

Researches in Chemotherapy

CHEMOTHERAPY, which forms the subject of Dr. F. L. Pyman's presidential address before Section B (Chemistry), may be regarded as the treatment of disease by chemical substances, which have been shown by biological methods to be relatively much more toxic to pathogenic organisms than to human or other animal hosts.

Chemotherapy was developed by Paul Ehrlich, and its most outstanding achievement has been the introduction of the arsenic group of spirochæticides.

In the field of bactericides, the introduction of phenol as an antiseptic by Lister in 1867 has led to the study of many derivatives of phenol. Recently systematic studies of various homologous series of phenols have resulted in the introduction into medicine of hexyl-resorcinol and amyl-*m*-cresol, the latter having a Rideal-Walker coefficient of 280.

The chemotherapeutic investigation of amœbicides was greatly facilitated by the *in vitro* test for amœbicidal efficiency developed by Dobell and Laidlaw. Using this test, Coulthard studied a series of alkyl derivatives of harmol prepared in Messrs. Boots' laboratories and showed that peaks of bactericidal efficiency were reached at butylharmol for *B. typhosus* and at amylharmol for *S. aureus*, whilst peak amœbicidal activity was found in *O-n*-nonylharmol. Salts of members of this series were, however, very sparingly soluble in water, and in order to obtain more soluble compounds the corresponding dialkylamino derivatives were prepared and their amœbicidal activities compared with that of emetine. Although the most active member was not as active as emetine, it had several times the activity of *O-n*-nonylharmol and it was suspected that the harmol residue might not be the important contributor to the amœbicidal properties of the molecule and that the dialkyl-aminoalkyl group might play an important part. This led through various intermediate stages to the preparation and study of a series of tetra-alkyldiamino paraffins and of these α -tetra-*n*-amyl-diaminodecane was found to be the most efficient. For brevity, the compound is referred to as T.A.D.D.

The preceding results had shown that, when tested by the Dobell and Laidlaw technique, T.A.D.D. was the most active amœbicide so far prepared. It now became necessary to compare the efficiency of this compound with that of emetine under conditions as similar as possible to those found in the intestine of a dysenteric patient. When tests were carried out under these conditions T.A.D.D. was found to be more active than emetine. As originally pointed out by

Ehrlich, the therapeutic value of a substance is a function of its toxicity to both parasite and human host. It became necessary, therefore, to determine the relative toxicities of T.A.D.D. and emetine to mice. The results of such a test showed T.A.D.D. to be from one third to one eleventh as toxic as emetine, depending on the method of administration.

T.A.D.D. had thus a greater *in vitro* amœbicidal activity and was less toxic to mice than emetine. These results appeared to justify the clinical trial of the compound in the treatment of amœbic dysentery.

Such a trial was carried out by Prof. Warrington Yorke, at the request of the Therapeutic Trials Committee of the Medical Research Council. Unfortunately, T.A.D.D. proved to be too irritant for parenteral administration and it was not sufficiently active to be of any real value when given orally.

Whilst this investigation has not yielded a compound of clinical value, it has resulted in the accumulation of valuable data which will be of value in further work on this subject.

The account of such an investigation indicates the enormous amount of chemical and biological team work involved in attempts to evolve new drugs for the treatment of disease.

The Glaciation of the Midlands

IN his address to Section C (Geology), Prof. L. J. Wills discusses the Pleistocene history of the West Midlands with the object of discovering how many glaciations are represented, and of linking these up with the better-known sequences of East Anglia.

It has long been recognized that the boundary between the 'Newer' and 'Older' Drifts crosses the district from Church Stretton through Bridgnorth to Wolverhampton. Prof. Wills devotes attention mainly to the Older Drifts, which have undergone enormous denudation in the vales but have in varying degrees survived on the Midland Plateau and on watershed areas. The evidence of the former great extension of the present outcrops is scattered, but is *en masse* sufficient to allow the assumption that the vales of Severn and Avon were ice-filled during the older glaciations, though it must be realized that they were far shallower then than now.

In the Midlands three principal types of drift can be recognized: *Irish Sea* in the north-west, and belonging to the Newer Drifts; *Western* or *Welsh* on the Midland Plateau (this occasionally contains Irish Sea boulders, and in the Trent