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IS THE CURRENT SYSTEM OF SCIENTIFIC COMMUNICATION ADEQUATE TO THE AGE OF PLASMID ENGINEERING?

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In order to deal with both the general problem of scientific information, as well as the specific problem of information on Recombinant DNA, we have divided our paper into two parts. The first part will deal with the problem of information retrieval and the second will outline some of the special sources on plasmids not published in available journals.

In order for scientists to function effectively today, they must have the assurance that they are aware of all research which may have some bearing on their activities. Whether the topic is antibiotic resistance in bacteria, cloning of unnatural molecules, recombinant DNA or any other aspect of science, we must insure that maximum advantage is taken of the new methods that have been developed in the past decade for general and selective dissemination of information. Undoubtedly, the import of this assertion is of greatest significance to our scientific colleagues throughout the underdeveloped world. For a variety of reasons, many of them may not have been exposed to many of these more modern methods.

The reasons why scientists in many countries have not had the benefits of these new services are fundamentally economic and political. Scientific information dissemination and publication oftentimes receive a very low priority in countries where hard currency is in limited supply. In particular hard currency has not been made available on a large-scale to the scientific community to purchase foreign information services. Those of you who are from the U.S.A. and those other nations who are familiar with *Current Contents*® and other information methods must forgive us if we do not take for granted these systems are known to you. The large number of new subscriptions to *Current Contents* received each year, particularly from the newly developed areas, indicates that, at least, a brief summary should be provided.

Current Contents is a weekly service of the Institute for Scientific Information®. Its basic purpose is to include the contents of over 1,000 leading journals in the life sciences. Five other editions of *CC*® provide similar coverage of their respective fields. As a weekly publication, *CC* provides prompt access to the content of the most important journals in the pre-clinical, clinical and natural sciences. Biochemistry and molecular biology have always been regarded as focal points of coverage as well as immunology, pharmacology and microbiology. All aspects, therefore, of antibiotic resistance research are covered. By scanning *CC* each week the research scientist can not only find out about papers of specific immediate relation to his research, but also keep in touch with ancillary fields.

An optional Weekly Subject Index was added to *CC* a few years ago and has become very popular. Assistants or secretaries can be used to check lists of key words such as cloning, recombinant DNA, etc.

Perhaps the most important and widely used part of *CC* is the Author Adress Directory. Through this directory millions of reprint request cards and letters are initiated each year. ISI® sells several million of its own *Request-A-Print*® cards. The use of *CC* in combination with reprint requests has enabled thousands of scientists, especially in developing countries to build up extensive reprint libraries. On the other hand this has meant that authors had to order more reprints than before. It is not unusual for an eminent scientist like Spiegelman to send out 2,000 reprints of an article. An average is closer to 300 these days though 500 is not uncommon.

CC has in fact also fostered greater use of journals and is particularly important to the establishment of new journals. The average *CC* reader subscribes to many journals and uses his institutional library quite heavily. It is noteworthy that the largest library of its kind, the British Lending Library, attributes 20% of its requests to *Current Contents*.

About three years ago we added the ISI Press Digest to *CC*. This has become vital to the scientist interested in following developments reported in mass circulation journals or in journals which publish on the social implications of science, science policy, etc.

It is unfortunately true that *CC* has become a powerful force in the lives of authors and editors. Many will refuse to publish in a journal that is not covered in *CC* knowing its worldwide impact on reprint requests. On the other hand, *CC* has been able to exercise its influence to raise the international standards of journals. But it has a long way to go. Our most significant recent accomplishment has been to convince French journals to use English contents pages and abstracts. We also make a large scale effort to improve editorial details such as addresses of authors or style of bibliographic citation.

Recognizing that there are limits to titles and limits to the ability to scan or browse through *CC* we also urge *CC* readers to use our *ASCA*® service. This is possible now for a very nominal extra cost. At the least, this enables each scientist to learn who is citing the work of his or her laboratory. The *ASCA* system is made possible by the existence of the *Science Citation Index*®. Space and time do not permit me to go into the details of the *SCI*® or *ASCA*, but perhaps this will be possible during the discussion periods. The implications of the *SCI* in science policy studies has received considerable attention in the press lately. The use of citation analysis for identifying significant science has become a distinct field of research. Its applications can only be illustrated by reference to examples that may interest this audience. By using methods of numerical taxonomy we are able to monitor the growth and decline of fields such as recombinant DNA.

A variety of citation based studies are indeed reported through a weekly column which appears in *CC* each week. These *Current Comments* provide an opportunity to editorialize on a variety of subjects. Indeed, it was an editorial on genetic engineering which led to the invitation to present this paper. That particular editorial, copies of which I have brought with me, illustrates the type of information problem faced by the science journalist who wants access not only to technical journal material but also items that have appeared in significant lay publications.

The *SCI* data base I have mentioned briefly is now also available, in part, on international on-line computer networks. I have no doubt that by the end of the next decade most scientists in the world will have access to this data base, and many others. The use of such information retrieval facilities will greatly modify the pace and character of research everywhere. It will also require some reorientation in the training of scientists. Scientists must not only learn to write technical articles but also to use the newer informational facilities. While *Current Contents* requires a minimum of training or instruction the use of on-line facilities does require considerable orientation. That is why intermediaries provide such services at the present time. This is true for MEDLINE as well as for *SCISEARCH*®.

Obviously, a very substantial portion of the scientific journal literature concerning cloning, or Recombinant DNA, etc. will be found by the regular use of services like *CC* and the others described. However, we can single out information on these topics, as with any other topic, to provide all concerned scientists a special alerting service. If deemed necessary, such an alerting service could even become daily. But such an *SDI* service can only be as responsive to current developments as are the journals that report such information.

It, therefore, is imperative that the world's primary scientific communications system include means whereby such information can be transmitted on an almost instantaneous basis. While we would hope that journals like *Science* and *Nature*, and others of a weekly frequency, would make certain to report such information promptly, there can be no doubt that, at the present time, the only prompt outlet for such information of necessity is the *New York Times* and comparable publications elsewhere. The scientific community, at the present time, still lacks its own voice at the daily level, a shortcoming which I hope ISI may rectify some day. We have no doubt, however, that should some emergency development occur, responsible newspapers in each country would report this information to assure rapid dissemination. Unfortunately, the use of newspapers or even television or radio might produce an uneasiness amongst the public which might be unnecessary and unjustified. It is not inconceivable that for this reason, we may wish to consider utilizing the computer networks that are accessible to most centers of molecular biology research to disseminate such information on an instantaneous basis. For example, the SUMEX system at Stanford [1] is capable of transmitting primary communications as would be the case for other developing computer and communication networks.

In the final analysis, while ISI and other organizations can improve the channels of communication, it is the responsibility of scientists themselves to utilize information that is placed in front of them.

The discovery in Japan of the transferable antibiotic resistance factors (R plasmids) in bacteria was eventually followed by intensive investigations on every aspect of their biology and medical importance during the next decade.

New isolations were reported thoughout the world: first, in enteric pathogens and then extended to isolation from diverse genera of bacteria. Laboratory investigations proceeded to clarify the nature of these resistance factors as extrachromosomal elements, which could be transferred to other bacteria, even to less closely related species, by a mating or conjugative process just as the sex factor plasmid transfers the chromosome in the earlier example in Escherichia coli K-12. Many others aspects of genetic characterization were published as well as reports on enzymatic mechanisms by which antibiotic therapy could be foiled. Molecular methods soon were devised to demonstrate that such plasmids consisted of covalently closed circular (CCC) DNA, physically separable from chromosomal DNA. The DNA molecules could be examined in the electron microscope, their contour length determined and fine structure analysis of the DNA topology determined by the use of heteroduplex techniques for comparisons of DNA sequences for plasmids of different origin.

The correlation of these multifaceted efforts for understanding these ubiquitous extrachromosomal elements required access to numerous reviews, in addition to the primary experimental data scattered in various journals. International conferences were held, which dealt with the problem from the viewpoint of the geneticist, epidemiologist and pharmacologist. For the newcomer to the field, the rapid and simultaneous research developments of many laboratories are not easily assimilated. Many semantic difficulties arose — these included duplications and errors in plasmid designation and numerous terminological problems.

Because of the extraordinary interest in plasmid biology and its importance in the fields of theoretical genetics, on the one hand; and the practice of medicine for infectious disease, on the other, several informal meetings of some of the leading investigators were set up to coordinate these researches. One of these was the joint Japan-USA meeting on bacterial plasmids (Honolulu, November 1972), sponsored by the U.S. National Science Foundation for the Japan-USA Cooperative Scientific Program. These proceedings were not published as such. It was decided that some of the members should continue to meet as a plasmid nomeclature committee to resolve some of the confusions. A preliminary proposal was sent to over 200 interested scientists for their review and critique. In addition, the suggestion was made to establish an agency which would (1) coordinate certain aspects of plasmid investigation, (2) maintain a catalog of plasmids and help to avoid duplication of nomenclature, (3) provide information from the catalog on request, (4) maintain stocks of plasmid-carrying strains or, at least, those most widely investigated, encompassing the standard list of prototype plasmids and compatibility group standard strains. Such a Plasmid Reference Center will now be established at Stanford University in California.

Richard Novick [2] compiled a list of available plasmids and provided the synonyms and basic characteristics reported in the literature up to November 1973 and this list will be updated from time to time.

Public discussions of the draft proposal were held during the American Society for Microbiology Conference on Extrachromosomal Elements in Bacteria held in New Orleans, Louisiana, U.S.A. in January 1974. A second conference was held the following year at Squaw Valley, California.

The Nomenclature Committee published their proposal after receiving as much feedback as possible. [3] It is hoped that the broadest consensus of opinion derived from many discussions will serve as a useful guideline. This was exemplified by Demerec et al. when they recommended standard notation for bacterial genetics in 1966. [4] The second large group coordinating research on an international basis is the Commission on Chemoresistance which is sponsoring this Third International Symposium.

New experimental procedures in molecular technology have changed many aspects of this field in a startling manner. These may be summarized, in part, by the following:

(1) cloning of plasmid DNA molecules (whether conjugative or not) by transformation into $CaCl_2$-treated host bacteria.

(2) the discovery of several restriction enzymes which could be prepared and utilized to cleave plasmid DNA into subunits which could undergo enzymatic ligation to other DNA fragments. Not only could plasmid fragments be joined to distantly related plasmids from entirely unrelated host bacteria, but the technique could allow a new type of artificial DNA molecule, not so far found in nature, between bacterial plasmid genes and sequences of eukaryotic, viral, and bacterial DNA fragments. An unlimited supply of other chimaeric molecules may be anticipated as these techniques are explored and improved.

(3) the discovery of transposable elements by which a measured gene sequence may be inserted onto other plasmids, site-specific or not. This development provides new insights into the origin and evolution of plasmid gene sequences.

To keep up communication of these rapid new developments, the National Institutes of Health is attempting, on a trial basis, to distribute "Nucleic Acid Recombinant Scientific Memoranda", or NARSM, to interested USA scientists, who, in turn, will prepare summaries of their more recent findings for rapid and informal publication. It has also distributed working guidelines to their selected list of participants for research involving recombinant DNA molecules which may pose problems of biohazard. Two opposite

sides ot the new technology pose problems to science and society: the potential for the creation of dangerous entities because of their high antibiotic resistance and easy transmission to man. There is both the potential of serious biohazards in bioengineered molecules as well as dawning hope to overcome genetic difficiencies as well as the creation of a new tool for the precise definition of DNA sequences in laboratory investigation. This subject of biohazard and genetic engineering has aroused a great deal of thought-provoking controversy in the public press, as well as in the scientific media. [5] This was illustrated by the International Conference held at Asilomar [6] and is further illustrated by the forthcoming Miles Symposium entitled, "The Impact of DNA Recombinant Molecules on Society and Science". The political problem to be resolved is how to inform the public of those developments in the laboratory which bear on society, and also to keep the laboratory investigator aware of the social significance and possible dangers of new research. This danger concerns the creation of certain heretofore nonexistant molecules of unknown properties which can be carried by common intestinal bacteria. Moreover, scientists not concerned with either bacterial genetics, infectious disease, or antibiotics resistance, now hope to use plasmid engineering methods to amplify and clone particular genes.

Such scientists may be in special need of modern retrieval services since they are not as familiar with the basic literature. Hopefully, the types of discussions being conducted here in Bratislava will lead to the improvement of plasmid information services.

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