Antibiotic Sensitivity Testing

It is notorious that tests of bacterial sensitivity to antibiotics are done in an extraordinary variety of ways. Many variations of the usual methods are misconceived and inadequately controlled, or lend themselves to misinterpretation. False information has thus often been provided to clinicians, of which they have sometimes not been slow to complain. There are indeed some who have expressed the view that laboratory reports on this subject are better disregarded.

This problem was considered by an expert committee of the World Health Organization which met in 1960, and its report[1] recommended the definition of a standard routine method employing paper discs. The factors requiring control were defined, and the main features of a suitable method were laid down in some detail, but many questions on such matters as choice of antibiotics, disc contents, culture media, and procedures for interpretation and reporting were necessarily left unsettled. The task of furthering this project was taken up almost immediately by a working group sponsored by W.H.O., which has owed much to the leadership of Dr. Hans Ericsson, of Stockholm. From this an international collaborative study developed, in which representatives of many countries have taken part at various times. This study enabled almost every aspect of the subject to be investigated thoroughly, and the results of actual tests performed by prescribed methods in many different laboratories have been compared. The working group has had two formal meetings in Geneva and two in Stockholm, and informal meetings of such members of the group as were present during international conferences in Naples, Montreal, Vienna, Paris, and elsewhere. Various findings by individual workers have been published, but the progress of the study as a whole has been recorded only in reports for private circulation, though many bacteriologists have been aware of some of their contents.

This situation has now been remedied. A full report of the entire enterprise, with recommendations to which it leads, has been published by H.M. Ericsson and J. C. Sherris.[2] Techniques are proposed for two dilution methods, and for a disc method which can be used either as a routine or to check the accuracy of another already in use. This employs large plates and high-content discs, and thus resembles the Kirby-Bauer method,[3] in which diameters of inhibition zones are translated into categories of sensitivity or resistance by reference to tables. The present report proposes that these diameters should be converted to minimum inhibitory concentrations and thus into such categories, but no actual instructions are given about how this is to be done.

One of the tasks of the working group was to construct regression lines (plots of zone diameters against minimum inhibitory concentrations determined by a dilution method) for 12 antibiotics, and these enable the conversion to be made. These lines are reproduced, but not all are considered satisfactory, and among various proposals for further work is that there should be complete and elaborate restudy of this aspect of the subject. It is also suggested that there should be national reference laboratories with the duty of "preparing complete descriptions of current recommended methods and interpretative schemes", and of supplying fully characterized reference cultures with which the performance of a method can be checked. The proposal that each country should now shoulder this burden independently is in conflict with the policy of the original W.H.O. Committee, whose intention was that reliable methods should be proposed for "universal adoption". Nevertheless, it seems that steps have been or are being taken to carry out this proposal in France, Germany, Sweden, and the United States.

The slow progress made may be attributed to another departure from the original intention at Geneva. This was understood to be that a relatively simple procedure for a disc test should be so defined as to eliminate the known common sources of serious error. That could have been done in far less time, and the adoption of such a method might already have enabled innumerable illnesses to be shortened and even have helped to save many lives. The procedure which has been studied is more elaborate, much more costly in materials, requires the most rigid standardization, particularly in regard to the composition of the culture medium (another problem not yet finally settled), and its interpretation is still to some extent the subject of controversy. The kind of laboratory where most of the mistakes are made will have difficulty in practising it successfully. But this is a serious proposal, based on very extensive study and backed by leading world authorities, and at present there is no alternative to it. Since one thing on which almost everyone is agreed is that something needs to be done, Great Britain cannot remain idle while other countries implement the W.H.O. proposals. This is surely a matter in which official action is required to determine British policy.

[1] Standardization of Methods for Conducting Microbic Sensitivity Tests. *W.H.O. Technical Report Series*, No. 210, 1961.
[2] Ericsson, H. M., and Sherris, J. C., *Acta Pathologica et Microbiologica Scandinavica*, 1971, Supplement No. 217.
[3] Bauer, A. W., Kirby, W. M. M., Sherris, J. C., and Turck, M., *American Journal of Clinical Pathology*, 1966, **45**, 493.

Hepatic Hypoglycaemia

Among patients with fulminant hepatic failure due to viral hepatitis or the toxic effects of drugs occasional cases appear with spontaneous and profound hypoglycaemia. Since frequent monitoring of the blood sugar is still not a routine practice in the management of these patients, hypoglycaemia may pass unrecognized, its symptoms being attributed to hepatic encephalopathy.[1] This is tragic, for the hypoglycaemia leads to further brain damage. Restoration of the blood sugar to normal can result in an improvement in the level of consciousness and in the signs of disturbed function of the pyramidal tracts.

The cause of this hypoglycaemia is uncertain. Insulin is secreted into the portal system and probably much of it is enzymatically destroyed by the liver. In a case of fulminant hepatitis reported by R. L. Sampson and colleagues,[2] of Cape Town, enormous amounts of sugar (2·5 kg) were given at one stage over 24 hours with persistence of the hypoglycaemia. This together with the finding of a high level of insulin in the plasma suggested to them that failure of degradation of insulin by the liver played an important part in the hypoglycaemia. The patient subsequently died, and at necropsy the pancreatic islets appeared larger than normal, with increased cellular cytoplasm and nuclear variation, raising the possibility of enhanced production of insulin. Other mechanisms have been suggested. Synthesis of glycogen or its storage in the liver may have failed, as may its subsequent breakdown, which is the main process responsible for maintaining the blood sugar in the fasting state.

A recent report of P. Felig and colleagues[3] at Yale is of considerable interest, for they showed that hypoglycaemia