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AND
ANTICANCER
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PREFACE

The papers in the Proceedings include those presented at the 6th International Congress of Chemotherapy. Five hundred and four papers were read at the congress however 18 papers were not submitted for publication so that the Proceedings includes 486 papers which were arranged according to the classification of the congress program.

In order to commemorate the congress here, I ask the indulgence of the readers to include the Opening Address by H. Umezawa and the Address to the Post-Congress Symposium I "Chemistry, Biosynthesis and Transformation of Antibiotics" by Prof. J. C. Sheehan.

Opening Address

In the various fields of medical sciences, chemotherapy has made the greatest contribution to the welfare of mankind, saving lives endangered by numerous diseases caused by microorganisms. Experts from many different fields such as clinicians, medical doctors, microbiologists, pharmacologists, biochemists, chemists, and fermentation engineers are concerned with the different aspects of chemotherapy. Although the field of chemotherapy has made contributions for a long time, it was relatively late that a society for chemotherapy was organized. The establishment of a chemotherapy society in Japan took place in 1956, and an international society was organized in 1957.

Generally the field of chemotherapy is understood to include sciences relating to compounds which inhibit the growth or functions of pathogenic organisms, as well as the activities and applications of these compounds. In the last twenty years the field was extended to include antitumor compounds, their activities and their applications. Thus, the definition of chemotherapy now is extended to include all compounds useful for the treatment of diseases caused by microorganisms and malignant cells. The Sixth International Congress of Chemotherapy includes papers relating to this general definition. It does not include papers dealing with the treatment of other diseases using chemical or biological products though we received such papers from some people.

The characteristics of progress in chemotherapy during the last ten years include advances in the following areas: addition of new chemotherapeutic agents, mode of actions, genetics and biochemistry of resistant organisms, chemistry of antibiotics, and chemotherapy of viral diseases and cancer. Particularly, great progress has been made in the areas dealing with the mode of action of chemotherapeutic agents and the genetics and biochemical mechanisms involved in resistance which are now studied on the molecular level. These studies are rapidly progressing, and in the future we can expect that they will be analyzed on the chemical level, that is expressed by the stereochemical formulae of proteins, nucleic acids, and compounds participating in these actions. Then, we can predict the structures of active compounds. It will be the near future when we will see papers under the title of the stereochemistry of action. Papers relating to these rapidly progressing areas were received and symposia were organized.

Although at present there is no practically useful compound for virus diseases, virus chemotherapy is now studied on the enzymatic level, and new types of chemotherapeutic approaches such as the use of double-stranded RNA, interferon, or interferon-stimulators are appearing. In spite of a scarcity of participants, I believe that it is fortunate that we could organize one symposium on virus chemotherapy.

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Now, under clinical aspects, resistant organisms or resistant infections and cancer are the main subjects of present and future chemotherapy. The science of chemotherapy will start with the clinical observation. In other words, the clinical studies which identify the main pathogenic organisms causing present-day infections will provide the basis of fundamental progress. Symposia dealing with resistant infections and pharmacokinetics and the general sections will indicate the more important subjects in chemotherapy at the present time and in the future.

In the case of cancer, after the success in the chemotherapy of bacterial diseases, studies with antitumor substances were initiated over twenty years ago with a great hope for success. However, with no practical success in the clinical field, many people were disappointed in the last ten years. However, excellent clinical studies were recently made, and some types of cancer are now confirmed to respond to certain agents. In this congress the recent more effective cancer chemotherapy will be presented, and it will surely stimulate further rapid advances in the near future.

Beside the symposia we have two round table discussions, one concerned with problems in the determination of bacterial sensitivities to chemotherapeutic agents and the second dealing with the classification of antibiotics from different points of view. There are many antibiotics and chemotherapeutic agents of various origins with a variety of chemical structures and biological actions. If the classification is well done, the newcomer will find it easy to enter this field. In other words this kind of trial, if successful, will stimulate the newcomers. In order to encourage all of you to attend these round table discussions, they will be held after dinner.

The field of pharmacokinetics is of interest to all people studying chemotherapy. Therefore, this symposium was arranged in the evening.

In this congress, it is our great pleasure to have four plenary lectures, under clinical aspects by Prof. Finland, for the mode of action by Prof. Davis, for immunology and chemotherapy by Prof. Braun, and for new methods of screening by Prof. Navashin. These lectures will point to the future of chemotherapy. I hope that you will not be disappointed when you consider the very tight schedule during the day and evening. In this congress we have collaborators from thirty-four countries. In all, 510 papers will be presented at the congress including two post-congress symposia. Two years ago in Vienna, I was told by many people to select papers carefully for presentation at the congress in Tokyo. Truly, it is an ideal thing if one can do so. Here, four lecture halls will be used for the presentations. Many of you may be disappointed in missing certain papers because of the overlapping schedule. I personally had hoped to have two lecture halls for the congress. However, we found it impossible since we received many abstracts of excellent papers. After the congress is over, we will publish a volume of the proceedings if we have all of the completed manuscripts of the papers in the four lecture halls as soon as possible.

In closing I again express my hearty thanks to all of our participants in the congress, and in particular, the foreign guests. I also wish to thank our Japanese participants for their cooperation in the preparations of the congress. Further, I wish to thank Dr. Yukimasa Yagisawa, Dr. Keiichi Takeda and Dr. Kenji Maeda for their invaluable assistance in editing the Proceedings.

HAMAO UMEZAWA, *President*
The Sixth International
Congress of Chemotherapy

CHEMICAL MODIFICATION OF ANTIBIOTICS

Opening Address to the Post-Congress Symposium I "Chemistry, Biosynthesis and Transformation of Antibiotics"

Thank you Professor Sumiki, it is a real pleasure to give the opening address at Symposium I. As some of you are aware, we have been interested in the chemistry, biosynthesis and transformation of antibiotics for almost thirty years. I can't claim quite the seniority that Professor Sumiki has but I am getting dangerously close, I sometimes think.

We have been interested in natural product structure determination and have worked out the structures of a number of antibiotics. We have also been interested in synthesis and have completed several syntheses of antibiotics; we have also made some modest efforts at the modifications of certain antibiotics and in particular, of course, the penicillins.

I agree with Professor Sumiki that things have changed a great deal in the last thirty years, even from the year 1957 when he worked with the peptide antibiotic Etamycin. We used totally different techniques when we studied Telomycin only a few years later, and if we were attempting similar types of structure determination, I am sure there would be a greater reliance on physical methods. Still in the area of synthesis chemists have not made quite as spectacular advances; except possibly in a few limited areas.

Let us first consider why the chemist or medical scientist might like to modify by one means or another the structure of an antibiotic. After all the microorganisms did not make these antibiotics just for our chemical or medical use, if indeed they have any particular directed function.

1. Broadened (or narrowed) microbial spectrum
2. Activity against resistant organisms
3. Lessened side effects
4. Greater metabolic efficiency (better absorption, slower excretion, less serum binding, lowered chemical and biochemical degradations, etc.)

Fig. 1. Possible Objectives for Transformation of Antibiotics.

Figure 1 sets forth possible objectives for transformation of antibiotics by various methods. One might, for example, most obviously look for the broadening of microbial spectra; that is, for an agent that is more effective against a wider range of microorganisms. But I think what is not fully realized is that perhaps in some cases one would like to narrow the microbial spectrum. One talks about broad-spectrum antibiotics but these have certain disadvantages and they may interfere seriously with the natural flora, for example, so perhaps the direction of the future will be to look for a narrower antimicrobial spectrum. In fact I have asked some clinical researchers exactly what properties they would like to have in certain antibiotics. One would be surprised at the variety of answers. One answer almost never obtained from a top authority is that we want something that is effective against everything.

A second objective is action against resistant organisms. As you are well aware, organisms are in many cases able to adapt to the antibiotic and chemotherapeutic agents. By chemical transformations one might hope to increase the activity against resistant organisms. Third, lessened side effects. I won't go into this topic in detail. I think its more or less self-explanatory. Fourth, what might be called greater "horse-power," a greater metabolic efficiency that will help achieve higher blood levels.

1. By chemical or biochemical alteration of the fermentation-produced antibiotic or intermediate
2. Introduction of specific chemical features by addition of special precursors to the fermentation medium
3. Total chemical synthesis

Fig. 2. Methods Available for Producing Structural Variations in an Antibiotic Molecule.

In Fig. 2 we attempt to outline the methods available for producing antimicrobial spectral variations. First by chemical and biochemical modifications of the natural antibiotic or some intermediate along the route. Second, the introduction of the desired feature by the addition of precursors to the medium. In the penicillins this technique was used to produce penicillin V. The third scheme, which is perhaps the most powerful method of all, is by total chemical synthesis, and in some instances this is the method which has been used. A total chemical synthesis in principle is the most general since if one can synthesize the parent one should be able to vary the molecule essentially at will. On the other hand, total chemical synthesis of a complicated antibiotic is not an easy matter; it is necessarily a multistep procedure, so it may not be economically competitive unless the product has some very unusual features.

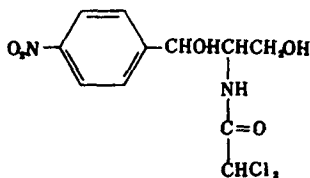


Fig. 3. Chloramphenicol.

In Fig. 3 and in the next few figures are the formulas of a number of antibiotics which are some of the leading ones from a clinical standpoint. It is not that you are unaware of the structures, but it is simply that I want to present the formulas so that I can illustrate a few points. I think it is fair to say, with an exception that we will come to later, that in the past attempts to improve, from a clinical point of view, the properties of a natural antibiotic have been less successful than one would have predicted. That is a value judgement on my part, but there it is.

Figure 3 is the formula for chloramphenicol, which has been around for upwards of 20 years. A large number of analogs have been made. Since it is a relatively simple compound, it could be synthesized totally by organic chemists, but I have been informed by Parke-Davis that none of the analogs had essentially improved properties over the natural antibiotic.

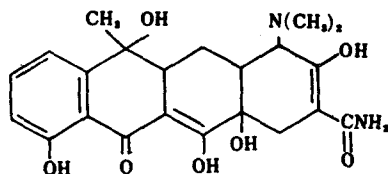


Fig. 4. Tetracycline.

Figure 4 shows tetracycline. Of course there are a number of natural relatives that can be produced directly by fermentation with precursors and also it is accessible by total synthesis so chemical modifications by various techniques are possible. In spite of all the opportunities, only relatively

limited success has been achieved, again in my opinion, in improving the properties of tetracycline in a dramatic way. There are some chemical modifications that have been taken advantage of clinically, but again I think it is fair to say that results in this area have not been as outstanding as one might have perhaps hoped for at the outset, especially considering the amount of effort which has been made in this direction.

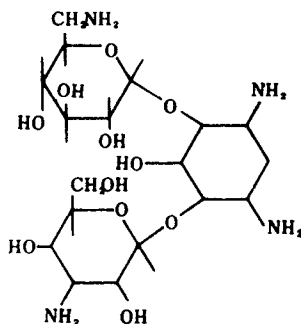
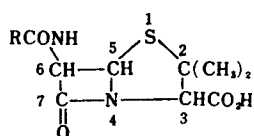
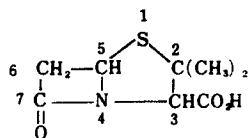


Fig. 5. Kanamycin.

Figure 5 illustrates Kanamycin, discovered of course by Professor Umezawa's group. This is an antibiotic related to streptomycin, and as in the case of streptomycin, dihydrostreptomycin was discovered early. It has some advantages over streptomycin itself, but there is no dramatic improvement, no substantial lessening of eighth nerve damage, for example. With Kanamycin the story is still a young one. As has been published by the Umezawa group, considerable effort has been put forth to obtain improved compounds in the Kanamycin area, and I can only wish them all success.

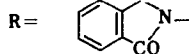
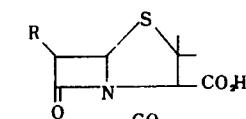


Penicillin (usually as a salt)

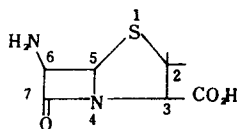


Penicillanic Acid

Sheehan, Henery-Logan and
Johnson, J. Am. Chem. Soc.,
75, 3292 (1953)



R = $\text{C}_6\text{H}_4\text{CH}_2\text{SO}_2$



6-amino ericillanic acid
6APA

Fig. 6. Penicillin Nomenclature.

The penicillin field (Fig. 6) is, of course, the area to which we have devoted the most effort. However, I might comment that less than 20% of my publications have to do with the penicillins, but these seem to be the ones popularly associated with my name. This figure sets forth the penicillin nomenclature because it is in the area of penicillins and cephalosporins, which we will come to a bit later, that the most dramatic improvement has been obtained.

In the upper left is penicillin acid where RCO is an acyl function attached to the penicillin nucleus. Back in 1953 we proposed the name penicillanic acid for the basic nucleus for the penicillins. Below is 6-aminopenicillanic acid (6 APA), which you are well aware is a renowned compound. One of the reasons we proposed the penicillanic acid nomenclature was that it was not possible to name 6-aminopenicillanic acid by the normal penicillin nomenclature except by some very awkward device such as desacyl penicillin.

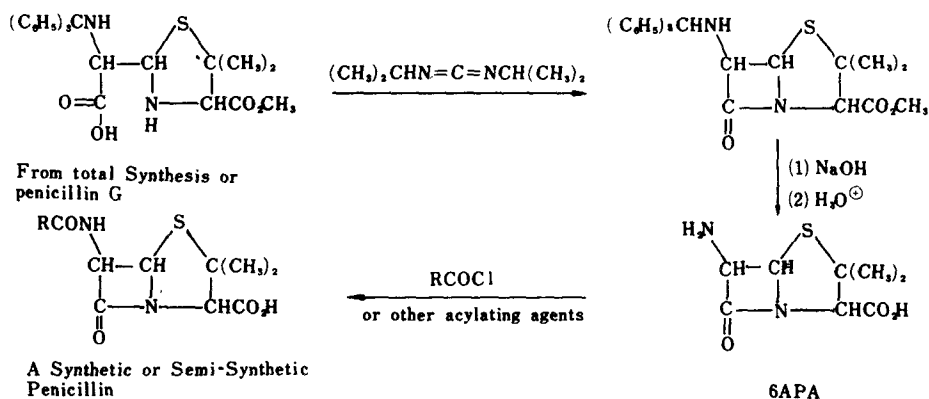
1. Acid stability
2. Broadened microbiological spectrum
3. Activity against resistant organisms
4. Less allergenicity
5. Greater metabolic efficiency (better oral absorption, slower excretion)

Fig. 7. Desirable Properties in an "Improved" Penicillin.

Figure 7 bears some resemblance to one presented earlier. I am very proud of this figure. It was not prepared especially for this symposium but was actually prepared in 1953 when I was giving one of the talks at the Organic Symposium in Ann Arbor, Michigan. The figure shows the properties that were set forth as what one might hope for in a penicillin, and I must say that my "crystal ball" was working much better the day when I prepared that slide than it has on some other occasions. The acid stability, of course, was easily predictable because the acid catalyzed rearrangement to penillic acid was well known and one could block this chemically.

As to a broadened microbiological spectrum, there was also an indication that this could be accomplished. Activity against resistant organisms was possible since the reason for the resistance was known in the case of the penicillinase-producing staphylococci. It seemed that one might be able to defeat the penicillinase enzyme by altering the penicillin structure by steric factors.

Lowered allergenicity is the only one that perhaps has not been realized fully although there has been some progress. And third, was the greater metabolic deficiency which was referred to in an earlier figure.



J.C. Sheehan and K. R. Henery-Logan, J. Am. Chem. Soc., 81, 5838 (1959).

For final step see J.C. Sheehan, U.S. 3,159,617, original filing date March 1, 1957.

See also J.C. Sheehan, "Amino Acids and Peptides with Antimetabolic Activity",

G.E.W. Wolstenholme, C.M.O'Connor, eds. p.258, J.A. Churchill, London, 1958.

Fig. 8 and 9. The Total and Partial Synthesis of 6-Aminopenicillanic Acid and a General Synthesis of the Penicillins.

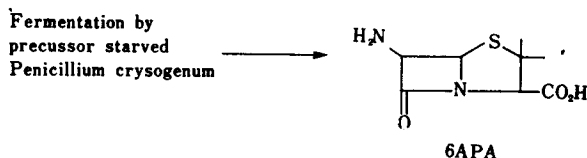
Figure 8 illustrates the last sequence in our total and general synthesis of the penicillins, the first and still the only such synthesis of the penicillins. In 1957 we synthesized penicillin V. In that synthesis we used a carbodiimide (which we originated for peptide synthesis) to close the β -lactam ring, and it was this step that had defeated the very extensive and intensive efforts during World War II. One simply cannot construct the β -lactam ring by the ring closure of the open compound, called penicilloric acid, by conventional reagents. We were able to prepare the derivative in the figure by total and partial synthesis. You will note that there are three asymmetric centers making possible four racemates; we prepared all these racemates, the one which is the α -series corresponds to the natural penicillins.

The chemical determination was not easy; one did not have NMR at that time which could tell one, for example, whether the two protons, 5 and 6, were *cis* or *trans*.

The blocking group on the amino function is trityl, which replaced the phthaloyl group used earlier in the synthesis. The penicillamine carboxyl is covered either by methyl, or better by benzyl. The carboxyl group which is to form the β -lactam ring is protected by *t*-butyl. Diisopropylcarbodiimide was used to close the β -lactam ring. The reason for this reagent rather than dicyclohexylcarbodiimide, which we used earlier in peptide synthesis and in penicillin chemistry, was that it is relatively volatile and on freeze-drying the mixture eliminates the excess reagent. This cyclization gives approximately a 70% yield, in fact in all the synthetic steps in the total synthesis no yield is lower than approximately 70%, and some were close to quantitative.

The effects of the bulky trityl group is to enhance the ring closure of this substance. It is well known that bulky substituents on a small ring help the ring closure. The next step is something that would have bothered the conventional penicillin chemist; we simply saponified the methyl ester without affecting the β -lactam ring seriously, and this again was made possible by the bulky trityl group. In more recent work we used the benzyl group and some other ester groups on the carboxyl function and have obtained still higher yields. This produced 6-APA which we then proceeded to condense with various acid chlorides and other acylating agents.

In the last step of the synthesis, treatment of 6-APA with an acid chloride or other acylating agents, one is able to obtain either a totally synthetic or semi-synthetic penicillin because we had also developed a method, not a very efficient one, of going from, for example, penicillin G to 6-aminopenicillanic acid. It involved opening the β -lactam ring and a re-closure. But at any rate both methods were available. This was reported in London in the Spring of 1958, and all this work had been completed in 1957, in fact, a little earlier than that.



Batchelor et al., *Nature*,
183, 257 (1959).

Fig. 10. 6APA by Direct Fermentation.

Meanwhile, a major development (Fig. 10) came from England and the Beecham group of Batchelor et al., see footnote 1, in which they made the important observation that if one did not add a precursor to the penicillin fermentation broth, one would obtain the same compound which we had prepared previously by total and partial synthesis, namely 6-APA. The Beecham group also proceeded to condense 6-APA with a large variety of acylating agents and prepared a substantial quantity of the products for clinical investigation.

The two processes complemented each other very nicely. The pioneering one in which we illustrated the principle that one could obtain synthetic penicillins is of great scientific interest and the British process for preparing 6-APA, the new penicillin available on a substantial scale for clinical testing. As you know, there are at least a half-dozen semisynthetic penicillins in routine clinical use and they have fulfilled most of the predictions which we made in 1953. By taking advantage of steric hindrance, methicillin and oxacillin are effective against penicillinase-producing clinically-resistant staphylococci. Ampicillin α -amino penicillin G, has a widened bacterial spectrum and is effective against a significant number of gram-negative as well as gram-positive microorganisms. These are areas in which a so-called wonder drug has been improved markedly from a medical standpoint.

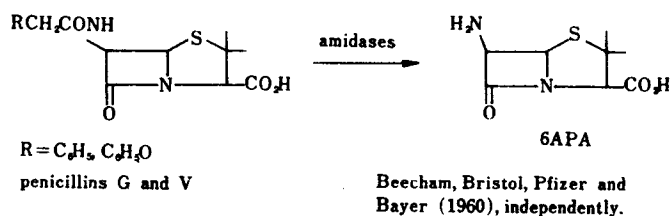


Fig. 11. 6APA from "Natural" Penicillins.

Another process (Fig. 11) to obtain 6-APA, and thereby the semi-synthetic penicillins, is to use an amidase to remove enzymatically the side-chain from penicillin G or from penicillin V, and this for a considerable period of time was the favorite commercial method. More recently, an effective chemical method has been devised which appears to have a marked advantage over either the precursor technique or the enzymatic splitting of the side chain.

These (Fig. 12) are some of the new types of penicillin.

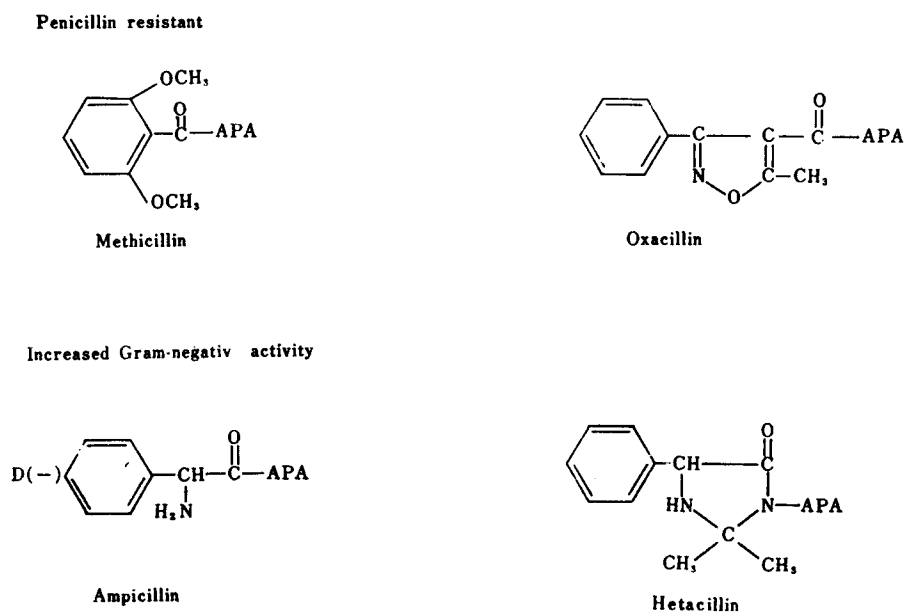


Fig. 12.

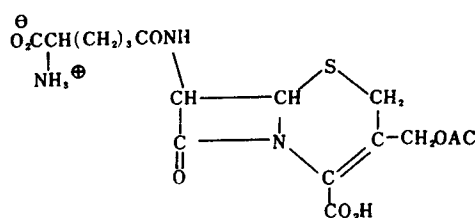


Fig. 13.

This (Fig. 13), of course, is Cephalosporin C, a closely related antibiotic, with a β -lactam ring. The story here has essentially duplicated the penicillin saga and there are a number of clinically important cephalosporins which are related to 6-APA, so the analogy is very close.

I would like to thank you for listening attentively and hope that out of this symposium and future ones come some outstanding examples of the improvement of the properties of an antibiotic by chemical, microbial or other transformations.

JOHN C. SHEEHAN
Massachusetts Institute of Technology

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