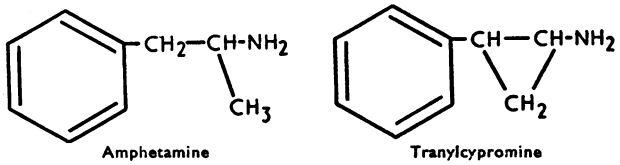
To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in common use.

Tranylcypromine

" Parnate " (Smith Kline and French).

Chemistry.—This drug, which is trans-(±)-2-phenylcyclopropylamine sulphate, is closely related to amphetamine, as the following structural formulae show:



Amphetamine Tranylcypromine

Pharmacology.—Tranylcypromine stimulates the central nervous system. It is a monoamine oxidase inhibitor, but unlike iproniazid and its analogues it is not a hydrazine. It seems unlikely that all the pharmacological effects of these drugs are related to inhibition of monoamine oxidase; other enzyme systems also appear to be involved.

Therapy.—Like other monoamine oxidase inhibitors, tranylcypromine is useful in mild depressive states, particularly those accompanied by symptoms of anxiety or feelings of fatigue. It should not be given alone for severe depression: E.C.T. is still necessary for many cases of endogenous, and certainly all of severe, depression. Given in conjunction with E.C.T., tranylcypromine may reduce the number of shocks needed and prevent subsequent relapses, but in general imipramine is a more effective drug in such cases. Depression occurring in schizophrenia controlled by phenothiazines may respond to tranylcypromine; careful supervision is essential because of the danger of causing the schizophrenia to flare up. Tranylcypromine may act within 24–48 hours, which is quicker than other monoamine oxidase inhibitors, such as phenelzine (" nardil ") and isocarboxazide (" marplan "); but there is no evidence that parnate is otherwise superior clinically.

A dose of 10 mg. (1 tablet) b.d. should produce a response within a week. If there is no response, the dose may be increased to 10 mg. t.d.s. for a further week, and then to 20 mg. b.d. There is rarely any therapeutic advantage in giving more than this, and side-effects become increasingly prominent. The time for which the drug must be continued varies from patient to patient, and a suitable maintenance dose for each patient should be found by trial and error.

Side-effects.—These are similar to those of other monoamine oxidase inhibitors. The most common are: feeling of faintness, sleepiness or decreased need for sleep, dry mouth, constipation, excessive flatus, sexual difficulties, headache, rashes, restlessness, neuromuscular and sensory disturbances, and oedema. Mania has not been reported, but is a possibility when high doses are given. Most of these complications can be relieved by reducing the dosage. Oedema responds to diuretics.

N.H.S. Basic Price.—100 tabs., 35s. 6d.

An account has now been printed of the First All-Asian Congress of Paediatrics, which was held in New Delhi, India, from January 2 to 6 this year. It includes the address of the President of the Congress, Dr. K. C. CHAUDHURI, and synopses of papers given under the sectional headings of cardiology; diseases of the gastro-intestinal system; haematology; infectious diseases; the nose; miscellaneous; diseases of the nervous system; nutritional disorders and infant feeding; social paediatrics; surgery; and tuberculosis. The congress was sponsored by the Indian Paediatric Society and the Association of Paediatricians of India.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Research on Prescribing Habits

SIR,—A number of serious and urgent health problems are arising in connexion with the current revolution in our use of drugs. This revolution would appear to be far from bloodless, and we are obviously in grave danger of doing more harm than we might suspect. For this reason, we consider that your suggestion (May 27, p. 1520) for a register of drugs capable of producing blood dyscrasia is timely, and we feel that the existing machinery for the notification of disease might well be employed. If these blood dyscrasias were made notifiable, it is probable that the clinical picture is spectacular enough for a high proportion of them to be reported.

From a rather cursory study of the disposal of E.C.10's in this area, we are inclined to believe it possible to intercept prescriptions which had been dispensed to the patient concerned during the months preceding notification, and in this way establish an association between disease and drug.

Furthermore, your leading article on drug-induced blood dyscrasia should make us think yet again about *all* the unpleasant side-effects of our new treatments. That they are not confined to organic damage alone is shown by the Brain Report,[1] with its emphasis upon drug dependence and minor addiction. While more pharmacological research is obviously needed, we would also like to see studies of every aspect of our national prescribing habits, so that a more rational social policy governing the purchase, distribution, prescription, and evaluation of drugs may be developed.—We are, etc.,

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REFERENCE

1 *Drug Addiction: Report of the Interdepartmental Committee*, 1961. H.M.S.O., London

Connective Tissue

SIR,—In his letter (May 20, p. 1459) Dr. C. H. Lack suggested that degradation of periendothelial matrix by plasmin may be the basis of certain disorders of connective tissue. As an alternative to " auto-immune " hypotheses, his concept of a primarily " autolytic " pathogenesis is favoured by evidence emerging from several lines of investigation.

Capillary resistance, measured by negative-pressure tests, was frequently found to be subnormal in patients with rheumatoid arthritis. This abnormality could result from a structural weakness of connective tissue ensheathing small cutaneous blood-vessels.[1] In many individuals the level of capillary resistance showed rapid fluctuations, indicative perhaps of changes occurring primarily in the amorphous ground substance rather than in the relatively inert fibrillary components of the sheath.[2] Thus the low level of capillary resistance in rheumatoid arthritis might well reflect the occurrence in periendothelial matrix of the enzymatic damage envisaged by Dr. Lack. The collapse of rabbits' ears following intravenous papain, first reported by Thomas in 1956,[3] is a closely analogous experimental situation, where loss of rigidity in cartilage is the clinical sign of

reversible enzymatic damage to the amorphous component of matrix. Dr. Lack mentioned that cortisone delayed restoration of the matrix following chondrolysis. McCluskey and Thomas[4] have reported a similar action of cortisone, hydrocortisone, and prednisolone upon the cartilage of papain-treated rabbits.

At least one of the serological features of rheumatoid arthritis may have an enzymatic basis. The "antinuclear factor" found in the serum of the majority of patients[5] appears to be a basic protein closely related to or identical with an enzyme or family of enzymes with bacteriolytic activity.[6] Concerning Dr. Lack's concept of a release of plasminogen due to increased vascular permeability, it is relevant that lysozyme present in normal serum has no "antinuclear" activity, and, from the analogous behaviour of papain protease, it can be inferred that lysozyme is normally bound to other proteins in serum. It was concluded that the effects of intravenous papain on cartilage in rabbits were produced by molecules of enzyme which remained—briefly—in an unbound, readily diffusible state after entering the circulation. The remaining molecules were bound by alpha-2-globulin, presumably forming a complex molecule sufficiently large to be incapable of entering cartilage.[7] Similarly, a positive test for "antinuclear factor" in rheumatoid arthritis may reflect inadequate binding of lysozyme in serum, and signify the presence of free enzyme capable of passing from the circulation and into tissues. It is likely that potentially harmful enzymes do enter the circulation in the course of tissue breakdown due to injury or infection. Any tendency for these enzymes to act upon susceptible substrates in healthy tissue may normally be obviated by binding mechanisms capable of retaining enzymes within the circulation.

We would agree with Dr. Lack's suggestion that autoimmunity could be a consequence rather than the cause of disorders of connective tissue; the possibility that immune responses might also maintain systemic disease initiated by enzymatic damage has been considered.[8] The hypothetical role of the reticulo-endothelial system could be the development of cell-borne or humoral hypersensitivity to antigens created by enzymatic degradation of components of tissue. In this way the immune response would be qualitatively similar to that occurring under the stimulus of other foreign proteins; the concept of hypersensitivity to truly *native* components—that is "auto-immunity"—may be irrelevant. Finally, Dr. Lack's ideas and those outlined above have evolved on the basis of independent clinical and experimental studies. Though differing in detail, they have in common the concept that some abnormality of the distribution and fate of enzymes *in vivo* may be of fundamental importance in the development of the disorders of connective tissue.—We are, etc.,

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REFERENCES

1 Potter, J. L., and Wigzell, F. W., *Ann. rheum. Dis.*, 1957, **16**, 357.
2 —— and Duthie, J. J. R., ibid., in press.
3 Thomas, L., *J. exp. Med.*, 1956, **104**, 245.
4 McCluskey, R. T., and Thomas, L., *Amer. J. Path.*, 1959, **35**, 819.
5 Alexander, W. R. M., Bremner, Joan M., and Duthie, J. J. R., *Ann. rheum. Dis.*, 1960, **19**, 338.
6 Potter, J. L., Alexander, W. R. M., and Duthie, J. J. R., *Arthritis and Rheumatism*, abstract in press.
7 —— McCluskey, R. T., Weissmann, G., and Thomas, L., *J. exp. Med.*, 1960, **112**, 1173.
8 —— *Arthritis and Rheumatism*, review in press.

SIR,—May I support the remarks of Dr. C. H. Lack (May 20, p. 1459) on the role of the ground substance in connective-tissue disease? We have been studying this for some time, and have found that agents which preclude polymerization of mucopolysaccharide prevent collagen-deposition in newly formed granulation tissue of healing. The agent we have used principally has been testicular hyaluronidase, which contains a hyalase and sulphatase. This has no inhibiting effect on the contraction of a superficial wound. This process is brought about by cellular activity. (Contraction also takes place in scurvy, where again collagen is not formed.) We are now endeavouring to determine which of the mucopolysaccharides are important.

We have also been interested to study the significance of blood factors, such as plasmin. We are currently studying the effect of the polypeptide bradykinin. Although this appears to produce an early and increased exudation in a wound, we have not found any increase in collagen formation when the drug is locally exhibited repeatedly. (We are very much indebted to Dr. Holgate, Research Director of Sandos Ltd., for our supplies of this drug.)

It is our conviction that although collagen-formation may be a useful or important and obvious change in the process of wound-healing and in connective-tissue disease, it is not the most significant change, but is a by-product of inflammatory processes. Like Dr. Lack, we feel that the term "collagen disease" is a poor one. It describes a biochemical symptom, but is of no more value in classification than the "fever" of the ancient physicians.—I am, etc.,

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Evolution of the Mental Hospital

SIR,—I should like to congratulate Dr. A. B. Cooper and Dr. D. F. Early on their article, "Evolution in the Mental Hospital" (June 3, p. 1600). I wish particularly to endorse their view that the mental hospital must not become a hostel or a geriatric or a chronic-sick unit.

In my view the modern hospital, probably in the future, associated with its own psychiatric unit in a near-by general hospital, is an active treatment hospital first and foremost. It is there primarily to treat and cure the mentally ill. Its discharge rate should nearly equal its admission rate. It will, of course, have to care for a small number of long-term incurable cases, but these cases must primarily be psychiatric cases which require the support and skill of the psychiatrist and psychiatric nurse and not just elderly or infirm people.

Dr. Early has ably demonstrated that probably 30% of our long-stay patients do not require psychiatric care. It is therefore most essential that local authorities, in close co-operation with mental hospitals, provide hostels, but, above all, that the geriatric service, both chronic sick and Part III, realize that they must provide the necessary accommodation for many patients who would not be remaining under psychiatric care.

The psychiatrist and the psychiatric nurse must not be wasted looking after the elderly—they must be freed for the treating of the neurotic and psychotic. Facilities for the proper and time-consuming work of treating neurosis, which includes character disorders and psychopathy, are still sadly lacking. It may well be that parts of mental hospitals in the future could be used for the care of the elderly and infirm, but the medical and