Papers and Originals

REFLECTIONS OF A MEDICAL EDITOR*

BY

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Looking back to 1946, when it was first suggested that the Association of Clinical Pathologists should launch its own journal, I am left wondering why we thought it so necessary at that moment. The association was not quite 20 years old, was not yet expanding into its post-war boom, and the National Health Service, which was to play such a great part in the development of clinical pathology in this country, was only just being introduced by Act of Parliament. Could it possibly have been that the sponsors of the new journal felt that pathologists at that time did not have enough reading material? Was it possibly because the existing journals were so heavily oversubscribed that pathologists found difficulty in getting their papers accepted and published? Was it perhaps to be a "status symbol" for the association itself? Or was it really, as the council of the day was persuaded to accept, that with the increasing pressure on the four main disciplines in clinical pathology it was becoming essential to provide a platform on which some unification of those disciplines could be maintained and encouraged?

Objectives

Until now, therefore, we have tried to maintain the *Journal of Clinical Pathology* as a general journal in clinical pathology, carefully allocating approximately one-quarter of the available space to each main subject. Although the objective of the editorial board remains the same, as each discipline becomes more specialized we shall find fewer general practitioners in clinical pathology and more of our readers will be turning to their own specialized periodicals. I have therefore been examining the needs of pathologists as writers and readers with a view to making tentative proposals for the future of the journal, and I have been especially concerned with its place in the general medical literature of the day. Inevitably I have been drawn into the whole question of scientific, and particularly medical, literature, and though I shall make generalizations I shall attempt to particularize where possible for pathology.

I have asked myself a number of questions, to some of which I found no answer. (1) Why do we as an association of clinical pathologists need to maintain a journal, and should we go on doing so? (2) Why do so many people wish to write for medical journals, and why do they wish to see their papers published in the *Journal of Clinical Pathology*? (3) Why do other subscribers take our journal? (4) What other journals of pathology do pathologists read? (5) If the journal is to continue, should it maintain its present form? If not, what changes are possible, or can we offer any suggestions for easing the burden of the pathologist as a reader as well as a writer?

The *Journal of Clinical Pathology* was started in 1948 with a single issue published privately by the

Association of Clinical Pathologists. This proved such a costly business that we quickly sheltered under the umbrella of the *B.M.J.* through the B.M.A. and became one of its scientific quarterlies. Therefore the journal, although it is the official journal of the Association of Clinical Pathologists, is really run as a joint venture with the B.M.A.

If you look at the slim first volume and compare it with the 1961 volume you will see that we conform to the normal in rate of growth. The first volume (1948) was devoted to 38 scientific articles contained in 231 pages, whereas the 1961 volume contained 111 papers in 588 pages, not including abstracts, technical methods, and book reviews. The increase in sales also suggests that the journal is meeting a demand from pathologists not only in the United Kingdom but from all over the world. Its scope and orientation is to some extent dictated by the editorial board, but in fact the face of any scientific periodical reflects much more the interests of its readers. What then is the face of the *J. clin. Path.*, to give it its familiar abbreviation? What does it reflect to-day?

Each year we look at the pattern of the papers which have been offered and accepted or rejected. We see a surprising consistency in the last few years, with a fairly equal number of papers offered in each subject, some 50% of all papers being rejected. The standards of the papers published I believe to be higher than before; I believe, too, that there has been something for everybody in the journal. If I am right in my guess then one of the aims of the Association of Clinical Pathologists has been successful—to bring under one cover material in all the four disciplines of pathology.

If we now assess all this activity, and especially the astonishing growth and development of the *J. clin. Path.*, I suppose we should be congratulating ourselves. But as I surveyed the general medical literature I began to feel certain qualms. Does the journal's success reflect an expansion of our specialty or even the vigour of our association? I began to fear that perhaps our success was merely a reflection of the general pressures being exercised on editorial boards of journals all over the world to increase and multiply. There is undoubtedly a mad rush to get papers published, and all periodicals, however recondite, are to-day basking in this era of prosperity.

We can, I suppose, enjoy the credit of being one of the more important journals which must be read by those wishing to be well informed, and we can answer the earlier critics who were doubtful of the wisdom of launching another journal at that time. But I wonder whether this is not the moment when we should be looking forward instead of backward and thinking about the possible modification of the journal and thereby of the writings of pathologists. So let us first examine the present purpose of the writers for this journal.

*Abridged version of the presidential address in 1962 to the Association of Clinical Pathologists under the title "The Pathologist and his Writings."

Purpose of Scientific Writers

There appear to be two main forces which drive people to write papers. First, all scientific workers have a public duty to relate and to offer to the world the results of investigations, original observations, and research work. This is both legitimate and praiseworthy, and should be encouraged at all levels. Highest priority on space should be given to such work, but not, I venture to think, until it has been critically assessed and is complete. Dr. J. Ralph Audy (Conference, vol. 1, no. 1, August, 1960) says: "Research which remains uncommunicated to others is work for private edification and may be discounted." This is a little harsh—and, anyhow, I see nothing wrong with private edification. Clearly we must aim at a middle path. There is a place for preliminary communications, which must be so titled, and I hope that our journal will soon accept such notices, rather like those which are offered to *Nature*; but, alas, the pages of our journal and of most scientific journals frequently contain records of half-finished or jejune work. Why do authors submit such work, and, even more so, the sort of work which is inevitably rejected? This is the effect of the second force which urges people to write to-day. It is reflected in such phrases as "publish or die," or, conversely, "publish to survive," or, at its worst, "publish to get on or get known."

There is also abroad the idea that it is important to get in first or to establish priority. Mr. A. L. Bacharach (1962) mentions the need for preliminary notices of important new advances, but says that the insistence on speed of publication is a "pathological development in science with a bad influence." The pressure arises from a number of causes. Some directors of research and some research grant committees demand as a prerequisite for continued employment or further grants regular publications from their workers. This demand is, I think, most objectionable from any point of view. University departments of pathology must indeed foster the drive for research and everything must be done to encourage not only the research project and team but also each research worker, and there must be available a medium in which to publish the results of these researches. But I should like to quote a distinguished authority on the subject in this society who once said to me: "When a man is appointed to a university department part of his duties should always be recognized as research, and thereafter the need to publish is instilled into the man because it is essential for the man and the department." Publication then becomes more important than the research itself. This is surely a wrong and unbalanced way of thinking about publication. Even if a young man must strive to become known, I hardly think we should get ourselves into the state of mind which believes that research committees or university departments of pathology need this kind of regular publicity.

In Britain at present the necessity to publish something is also exaggerated by the method of appointing consultants in the National Health Service. On each application form the candidate is asked to provide details of his publications. This stresses to both candidate and committee that publications are essential before consultant status can be attained and that quantity may be more important than quality, because the actual papers are not asked for or assessed by the professional committee.

The Problem of Priority

May I return to the difficult problem of establishing priority? An editor has to weigh carefully and privately with his assessors the claims of any author for priority, bearing in mind that important advances should be brought to the attention of all workers in the same or related fields as soon as possible. Most editors are human enough to wish their journal to make an occasional hit, and they would therefore accept avidly any paper which advances scientific knowledge and offer it early publication. In this I disagree with Professor W. V. Thorpe (1962), editor-in-chief of the *Biochemical Journal*, who suggests that editorial boards must refrain from selecting topical and interesting papers in preference to unexciting routine work, "for," he says, "what is dull to a man working in one field may be of vital importance to those working in others."

It is not always easy or equitable to accept for priority the first paper on an apparently new subject which appears on the editorial desk. We probably all feel that most new observations seem to come rather suddenly and to have occurred almost simultaneously to several groups of workers who have probably all been stimulated to the same line of research because of a chance remark, chance thought, or deductive pieces of reasoning which followed naturally on some other publication. M. L. Johnson Abercrombie in the *Anatomy of Judgment* (1960) says: "It is difficult for scientists to question the basic assumptions of their age. They are taken for granted because enough competent people have held them for long enough. Like the mores of a culture they are anonymous and so all pervasive as to be almost imperceptible. It requires an Einstein to offer any alternative." All editors have to go on in most questions of priorities is the sense of a move forward in an existing pattern which makes for a furthering of our understanding of a disease process.

A group of serious workers who may be working on a problem and its ramifications from first principles must feel frustrated indeed when a journal rather lightly publishes a preliminary communication from another author which may even incorporate some of their own as yet unpublished data and therefore establishes priority for another group of workers. Editors are often blamed for this state of affairs, but, however careful the assessors are, somebody who is quick off the mark can sometimes beat the gun unfairly. I therefore feel very sceptical about priority for its own sake. An editor can only try to take a judicial and impersonal view, hoping that he does not make too many mistakes and ignoring whenever possible the pleas of the author as opposed to that of the assessor for priority in publication. Other less laudable reasons in asking for quick publication are sometimes offered, such as an application for an imminent vacancy, the need to tell the world quickly, or because "the Americans," that nebulous body of prolific pathologists across the Atlantic, are working on the same theme and are due to come out in print "at any moment now."

Another but less important difficulty an editor has to face occurs when, after a preliminary note in the journal, a number of people are reminded that they have in fact also seen or been aware of a particular item of interest. There follows a spate of papers on the same subject. Some of these papers incorporate the results of years of study which the author feels will be lost if not offered at this precise moment; others have been incubating for

a shorter period; and the last and worst papers are those which have been put together very rapidly in order to hit the headlines. This is gamesmanship, and a particularly odious form of plagiarism which is difficult enough to spot at the time. After an editor has accepted two or three offerings on the same topic, he may feel bound to close his columns to any further papers which merely repeat the same thesis with a larger or smaller series of cases.

While talking of repetition, may I also draw your attention to the sort of paper which is repeated with slight alterations in a number of different journals? It is becoming fashionable for pathologists to write in the periodicals of their specialist subjects; for example, we now have paediatric pathologists, gynaecological pathologists, and pathologists working in special hospitals for diseases of the heart, chest, bone, etc. These pathologists may feel the need to report their work in the journals of paediatrics, chest diseases, etc., as well as in the journals of pathology. And so we frequently encounter almost identical papers by the same authors in the general clinical journals, the journals devoted to the study of individual organs, and the journals of pathology, with slight variations in accent each time.

Literary Style

I should like to discuss briefly the question of literary style as it affects the pathologist. Sir Thomas Lewis in 1944 said that "a disquieting proportion of what is offered to the student in conversation and in the generalities of journals and books is inaccurate, slovenly, and redundant." Although I think that this is an exaggerated and rather sweeping statement I quote it because I believe there is a tendency among pathologists to-day towards slovenly writing, which is increasingly difficult to correct. In a recently offered paper an author wrote "G.O.D. splits glucose into gluconic acid and hydrogen peroxide (H_2O_2), the latter is split by a peroxidase into water"! He went on to say that "since 1956 test papers impregnated with G.O.D., P.O.D., and O-toluene have been commercially available and have found extensive use." I am perhaps a little oversensitive to the form of abbreviation by capital letter which is so widely used to-day without explanation.

It is difficult for writers to allow themselves the prose style of the earlier medical writers, whose descriptions of pathological lesions were such masterpieces. This is because many modern editors have little feeling and ear for good prose and are relentlessly urged to save space. Loose and slovenly writing is particularly unfortunate in descriptions of techniques, and we have found it disturbing when assessors or readers attempting to repeat an experiment fail to reproduce results, whereas a few minutes of personal contact with the author would clear up the difficulties. The fault is partly the authors', and partly the editors', who have not tightened up the description of the method sufficiently to ensure that it can be easily followed. Scientific writing to-day in national journals must be written in a manner that is capable of being read and understood in China and Russia as well as in America and Britain. Therefore authors must avoid the temptation, and editors must ruthlessly blue-pencil all attempts at parochial writing and allusions, whether they are locally accepted short cuts with ancient Anglo-Saxon terminology, Gaelic innuendo, or lilting Welsh descriptions. These and slang, personal abbreviations, and jargon used by pathologists in local discussion groups among themselves have no place in international scientific writing.

In purely technical writing I feel that clarity is helped by brevity. I must add that editors are only human, despite suggestions to the contrary. They are impressed by papers which are well thought out and planned and clearly and succinctly presented. Such a paper has a greater chance of acceptance than one which has been badly typed in a hurry on poor paper and is full of scribbled corrections and insertions. These papers deserve to be rejected because at the very least they show discourtesy to the editors.

Surmounting the Literature Problem

I now come to certain suggestions which might help pathologists to attack the mounting problem of the literature. How do most of us surmount it at present? I suppose that some pathologists subscribe to one of the abstracting journals as a means of keeping abreast of new work. These are laboriously prepared, but they are increasing in size so rapidly that it is a major effort to read through the abstracts provided in order to find which papers have to be read in full. I do not think that abstracting journals are generally selective enough and they are frequently repetitive. I believe that abstracts are better if they are produced infrequently and more comprehensively than at present.

Many pathologists belong to local abstracting clubs, so that the burden of reading a large number of journals is shared. Many of these clubs have died a natural death after differing periods of longevity, or have kept alive because of the driving force of one or two people. Many who work in the larger cities come to rely on regular meetings of medical societies, learning more from the spoken word and personal contacts (with much less effort) than from the laborious reading of journals. And as an addict to meetings, and a laborious reader, I find this a better alternative.

There has been a remarkable growth in recent years of clubs which are designed to bring together workers in different branches of science but confined to a single field such as the Renal Club, the Central Sterilizing Club, the Thyroid Club, and these certainly maintain high standards and help to inform members of new and developing work.

How to maintain an up-to-date interest and knowledge of the literature is becoming an impossible problem for many pathologists, and I would like to summarize some suggestions that have been made to solve it. Professor Bernal (1939) has suggested that there should be better abstracting services and private circulations of papers rather than more journals run on conventional lines. Dr. Rutstein (1961), of Harvard, is also greatly in favour of reducing the numbers of original contributions, proposing editors should only accept those of the highest order after a severely critical assessment. Dr. Rutstein also hoped for a greater exchange of information between journals to avoid duplication. I believe this is of paramount importance, but it is very difficult to achieve at present because of the competitive spirit which exists between journals in any country and between journals of different countries. Dr. Rutstein also pleads for classification of papers and even different parts of any one paper by editorial boards so as to achieve a national or even international system of indexing, thus making it possible to feed such standardized information into a computer system of some sort.

Dr. Shiloh (1962), of Jerusalem, on the other hand, feels that things have gone too far already and that publica-

tions as we know them to-day are already outmoded. He recommends that, apart from certain original observations (not defined), publications should now be replaced in large measure by carefully programmed international seminars, at which groups of scientists interested in the same subjects could exchange ideas. These could be held at a national as well as an international level, and he points out that if scientific governors encouraged travel the communications so achieved would probably be more profound and detailed than any resulting from the struggle through the literature. I would support this view up to a point, but many of the larger international meetings fail because of poorly planned programmes and the unnecessary compulsion on participants to offer a paper, however ancient and repetitive, because without it the universities and other authorities would not meet the expenses involved. Sir Francis Walshe (1959) maintains it is probably true to say that no original discovery ever takes the air for the first time at a symposium. "It usually appears in print as an original contribution in an appropriate journal, but nowadays it goes on tour" with what he calls the "wandering symposiast." Smaller meetings, such as those arranged by the Ciba Foundation, are clearly of a much higher standard, but I believe that the reports for the non-participant are too detailed and too colloquial, and many would prefer a summary of the proceedings.

Suggested Changes

And so at last I come to certain suggestions for changes that may incidentally lighten the burden of the reader as well as of the author and editor.

First, we must adopt a firm attitude towards specialized scientific publications, reducing the number of references to the most relevant only, and not pretending that long introductions covering the literature, with pages of references to follow, indicate erudition. I would like to see this adopted by all our contemporaries, reserving only, say, the *Journal of Pathology and Bacteriology* and the *Quarterly Journal of Medicine* for lengthy philosophical contributions. Any other long papers should be published as monographs with abstracts sent to the appropriate journals. Secondly, we must discourage authors who divide their work into sections, distributing their largesse to a number of journals. We should set up a clearing-house so that papers appear whole in the most suitable journal, and abstracts provided by the author and editor then be sent to all other interested journals. Usually the abstract would be the author's carefully prepared summary. I believe that this one measure could reduce published articles by about a quarter.

You may have noticed that last year we, conforming to the practice in many other journals, transposed the authors' summaries from the end to the beginning of the paper. If an author is enthusiastic about his paper he can often transmit this enthusiasm to his reader in his summary, and we are encouraging authors to make their summaries their "shop front." There is a great art in writing synopses, and this will have to be developed by us all. Summaries must, of course, summarize; they must not be discursive or go into great detail, and their statements must be so simply and lucidly made that anyone, whether working in a particular field of study or not, should be able to assess at once what the paper has to say and whether he is interested enough to read it. Some people have suggested that, if things continue as now, in the not-too-distant future we shall in any

case only be able to print the summaries of papers. The whole of the paper with full data could then be deposited, say, with the British Museum or in some bottomless well, and anybody who really wished to consult the original manuscript could be provided with cheaply made photostats. These would be paid for by the applicant, and this practice in itself could go a long way to putting an end to the spate of cards which arrive almost automatically from the whole American continent requesting reprints made at the author's expense.

We have to decide for our *Journal of Clinical Pathology*, just as every editorial committee should decide, whether the object of publication is to provide opportunity and space for workers to publish the results of their observations and experiments—that is, for the recording of data—or whether the main object of the periodical should be for the information and education of its readers. The two objectives are not necessarily mutually exclusive, but the main orientation of the journal will have to be defined, otherwise contributors become frustrated by what they think unreasonable rejection of their material and assessors cannot carry out their duties properly. On the whole, the *Journal of Clinical Pathology* does provide a platform for both types of contribution, but perhaps we should allocate more space to the second type of offering than we have done in the past.

This brings me to my third suggestion, which concerns review articles. We adopted the technique of reviews very early in the life of the *Journal of Clinical Pathology*—in fact, in the first volumes—and were so pleased with the reception of these that they have become a regular feature of the journal. Their appearance should coincide with that stage when enough is known of new work, or when important changes have come about in older and established theories or techniques to make it imperative for every pathologist to be acquainted with the new views. Such reviews would ideally not only summarize recent work but evaluate it and comment on its implications, so that a pathologist can readily assimilate it into his routine practice if recommended. Review articles we have published have done a great deal to enhance the reputation of the journal and help to keep pathologists informed in the four branches of pathology.

We have on three occasions devoted a whole number to a special subject, and on those occasions some of the contributions were commissioned and others offered. The first such number was in 1953, when we reserved a whole issue to papers on coagulation defects; and the Oxford "school of coagulationists," so ably led by MacFarlane and Biggs, helped to provide an outstanding number of vital interest and importance. The second, in 1961, was a number which commemorated the life and work of Virchow. The third, also in 1961, published as an extra number, was devoted to the problem of hospital cross-infection and collected in one volume a wealth of information on one of the most important problems of to-day. This issue became overnight a best-seller and is still used as an authoritative reference by administrators as well as by doctors.

Conclusion

I believe we should now anticipate some modifications in the *Journal of Clinical Pathology*, and, I would hope, in many other periodicals which cater for the writings of pathologists in particular and of medical writers in general. If the journals would concentrate more on

up-to-date information and critical reviews, abstracts of important papers recently published by sister journals, and more streamlined less discursive articles, we could take a bold step forward in reducing the volume of reading material for our long-suffering colleagues. We would hope also to co-operate with other editors in defining the field of interest in our journals and at all times attempt to cater at least as much for the reader as for the author.

We may feel that these problems are becoming more and more urgent in the medical sciences, but more than two thousand years ago, in the heyday of Pompeii, the matter was already causing concern. On a wall of the Meeting House which was used as a wall newspaper there is a clear inscription, which freely translated reads: "It is a miracle O wall that thou has not yet crumbled under the weight of so much written nonsense."

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IN-VITRO AND IN-VIVO STUDIES OF A PREPARATION OF UROKINASE

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At the present time there is much interest in the possible use of fibrinolytic enzymes in the treatment of intra-vascular thrombosis. One such enzyme, urokinase, is the physiological fibrinolytic substance present in a normal urine. Urokinase owes its fibrinolytic activity to its property as an activator of plasminogen (Fig. 1). Plasminogen, a natural plasma globulin, inactive in its native state, is converted by urokinase to plasmin, a proteolytic enzyme with wide substrate specificity. As suggested by Sherry *et al.* (1959a), clot lysis *in vivo* probably takes place by diffusion of activator—for example, plasma activator—into the thrombus, with conversion of clot plasminogen to plasmin. The plasmin so produced is close to the substrate of choice, fibrin, which is digested. Inhibitory mechanisms in the plasma normally prevent the appearance of free plasmin in the circulation.

Urokinase, itself a proteolytic enzyme, activates plasminogen by first-order kinetics probably by splitting lysine and/or arginine bonds (Kjeldgaard and Ploug, 1957; Alkjaersig *et al.*, 1958). It is a colourless protein with a high degree of stability over a wide pH range (Ploug and Kjeldgaard, 1957).

Bjerrehuus (1952) has shown that urokinase concentrations are similar in bladder urine and urine obtained from the renal pelvis. The work of von Kaulla and Swan (1958) and of Smyrniotis *et al.* (1959) suggests that urokinase may represent in part at least excreted plasma plasminogen activator. There is evidence to support the concept that it has a physiological role in maintaining the patency of the urinary tract by promoting the lysis of fibrinous deposits (McNicol *et al.*, 1961).

Because of its human origin, it has been hoped that urokinase might have many advantages, including freedom from toxicity and antigenicity, as a therapeutic fibrinolytic substance (*British Medical Journal*, 1962). Interest in the use of urokinase was stimulated by its isolation and purification by Ploug and Kjeldgaard (1957). There are reports in the literature of the use of urokinase-activated plasmin—for example, Sokal *et al.* (1958) and Sussman and Fitch (1958)—and Hansen *et al.* (1961) also report on the infusion of urokinase to 22 subjects, though they present no data on the biochemical effects induced.

Recently a commercial preparation of urokinase, intended for trial by clinical investigators, has become available (Leo urokinase), and the present paper gives the results of study of this preparation *in vitro* and *in vivo*.

Materials and Methods

Urokinase.—A purified preparation, isolated from the urine of normal males, was made available by Leo Laboratories Ltd. The preparation, supplied as sterile yellowish-white pellets, was freely soluble in 0.9% sodium chloride. The manufacturers state that potency, in arbitrary units (Ploug and Kjeldgaard, 1957), varies from batch to batch from 5,000 to 12,000 units/mg. The materials used in this study had a potency of 7,100 units/mg. Calcium content of a 10,000-unit/ml. solution was less than 0.2 mEq/litre.

Fibrinogen was prepared from the expired bank plasma by a phosphate buffer method (Biggs and Macfarlane, 1962a).

¹³¹I-tagged fibrinogen was prepared by the method of Clement and McNicol (1959). Clottable radioactivity varied from 90 to 93%. Samples were counted in a well-type scintillation counter with a pulse height analyser.

Plasminogen.—A preparation of human plasminogen, soluble at neutral pH, was made available by the Kabi Pharmaceutical Company.

Thrombin.—Parke Davis thrombin topical.

Citrated Blood.—This was collected by clean venepuncture. Nine volumes of blood were mixed with one volume of 3.8% sodium citrate in a graduated centrifuge tube.

Plasminogen assays were carried out by the caseinolytic technique of Remmert and Cohen (1949) as modified by Alkjaersig *et al.* (1959a).

Activator assay, with plasminogen-enriched ¹³¹I-tagged clots, was performed by the technique of

FIG. 1.—Showing how urokinase converts plasminogen to plasmin. Plasmin, a proteolytic enzyme with wide substrate specificity, digests fibrin to give soluble products.