PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Concluding Remarks

M. R. Pollock and E. P. Abraham

Phil. Trans. R. Soc. Lond. B 1980 **289**, 377-378
doi: 10.1098/rstb.1980.0054

Phil. Trans. R. Soc. Lond. B **289**, 377–378 (1980)
Printed in Great Britain

Concluding remarks

M. R. Pollock, F.R.S.

For two days we have been hearing about advances, over the last 50 years, in our knowledge of β-lactams and β-lactamases which, in regard to chemical structure and (to a lesser extent) mechanisms of biosynthesis, have been truly remarkable. There has also been striking (if less complete) progress in our understanding of the genetics of their production and the mechanisms of their actions at a broad biochemical level. But we still know little about where they are located within or around the cell, their permeability properties or what might be termed their natural ecology, and practically nothing about the probable pathways of their evolution.

These deficiencies illustrate the types of research that one may hope will develop during the next 50 years.

From a practical point of view we appear to have a situation involving three distinct classes of entity, two of which (the β-lactam-sensitive centres and the β-lactamases themselves, possibly related to each other chemically) are specific receptors of the third (the β-lactams). What happens to the potential patient depends upon the effective interaction of these entities in the micro-environment within and around the human body. Studies *in vitro* involving huge numbers of molecules of these substances under artificial conditions may be a poor guide to the situation *in vivo*. Moreover, related to the *in-vivo* situation itself, at further remove and on a much longer time-scale, is that in the exceedingly complex natural environments in the soil and other locations outside the body. We know practically nothing about these environments. Indeed, they are barely susceptible, at the moment, to a proper experimental approach. Yet, until we do know more we shall never be able to feel that we have the problem of bacterial infection under satisfactory control.

E. P. Abraham, F.R.S.

This meeting should not be allowed to end without an expression of thanks to our speakers and chairmen, so may I thank them now on behalf of us all. Although the meeting was timed as a commemoration of the first observation of penicillin it has been concerned almost entirely with recent developments in the chemistry, biosynthesis, mode of action and enzymic hydrolysis of what are now known as β-lactam antibiotics. These developments have been astonishing and extensive in the last decade, stimulated by the value of the penicillins and cephalosporins in medicine and the promise of new substances to cope with the problems presented by resistant organisms. The fact that discussions of such diverse topics could be brought together and hold the audience at a single meeting is an indication of the wide interest of the subject and a tribute to the quality of the speakers.

May I add a final comment to those of Professor Pollock. The achievements of the chemists have given us reason to believe that almost any small β-lactam molecule can now be made by total synthesis, if its stability is sufficient for it to have more than a transitory existence. The routes used in total chemical synthesis have been somewhat different from the corresponding biosynthetic pathways in fungi and *Streptomyces*. Although little is yet known about the precise mechanisms of the enzyme-catalysed ring closures involved in the formation of β-lactam antibiotics, the time seems to be approaching when these mechanisms will be elucidated and when

it may be possible for organic chemists to think of using them as models. But what compounds should be made in searches for molecules with the desirable attributes of the known penicillins and cephalosporins but with new and valuable biological activities? Here one of the wide gaps in our understanding, which hinders a rational step forward, is the lack of knowledge of the structural detail of the active site in the specific proteins with which the β-lactam compounds react, although many of these proteins have now been identified and some have been shown to contain a serine residue which is involved in the formation of an acyl-enzyme complex. There are indications that this gap will be partly closed within the next decade.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES