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1924-1959. II. SCIENTIFIC CONTENTS**

Philip K. Bondy

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HISTORY OF THE JOURNAL OF CLINICAL INVESTIGATION, 1924-1959

II. SCIENTIFIC CONTENTS

By PHILIP K. BONDY, M.D.

Editor-in-Chief, Journal of Clinical Investigation

The most interesting aspects of the history of the JOURNAL OF CLINICAL INVESTIGATION are those pertaining to its contents. Since the editors have, from the beginning, printed unsolicited manuscripts, the subjects of the papers which have been published have depended to some extent on the interests and attitudes of its authors. One might speculate at length as to what passes through an author's mind when he decides where to send his manuscript. Certainly, such considerations as the nature of the article, the audience for which it is intended, the probability of its acceptance, and the prestige of the journal as compared with others in the field enter into his decision. Undoubtedly all of these factors have influenced the material available to the editors of the Journal. The interests and critical abilities of the editors have, in turn, modified the selection of the articles which have finally been accepted. In order to evaluate the pattern which has resulted, I have reviewed briefly the contents of the Journal over the past 35 years. I have paid particular attention to evidence of changing interests of the contributors and to the introduction of new attitudes and techniques into the field of clinical investigation, as mirrored by the articles published by the Journal.

One of the most clear-cut results of this survey is the unexpected fact that little change has occurred through the years in the distribution of articles among most of the major fields of interest. Within fairly narrow limits, the percentage of papers dealing with problems in gastroenterology, infectious diseases or the processes of metabolism has remained unchanged. There has, however, been a gradual reduction in the proportion of papers dealing with the circulatory system. Since "competing" specialty journals in all of these fields began publication after the establishment of the Journal, it appears that the availability of other channels for diffusion of scientific knowledge has

had a variable effect on what is submitted to the Journal for publication.

The major interests of our authors have, of course, changed with the years, but certain problems appear to have exerted a continuing fascination on clinical investigators. Throughout its 35 years, the Journal has carried papers concerned with such topics as the measurement of body fluid compartments, the factors regulating the balance of electrolytes, the mechanism of edema and ascites formation, the nature of "shock" and factors which determine its reversibility, the cause of arterial hypertension, and the measurement and clinical significance of a variety of pulmonary functions. Although the methods which have been brought to bear on these subjects have evolved greatly, satisfactory answers to certain of the problems have still not been obtained. In other cases (such as those concerned with body fluid compartments) the determination of acceptable normal values has been followed by investigation of clinical and physiological situations of increasing complexity. The introduction of new techniques has usually called for re-investigation of previously determined data. For example, plasma volume was first investigated by the dyes "brilliant vital red" and later with "Evans blue" (T-1824), introduced into clinical investigation by Gibson and Evans, *J. clin. Invest.*, 1937, 16, 301. The results obtained by these methods were later confirmed by measuring the distribution of I¹³¹-labeled human serum albumin (Crispell, Porter and Nieset, 1950, 29, 513) and by the use of radioiron or chromium-labeled erythrocytes (Sterling and Gray, 1950, 29, 1614) combined with the hematocrit.

Although these general topics have continued to occupy the attention of our authors, the degree of interest in the different problems has varied as techniques have changed, and as external influ-

ences have provided impetus for special "practical" studies. The investigation of shock, for example, was greatly expanded during the Second World War and the Korean War. The intensive study of agents to protect against arsenical poison gases resulted in the publication of a mass of material related to "British Anti-Lewisite," which appeared as a supplement to the Journal. The wartime interest in blood preservation and the therapeutic use of plasma, either in its native form or after fractionation, resulted in a flood of papers related to these subjects. Our authors have always been interested in the study of infectious diseases, but the mobilization of large numbers of soldiers and their maintenance in tropical regions sparked a particularly intense study of such diseases as infectious hepatitis, malaria and influenza. Although some of these manuscripts were gathered into special supplements, many appeared separately in the general pages of the Journal during the later part of the war and immediately thereafter.

Certain other topics have apparently been of interest for only restricted periods of time. If one divides the past life of the Journal into three parts, beginning in 1924, 1938 and 1948, it becomes apparent that certain issues which occupied the energies of investigators during the first period had ceased to interest them in later periods. Studies of the electrocardiogram, for example, have occupied only a very small amount of space in our pages during recent years, although when the Journal first began publication, many papers were concerned with the mechanisms and interpretation of cardiac electrical phenomena. A great deal of attention was paid to the measurement and evaluation of the concentrations of plasma electrolytes and proteins in the early years. The pioneering work (Volumes 1-11) of J. P. Peters, F. W. Sunderman, J. H. Austin, and their colleagues in adults, and of A. F. Hartmann and D. C. Darrow in children, applied scientific principles to the study of the changes of body composition in disease states, and laid the foundation for modern clinical chemistry. The application of similar techniques by Atchley, Loeb, Richards, Benedict and Driscoll (1933, 12, 297) to the study of diabetic acidosis underlies all modern concepts in the treatment of this disease. Laboratory methods intro-

duced by these and other workers have proved so successful in the clinic that they have tended somewhat to supplant the Oslerian tradition of bedside diagnosis. The gradual progression of these techniques from the experimental laboratory to the routine care of patients represents a triumph of the principles to which the Society and the Journal are dedicated. But, as these methods met with widespread acceptance, they have ceased to be of much interest to those in the forefront of medical research. Very little material related to the concentration of plasma electrolytes and proteins has appeared in the pages of the Journal during the second two periods of its existence. Similar remarks might be made regarding the evaluation of tests of gastric analysis or the mechanism of action of the anti-anemic fraction of liver extract. The latter returned to a position of interest, however, when the isolation and characterization of vitamin B₁₂ provided an opportunity for the specific studies of utilization and transport which have appeared in recent years.

The study of renal physiology has pursued an interesting pattern. During the early years, the study of urine morphology and the total quantities of various urinary constituents occupied most of the interest of our authors. With the introduction of the urea clearance technique, interest in renal function began to assume a somewhat more modern aspect. It was not until the second period of the Journal's life, however, that the introduction of specific renal clearance techniques such as the inulin clearance (Shannon and Smith, 1935, 14, 393), diodrast clearance and para-amino hippurate clearance (Smith, Finkelstein, Aliminoso, Crawford, Graber, Goldring, Chasis, Ranges and Redish, 1945, 24, 388 and 583) inaugurated the flowering of renal physiological investigation which continues to the present.

From 1938 to 1948 new problems occupied our authors. During this time, the ballistocardiograph was studied intensively. The relation of the kidney to hypertension was investigated by elucidation of the renin system. The relationship between streptococcal disease and rheumatic fever was elaborated. New methods permitted a study of the nature of the plasma lipids and their change in disease. The sulfonamides, followed by penicillin and streptomycin, came in for increasing atten-

tion. The pattern of medical science and clinical practice was changing so rapidly during this period that often by the time studies were published they were somewhat outdated. For example, the highly informative paper by Wood (1940, 19, 95) on the clinical estimation of antiserum titer in patients with pneumonia appeared after the development of sulfonamides and penicillin had begun to render interest in antipneumococcal serum of only theoretical interest.

The recent interest in the application of radioactive substances to the measurement of physiological processes was foreshadowed by the experiments of Blumgart and Weiss, who used radium-C to measure the circulation time (1927, 4, 15). Aside from their series of experiments, which lasted until 1930, however, radioactive measurements were not used until the late 1930's. The real spurt of interest in the techniques made possible by these substances, however, belongs to the postwar period. During the past 10 years, few fields of experimental medicine have escaped the influence of the counter or mass spectrometer. The availability of isotopic tracer substances has encouraged another recent development, namely the introduction of elaborate mathematical systems for the treatment of kinetic data which could be derived from such tracers. In leafing through the pages of the Journal, one is struck by the rarity with which mathematics was applied to the analysis of experimental data during the first two-thirds of the Journal's existence. Even the use of statistical analysis, a shibboleth of present scientific writing, did not appear until about the twelfth volume (1933) when Starr, Collins and Wood defined for their (presumably statistically naive) readers such parameters as the standard deviation, coefficient of correlation, slope of a regression line, and so forth. In the beginning, when mathematics was applied, it often took the form of a simple repetition of basic laws of physics, usually dealing with pressure, flow, viscosity and other parameters of the circulatory system. The introduction of differential equations to our pages has been a recent and (for some) traumatic experience. It is little solace to reflect that the mathematics commonly employed by our authors is usually of a variety which mathematicians find most pedestrian. It seems likely that the present

trend toward the erection of mathematical models will expand, and that the days of simple arithmetical innocence are gone forever from our pages.

Experimental techniques have changed during the past 35 years, but not, perhaps, so basically as might have been expected. We still have today, as we did in the beginning, the metabolic balance study, the Fick Principle, and the epidemiological study. The application of these methods is somewhat different, however. Whereas, in earlier days, one studied the balance of sodium or nitrogen, one is now likely (in addition) to study the balance of steroids, amino acids, trace metals or vitamins. No longer does the cardiologist ventilate his subject with ethyl iodide; he transfixes him with a cardiac catheter instead. But he still applies the time-honored mathematics of Fick (published elsewhere in 1870). The fact that many of the early papers concerned with the development of the cardiac catheter technique were published in this Journal (Courmand, Riley, Richards and their co-workers, Volumes 24-28) probably accounts for the presence of papers which have expanded and extended the methods to include the study of congenital heart disease (Dexter, Haynes, Burwell, Eppinger, Seibel and Evans, 1946, 26, 547), estimation of hepatic blood flow (Bradley, Ingelfinger, Bradley and Curry, 1945, 24, 890), coronary blood flow and extraction of various substances by the kidney. But all of these extended catheterization methods still hark back to Fick.

The study of infectious disease, especially in its epidemiological aspects, has changed very little, but the weapons now used are virus isolations and complicated immunological techniques, whereas years ago bacterial cultures and fairly simple antibody tests were used.

As clinical researchers have become increasingly basic-science minded, they have tended to introduce an increasing interest in biochemistry and particularly in enzymology, specific chemical isolations and accurate fractionation procedures. An interest in enzymes has been present from the beginning, but originally it was the digestive enzymes which were studied. Later, the presence of certain enzymes in the blood was related to disease processes. A case in point is the description, by Gutman and Gutman (1938, 17, 473), of the ele-

vation of serum acid phosphatase in patients with metastasizing prostatic cancer. Other enzymes have entered the picture until at present the study of plasma enzymes is, in itself, an overwhelming preoccupation of a certain part of the medical community. The Journal has recently published a number of papers concerned with this phase of clinical research. But more basic has been the increasing number of papers which have applied the disciplines of enzymology to the explanation of disease processes. For example, we have recently published several papers concerned with the relationship of the anaerobic metabolism of carbohydrates in erythrocytes to hemolytic disease.

The interest in purification and fractionation of complex biological substances is, perhaps, best exemplified by the extensive studies concerned with the separation of the various protein fractions of plasma. Most of the papers emanating from the laboratory of Cohn and his successors have appeared in the Journal; indeed, an entire supplement was devoted to them in 1944. The expansion of this type of study to provide information about the protein-binding of trace substances such as iron and copper, and to supply useful products such as antihemophilic globulin, gamma globulin, fibrin, fibrinogen and albumin, is a story which has been written, for the most part, in the pages of the Journal.

Considering the fact that the Journal was established specifically to publish the results of investigations of clinical problems; it is not surprising that most of the material published in its pages can be related in some way to disease processes or to the establishment of normal values against which impaired function may be measured. There has, however, been a notable paucity of papers concerned with the presentation of clinical observations based on bedside observation. Moreover, such observations have tended to become even rarer as the years have progressed. In spite of this, purely clinical papers continue to appear occasionally in the pages of the Journal, usually in conjunction with a related experimental or epidemiological study. The plaintive comments of some of our readers that "there is nothing very clinical about the JCI any more" are not supported by the facts. Many of the studies reported in these pages have originated in attempts to answer

clinical questions. The continuous progress of clinical medicine has been based on apparently "impractical" scientific studies of disease.

From the very beginning, the editors have attempted to publish only "worthwhile" papers. Since mere repetition of previous studies is not likely to be rewarding, most of the material in the Journal represents a "first" (or at least a fairly close "second") of some sort or other. It is undoubtedly brash, therefore, for me to attempt to select from our archives specific papers which seem particularly important. In spite of this, I have been so impressed by the impact of a few of the papers on present scientific or clinical thought and practice that I could not refrain from singling out one or two for particular mention. I have already cited some of them. Others, which were published within the past 10 years or so, are so recent that it seems too early to single them out. But among the early papers were several more which seem worth mentioning.

The introduction of a new viewpoint may be of great importance. The diagram of the plasma ionic pattern in a paper by Gamble and Ross on page 419 of Volume I must represent one of the very earliest uses of what later generations of medical students were to know as the "Gamble-gram."

The fact that parathyroid hormone exerts a primary effect on the renal excretion of phosphorus was described by Albright, Bauer, Ropes and Aub (1929, 7, 139). The subsequent studies of calcium metabolism and parathyroid function by these and other authors resulted in a remarkable piece of scientific investigation and cross-country cooperation when a pair of papers were published by Hannon, Shorr, McClellan and Dubois (1929, 8, 215) and Bauer, Albright and Aub (1929, 8, 229) describing the same patient, Captain Charles Martel, who represented the first case of hyperparathyroidism diagnosed in the United States.

The "iron lung" is a familiar (and, we hope vanishing) piece of apparatus in most hospitals. It first saw light in the laboratories of Dr. Philip Drinker, and was launched in the Journal (Drinker and Shaw, 1929, 7, 229). The prolonged studies of acidosis in children carried out in Hartmann's laboratory culminated, in a prac-

tical sense, in the introduction of the use of sodium lactate for the treatment of acidosis in children by Hartmann and Senn (1932, 11, 327).

If these selections seem biased and arbitrary, it must be remembered that they are personal. Other reviewers would doubtless select other papers, for there is a huge store of information in the past issues of the Journal. A large part of this information is still as fresh and valid as it was years ago when it first was published. This continuing value arises from the high standards set by the editorial committees in conformity with the objectives of the Society. The Journal has been one of the most important vehicles for the expression of the Society's ideals, and (together

with the annual meetings) has kept constantly alive the principles of excellence which impelled the founding fathers to form the Society. The struggle to maintain high standards has not always been easy, and the fact that they have been sustained is a tribute to the authors, reviewers and editors who have labored to bring this about. If your present editor ends this brief note with a feeling of pride it is for the traditions of the institution which he serves, rather than for any personal feeling of accomplishment. And this pride can be shared, not merely by members of the Society, but by all who have contributed to the progress of medicine in the past years, in whatever capacity they may have functioned.