Progress in Clinical Pathology

Mario Stefanini, Editor

VOLUME VII

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GRUNE & STRATTON
A Subsidiary of Harcourt Brace Jovanovich, Publishers
New York San Francisco London

Grune & Stratton, Inc.
111 Fifth Avenue
New York, New York 10003

Library of Congress Catalog Number 66-11412
International Standard Book Number 0-8089-1037-X
Printed in the United States of America

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Preface

This Volume, like the previous ones of this series, is directed primarily, although not exclusively, to the pathologist who practices in the community hospital. His needs and interests are of necessity different from those of the pathologist in the large university hospital or within the walls of a medical school. However, two fairly recent trends have narrowed this gap. One is the increasing role of the pathologist as a teacher of medical students. While some medical schools are experimenting with the idea of a university without walls and decentralizing their programs, they are emphasizing instruction directly at the bedside and by the practicing physician. The other trend is toward continuing medical education at the postgraduate level. A practicing physician is confronted by the increasing cost of organized educational courses and of traveling, the difficulty of leaving an established practice even for a few days, and the problem of relating much of the material offered to his own specific needs. Thus, it is to be expected that great interest is displayed in programs of continuing medical education at the level of the community hospital. By his participation in these dual programs the pathologist extends his traditional role from the confines of the laboratory to the broad reaches of the medical community. The Editor is involved in one such program and finds it both stimulating and rewarding. However, the gathering of information for this purpose is a Herculean task. We are told by many readers involved in the educational process that the volumes of this series have been quite useful to them, a fact that gives this series a new and welcome dimension and may explain somewhat its acceptance and durability.

Volume VII features shorter articles than previously presented to allow broader coverage of areas of greatest interest or of most rapid progress. Instrumental in the selection of contributions and contributors were the co-editor, Dr. Ali A. Hossaini, who obtained the cooperation of many members of the Medical College of Virginia, and the Consulting Editor, Dr. Henry D. Isenberg. Their input greatly affected the contents of this volume.

The applications of computers to diagnostic microbiology are evaluated by MacLowry and co-workers, who discuss advantages and disadvantages of a tool which may ultimately offer the ease and precision of diagnosis that are sometimes lacking with classical methods. After many years of relative stagnation, medical microbiology is experiencing a revival, triggered largely by the introduction of new techniques. Brenner discusses the relatively new method of hybridization in the study of bacteria, with special reference to Enterobacteriaceae, some of the more perplexing organisms in diagnostic microbiology.

From the University of Leeds, Broughton, well-known for his pioneering work in biochemical methodology, presents excellent reading on a rather abstruse subject and provides a number of valuable hints regarding the everyday routine

of the biochemical laboratory. The Editor finds that practicing physicians are increasingly curious about the workings of the tests they request and about the role of standards and of quality control in the performance of biochemical procedures. Broughton's chapter offers valuable background reading for all interested in this field. Kassirer presents a clinically oriented discussion of renal function evaluation which would seem to clarify ideas in a field of increasing complexity.

A number of contributions are related to the rapidly expanding field of immunology, which, like all other fields of human endeavor, is splitting into a number of subspecialized areas of interest. Lange presents an authoritative discussion of the immunologic aspects of aging in an informative and readable style. For the pathologist 40 years of age and over the chapter has a direct personal interest and application! Issitt reviews newer aspects of the autoimmune hemolytic anemias and discusses in detail the syndrome of cold autoimmune hemolytic anemia which is attracting renewed interest. The diagnosis of neoplasms through immune tests has been discussed previously in this series. However, the field is evolving rapidly and the presentation by Moncure of more recent advances complements the earlier review and updates the subject quite satisfactorily. It should be valuable to our readers. Kohout and Dutz review lymphocyte receptors, the role of B and T lymphocytes, and disorders related to their altered functions. An addendum of test procedures outlines techniques soon to become part of pathology laboratories at all levels. Cannady and colleagues discuss transplantation immunity and present in detail ideas and methods which will be increasingly useful, not only in the rather selective area of tissue transplantation, but also in the more routine practice of transfusion of blood and its components. The rapid advances in the blood Lewis system and the interesting phenomenon of albumin autohemagglutination, which has practical importance in the day-to-day operation of a blood bank, are discussed by Hossaini.

Chromosome studies were discussed by Ian Porter in a previous volume. Since the field is exceedingly dynamic, it was felt that the newest ideas and procedures (including the technique of high resolution for the analysis of chromosomes) should again be directed to the attention of the pathologist. This is aptly done by Yunis and Chandler.

The last part of the volume contains a number of contributions of a miscellaneous nature. Qureshi and colleagues discuss the diagnosis of venous thrombosis by laboratory methods, a field which the pathologist must tread more and more often. The importance of cyclic nucleotides in the understanding of medical problems is such that it was felt that the subject should be explored in depth. This has been so aptly done by Escobar that it should have wide appeal. Amador discusses the pros and cons of shared laboratories, a potential bone of contention between government agencies and pathology groups. The final chapter, by Martinek, is offered as a contribution "without time," wherein inept definitions and words are shown to be retarding progress and contributing to the confusion in some fields of endeavor within the laboratory. It represents an indictment of words and of ideas that have outlived their usefulness and outgrown their meanings.

A book such as this has problems of duplications, repetitions, and, at times,

contradictions. The Editor and his staff have tried to keep such problems to a minimum and request your indulgence where this has not been possible. The interest and encouragement of the Publisher were essential to the accomplishment of our goal.

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INTRODUCTION: WHY EVALUATE METHODS?

Most clinical pathologists would agree that the standard of performance of many laboratory tests is not good enough, but there seem to have been few, if any, systematic investigations into the reasons for this. Inadequate and inferior equipment, staff deficiencies, overwork, and overcrowded laboratories all play a part, but the major cause is almost certainly the use of unreliable methods. All agree that these exist, but since they are rarely named and the exact nature of their deficiencies is not always clear, nobody need admit to using them or, if he does, he can find good excuses for doing so.

Methodology in clinical chemistry has been aptly described as a jungle [60]. (It may be in other branches of laboratory medicine as well, but they seem to have attracted less comment.) Textbooks contain a bewildering choice of methods, some of historical interest only, and many of those in widespread use were chosen for their convenience or popularity rather than

for their scientific merit. On some occasions sound chemical principles have been sacrificed in an attempt to overcome the limitations imposed by the design of an instrument or an automated system; and demands for simplicity, at minimal capital cost, have led to the proliferation of kits, some of which give completely unacceptable results [6]. Sometimes the evidence about the relative merits of different methods is conflicting or lacking entirely, but in other cases (Fig. 1) the information is clear but apparently not always used. The analyst may believe that by a combination of insight and special skill he can obtain good results when others cannot, and occasionally this does happen. He may feel that the method is good enough for clinical purposes, although others do not, and that with his overwhelming work load, speed and convenience are more important than accuracy and precision.

Although it is not usually possible—or even advisable—to specify a "best" method, there is now wide agreement on the need for standard, selected, or recommended methods which have been thoroughly investigated and shown to give consistently reliable results [33, 61]. This approach is widely used in other branches of analytical chemistry, and in some countries only approved methods may be used for tests on patients. However, many analysts fear that this standardization would inhibit the development of new and better methods and thereby remove some of their interest in and enjoyment of laboratory work.

There are remarkably few guidelines published on how to select a method for routine use, probably because this decision is normally assumed to need only common sense and a good textbook. In practice, it is a complex process, more often governed by pragmatism and intuition than by purely scientific considerations. Many psychological influences play a part: the need for simplicity, convenience, and ease of use; faith in the reputation of an eminent author or large manufacturer; fashion, and the elegance of a novel technique or the glamour associated with a new instrument; resistance to change by some and a constant search for improvements by others.

The selection of a reliable method from the plethora available requires information about the quality of each, as well as the knowledge and experience to judge which factors are important, so that the laboratory's ideal requirements can be balanced against a realistic assessment of what is available. The analyst can only do this if given adequate information about the quality of methods; if this is not available or

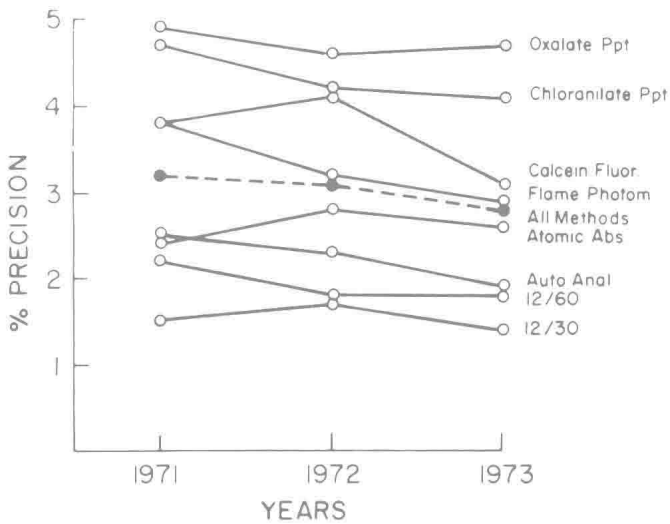

Fig. 1. Within-day coefficients of variation of eight methods for serum calcium determination for the period 1971–1973, calculated from data obtained in the College of American Pathologists survey program. (Reprinted from Gilbert: Am. J. Clin. Pathol. 83: 960–973, 1975.)

is unconvincing, it must be obtained. Any method, no matter how well documented or highly recommended, needs to be evaluated before it is adopted for routine use. Surprisingly few publications have described how to do this [7, 24, 75], and in some respects these differ. There is therefore a need for a better understanding of the factors that should be considered in judging analytical methods and the procedures for obtaining the information necessary to make a wise choice. This chapter discusses these problems from the viewpoint of the clinical chemist who wishes to select an analytical method for routine use, but some of the concepts and general principles also apply to other branches of laboratory medicine.

WHAT FEATURES ARE IMPORTANT?

A clear distinction must be made at the outset between the relevance of the *test* to the clinical needs and the performance characteristics of the analytical *method*. These two concepts often use the same terms, such as sensitivity and specificity, but their assessment is entirely different. The diagnostic usefulness of a test [36] will, of course, be influenced by the analytical performance of the method, but this issue will not be considered further here.

As a first step, the user must decide what type of method he requires and whether his needs would be met by a kit, a manual method, or an automated system. In selecting automatic equipment, he may be influenced by the inclusion of other tests as a bonus, but this feature should not detract from the quality of performance of the test which is primarily wanted. Having found a method, he must ask whether it requires readily available equipment and reagents and if he is capable of using it. He must also decide whether the volume of specimen required is satisfactory and if the method covers the range of values expected in these specimens. Although all these factors are important, they depend essentially on the individual laboratory's capabilities and particular problems. The evaluation itself must be based primarily on features which can be measured and expressed in numerical form so that one method can be compared with another and with the required standards of performance.

Those who try out a method before adopting it are often not clear as to what they are looking for. It is evident from the claims made by some authors and from published evaluation schemes that opinions differ on the importance of different features. A wide range of virtues have been used to describe analytical methods, and it is useful to distinguish between those which can only be judged subjectively (such as simplicity) and those which can be experimentally measured. The latter have been called *performance characteristics* [82]; the following ones have been listed by the IFCC (International Federation of Clinical Chemistry) Expert Panel on Nomenclature and Principles of Quality Control in Clinical Chemistry [23]: *speed, cost, technical skill requirements, dependability and laboratory safety* (jointly referred to as practicability criteria), *precision, accuracy, specificity*, and *sensitivity* (reliability criteria). Although this is not the place to discuss terminology, some of their definitions are given below to aid in understanding the rest of this chapter.*

Precision is the agreement between replicate measurements. It is conventionally expressed in terms of the standard deviation (SD) or coefficient of variation (CV), and both these increase as precision decreases. To describe a method as having high precision could therefore be ambiguous; for example, a statement that precision decreases with increasing concentration could mean that it got worse or that the SD or CV (or both) became smaller. Consequently, it has been proposed [23] that the SD or CV should be called *imprecision* (synonymous with scatter or variability), and no numerical value should be ascribed to the general term precision. The terms reproducibility and repeatability have been used to distinguish different types of precision, but these tend to obscure the many factors which can affect precision, and they have not so far found wide acceptance in clinical laboratories.

Accuracy is the agreement between the best estimate of a quantity and its true value. For similar linguistic reasons it is *inaccuracy* or *bias* which is commonly measured—that is, the numerical difference between the mean of a set of replicate measurements and its true value.

Specificity is the ability of a method to determine solely the component it purports to measure. It has no numerical value, but is expressed in terms of the unwanted components which contribute to the result. A nonspecific method will give falsely high results.

* See Chapter 15.