general use throughout most of the world; the problem of
Manual fur die Praxis.

or even the same company >

Boston, on Wednesday evening, October 30 at 6 p.m.

This book is not designed as a comprehensive atlas, but is

the contribution by Priv.-Doz. Dr.med.Jürgen Stoffregen.

specialists in these specific areas,

by

— ED.

Notes: To mention the useful Physicians’ Desk Refer-

on Kidney Problems in Diabetes, 31.

G.,

35 Binney Street, Boston, on Tuesdays at 12 noon:

with Dr. Louis Lasagna, professor of

Boston Chapter. M.H.A., 650 Beacon Street, Boston, Massa-

conferences were held on November 5 and 6. Asthma Symposium, New York City: and "Route to Drug Discover* *' Ik

November 18-20, Southern Medical Association, New

17.

York City: and "Route to Drug Discover* *' Ik

Boston. The first three conferences were held on Novem-

Medicine: Efficacy, Potentials and Hazards of Vaccines,

Clinical Pharmacology, Johns Hopkins University School

Second, immunologist by immunological be-

By the proclivity of a country often

The application of mathematical concepts

Alvyn R. Feinstein, M.D.*

PHYSICIANS may be startled to discover that

many of them think in mathematical sets and with

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BOOLEAN ALGEBRA AND CLINICAL THERAPEUTICS

J. Analytic Synthesis of the General Spectrum of a Human Disease

by

A NEW ENGLAND JOURNAL OF MEDICINE

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Number 18

PHYSICIANS may be startled to discover that

many of them think in mathematical sets and with

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more from studying grammar than the foreigner who
gets a little from each.

The "foreigner" that comes to clinical medi-
cine today is the computer. It brings with it poten-
tial capacities for facilitating diagnosis, for making
multiple correlations with rapidity and extensions hitherto impossible and for providing storage back-
grounds for the clinician. It can bring science to the formation
of diagnostic, prognostic therapeutic judgments.

Like a foreigner learning a new language, the com-
puter must be taught the construction of elementary sentences. But also
have either elegance or poetry.

Like the foreigner, the computer must be taught
abstract mathematics has any real value in medicine.

But also have either elegance or poetry.

The number of possible patterns increases marked-
ly for relations of 3 sets. The chart contains 2 rela-
tions to either of the first 2, to both or to their
intersection, by being disjoint, subordinate, encom-
sions, or inclusion. It is obvious that the possible types of pattern formed in these relations
among 3 sets are shown in Figure 2.

The 15 illustrations in Figure 2 are a partial sam-
ing of the many potential relations. Addition-
al patterns obtainable by identical set relations and by the
set of brown-haired but not men having cholesterol levels higher than 250 mg. per 100
mL. A woman is excluded from any set that con-
tains only men.

Sets are always considered within some frame-
work of reference called a universe. Thus, the sets of
different human diseases are considered in the
universe of human beings. The universe of human
mortality includes sets of patients who have polydipsia, sets of patients with diabetes, and
sets of patients with vascular lesions. In any given
universe the complement of a set is whatever is in
the universe contains that is not part of that set.

Thus, in a universe composed of the set of all
human beings, the complement of the set of all
men is the set of all women. In the universe com-
promised of patients with diabetes mellitus, the comple-
ment of the set of patients with vascular lesions is the
set of all diabetic patients who do not have vas-
cular lesions.

Since sets are not individual objects but instead
be subjected to addition, subtraction, multiplica-
tion or division in exactly the same way that these
processes are used for numbers in elementary algebra. Sets (or collections of objects) have polydipsia, sets of patients with diabetes, and
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the universe contains that is not part of that set.
Classification of Human Disease According to Pattern of Discovery

To be identified and studied, a disease must first be discovered in the patient who has it. Its accurate identification often requires various laboratory tests. At the same time that they help identify (or diagnose) the disease, these tests provide results that help classify cases into subgroups according to data derived from pathological, biochemical, hematologic, immunologic, radiographic, electrophysiological and other tests performed in the laboratory. None of these tests, however, classify a specific distinct variation of each case of a disease: the way in which it is clinically discovered.

Diseases are discovered; others are not. Some diseases are found "early," and others are found "late." Some are found because the patient has definite symptoms that brought him to a doctor, others are discovered accidentally in asymptomatic patients. The possible ways in which a disease can be discovered are considered and classified below:

Defective:

Most of the terms defined here are familiar and are used in their traditional, familiar sense; some are familiar but are used with specific shades of meaning; some are new, created for present needs.

Almost every disease has a basic lesion, usually a departure in some cell, tissue or chemical, that gives the disease its name and the patient a diagnosis. The basic lesion, which must be demonstrated or assumed to be present in all patients with the disease, is best shown by gross, microscopic or chemical pathology. When it cannot be shown in this way, its existence is inferred from some of its effects described below.

The effects of the basic lesion are manifested by symptoms, signs and laboratory abnormalities. Symptoms are subjective clinical abnormalities, observed by the host and noted by the physician in history taking. Signs are objective clinical abnormalities, sometimes not always observed by the host and noted by the physician on physical examination. Notable signs are those that are visible or palpable (sometimes audible) and detectable by host as well as by the physician.

Laboratory abnormalities are defined here as abnormalities of tests performed by devices or procedures other than usual clinical examination. Such tests include electrocardiography, electroencephalography, radiography and laboratory analysis of bodily fluids.

When present, a disease may or may not produce symptoms or notable signs. When present, symptoms or notable signs may be noted or not noted by the host; when noted, they may be ignored or ignored. Symptoms and notable signs become symptoms of the disease only when they are noted by the host and cause the host to seek medical attention for them.

In the universe of all persons with a specific disease, a randomly selected host is one who has no complaints referable to that disease. His condition of health may be recognizable through its laboratory abnormalities, and he may even have some of its symptoms and signs. Unless he has noted these features and has come to a doctor complaining of them, he is latitudinal. Thus, the latitudinal set of a specific disease contains patients who may be "clinical" or "subclinical," but who are discovered without coming to a doctor because of his complaints of that disease.

A living latitudinal host is medically discovered and becomes a patient in one of two ways: he comes to a doctor with complaints due to some other disease and the abnormalities of his first disease are discovered in the course of the routine examination; or a purposeful but accidental examination (done for routine, epidemiologic, insurance, military, employment, premarital or other reasons) discloses the symptom, sign or laboratory abnormality that evokes further examination and ultimate diagnosis.

In the latitudinal dead host, previously undiagnosed disease can be accidentally discovered at autopsy; it remains undiscovered if there is no autopsy or no lesion demonstrable at autopsy. A lesion may not be found at autopsy if the disease is located at a site not routinely examined by pathologists (such as the temporal bone or calf veins) or if the disease has no visible lesion (for example, porphyria or any completely healed previous acute inflammation).

The primary features of a disease are symptoms, signs or laboratory abnormalities directly caused by immediate effects of the basic lesion. The secondary features (or complications) are attributable to the long-term or indirect effects of the basic lesion. Table 1 shows how the terms "basic lesion," "primary features" and "secondary features" are used in various diseases. The illustrations chosen here and the division of features into "primary" and "secondary" categories are entirely arbitrary and have been proposed solely for the purposes of this discussion. In some of the diseases listed in Table 1 the basic lesion is the cause and site of the disease, and in others the basic lesion is anatomically diffuse or chemical; it is cellular in some and unknown in others. Since the discussion here is concerned with clinical aspects of how disease is discovered, laboratory abnormalities have been omitted from citations of primary and secondary features. Some of these features are almost invariably associated with specific laboratory abnormalities (for example, jaundice with hyperbilirubinemia, renal failure with azotemia, pathologic fractures with x-ray signs); whereas other laboratory abnormalities (such as electrocardiographic Q waves or lupus globus tests) have no precise clinical correlations but are often used by clinicians to infer the existence of a basic lesion not otherwise demonstrable.

Spectrums of Discovery of Disease

Clinical discovery. As noted above, the patients with a specific, identified disease can be divided into types.

FIGURE 2: Relations in Intersections of Three Sets.

In each illustration set A is hatched vertically, B diagonally, and C horizontally. The overlap of hatching indicates the overlap, or common subset, of intersecting sets. In some instances, a set exists alone without being involved by any other. The total number of distinct subsets present in each illustration depends on how the three sets interrelate. Thus, the subsets formed in these illustrative intersections are as follows: 1, A; 2, B; 3, C; 4, A,B; 5, A,C; 6, B,C; 7, A,B,C; 8, A,B,C; 9, B,C; 10, A,C; 11, A,B,C; 12, A'; 13, B'; 14, C'; 15, A,B,C.'
3 main sets with the clinical properties of no complaints, primary features and secondary features. Each of these sets can be further subdivided. The lanthanatic set, which has no complaints, may be divided into 4 subsets of patients who also have primary features, secondary features, both or neither. The primary-features set may be divided into 4 subsets according to the presence or absence of complaints or of secondary features. The secondary-features set may similarly be divided into 4 subsets according to the presence or absence of complaints or of primary features.

Actually, of course, these 3 main sets do not exist separately: they overlap, and their subsets coexist. Their synthesis into the spectrum of clinical discovery of a diseased patient is shown by the Venn diagram of Figure 5. Each circle represents the set previously defined; everything outside that particular circle represents the complement of the set: the crosshatching of the overlap shows the subset. Figure 4 is a simpler demonstration of Figure 5, with the crosshatching removed. The interaction of the circles divides the spectrum into 7 subsets, each representing a different group of patients. A specific listing of the properties of these subsets is given in Table 2. In the diagram of Figure 4 the complement of the lanthanatic set consists of all patients who have complaints, so in subset 5, which represents the complement of the primary-features set consists of the patients shown in subsets 1, 4 and 7; the complement of the secondary-features set is subset 2 and 3. A few clinical illustrations, using coronary heart disease as an example, will help demonstrate their properties of discovery — found in life, at death or not at all — cannot occur in combination, lanthanatic disease can be found in only one of these ways. Hence, these properties do not overlap and are mutually exclusive. The sets of their patients can thus be shown conveniently as nonoverlapping concentric circles within the main lanthanatic circle.

The addition of these sets to the diagram of Figure 5 produces the changes shown in Figure 6, which depicts the total spectrum of a disease. (The Venn diagram of Figure 5 is not strictly accurate in its arrangement of subsets since disease first discovered at autopsy and undiscovered disease have both been shown correctly as subsets of the lanthanatic set but undiscovered disease is not, as depicted, a subset of disease first discovered at autopsy, nor is the latter a subset of disease discovered during life; to indicate these minor distinctions, the diagram would have required greater complexity but, in its present form, it is equally clear and maintains a useful symmetry that would otherwise be lost.)

In Figure 5 the area in white contains all patients discovered during life, the stippled area those first found at death (surviving informants can, when necessary, provide the history of previous presence of primary or secondary clinical features), and the black area those who are not found at all.

These additional circles produce 4 more subsets, numbered 8 through 11, and a twelfth, that has 4 unnumbered subsets of undiscovered disease. For clinical classification of the stages of disease at time of discovery, the original 7 subsets will suffice. For classifying all possible stages the additional subsets are needed.
The diagram of Figure 5 can be used to show the evolution of a disease in its host. Disease always begins in the (black) undiscovered core. As it develops, it moves outward to subsets 8-11 in which it can be found by pathologists before it is clinically discovered. It may then advance to subset 1, where it is discovered by clinicians while it is still subclinical. The disease may then pass the point beyond which the patient seeks medical aid (subsets 5-7), when the disease is no longer latent.

Numerical size and medical view of the spectrum of a disease. It should be emphasized that the relative sizes of these diagrammatic circles, and of the subsets formed by their intersections, do not in any way indicate the actual or relative number of patients in each subset. The diagrams show only that characteristic groups of patients with different properties. The true size of each group or subset must be determined by surveys of the disease. These sizes can be distorted both numerically and proportionately by the material available to the examiners who study the disease.

Because observers at these different points will inevitably see different parts of the spectrum, disease can be divided into subsets 1 through 11. invisible to all other observers. The pathologists view of other subsets is restricted to the portions that come to autopsy with demonstrable lesions. Pathologists may see other rare lesions, but they rarely see subset 1. On the ward clinicians are like pathologists in subsets through biopsy in living patients, but they rarely see subset 1. In the outpatient clinic, where mild cases are often seen, they may find it more difficult to recognize disease than they see in the inpatient clinic, where mild cases are more commonly seen. This diagram can be used to show the numerical size and medical view of the spectrum of a disease.

The diagram of Figure 6 can be used to show the site of survey affects the size of the total spectrum of a disease. The disease is seen by different medical observers. The disease in subsets 2 through 4, 5 through 7, and 8 through 11. invisible to all other observers. The pathologists view of other subsets is restricted to the portions that come to autopsy with demonstrable lesions. Pathologists may see other rare lesions, but they rarely see subset 1. In the outpatient clinic, where mild cases are often seen, they may find it more difficult to recognize disease than they see in the inpatient clinic, where mild cases are more commonly seen. This diagram can be used to show the numerical size and medical view of the spectrum of a disease.

Summary of Conclusions
A branch of modern abstract mathematics and symbolic logic, dealing with the interrelations of sets of objects and illustrated by appropriate diagrams, is a useful tool for studying various aspects of human disease. The relations, called Boolean algebra, and the graph patterns that they form, called Venn diagrams, offer a method for conceptual and visual demonstration, analysis and synthesis of components and overlapping parts of a complex structure. The techniques are applied here to construct a system for classifying human disease according to how patients with the disease are discovered. Three major properties of a disease involved in its clinical recognition and identification are the presence or absence of complaints, the presence or absence of complications, and the presence or absence of secondary features or complications, appearing simply from the part that they saw, and yet not recognized as a disease. Many contemporary therapeutic controversies such as those regarding antimicrobial therapy for coronary heart disease subsets 2 through 4, 5 through 7, and 8 through 11. invisible to all other observers. The pathologists view of other subsets is restricted to the portions that come to autopsy with demonstrable lesions. Pathologists may see other rare lesions, but they rarely see subset 1. In the outpatient clinic, where mild cases are often seen, they may find it more difficult to recognize disease than they see in the inpatient clinic, where mild cases are more commonly seen. This diagram can be used to show the numerical size and medical view of the spectrum of a disease.

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BELOW-KNEE AMPUTATIONS IN PATIENTS WITH SEVERE ARTERIAL INSUFFICIENCY

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Surgical opinion varies widely as to the advisability of performing below-knee amputations in limbs that exhibit diminished circulation at the level of amputation. It has been shown that below-knee amputations can heal by first intention in patients with severe arterial insufficiency, but failure of the stump has been reported in the majority of patients who did not have either a popliteal pulse or calf oscillations. At present many surgeons believe that below-knee amputations are contraindicated unless there is good arterial circulation at the level of amputation, as evidenced by the presence of calf oscillations and a palpable popliteal pulse. A recent book on peripheral vascular disease summarizes the problem as follows: "This site of amputation (below-knee), useful enough in other conditions, is rarely advised in peripheral vascular disease — indeed, the author has not seen a below-knee amputation in arteriosclerosis that could be described as functionally successful." It has been our belief that below-knee amputation has a definite place in the treatment of peripheral arterial disease, even in patients with marked reduction in circulation at the level of amputation. Furthermore, the functional advantages derived from below-knee amputation are of particular benefit in the rehabilitation of this group of patients, who are usually elderly and may have bilateral disease. This impression is confirmed by the results, described below, of 16 consecutive below-knee amputations carried out on patients with no palpable popliteal pulse and no trace of calf oscillations. In analyzing the results, we have particularly emphasized rehabilitation, the ultimate aim of amputation.

CLINICAL MATERIAL

Sixteen consecutive below-knee amputations were carried out in 15 patients because of actual or impending gangrene. A second patient was operated upon after the interval from operation to death varied from three to nineteen months. The follow-up period varied from five to twenty-four months, with a mean of forty-eight weeks.

Operative Technique

The features of technic emphasized were exposure gentleness in handling ischemic tissues, careful heeding of the anterior skin of the tibia and of the skin to avoid suture-line tension and to allow evacuation of blood. All operations were carried out by the resident staff, with supervision by the attending staff. The standard description is repeated below.

The patient was placed in the prone position with the knee flexed to a right angle. Equal anterior and posterior skin flaps were made, with the most proximal point of incision extending to the level of division of the tibia (10 to 15 cm. below the joint line, depending upon the height of the patient). The incision was carried down through the skin, with no conscious attempt to avoid the underlying muscle. The skin was elevated free from the anterior surface of the tibia by careful dissection in the bloodless plane just above the periosteum. The incision was deepened to a level 3 cm. above the point of division of the tibia, and the interval from operation to death varied from three to nineteen months.

With the exception of 1 patient in whom symptoms of cerebral vascular insufficiency developed, all patients remained hospitalized for 4 to 30 days. Three patients failed to heal, necessitating re-amputation at a supracondylar level (Table 1). Although there was no operative mortality 4 patients died during the follow-up period. The clinical diagnosis was acute myocardial infarction in each, and the interval from operation to death varied from three to sixteen months.

Operative Results

Ten of the 16 amputations healed primarily. Three amputations exhibited delayed healing, and 2 of these 3 stumps required revision of the wound.

Three amputations failed to heal, necessitating re-amputation at a supracondylar level (Table 1). Although there was no operative mortality 4 patients died during the follow-up period. The clinical diagnosis was acute myocardial infarction in each, and the interval from operation to death varied from three to nineteen months.

Three patients required readmission to the hospital.