Clinical research and the toilsome discoveries of new technical methods are as fully entitled to the term "scientific" as any of the good work done in our laboratories. The complexities of clinical research are so intricate, and because of the human material upon which they are conducted are so bewildering as perhaps to surpass all forms of laboratory research in difficulty. They call for qualities of insight, imagination, patience, and intellectual integrity to a no less considerable degree. The practice of clinical medicine or surgery makes a further heavy demand upon qualities of temperament and of character which are little exercised in the clustered tranquility of the laboratory. Yet the rewards open to the clinical investigator by the only scientific body competent to give them, the Royal Society, are consistently withheld. The present President of the Royal Society is a medical man whose life has been spent in the laboratory, with the result that physiology and general medicine have been permanently and very greatly enriched by his labours. But there are physicians and surgeons whose lives have been spent in the wards and in the operation theatres of our hospitals whose contributions to "scientific" medicine are entitled to rank even with his. The joint and separate labours of the laboratory worker and of the clinician are both, perhaps equally, necessary for the future progress of medicine in all its branches. Both are deserving of recognition at the hands of those empowered to confer it; in "scientific" value one does not surpass the other.—From MOYNIHAN, BERKELEY: Letter to the Editor. The Times, London, July 27, 1923.
Minuscule Review

Drug-Related Pulmonary Vascular Disease


These two papers present in detail the clinical findings and studies of cardiopulmonary function of 31 patients with an entity which in many respects resembles primary pulmonary hypertension. Of particular note is that 23 patients were examined in 1967 and the first half of 1968 while only eight had been admitted between 1955 and 1966. Seventeen of the last 23 patients had received a new anorectic for weight reduction (aminorex fumarate [Menocil]) prior to the onset of symptoms.

RÉJANE M. HARVEY

Correction

In the list of “Participants” in the supplement on “Research on Acute Myocardial Infarction” (Circulation 40 [suppl IV]: IV-1 to 338, 1969) the entry concerning Dr. Reid should read:
Donald D. Reid, M.D., Professor of Epidemiology, instead of Professor of Statistics, London School of Hygiene and Tropical Medicine, London, England.
Minusculc Review


The practice in clinical laboratories of specifying two numbers as "normal limits" is sufficiently common to justify examination of the procedures used in their determination and, if any such procedures are found wanting, to present the case, against them.

This cooperative effort of biostatistician and internist is first, a consideration of a procedure recommended by Hoffman and secondly, an attempt to dissuade those responsible for the specification of "normal values" (or, as the authors prefer, "clinical limits") from using it. Hoffman's method is to obtain a mean and standard deviation based on the behavior of the frequency distribution near the primary mode, and then to calculate the "limits" as the mean ± 2 standard deviations.

Elveback, Guillier, and Keating compared the "limits" obtained from applying Hoffman's method to routine laboratory data from the Mayo Clinic with the 2% and the 97% percentile values obtained from a set of data for several hundred "healthy adults." Of the seven examples—serum calcium, inorganic phosphorus, total protein, albumin, alkaline phosphatase, urea, and magnesium, the standard deviation via Hoffman's method was an overestimate in six of them (for albumin as high as 67%) and resulted in excessively large normal ranges.

The setting of norms can, and in the view of some, should be expanded to consider more than a single variable at a time, that is, it should be multivariate in character. Also, questions arise as to the optimality, possibly the appropriateness, of the usual definition of limits even in the single variable case. More relevant reference information accompanying a single reading might be the risk, or relative risk, of various diagnoses. Argument over the nature of the population on which to establish reference data, whatever its form, continues and is likely to continue until there is a greater degree of convergence among (1) how limits are defined, (2) how they are, in fact, determined, (3) what the physician thinks the limits represent, and (4) what, if any, actions he takes as a result of referring to these limits. Much remains to be done before achieving a satisfactory operational resolution to these rather general considerations and to that hopefully not too utopian concept, international standardization.

In this paper, the focus is limited to a particular method for determining limits univariately on data from clinical laboratories, using as a standard the 2% and the 97% percentile values in a "healthy population." Supported by considerable data, its conclusion that, for this type of limit determination, the Hoffman procedure is inadequate, seems justified.

Marcus O. Kjelsberg, M.D.
Minuscule Review

Polley HF: Evolution of steroids and their value in control of rheumatic disease.

Dr. Polley outlines the development of the clinical use of steroids in the treatment of the rheumatic diseases at the Mayo Clinic and draws from his extensive experience, guide lines for approved current practices. He was closely associated with Dr. Hench in the early use of cortisone, the first patient being given "compound E," to be named cortisone, on the autumnal equinox, 1948. Within 2 years, the award of the Nobel prize was announced. This short interval belies the long years of clinical observation on rheumatoid arthritis by Dr. Hench, a man with penetrating powers of observation and a discerning curiosity concerning the natural phenomena of disease.

From the historic viewpoint, it is noteworthy that the Nobel award in 1950 coincided with the year of publication of Hans Selye's book Stress. In the preceding decade there was considerable difference of opinion, at times amounting to acrimonious debate, concerning the clinical significance of Dr. Selye's theories. It is possible that such controversy helped to polarize the community of scientists into differing schools concerning the significance of the reports on the dramatic anti-inflammatory effect of cortisone. Possibly the most revolutionary jarring of the entrenched thoughts of some scientists related to the new idea of hormonal material, effective in minute doses, in the general functioning of the body, as having unpredictably gross physiologic effects; or the metamorphosis from a physiologic to a pharmacologic agent. To illustrate the resistance of some persons with high intellect and research minds, I heard one internationally renowned endocrinologist make this statement in 1948 concerning cortisone and its possible action in rheumatoid arthritis "I hope it doesn't work. I don't see how it should." In 1952 an eminent research scientist observing the baleful effects of cortisone in modifying the reaction to bacterial toxin in rabbits feared great harm (an opening of Pandora's box) from the clinical use of the drug. Such islands of resistance to the acceptance of the discovery are mentioned, as Dr. Polley properly emphasizes the "initial widespread overenthusiasm and the subsequent rebound of disillusionment that followed."

Dr. Polley's review touches briefly on the very real problem of hypercortisonism and outlines present concepts of the nature of the anti-inflammatory and anti-rheumatic effects emphasizing, "The most definitely established one to date is that of increasing the stability of lysosomes." Under the section entitled "The Future," Dr. Polley touches on "the unsolved etiology of rheumatic disease," "the possible refinements of steroid structure," and "the health problems of chronic disease." The short review is followed by a select list of 20 references which presumably are believed by the author to be the key papers illustrating the development in corticosteroid therapy over the past two decades.

H.B.B.


---

**Advice in Times of Adversity**

**Milton 1644**

... that then, the people, or the greater part, more than at other times, wholly taken-up with the study of highest and most important matters to be reformed, should be disputing, reasoning, reading, inventing, discoursing, even to a rarity and admiration, things not before discoursed or written of, argues, first, a singular good-will, contentedness, and confidence in your prudent foresight, and safe government, ... as in a body, when the blood is fresh, the spirits pure and vigorous, not only to vital, but to rational, faculties, and those in the acutest, and the pertest operations of wit and subtlety, it argues in what good plight and constitution the body is; so when the cheerfulness of the people is so sprightly up, as that it has not only wherewith to guard well its own freedom and safety, but to spare, and to bestow upon the solidest and sublimest points of controversy and new invention. ...—MILTON, JOHN: *Areopagitica: A speech for the Liberty of Unlicensed Printing, to the Parliament of England* (1644). In *Occasional Essays on Various Subjects, Chiefly Political and Historical; Extracted Partly from the Publick Newspapers*. London, 1809, p. 236.
The Double Murmur of Aortic Insufficiency
Duroziez (1861)

The double murmur can be produced in two ways, by means of the stethoscope or by means of the hand. With the stethoscope pressure is exerted to completely compress the artery; at a certain moment the double murmur will appear; only when the second murmur can be readily produced is it possible to place the stethoscope on the artery without pressure and then gradually slight pressure can be exerted with the hand above and below the stethoscope. Pressure above will produce the first murmur, while pressure below will produce the second murmur; it is evident that the second murmur is produced by the arteries of the legs, which propel the blood backwards and in some manner empty the capillaries.—P. Duroziez: The Double Intermittent Murmur over the Femoral Arteries as a Sign of Aortic Insufficiency. In WILLIUS F A, AND KEYS T E: Classics of Cardiology, vol. 2. New York, Dover Publications, Inc., 1941, p. 495.
Obstruction of the major airways by blood vessels may be caused by one of several entities including (1) aortic aneurysms, (2) enlarged pulmonary arteries in instances of pulmonary hypertension from any cause, and (3) certain varieties of anomalies of the aortic arch system, collectively called “vascular rings.”

Yet another example is the so-called “vascular sling” of which an example in an adult was described recently by Kale and associates.

The “vascular sling” is characterized as follows (fig.). The pulmonary trunk does not bifurcate but, instead, continues as the right pulmonary artery. Before the right pulmonary artery enters the right lung, it gives off the left pulmonary artery. The latter passes posteriorly in the upper angle between the right main bronchus and trachea. It then turns leftward between the trachea, in front, and the esophagus, behind. From this position, it proceeds to the hilus of the left lung.

Two important features characterize this condition. The first is that the anomalous artery may cause broncho-obstructive effects in the right lung. The other is that it is responsible for an indentation in the anterior aspect of the esophagus at the level of the carina. In this characteristic, the “vascular sling” differs from the usual “vascular ring” which, classically, causes deformity of the posterior aspect of the esophagus.

Among the reported cases of the “vascular sling,” the characteristic period in which symptoms begin is infancy. An exception to this rule is the case of Kale and associates in which the patient was 54 years old. In that case in which the characteristic indentation of the esophagus was shown clearly and in which the condition was identified angiocardiographically, symptoms did not seem related to the vascular malformation. Of importance to physicians dealing with adult patients, however, was that the malformation was responsible for a right-sided mediastinal mass.

Jesse E. Edwards, M.D.
gram and its hemodynamic correlation in 100 proved cases. Amer J Cardiol 2: 698, 1958

Routine and Change

There are, of course, in every calling, those who go about the work of the day before them, doing it according to the rules of their craft, and asking no questions of the past or of the future, or of the aim and end to which their special labor is contributing. These often consider and call themselves practical men. They pull the oars of society, and have no leisure to watch the currents running this or that way; let theorists and philosophers attend to them. In the mean time, however, these currents are carrying the practical men, too, and all their work may be thrown away, and worse than thrown away, if they do not take knowledge of them and get out of the wrong ones and into the right ones as soon as they may.—OLIVER WENDELL HOLMES: CURRENTS AND COUNTER-CURRENTS IN MEDICAL SCIENCE. Boston, Ticknow and Fields, 1861, p. 6.
Aspects of the Physician-Patient Relationship
as Seen by a Philosopher-Novelist

Sympathy between doctor and patient is surely desirable, and a case might be made out for the view that only he who suffers can be the guide and healer of the suffering. And yet—can true spiritual mastery over a power be won by him who is counted among her slaves? Can he free others who himself is not free? The ailing physician remains a paradox to the average mind, a questionable phenomenon. May not his scientific knowledge tend to be clouded and confused by his own participation, rather than enriched and morally reinforced? He cannot face disease in clear-eyed hostility to her; he is a prejudiced party, his position is equivocal. With all due reserve it must be asked whether a man who himself belongs among the ailing can give himself to the cure or care of others as can a man who is himself entirely sound.—THOMAS MANN: In Familiar Medical Quotations, edited by Maurice B. Strauss. Boston, Little, Brown and Co., 1968, p. 415.
Plimsoll's Mark

Before 1866 there sailed from English harbors what were known as “coffinships.” They were old, unseaworthy, overloaded vessels, heavily insured by their unscrupulous owners, who freely risked in them the lives of the helpless crews. The unceasing efforts of Samuel Plimsoll finally brought about a reform, and thenceforth vessels were inspected and marked with a line indicating the safety point for loading. This is called “Plimsoll’s mark.”

It seems possible that things other than vessels on the high seas have a safety load line and might well be examined to determine and fix their Plimsoll’s mark.

. . . not all the little vessels that put into the harbor of our public schools can go out with the same weight of cargo. They can all navigate safely if the schools and parents and society do not demand too much of them. Brain as well as brawn has a Plimsoll’s mark, and the quicker that is recognized, the happier and more useful will be those whose load in the social scheme is fitted to it. But we must allow for the fact that when character and purpose walk the quarter-deck of even mediocre brains, they make it possible to sail them with heavier loads than any intelligence test would indicate.—Guy Stanton Ford: On and Off the Campus. Minneapolis, University of Minnesota Press, 1938, p. 432.

Addendum

Authors too might have their Plimsoll’s mark for tolerance of criticism—the stronger the authorship the larger load of criticism an editor might transmit. The editor should be certain that not only the total load of criticism, but also that this cargo be properly packaged and labeled and be transferred slowly enough to allow careful stowage or jettisoning.—H.B.B.