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LIVER EXTRACTS AND THEIR
BIOLOGICAL EFFECTS

Since the discovery of the therapeutic effect of liver in pernicious anaemia it has been the aim of the pharmacologist to produce ever more concentrated extracts with the ultimate view of synthesizing the active principle. Clinicians, on the other hand, always on guard that the chemist in his rejection of unnecessary molecules should not render his remedy less potent, suspect that preparations become less active when they exceed a certain degree of concentration. The work of Subbarow and Jackson¹ suggests that the therapeutic potency of liver extract depends upon one principal factor which, if given in sufficient amount, can alone bring about a remission, and several subsidiary factors which, themselves without anti-anaemic effect, yet intensify the therapeutic efficacy of the extract. A recently published investigation² from Copenhagen throws some light on these subsidiary factors and their relation to the anti-anaemic principle. Barfred began his research in order to elucidate the causes of the disagreeable effects so often observed after injections of liver extract. He found that these reactions occurred especially with the use of preparations containing a relatively high amount of dry substance. He showed also that extracts rich in dry substance are highly toxic to mice, and that by employing a preparation 1 c.cm. of which was not lethal to mice it was possible to avoid most of the unpleasant reactions in patients with pernicious anaemia. This led to a study of other biological effects of liver extracts, with interesting results. Confirming and amplifying the work of previous workers, Barfred showed that certain liver preparations were capable (1) of increasing the volume and HCl content of the gastric secretion of normal and achlorhydric subjects, (2) of producing positive intracutaneous reactions, and (3) of inducing leucocytosis. The factors responsible for these effects have certain features in common, such as solubility in butyl alcohol and resistance to boiling and action of erepsin. An attempt was made to identify the substances responsible for these biological effects. Histamine, acetylcholine, adenosine, nicotinic acid, and other members of the vitamin B complex were studied, and it was shown that not one of these substances taken singly could produce all the subsidiary effects of liver extracts, although it was possible that a combination of the first four might. It is evident, however, that the subsidiary actions of liver extracts are not peculiar to this organ, as an extract of the thymus gland prepared in the same way produced the same results without any influence on the course of pernicious anaemia. Of interest for the future synthesis of the anti-anaemic principle is the finding that prolonged treatment of potent liver extracts by erepsin did not diminish the anti-anaemic potency, suggesting that the principle is not a simple polypeptide.

The subsidiary substances found in the butyl alcohol solution have no effect on pernicious anaemia, but by the use of the double reticulocyte reaction introduced by Minot and Castle it was shown that they increased the response obtained from the use of the residue left after

treatment with butyl alcohol. If by further concentration of an active liver extract the stimulating effect of HCl secretion was abolished a reduction of the anti-anaemic effect was invariably found. This indicates a method whereby the limit to concentration can readily be determined. It also has led Barfred to put forward the interesting hypothesis that the gastric factor may be of importance in stimulating the stomach to produce the intrinsic anti-anaemic factor. With highly purified extracts containing but little of the subsidiary substances the therapeutic effect would be due merely to the haemopoietic principle contained in the extract. With less concentrated preparations, on the other hand, the patient would derive benefit not only from preformed anti-anaemic substance but also from the extra amount of intrinsic factor secreted by the stomach under the influence of the gastric factor contained in the extract.

The painstaking investigations of Barfred, while of considerable theoretical interest, may lead to results of some immediate practical value in providing a method for determining the optimal limits of concentration of a liver extract. It is obvious that all extracts should have some stimulating effect on the gastric secretion, thus limiting the degree of concentration upwards. At the same time they should be so purified that a dose of 1 c.cm. is not lethal to mice, thus ensuring that unpleasant reactions in the human subject are reduced to a minimum.

SOME PROBLEMS OF MEDICAL EDUCATION

Last year, following a request from the Interdepartmental Committee on Medical Schools, the Council of the British Medical Association set up a compact committee of fourteen to prepare evidence, and the result, under the chairmanship of Prof. Sydney Smith of Edinburgh, has been the memorandum printed at page 702. It is a clear and concise report, moderate and constructive in tone. While covering the five specific points referred to it, the committee goes into some broader considerations, recognizing that, although the organization of medical schools and of the facilities for clinical teaching poses problems of its own, the matter should be studied not as a thing apart but in relation to the whole question of the future organization of medical services. The problem is one not merely of devising methods of linking the present voluntary and local authority hospitals for the purposes of medical education, but of considering the place of the teaching hospital in the future hospital service and the method of associating other types of hospital and medical institutions with the teaching hospital. The method of recruitment to the profession and the needs of practitioners of the future, whose conditions of work may well differ from those we know to-day, must also be kept in mind.

Starting with the axiom that a medical teaching centre should be one from which medical education, both undergraduate and postgraduate, and research are organized for an area, the committee lays down general criteria to which the centre must conform if it is to fulfil its important functions. This conception of a medical teaching centre is elaborated under several subheadings. The memorandum next sets out desiderata in respect of the teaching staff, their selection, appointment, and status, and then passes to the question of how far general practitioners might assist in the training of medical students. Two frequent complaints are succinctly noted: one is that the future family doctor is not given knowledge that he will find to be essential in his daily practice; the other is that the newly qualified man may enter general practice without any previous instruction in his ethical relationships with his patients and his colleagues or in his rights and obligations under the Health

¹ *J. clin. Invest.*, 1937, 16, 573.² *Acta med. scand.*, 1942, Suppl. 131, 1.