altered the concepts and names of "disease." The frequent use of necropsy, which had been pioneered by Morgagni and Bichat, began to reveal a gross morbid anatomy that helped explain the clinical manifestations of the bedside. Later on, Virchow and others began using microscopy to demonstrate the many anatomic abnormalities that could not be discerned by naked eye. As these new forms of medical evidence became available, disease was transformed from a clinical to an anatomic entity. The gross and microscopic manifestations of histopathology became regarded as the new "diseases" that accounted for the old abnormalities of clinical *dis-ease*. While histopathologists were delineating these morphologic entities of disease, clinicians were developing such new bedside examining methods as percussion, auscultation, thermometry and sphygmomanometry; and the new forms of clinical data were correlated with the new diseases of histopathology.

By the end of the 19th century, these developments had established the concepts and procedures of *physical diagnosis* in much the same format that we use today: the clinician observes a series of bedside phenomena from which he deduces the name of a disease that is demonstrated in the morgue or under the microscope. As a result of this transition in concepts of disease, the clinician's diagnostic activity became a process of reasoning rather than a description of observations. Before these changes, a clinician did not need to use reasoning to name a disease: he classified the clinical phenomena that he observed in the patient. As disease became an entity of histopathology, the diagnostic process became an act of inferential logic, with clinical evidence as "input" and morphologic names as "output."

With further advances in technology during the late 19th century and thereafter, the morphologic concepts of disease were expanded to include many additional entities: the microbial substances revealed in bacteriology and virology, the functional abnormalities revealed with physiology and biochemistry, and some of the "new" modern abnormalities demonstrated with immunology, electron microscopy, and biophysics.

During these technologic and conceptual changes throughout the centuries, certain names of diseases have been converted from one type of entity to another, whereas other names have persisted because the new nomenclature did not offer satisfactory substitutes (13, 17). Thus, the old *consumption* has become the new *tuberculosis*, *lung cancer*, or other modern diseases; the old *angina pectoris* has become the new *coronary artery disease*; and the old *familial hemolytic jaundice* has become the new *spherocytosis*; but the old *gout*, *diabetes mellitus*, *rheumatic fever*, *measles*, *cerebral palsy*, *coryza*, and *epilepsy* still remain servicable as diagnostic names of modern disease entities. Because of the many alterations and adaptations imposed during different medical eras, our current nomenclature of disease contains a chronologic and intellectual polyglot of diverse diagnostic terms.

Many names of diseases are less than two centuries old, representing abnormalities of morphology (*carcinoma*, *arteriosclerosis*, *cholelithiasis*, *appendicitis*), microbiology (*amebiasis*, *streptococcal infection*), biochemistry (*porphyria*, *phenylketonuria*, *hyperlipemia*), or physiology (*achalasia*, *atrial fibrillation*). The most recent of the "new" diseases are being detected with electron microscopy (*cytomegalic inclusion disease*), immunology (*lymphocytophthisis*), or chromosome analysis (*21-trisomy*). But many ancient veterans of diagnostic nomenclature (*gout*, *measles*) still remain in service, together with the clinical clusters called "syndromes" (*chronic brain syndrome*, *superior vena cava syndrome*). Some diseases still bear the names of physical signs (*erythema multiforme*, *hypertension*) or symptoms (*pruritus ani*, *myasthenia gravis*), and some are cited according to personal habits (*chronic alcoholism*, *narcotic addiction*) or body habitus (*obesity*). A clinical nosography is still the basis for all the behavioral terms used to diagnose psychiatric disorders (*schizophrenia*, *anxiety neurosis*, *passive aggression*, etc.).

In addition to this generic variety of names for disease, nosographers have regularly employed eponyms when the constituent description was too complex or cumbersome for the entity to be cited generically. Some of the current eponyms are about a century old (*Hodgkin's disease*, *Horner's syndrome*, *Von Recklinghausen's disease*) and others are much newer (*Klinefelter's syndrome*, *Reiter's syndrome*, *Franklin's disease*). In some of the newest approaches to nomenclature, the disease is named after the patient in whom it was first detected (*Christmas disease*, *Hageman factor*), or the city in which the discovery occurred (*Philadelphia chromosome*).

Since this potpourri of disease nomenclature was developed chronologically rather than logically, at least four major intellectual barriers will thwart any attempts to depict the diagnostic process in a simplistic scheme based on a single sequence of logic or a single statistical formula.

Intellectual Barriers to Simplified Schemes of Diagnosis

The altered spectrum of an altered disease. No matter what scheme of reasoning is developed to attain a particular diagnosis, the scheme will immediately lose its validity if the name of the disease is altered from a clinical to a morphologic designation, or from a morphologic to a biochemical term, because such changes will immediately change the spectrum of patients who have the disease (13). For example, the disease *angina pectoris* is defined by certain symptoms, but *coronary artery disease* can often occur without producing symptoms; similarly, *spherocytosis* can be present without the jaundice of *familial hemolytic jaundice*, and infection with *poliomyelitis virus* can occur without any of the neurologic manifestations of *infan-*

tile paralysis. Consequently, when disease *A* becomes converted to disease *B*, any statistical data based on clinical or other manifestations of disease *A* will no longer be valid for the new clinical spectrum of *B*; and any clinical sequence of logic leading to a diagnosis of *A* must be altered to account for the new manifestations or lack of manifestations associated with *B*.

The choice of pathognomonic evidence. One of the main reasons for changing the names of diseases from clinical to paraclinical entities has been the availability of technologic evidence that is more specific, objective, and preservable than clinical symptoms or signs. Moreover, the same symptoms and signs can often be explained by several different diseases, each with its own pathognomonic evidence. Consequently, many traditional concepts of purely physical diagnosis have become archaic, and a clinician who seeks diagnostic precision today will often rely on an appropriate technologic test rather than on diagnostic reasoning alone. For example, the combination of hemoptysis and pulmonary rales that may have led to a diagnosis of tuberculosis 50 years ago will often be "worked-up" today with cultures for tubercle bacilli, cytologic smears for lung cancer, bronchograms for bronchiectasis, or cardiac examinations for mitral stenosis.

For a modern diagnostician who knows how and when to order the appropriate specific tests, any statistical scheme of diagnostic probabilities based only on clinical symptoms and signs will inevitably yield results that are too imprecise. Conversely, if the critical pathognomonic test is obtained in advance of any mathematical diagnostic calculations, the calculations become unnecessary. Thus, if a paraclinical specimen provides unequivocal evidence of lung cancer, the patient has lung cancer, regardless of the clinician's logic or the statistician's probabilities. Similarly, if a suitable test demonstrates unequivocal evidence of gall stones, porphyria, brucellosis, hyperthyroidism, or lupus erythematosus, these diseases will usually be diagnosed regardless of the associated clinical manifestations.

Thus, as the technologic tests have become more widespread, safe, and readily applicable, clinicians have begun to use the results as diagnostic evidence; and the clinical "end-point" of diagnostic reasoning has often been the selection of a diagnostic test, rather than the selection of a diagnostic name.

The choice of a diagnostic end-point. As diagnostic nomenclature has progressively changed from clinical to morphologic to etiologic entities, the clinician may have great difficulty deciding when a diagnostic "end-point" has been reached. Should he stop when he has named an entity that accounts for the main clinical manifestations, or should his diagnosis extend to each entity that might be regarded as causal for the one he has just cited? Thus, is *myocardial infarction* a satisfactory diagnostic "end-point" for an appropriate type of chest pain? Or should the array of diagnostic terms extend onward sequentially from *myocardial infarction* to *coronary thrombosis*, *coronary atherosclerosis*, *hyperlipemia*, *nutritional imbalance*, and *neurotic personality*? The problem of where to stop confronts any design of a logical sequence for diagnosis, and is insurmountable in any statistical schemes of probability.

The concurrence of diseases. The last main barrier to any simplistic concept of the diagnostic process is the frequent co-existence of multiple diseases in a single patient. The discovery of such polypathic patients has become an increasingly common event in modern medicine, particularly as more and more patients receive the screening tests and technologic "work-ups" that provide evidence of multiple diseases. If the diseases have no symptomatic or anatomic overlap, their different

clinical contributions can readily be distinguished. Thus, difficulty in hearing can be ascribed to otosclerosis, and pedal pruritus can be attributed to dermatophytosis, without any problems in deciding which disease accounts for which symptom. But many patients have multiple diseases that can overlap in manifestations or location, and that make impossible a specific diagnostic explanation for a specific symptom (18).

The clinician may therefore have no definite way of deciding which disease was responsible for the hemoptysis of a patient who has unequivocal evidence of primary lung cancer, active tuberculosis, and bronchiectasis. Similarly, the clinician may be unable to assign the exact cause of rectal bleeding in a patient who has diverticulosis, hemorrhoids, and rectal cancer. In such circumstances, neither a mathematical calculation of statistical probabilities nor a straightforward scheme of clinical logic will solve the clinician's diagnostic dilemma, and he will plan his further management of the patient on the basis of data that refer to prognosis and therapy, rather than information dealing with diagnosis alone.

THE LOGICAL DIRECTION OF DIAGNOSTIC REASONING

For the reasons just cited, a statistical calculation of diagnostic probabilities will inevitably be too crude for precision in modern problems; a logical sequence of reasoning often cannot provide the specificity of technologic tests; and neither procedure can regularly detect disease in asymptomatic patients or delineate the symptomatically "active" component of multiple diseases. If the diagnostic process merits scientific analysis today, therefore, the analysis should be aimed not just at selecting the name of a disease, but also at helping the clinician choose suitable paraclinical tests from the enormous technologic array that has now become available. The clinician's additional decisions about when to "screen" for asymptomatic disease and how to treat multiple diseases require judgmental concepts of management, not just diagnosis alone.

For the purely diagnostic activities of modern clinicians, a scientifically and pragmatically useful scheme of reasoning is one that can lead, if possible, to the explanation provided by the diagnosis of a specific disease, or, if not possible, to an intermediate point at which further diagnostic tests or therapy can be chosen. Since current Bayesian formulations are based only on the "end-points" of diagnosis, the probabilistic approach cannot discern the intermediate stages of the diagnostic process.

To indicate these stages requires a clinical outline of the successive logical branchings that reflect traditional diagnostic reasoning. For this outline, the diagnostic process can be defined as a sequence that begins with the names of manifestations, and that ends with the names of entities regarded as satisfactory for diagnosis or therapy. A *manifestation* is defined as any item of medical evidence that is regarded as pertinent; the term includes entities that are sometimes called "positive findings," "abnormalities," or "pertinent negatives." (The process of selecting these pertinent manifestations will be described in the next paper of this series (19).) A satisfactory *diagnostic entity* is defined as the name of a condition chosen as the "end-point" in labelling or explaining a manifestation or cluster of manifestations. If there are no manifestations to be accounted for, the diagnostic entity may be expressed in such terms as "normal," "negative," or "healthy." *Diagnostic reasoning* comprises the strategy and tactics of evaluating evidence, selecting manifestations, evaluating the manifestations, ordering adjunctive tests to obtain addi-

tional evidence, evaluating the results of those tests, and ultimately choosing the names of diagnostic entities.

The sequence of diagnostic reasoning follows a rational direction opposite to that used in explaining the process of pathogenesis. In pathogenetic reasoning, the logical direction goes from cause toward effect. An example of such a sequence, showing the possible consequences of a thrombosis of calf veins, is portrayed in Fig. 1. At each step in the reasoning, a causative event is noted, and the arrows point to the effects that may follow. The sequence noted here is incomplete; it does not continue its pathway to cite such possible clinical consequences as fever, limping, jaundice, incapacitation, or death.

In contrast to this order of logic, diagnostic reasoning proceeds in the opposite direction: from effect toward cause. An example of such a sequence is shown in Fig. 2. In this illustration, an attempt is made to explain the causes of a patient's three concomitant manifestations: dysuria, fever, and tenderness in the region of

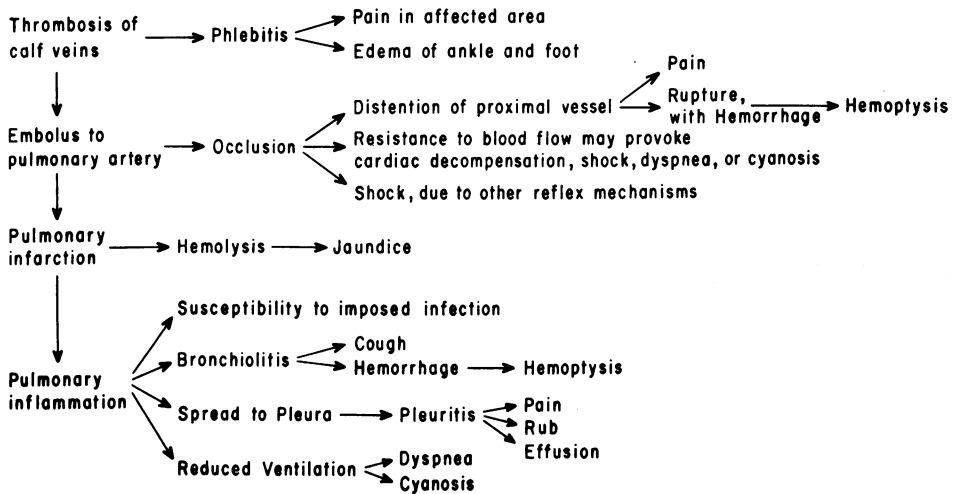


FIG. 1. Consequences of thrombosis of calf veins (for details, see text).

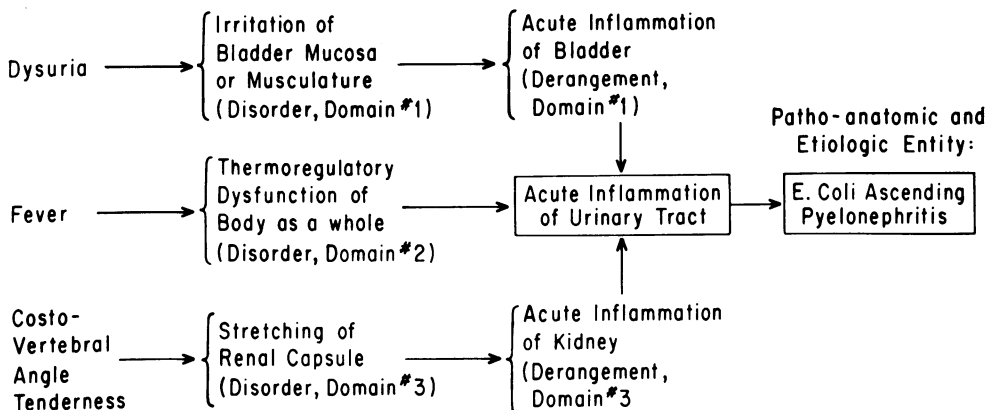


FIG. 2. Diagnostic explanation for the manifestations of dysuria, fever, and costovertebral-angle tenderness. The entities identified as domains, disorders, or derangements are discussed later in the text.

a costovertebral angle. The pathway demonstrates the logical sequence of the reasoning, and the arrows are used here in the logical sense of “implies,” rather than in the chemical sense of “causes.” Each manifestation is attributed to a functional abnormality at a particular site in the body (or in the body as a whole). Each of these abnormalities is then attributed to an underlying abnormality, and the latter abnormality is ultimately ascribed to a particular diagnostic entity. (In this example, a single diagnosis accounts for all the abnormalities.)

This sequential search for entities that are “immediate causes,” each providing an explanation for its antecedent entity, is the intellectual characteristic that distinguishes diagnostic reasoning. In this scientific quest, a clinician constantly makes use of his knowledge of the anatomy and physiology of grossly intact structures, and he constantly thinks about phenomena that cannot be discerned in fragments of tissues, in cells, or in intracellular substances. In the rational pathway of Fig. 2, for example, such functional terms as *stretching* and *irritation*, and such structural terms as *renal capsule*, are strictly entities of macrobiology.

The macrobiology of intact structures is constantly contemplated during diagnostic reasoning, although seldom considered in the molecular microbiology of “basic science.” Diagnostic concepts deal with gross structures and intact functioning systems; “basic science” deals with cells, membranes, and other fragmented models. The reasoning of clinical diagnostic activities proceeds from effect to cause; the reasoning of experimental cellular biology and pathophysiology proceeds from cause to effect.

Although medical students are often exposed to excellent diagnostic reasoning by clinical instructors, the concepts of macrobiology and of other constituents in the diagnostic process may not be formally identified. The instruction is usually based only on direct precept in individual cases, and no general principles have been established. For example, when a series of diagnoses are collected and analyzed (20), the diagnostic tactics may be splendidly illustrated for each particular case, but the sequential strategies are not formally organized and specified as principles suitable for application in a more general approach.

In the absence of a delineated logic, clinicians develop their own diagnostic techniques in an *ad hoc* individualized manner and are then often unable to recall all the intellectual mechanisms that must be discerned and stipulated. Consequently, when asked by medical students—or by statisticians or computer specialists—about the ingredients of the diagnostic process, a clinician may reply that it is a non-descript act of artful judgment. The remainder of this paper is concerned with the basic constituents and sequential reasoning of that judgment.

THE ARCHITECTONICS OF CLINICAL MACROBIOLOGY

Although the end stage of diagnostic reasoning contains the names of various diseases, the initial stages can be classified into architectonic entities that are unique to clinical macrobiology. These entities are a group of *domains*, comprising gross structures and functions of the body, and a group of *disorders*, which represent gross abnormalities in those domains.

Clinical Domains and Foci

A clinical *domain* is a portion of the body that is the structural or functional source of a manifestation. A single domain can be composed of more than one structure or function, and a single structure or function can be a part of many

different domains. Domains can be classified in the four categories of *organ*, *region*, *channel*, and *system*.

Organs. An organ is a discrete gross structure, consisting (usually) of a cover, a distinctive “parenchyma,” an interior “lining,” and certain enclosed vessels and ducts. The stomach, brain, lung, heart and skin are examples of organs; the eye and ear are examples of sensory organs.

Regions. A region is an anatomically defined part of the body, containing more than one organ. The head, chest, mediastinum, abdomen, and pelvis are regions.

Channels. A channel consists of a group of structures or organs connected in a direct anatomic sequence for the functional purpose of transmitting a “flow” from one part of the channel to another. The “flow” can contain solid, liquid, or gaseous substances, and, in the case of the nervous system, neural impulses. Thus, the “respiratory tract” is a channel composed of mouth–nose–pharynx–larynx–trachea–bronchi, and other structures down to the alveoli. The “digestive tract” is a channel that begins at the mouth and extends through pharynx and esophagus to stomach and intestines, ending in the rectum and anus. The “central nervous system” is a channel extending from brain and medulla through the peripheral nerves. Other examples of channels are the “urinary tract,” “biliary tree,” “reproductive tract,” “arterial system” (comprising the aorta and its branches), the “systemic venous system” (comprising all venous branches leading to the heart), and the “portal venous system” (comprising the intra-abdominal veins leading to the liver).

Systems. Unlike the three types of domains just cited, which are defined anatomically according to location and construction, a system is defined physiologically according to its action. A system comprises a group of organs or structures that work collectively in performing certain functions. The participating structures in a system need not have a contiguous anatomic relationship, and the number of structures will depend on the functional role of the system. For example, the cardiopulmonary system, composed of heart and lungs, oxygenates blood; the cardiovascular system, composed of heart and blood vessels, circulates blood; the cardiovascular-pulmonary system circulates oxygenated blood. Examples of other systems are the hematopoietic system (which is responsible for the quantity and components of blood), the endocrine system (which regulates other systems), and the body as a whole (which maintains temperature, physical energy, etc.).

Diagnostic reasoning begins with the decision that a particular manifestation arises in a particular domain. If the domain contains many structures or functions, a *focus* within the domain will next be selected as the particular structure or function responsible for the manifestation. In certain circumstances, the entire domain can be the focus, and vice versa.

Clinical Disorders

A disorder is a gross abnormality in the structure or function of a domain. A disorder of structure is called a *lesion*, and, of function, a *dysfunction*. Disorders can occur in the quantity, quality, or orientation of either a structure or a function.

Lesions.

(1) *Size.* In quantity, the size of a structure can become larger or smaller than normal. A solid structure can become hypertrophic or atrophic; the volume of a hollow structure can become larger by dilatation or distention, or smaller by stenosis, narrowing, compression, or occlusion. The capsule that covers a solid structure

can be stretched. The suffix *-megaly* is often used for describing enlargements of certain structures (such as heart, liver, spleen, and thyroid) but the suffix is not applied consistently. Enlargement of lymph nodes is often called *lymphadenopathy* and no name other than *distention* is generally used for the enlargement of the lumen of thin-walled hollow organs, such as bladder or stomach.

These changes in the size of structures can often be determined by the physical examining techniques of inspection or palpation. Other changes can be observed with endoscopy, with radiography, or inferentially with auscultation (for dilatation of cardiac valves) and percussion (for distention of stomach or bladder).

(2) *Composition*. In quality, the composition of a structure can become abnormal because it is absent, replaced, infiltrated, irritated, consolidated, disrupted, or distorted. The distortions can take such forms as sacculations, aneurysms, perforations, shunts, and fistulae.

(3) *Location*. In orientation, a structure can be pushed, pulled, herniated, prolapsed, involuted, or otherwise displaced from its normal location. Such a change may be caused by a change in an adjacent structure, or by a congenital or acquired anomaly of the structure itself. For example, pulmonary atelectasis or a pneumothorax can cause a shift in the mediastinum; an accident of embryonic development can cause an ectopic breast or spleen, a duplicated bowel, or a situs inversus.

Dysfunctions. The diverse parts of the body have a variety of gross functions. The functions are expressed in such transportational movements as the contraction of skeletal muscles, the circulation of blood, the flow of intestinal contents, and the ventilatory passage of air. Regulatory functions are exemplified by the various exchanges that occur during absorption, secretion, filtration, perfusion, diffusion, hemolysis, and hemostasis. Supply functions occur during the formation, decomposition or alteration of such products as blood cells and chemical substances. Abnormalities in function, which are discussed in greater detail in suitable textbooks of physiology or pathophysiology (21–23) can be classified according to their effects on these acts of transportation, regulation, and supply.

(1) *Amount*. The quantity of a function can be abnormal in rate of movement, balance of exchange, or magnitude of product. Thus, the rate of menstruation, breathing, heartbeat, hemolysis or intestinal passage may be too fast or too slow; and an excess or deficit of a system's balance or creation of a product is reflected in such terms as anemia and polycythemia, leukemia and leukopenia, hyperthyroidism and hypothyroidism. The volumetric flow in a channel can be increased or decreased; and the rates of absorption or secretion in an organ or system can be excessive or inadequate.

(2) *Operation*. In quality, a function can be abnormal in the vigor and regularity of movement, or in the achievement of its product or general regulatory performance. Examples of abnormal movements are cardiac arrhythmias, achalasia, myotonia, metrorrhagia, and spasm of striated muscle. Bence Jones protein and galactosemia are examples of abnormal products, and cardiac or renal decompensation illustrate an abnormal regulatory performance.

(3) *Direction*. The orientation of a function refers to the direction in which a movement is transmitted. With appropriate abnormalities, a "flow" can be obstructed, regurgitated, refluxed, diverted, or reversed.

Interrelation of disorders. Because disorders are both structural and functional, one disorder is often causally associated with another. Thus, a narrowed lumen in the pylorus may cause obstruction to the flow of gastric contents; the gastric

contents may then regurgitate and cause irritation to the esophagus. Dilatation of the mitral valve ring may produce a partial reversal of blood flow, leading to cardiomegaly, and eventually to arrhythmias and cardiac decompensation.

PATHOLOGIC CAUSES OF CLINICAL DISORDERS

Although one disorder can often lead to another, each disorder or array of disorders is attributable to an underlying immediate cause, which may or may not be identifiable in specific terms. Thus, an immediate cause can not always be specified for such disorders as hyperthyroidism, but can usually be found for such disorders as cardiomegaly or congestive heart failure. These underlying causes of disorders can be identified with several sequential degrees of pathologic specificity.

Pathologic Derangements

A derangement is a general pathologic process responsible for a disorder. Such entities as inflammation, infarction, neoplasia, trauma, and congenital and certain biochemical abnormalities are all derangements.

A derangement differs from a disorder in three main ways. Although a disorder can almost always be identified by gross observation, many derangements must be examined microscopically or chemically for the abnormality to be specified precisely. A second distinction is that derangements, in contrast to disorders, are seldom expressed in functional terms because they are identified as either morphologic or biochemical entities. A third distinction is that a single disorder can be caused by several different derangements. Thus, in the previous examples, the disorders of a narrowed pyloric lumen or dilatation of the mitral valve may each be due to such derangements as inflammation, neoplasia, or a congenital anomaly. Like disorders, one derangement is often associated with another. Thus, a zone of tumor or trauma may be surrounded by a zone of inflammation.

As additional illustration for some of these distinctions in nomenclature, consider the manifestation of dysphagia. This symptom can be due to a variety of disorders, including such lesions as an internally narrowed esophageal lumen, external compression of the esophagus, or displacement of the esophagus; the symptom can also arise from such dysfunctions as esophageal spasm or esophageal obstruction. These lesions and dysfunctions can be due to disorders in structures outside the esophagus, or to inflammatory and neoplastic derangements involving the esophagus itself.

Patho-anatomic Entities

After derangements have been identified, diagnostic reasoning may often proceed to the specification of structural entities that are regularly cited as the names of diseases. A *patho-anatomic entity* can be defined as a specific topographic and morphologic abnormality that may lead to derangements and disorders. The following disease names are examples of patho-anatomic entities: epidermoid carcinoma of the upper lobe of the right lung; right pyelonephritis; cholelithiasis; atrial septal defect; rheumatic mitral stenosis; phlebothrombosis; pulmonary emphysema; slipped femoral epiphysis; and placenta previa.

Pathogenetic (or Etiologic) Entities

This last group of diagnostic terms refers to circumstances or agents that can cause, provoke, or predispose to the development of disorders, derangements, or

patho-anatomic entities. Such etiologic entities include microbial, immunologic, and certain biochemical abnormalities, as well as such behavioral or psychic features as improper nutrition and emotional stress.

The esophageal disorders and derangements causing the dysphagia described in previous examples can be due to some of the following patho-anatomic and etiologic entities: scleroderma of the esophagus; epidermoid carcinoma of the esophagus; an esophageal cicatrix after ingestion of lye; compression from metastatic carcinomatous lymphadenopathy in the mediastinum; displacement by a huge left atrium; chronic esophagitis associated with hiatus hernia; and achalasia.

SEQUENTIAL STATIONS IN DIAGNOSTIC REASONING

With these terms and concepts defined, the sequential stations of diagnostic reasoning can now be graphically demonstrated. The sequence is illustrated in Fig. 3, and the discussion that follows is based on the "flow-chart" shown in that figure.

The clinician begins by discerning that the patient has a manifestation for which a diagnostic explanation is to be sought. The manifestation is then referred to a domain and to a focus within the domain, although the focus may sometimes be selected directly. (For example, the manifestation of *difficulty in swallowing* is referred to the domain of the upper gastro-intestinal tract, and then to a focus either in the pharynx or in the esophagus. The manifestation of *pain in the eye* is referred directly to the eye, which is, in this instance, both a domain and a focus.)

The next decision is to choose a disorder at the focus. According to the type of disorder that is chosen, the next step may lead directly to a pathogenetic entity, or through a sequence that goes to a derangement, then to a patho-anatomic entity, and finally to a pathogenetic entity. After the disorder has been chosen, other disorders may be invoked as parallel or sequential stations in the reasoning, and these ancillary disorders may then be the point of departure for the identification of a derangement and the subsequent entities.

In the illustrative examples that follow in Figs. 4–7, the main purpose is to show the sequence of stations in diagnostic reasoning. The intricate reasoning used for the particular decisions made at each station has been deliberately omitted and reserved for subsequent discussion. In Fig. 4, the sequence of diagnostic stations is shown for a patient who has been noted to have the manifestation of pallor. After this manifestation was referred to an erythropoietic focus in the hemic system, the next step in the reasoning for this particular patient led to selection of anemia as a quantitative disorder in the amount of blood. This disorder was then

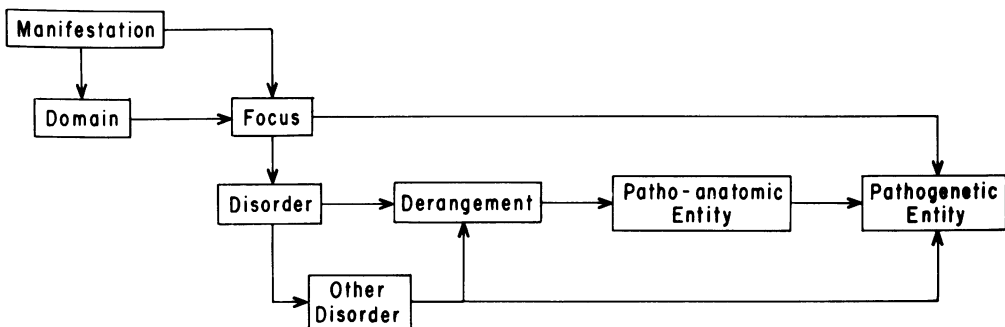


FIG. 3. Sequential stations in the intellectual pathway of diagnostic reasoning.

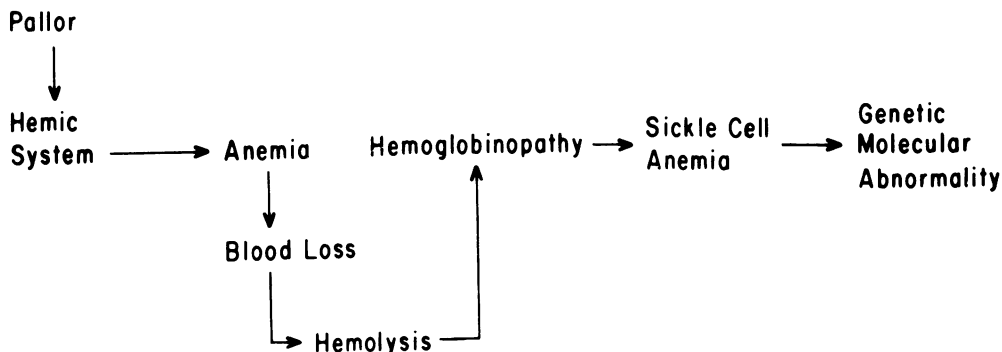


FIG. 4. Sequential stations in diagnostic reasoning for a patient with the manifestation of pallor.

ascribed to an operational disorder—loss of blood—which was attributed to another operational disorder, hemolysis. The hemolysis was then attributed to the derangement of hemoglobinopathy, for which the patho-anatomic entity of sickle cell disease was held responsible. A genetic molecular abnormality was then noted as the etiologic entity. All of these decisions might have been carried out with purely clinical reasoning, but appropriate paraclinical data would have been helpful to confirm the initial conclusions about the disorder of anemia and the subsequent conclusions about hemolysis and sickle cell disease.

Another example of sequential reasoning is shown in Fig. 5. The patient's presenting manifestation is the complaint of unilateral intermittent claudication. The selected domain is the arterial channel to the legs; the focus is a site below the aortic bifurcation; and the disorder is inadequate oxygenation of blood delivered to the leg. This much of the rational sequence is immediately implied by the patient's complaint; the rest of the sequence requires the use of additional clinical data and reasoning. In the instance shown in Fig. 5, this reasoning led to the decision that the inadequate oxygenation was caused by a lesion—a narrowed vascular lumen—and that this lesion was due to a derangement, embolus to the femoral

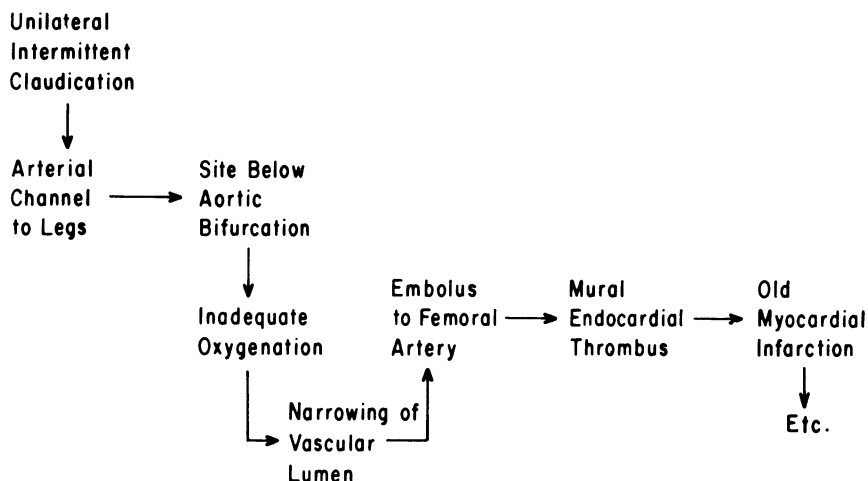


FIG. 5. Sequential stations in diagnostic reasoning for a patient with unilateral intermittent claudication.

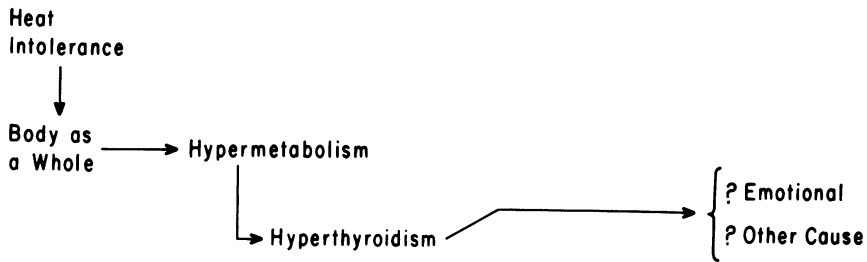


FIG. 6. Sequential stations in diagnostic reasoning for a patient with heat intolerance.

artery. The patho-anatomic source of this derangement was chosen to be a mural endocardial thrombus, and the etiology of the latter entity was attributed to an old myocardial infarction. (A separate path of diagnostic reasoning could then be used to assess the pathogenesis of the myocardial infarction).

A shorter diagnostic pathway is shown in Fig. 6, where the presenting manifestation is heat intolerance, for which the assigned domain is the body as a whole, and the general disorder is hypermetabolism. After further reasoning, the hypermetabolism is ascribed to the endocrine dysfunction of hyperthyroidism, and at this point a diagnostic end-point is reached, unless emotional or other events are to be conjectured as causes of the hyperthyroidism.

The last example to be shown here is in Fig. 7, where the patient's presenting manifestation is peripheral edema, originating in the domain of the cardiovascular system. A decision has been made that the focus is the heart and that the disorder is the dysfunction of congestive heart failure. From the physical finding of a displaced apex beat, a parallel decision has been made that the lesion of cardiomegaly is present. These two disorders are then explained, after appropriate further reasoning, by the derangement of rheumatic heart disease, and the patho-anatomic entity of mitral stenosis. If a further pathogenetic entity is sought for the rheumatic mitral stenosis, an antecedent streptococcal infection can be regarded as an etiologic entity.

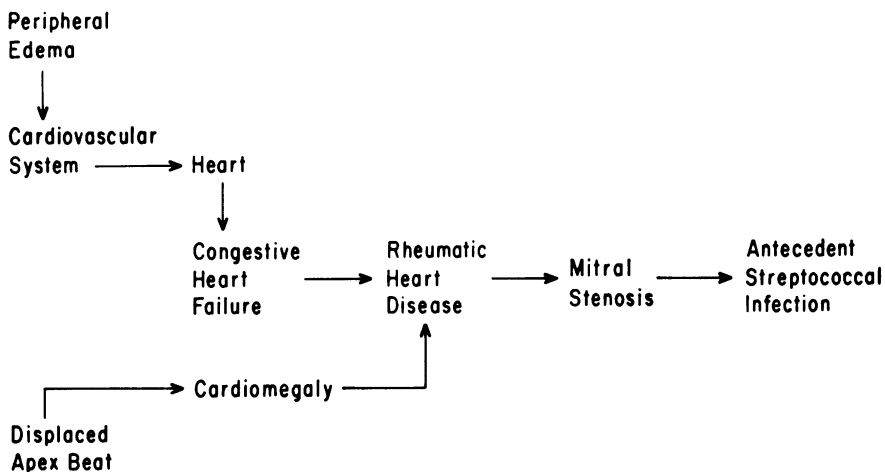


FIG. 7. Sequential stations in diagnostic reasoning for a patient with peripheral edema.

THE DIAGNOSTIC IMPORTANCE OF MACROBIOLOGY

Although domains and disorders are seldom specifically identified in contemporary accounts of the diagnostic process or of differential diagnosis, these entities of clinical macrobiology play a paramount role in diagnostic reasoning. They demarcate the major stations at which the intellectual pathway can change directions, reach conclusions, or make transfers to other modalities of thought, evidence, or action.

The Directional Referral of Domains

As an inevitable precursor of all the ensuing decisions, the choice of a domain is the first major step in diagnostic reasoning, and it establishes the subsequent direction to be followed. To choose a domain correctly, the clinician must be familiar not so much with biochemistry or microbiology, as with gross anatomy and systemic physiology. Without suitable attention to all the gross structural and functional distinctions that can account for the observed manifestations, a clinician may limit the list of candidate domains to the most obvious choices, thus creating errors of omission (24) in the diagnostic reasoning.

One of the hallmarks of a wise diagnostician is the broad scope he reviews before choosing a domain. This broad review is needed not only to include all the possible candidates, but also to detect the situations in which a manifestation in one domain is caused by a disorder at a site quite different from the most obvious choice. Such situations can arise during several types of macrobiologic "referral".

Diaphragmatic distortion. Because of the dome-like spatial configuration of the diaphragm and because of the way its two sides are innervated, certain intrathoracic abnormalities may appear to be manifested in the abdomen, and vice versa. For example, the pain of a splenic infarct may seem to be in the lower left chest, or the pain of a myocardial infarction may appear localized in the epigastrium. In a patient with a hepatic abscess, the increased dullness to percussion above the diaphragm may suggest a pulmonary lesion, and in a patient with emphysema, a cardiac impulse displaced in the epigastrium may suggest an abnormal right ventricle or a lesion in the abdominal aorta.

Thus, whenever the region (or organ) under preliminary consideration is either the lower chest or upper abdomen, the possibility should be considered that diaphragmatic distortion has "referred" a manifestation from one domain to the other.

Channel transmission. Another type of possibly confusing "referral" occurs when the product or consequence of a disorder in one part of a hollow channel is transmitted to another part of the channel.

Because the gastrointestinal, respiratory, and genitourinary channels have outlets at the surface of the body, a disorder within these channels can be reflected in the vomitus, feces, sputum, urine, or other substances extruded at the surface. For accurate diagnostic reasoning, every element in the channel must be considered as the possible source of the extruded substance. Thus, when blood appears in the urine, the sources to be considered are not just the obvious choices of kidneys or bladder, but also the renal pelvis, ureters, and urethra. For a patient with persistent vomiting, the anatomic scope of sources must include lesions not just in the upper gastrointestinal tract, but also in the colon and below.

When two channels have outlets that are common to both, or close together, a product that emerges from one channel may incorrectly be attributed to the other.

Thus, hematemesis may sometimes be mistaken for hemoptysis (and vice versa); and the blood found in a woman's urine or feces may have come from the vaginal orifice. A fistula in two neighboring channels may create diagnostic confusion until the possibility of an abnormal connection has been recognized. Thus, a tracheo-esophageal fistula may be neglected as a source of respiratory distress, and a recto-vesical fistula may be forgotten as a possible cause of dysuria.

For disorders in hollow channels that have no external outlet to the surface, an overt substance is not extruded to provide the clue that may link a peripheral manifestation to its central source, or a central manifestation to its peripheral origins. In this way, the heart may be "shielded" either as a source of arterial emboli or as a cause of increased hydrostatic pressure when manifestations occur at uncommon distant sites in the cardiovascular channels. Thus, although arterial embolus from a fibrillating or murally thrombotic heart is regularly considered in explaining the manifestations of stroke, such an embolus is less likely to be contemplated in explaining abdominal pain. In addition, although the manifestations of dyspnea and edema regularly suggest cardiac decompensation, a failing heart is not regularly considered as a cause of ascites and mild jaundice. For similar reasons, the prostatic and uterine venous plexuses are also often overlooked as sources of pulmonary emboli; and an appendiceal or diverticular abscess may be neglected as a cause of pyelphlebitis.

Neurologic peculiarities. The tree-like distribution of the central nervous system "channel" makes it particularly well suited to diagnostic analysis with sequentially branching logic. The frequent appeal of neurology to clinical logicians, and the recent appearance of a logically oriented account of neurologic diagnosis (25) can be attributed to this branching-channel construction of the nervous system. Although a tree-like search pattern can often be conducted for abnormalities in the arms or legs, certain peculiarities of neuroanatomic construction and interrelation must be contemplated in the "referral" of manifestations for underlying abnormalities in the thorax and abdomen. Thus, because of the peculiar pathway of the recurrent laryngeal nerve, a lesion in the mediastinum may be manifested by hoarseness; for analogous reasons in the route of the phrenic nerve, disorders of the pericardium or diaphragm may be manifested in the shoulder region or neck. Through connections of the involuntary nervous system, cardiac pain may be referred to the arm, gall bladder pain to the scapula, and appendiceal pain to the periumbilical region.

A knowledge of gross anatomy, system physiology, and neurologic function is thus a pre-requisite for the critical choice of domains that constitutes the first step in diagnostic reasoning.

Disorders as Diagnostic End-Points

In many instances of diagnostic reasoning, the process ends with the identification of a disorder, and does not continue on to the naming of derangements and patho-anatomic entities. Such conclusions—at the *disorder* stage of the reasoning—are particularly common for diagnostic entities of psychiatry, psychosomatic medicine, and endocrinology.

Many diagnostic terms of contemporary psychiatry represent disorders in the domain of the psyche (or, within that domain, in such foci as the id, ego, and super-ego). Thus, the manifestations of abnormal behavior patterns may be explained in terms of such disorders as *depression*, *passive-aggression*, and *neurosis*.

In "psychosomatic" medicine, such diagnostic phrases as *functional bowel distress* (or the *irritable colon syndrome*) *globus hystericus*, and *aerophagia* are the names of disorders commonly manifested with "organic" symptoms. Such disorders as *hyperthyroidism* are endocrinopathic diagnoses that are seldom carried beyond that level of identification, although specific derangements can often be found to explain the disorders of hypothyroidism, hypopituitarism, and hyperparathyroidism.

Disorders as Transfer Stations

Perhaps the most important intellectual role of disorders is the part they play as transfer stations at which diagnostic reasoning may pause for verification, or change to another direction.

Until a disorder is identified, the clinician is concerned with achieving an explanation for the overt manifestations of the patient. At this point, the clinician may pause for one or more paraclinical tests to help confirm the selected disorder. Thereafter, his reasoning often diverges to a new pathway, seeking evidence to explain the disorder rather than the overt manifestations. These intellectual verifications and transfers can be illustrated with the same series of examples shown in Figs. 4-7.

In the first example, in Fig. 4, after suspecting the disorders of anemia and hemolysis, a clinician would probably check the hematocrit and serum bilirubin levels for confirmation, but the subsequent history-taking, physical examination, and paraclinical tests would now lead into pathways that are based on explaining the proposed disorders, rather than the manifested pallor. Thus, the questions about family history, the inspection of skin of the patient's legs, and the request for a hemoglobin electrophoresis are aimed at explaining the anemia and the hyperbilirubinemia, not the pallor.

In the second example, in Fig. 5, the identification of a narrowed arterial lumen as the disorder might evoke appropriate roentgenographic tests, and would be followed by a shift in the reasoning, away from the claudication and toward an explanation for the arterial blockage. In this way, the focus of the history and physical examination might be transferred from the legs or aorta to the heart.

In the example depicted in Fig. 6, after choosing hyperthyroidism as the disorder, the clinician would probably order a confirmatory test to establish the diagnosis. If the gland shows no palpable abnormalities, the diagnostic reasoning might conclude at this point.

The last example, shown in Fig. 7, provides perhaps the best illustration of the logical shift that occurs in direction of the diagnostic process after a disorder is chosen. When the cardiomegaly and congestive heart failure have been identified as disorders to be further explained, the clinician now looks for evidence that he has not hitherto used. In this way, the presence of appropriate cardiac murmurs and the absence of symptoms and signs of other cardiac derangements become the evidence that lead to the diagnosis of rheumatic mitral stenosis. On the other hand, if the peripheral edema had been attributed to the disorder of hepatic decompensation, the reasoning would have shifted in the direction of symptoms and signs suggestive of causes for liver disease.

This ability to use disorders as a transfer station is another hallmark that distinguishes the knowledgeable clinician. During the activities of history-taking and physical examination, these transfers enable the search for data to expand into directions that are not well appreciated by the novice clinician, and that cannot

be recognized by a clinically unsophisticated statistician or computer programmer. Moreover, by ordering appropriate sequential tests to confirm disorders, a wary clinician can avoid both the pitfalls of erroneous diagnostic directions and the hazards and expense of an unselected “battery” of tests. This important shift in the middle of the reasoning—leaving the path that leads from manifestation to disorder, and changing to a new path that leads from disorder to pathogenetic explanation—has often been one of the unidentified aspects of “intuition” and “artistry” in diagnostic judgment.

Disorders as Therapeutic Targets

Disorders also have a fourth role that will not be further considered in this discussion of diagnosis. Many therapeutic actions are aimed at a disorder, rather than at a more specific disease entity. Thus, the performance of colostomy to relieve intestinal obstruction, the transfusion of blood for acute blood loss, and the administration of diuretics or digitalis for congestive heart failure are therapeutic actions that are planned and evaluated for their effects on the cited disorders, often regardless of the underlying diseases responsible for the disorders.

With this basic rational pathway described, we can contemplate many other decisions that occur during diagnostic reasoning. These decisions involve such activities as choosing and authenticating evidence, combining several manifestations into a single disorder, joining several disorders into a single derangement, and performing various other types of inclusion and exclusion. These procedures will be discussed in the next paper of this series.

SUMMARY

Diagnostic reasoning consists of sequentially passing through a series of intellectual explanatory stations during which the “input” data of a patient’s manifestations are converted to the “output” diagnostic entities or diseases. With advances in technology and nosology, major changes have occurred in the types of medical data used as “input” evidence, and in the names and concepts of the “output” diseases.

The diagnostic process cannot be depicted in any simplistic scheme of logic or of statistics because: (1) a change in the name of a disease will alter its clinical spectrum of manifestations; (2) the quest of modern clinical science is for precise pathognomonic tests that can accurately identify the presence of a disease, regardless of the associated symptoms; (3) the etiologic end-point of diagnostic reasoning will vary with each clinical situation; and (4) many patients have multiple diseases rather than one. For all these reasons, the process of diagnostic reasoning contains a complex series of logical branches, and the process often ends not with a diagnostic name, but with a decision to perform adjunctive tests or to administer therapy.

The early stations of diagnostic reasoning include a group of gross macrobiologic entities called domains and disorders. A domain, which is the structural or functional source of a manifestation, can be an organ, region, channel, or system. Each domain may contain a particular focus that is responsible for the manifestation. A disorder is a gross abnormality in the structure or function of a domain or a focus. A structural disorder is called a lesion, and a functional disorder, a dysfunction. Lesions can be caused by abnormalities in size, composition, or location of a structure; dysfunctions can be caused by abnormalities in the amount, operation, or direction of a function.

In the later stations of diagnostic reasoning, the sequence moves toward the pathologic derangements, patho-anatomic entities, and pathogenetic (or etiologic) entities that successively explain each other, and that account for the antecedent disorders. Thus, a common sequence of diagnostic reasoning is from manifestation to domain to focus, and thence to disorder and perhaps to other disorders. The next steps usually lead to a derangement, perhaps to other derangements, and thence (if possible) to patho-anatomic and etiologic entities.

Aside from their role as possible targets of therapy, the macrobiologic entities of domains and disorders have three paramount roles in the diagnostic process: (1) the choice of a domain determines the direction of subsequent reasoning, and must be made with awareness of the diaphragmatic distortion, channel transmission, and neurologic peculiarities that can "refer" a disorder in one domain to a manifestation in another; (2) in many psychiatric, psychosomatic, and endocrinopathic circumstances, the disorder represents the end-point in the reasoning; and (3) disorders are often used as "transfer stations" at which the clinician may pause to verify previous decisions, and change to new paths of reasoning for subsequent decisions.

The next paper in this series is concerned with the diverse strategies used in the intermediate reasoning that leads from each of these intellectual stations to the next.

REFERENCES

1. Neyman, J. Outline of statistical treatment of the problem of diagnosis. *Public Health Reports* **62**, 1449-1456 (1947).
2. Chiang, C. L., Hodges, J. L., and Yerushalmy, J. Statistical problems in medical diagnosis. Proc. Third Berkeley Symposium on Math. Stat. and Probability, Vol. IV, p. 121, (J. Neyman, ed.), Univ. Calif. Press, 1956.
3. Ledley, R. S., and Lusted, L. B. Reasoning foundation of medical diagnosis: Symbolic logic, probability and value theory aid our understanding of how physicians reason. *Science* **130**, 9-21 (1959).
4. Warner, H. R., Toronto, A. F., Veasey, L. G., and Stephenson, R. A mathematical approach to medical diagnosis: Application to congenital heart disease. *J. Amer. Med. Ass.* **177**, 177-183 (1961).
5. Scheff, T. J. Decision rules, types of error, and their consequences in medical diagnosis. *Behav. Sci.* **8**, 97-107 (1963).
6. King, R. E. Diagnostic analysis. *Bull. Math. Biophys.* **30**, 727-734 (1968).
7. Dudley, H. A. F. Pay-off, heuristics, and pattern recognition in the diagnostic process. *Lancet* **2**, 723-726 (Sept. 28, 1968).
8. Engle, R. L., Jr., and Davis, B. J. Medical diagnosis: Present, past, and future. I: Present concepts of the meaning and limitations of medical diagnosis; II: Philosophical foundations and historical development of our concepts of health, disease, and diagnosis; III: Diagnosis in the future, including a critique on the use of electronic computers as diagnostic aids to the physician. *Arch. Intern. Med.* **112**, 512, 520, and 530 (1963).
9. Baron, D. N., and Fraser, P. M. The digital computer in the classification and diagnosis of diseases. *Lancet* **2**, 1066-1069 (1965).
10. Jacquez, J. A. "The Diagnostic Process: Proceedings of a Conference Held at the University of Michigan." Malloy Lithographing, Inc., Ann Arbor, Michigan, 1963.
11. Jacquez, J. A. (ed.) "Computer Diagnosis and Diagnostic Methods." Charles C Thomas, Springfield, Ill., 1972.
12. Bruce, R. A., and Yarnall, S. R. Computer-aided diagnosis of cardiovascular disorders. *J. Chron. Dis.* **19**, 473-484 (1966).
13. Feinstein, A. R. "Clinical Judgment." The Williams & Wilkins Co., Baltimore, Md., 1967.

14. Bernard, C. "An Introduction to the Study of Experimental Medicine," p. 94. Trans. by H. C. Greene. Collier Books, New York, 1961.
15. Faber, K. "Nosography in Modern Internal Medicine." Paul B. Hoeber, Inc., New York, 1923.
16. King, L. S. "The Medical World of the Eighteenth Century," Chapt. VII. Univ. of Chicago Press, Chicago, 1958.
17. Feinstein, A. R. Clinical epidemiology: II. The identification rates of disease. *Ann. Intern. Med.* **69**, 1037-1061 (1968).
18. Feinstein, A. R. The pre-therapeutic classification of co-morbidity in chronic disease. *J. Chron. Dis.* **23**, 455-469 (1970).
19. Feinstein, A. R. An analysis of diagnostic reasoning. II. The strategy of intermediate decisions. *Yale J. Biol. Med.*, In press.
20. Harvey, A. McG., and Bordley, J. "Differential Diagnosis: The Interpretation of Clinical Evidence," 2nd ed. W. B. Saunders Co., Philadelphia, 1970.
21. Campbell, E. J. M., Dickinson, C. J., and Slater, J. D. H. "Clinical Physiology," 2nd ed. F. A. Davis Co., Philadelphia, 1963.
22. Sodeman, W. A., and Sodeman, W. A., Jr. "Pathologic Physiology. Mechanisms of Disease," 4th ed. W. B. Saunders Co., Philadelphia, 1967.
23. Brunson, J. G., and Gall, E. A. "Concepts of Disease: A Textbook of Human Pathology." Collier-Macmillan, New York, 1971.
24. Feinstein, A. R., and Niebyl, J. R. Changes in the diagnostic process during 40 years of clinico-pathologic conferences. *Arch. Intern. Med.* **128**, 774-780 (1971).
25. Renfrew, S. "An Introduction to Diagnostic Neurology. A Course of Instruction for Students," Vols. I-III. E. & S. Livingstone Ltd., Edinburgh, 1962.