The competing claims of staffing for service needs and for training are considered in some detail, particularly in the appendix on surgery. Since only a fraction of S.H.O.s and registrars in any specialty will eventually become consultants in that specialty, alternative careers must be offered. In the case of surgery, for example, it is suggested that about half the registrar posts should be earmarked for the training of future consultant surgeons in the N.H.S. This would maintain a ratio of registrars to senior registrars of about 5:4. The remaining surgical posts would be filled by Commonwealth trainees and trainees for general practice. This pattern is worthy of serious consideration.

The report is both realistic and practical. It deals largely with existing institutes, facilities, manpower, and staffing structure, and it suggests how we may make the best use of what we now have. For this reason the role of the teaching hospital is given most prominence and that of community medicine the least. The stimulus it offers to new developments in patterns of patient care is welcome. It expects that, before long, registration of specialists (which would include general practitioners) will be introduced as outlined in the 1967 Recommendations of the G.M.C. and suggests that active steps should be taken now to bring this about.

3 Ibid., 1966, 2, 125.
4 Recommendation as to Basic Medical Education, 1967. General Medical Council.

Origin of Penicillinase

Penicillins are attacked by two enzymes of microbial origin. One is amidase, which simply severs the side-chain leaving the nucleus intact, a reaction which is now the first step in producing the many new semisynthetic penicillins. The second is penicillinase, which opens the β-lactam ring of penicillin and deprives it of all antibacterial activity. It was recognized more than 20 years ago that this enzyme was formed by some strains of staphylococci, and that they owed to this their resistance to the antibiotic. These strains have little "intrinsic" resistance; it is not that they can tolerate penicillin, but that they can destroy it. All resistance to penicillin in staphylococci is of this nature. The formation of this enzyme at a site of infection can prevent the action of penicillin on another fully sensitive organism. Thus in mixed infections by staphylococci and haemolytic streptococci treatment with cloxacillin may be indicated, since it is both resistant to penicillinase and active against the streptococcus.

Soon after the recognition of staphylococcal penicillinase it was found that other bacteria form the same kind of enzyme. These include many Gram-negative bacilli such as species of Pseudomonas, Proteus, and Klebsiella, various Bacilli such as B. cereus and the anthrax bacillus, and even tubercle bacilli. In some of these organisms resistance to penicillin does not depend entirely or even largely on the enzyme; many of them also possess a high degree of intrinsic resistance. An exception is B. anthracis, which is intrinsically so sensitive that anthrax responds readily to treatment with penicillin. The structure of penicillinas—and cephalosporinases, corresponding enzymes attacking the nucleus of the cephalosporin group of antibiotics—is not exactly known, but it is clear that they are a family of enzymes and not a single substance. Many of these enzymes are inducible—that is to say, exposure to a penicillin will immediately cause them to be formed in much larger amount. It has also been established that different penicillinas vary in their capacity to act as inducers, and indeed nafcillin is claimed to have a therapeutic advantage in that it is a very weak inducer of penicillinase formation.

Professor M. R. Pollock, who has made extensive studies of penicillinas and the kinetics of their formation and activity, chose this subject for an Almroth Wright lecture which we print on page 71. His title refers to the origin and function of penicillinase as a "problem in biochemical evolution," and the main question which he asks is how it came about that some bacteria form such an enzyme, which is of no use to the cell forming it except as a means of eliminating an antibiotic from the environment. He reaches the interesting conclusion that formation of the enzyme may have resulted from an evolutionary change related to this very function. Some of his arguments will be appreciated only by those with a considerable knowledge of bacterial chemistry, but others will make a more general appeal. He points out, for instance, that the distribution of numerous moulds now known to form penicillin and of bacteria forming penicillinase is not dissimilar. Their habitats include not only the soil but the skin, where an interesting example is the reported coexistence of a penicillin-forming dermatophyte and a penicillinase-forming staphylococcus on the skin of hedgehogs. Two other pieces of evidence are derived from hitherto unpublished work. It has at last been shown that a Penicillum will actually produce penicillin in natural soil in the laboratory. Secondly, Pollock himself has shown in the same environment an antagonism between the growth of a penicillin-forming mould (P. chrysogenum) and a penicillinase-forming bacillus (B. licheniformis) in the sense that when growing together they attain lower total numbers than either growing alone.

This tentative conclusion has wider implications. Soil has been searched for antibiotic-forming species on a gigantic scale not only because it contains an enormous variety of micro-organisms but because it was originally regarded as a battle-ground of warring species, their weapons being antibiotics. Of late years this belief has lost many adherents, and antibiotics are commonly regarded as having no natural function—at least of any importance. In the words of S. A. Waksman and H. A. Lechevalier, "...we can conclude that the production of antibiotics, as we visualize it in the laboratory, does not occur in nature...too little solidly grounded information is available to warrant much more than speculation about the ecological significance of antibiotic production." If we are now to grant that penicillinase formation is the result of an evolutionary process of a

defensive nature, it follows that antibiotics themselves have a function in suppressing other species than those forming them and thus securing a more liberal supply of nutrient. "Nature red in tooth and claw," an expression intended to refer only to the animal kingdom, has thus an equivalent even among the lowest plants—a forbidding thought to the believer in peaceful co-existence as a natural way of life.

Spread of Influenza

The prognosis of an individual patient’s disease is always difficult even with a straightforward infection like influenza. Likewise to predict the appearance and course of epidemics is chancy. Nevertheless international co-operation, particularly through the World Health Organization’s Reference Centres, has given us a fairly complete picture of what is happening to the viruses causing influenza epidemics.

In 1947 and in 1957 completely new serotypes of influenza appeared—types A1 and A2—and these spread across the world, producing large epidemics. More epidemics followed in later years, and comparison shows that the virus strains have changed the antigens on their coats appreciably. This is presumably because new variants have a better chance of survival against the antibody induced by the last variety of influenza. Two distinct new antigenic modifications have occurred since the first A2 (Asian 'flu) viruses appeared, and have usually been associated with new epidemics.1,4

However, whether a virus spreads in a country depends not only on the “newness” or otherwise of its antigens but on the antibodies the inhabitants are carrying. Influenza A in Britain tends to recur at about two-year intervals,5 but recent years have shown exceptions to this rule (which is not followed in other parts of the world). It has therefore been suggested that if we know the immune status of the population of a country, in particular if we know the number of people carrying antibody against the current strain, then we may be able to predict an epidemic, and perhaps forestall it by vaccinating with the virus for which the population has no antibody. When new strains have appeared such studies have been made, and they are easy to interpret. In the 1957 pandemic only the very old had antibody against the A2 virus strain, and everyone else had no antibody and was susceptible. In the inter-pandemic period serological surveys are not so easy. Such studies have been made abroad, usually with the haemagglutination-inhibition tests to detect the antibody.6 The first of such studies from Great Britain are reported in this issue of the B.M.J. (p. 80). Dr. Marguerite Pereira and her colleagues report that sera were collected from October 1965 to May 1966 from routine blood specimens examined in public health laboratories, and were tested by a specific complement-fixation test for antibodies against the surface (V) antigens of recently isolated strains of influenza A2 and B. Only about one-half of the preschool children had antibody against influenza A and a quarter against influenza B, but over half the school-age children and adults had antibody. The peak level of antibody to recent strains was in the age group 15–24, possibly because they had been heavily affected by influenza and also because they had relatively little experience of the antigens of the earlier influenza serotypes which “condition” the immune mechanism to produce antibody against the earlier types rather than against the recent ones. This phenomenon was called “original antigenic sin,” and the mechanism has recently been studied by reproducing the phenomenon in rabbits infected successively with different influenza virus vaccines.10 It is thought to occur when clones of antibody-producing cells proliferate after the first antigenic experience of the virus, and are restimulated when partly cross-reacting antigens are met. But if large amounts of such new antigens are given they may not be adequately dealt with and may stimulate the formation of a new clone.

The second study, by Dr. G. C. Schild and Professor C. H. Stuart-Harris, appears at page 82. They used sera collected from children in South Yorkshire in three periods—namely in 1965, early 1966, and the winter of 1966–7. There was an outbreak of influenza due to both A2 and B viruses in the area in 1966, and the study therefore sheds light on the response of the “antigenically inexperienced” part of the population. In general antibody was less common and of lower titre in the younger children. Though most children had antibody against the 1964 influenza A2 before the epidemic, there was by 1966 a marked increase in the number with high titres, presumably as a result of natural exposure. Fewer children had antibodies against the 1965 influenza B strain, but the proportion of these with medium or low titres increased during the epidemic. The lowest frequency of antibodies was found in each case against the most recently isolated strain of influenza—that is, the 1966 strain—but by tests with sera prepared in the laboratory their antigenic composition did not seem to be particularly different from the viruses isolated one or two years before. The authors suggest, in fact, that tests with children’s sera may be the most delicate way of distinguishing between closely related influenza viruses, and certainly differences shown with human sera may well be important in epidemiology. On the other hand, sera from adults would probably distinguish between viruses less sharply than animal sera do.

The results of the survey by Dr. Pereira and her colleagues show that many people have antibody against the current influenza virus strains, and the authors say we are unlikely to have an epidemic due to these or similar strains. This is reassuring, but it leaves another question unanswered. How