A primary lesion in the colon is rare. Whatever its origin, the colonic lesion shows far less tendency to diffuse infiltration than when attacking the ileum, strongly tends to be localized, projecting and tumour-like and is less clinically outspoken so that secondary infection and ulceration have usually largely destroyed the typical submucous lymphoreticular hyperplasia some time before the specimen reaches the pathologist.

The search for the aetiological agent of Crohn's disease makes a sorry tale. More than one surgeon has made the challenging statement that M. tuberculosis has not yet been excluded as its cause. In this regard it is surprising how few cases have been thoroughly investigated by guinea-pig inoculation. In view of the apparently haphazard distribution of giant-cell systems in the regional lymph nodes this examination would necessitate the use of several, occasionally half-a-dozen, animals in the examination of each operation specimen. To investigate a significant number of specimens on this scale is a big undertaking but it should be carried out or vigorously encouraged by those who regard the uniformly negative evidence for tuberculosis as being too inconclusive for acceptance. One ingenious explanation which is difficult to disprove is that the initial event in the disease is an invasion of the intestine by M. tuberculosis followed by rapid and wholesale killing and disintegration of the bacilli *in situ*. The lipid material obtained by extraction of M. tuberculosis by fat solvents is unquestionably a powerful mesenchymal stimulant and the lesions which the tuberculolipids produce in the tissues of experimental animals contain giant-cell systems which show little tendency to caseate. It is just possible that an investigation recently carried out by Wells and Wylie may provide a clue to the aetiological basis of Crohn's disease. The serum of patients suffering from sarcoidosis in an active phase was found to be capable of modifying or completely neutralizing the ability of old tuberculin to evoke a typical reaction in the skin of persons known to be hypersensitive. The serum of a single case of Crohn's disease had a pronounced neutralizing effect.

Whilst the aetiology of Crohn's disease is still in the realms of speculation, our knowledge of its

clinical behaviour has been enriched by the published experience of many observers. In this issue we publish a detailed and fully documented survey of the literature of the disease by a surgeon, Mr. E. E. T. Taylor, and a critical review of the disease in all its clinical aspects by Professor T. L. Hardy.

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Annotation

'Compound E'

In October 1948 Philip Hensch delivered an oration to the Heberden Society entitled 'The Potential Reversibility of Rheumatoid Arthritis' in April of the present year he and his fellow workers at the Mayo Clinic have published a preliminary report² on the treatment of rheumatoid arthritis with 'Compound E', an adrenal hormone isolated by Kendall.

In his oration Hensch, drawing attention to the remissions of rheumatoid arthritis, described them as spontaneous, therapeutic, and accidental. Gold, first used on a false assumption, has the strongest claim to a place in the second group but induces a striking remission in only some ten to fifteen per cent. of cases, a figure which corresponds closely with that of spontaneous remissions. Because spontaneous remissions have happened to coincide with the trial of some new form of treatment, many therapeutic hopes have proved false; as a corrective to those assessing the value of any therapy in this condition, the results of simple supportive measures employed over a ten year period by Short and Bauer³ should be consulted. Certainly no form of treatment has hitherto produced rapid and convincing amelioration of the disease in a high proportion of cases treated.

Stressing the uncertainty of other measures,

Hench has repeatedly emphasized that two states, pregnancy and jaundice, give remissions in sixty to ninety per cent. of cases, a rate about five times that of spontaneous or therapeutic remissions. If we can find, he said in effect, some biochemical or hormonal change common to these two states, there may lie the way to effective treatment. A great deal of work has yielded negative results including bile salts intravenously, female sex hormones and transfusions of blood from pregnant donors. A pregnant woman's urine has even been administered, disguised as a cocktail. Only the deliberate induction of jaundice by icterogenic plasma or lactophenin has succeeded, but as the remissions produced are no more than temporary, it cannot be regarded as a practicable therapeutic measure.

Selye's Adaptation Syndrome and Collagen Disease. The understanding of rheumatic and allied disorders has been increased by two new forms of approach. By a series of experiments, which at first sight seem artificial, Selye⁴ was able to produce a number of changes in rats, including arthritis, Aschoff's nodes and polyarteritis nodosa. Exposure of animals to sudden stress, e.g. drugs, cold, acute infection, etc., produces 'shock'. When the stimulus is repeated in sublethal doses the animal becomes resistant to the stimulus to which it has become adapted, but abnormally sensitive to other damaging agents. If the stimulus is continued long enough, adaptation becomes exhausted and the animal dies. Selye thus distinguishes three stages of reaction to stress, the stage of 'alarm', the stage of 'adaptation', and the stage of 'exhaustion'. During adaptation the adrenal cortex hypertrophies and produces excessive amounts of cortical hormones; this change is mediated by the adreno-corticotrophic hormone of the pituitary. Selye claims that the arthritides and several other conditions are diseases of disordered adaptation to traumata of various kinds, in which excessive production of the salt-active hormone of the adrenal cortex plays an important part. The concept of disordered adaptation to non-specific traumata allows inclusion of allergic theories and at the same time covers the factors of psychological shock, prolonged physical

and mental strain, and exposure to damp surroundings, which loom large in the histories of patients with rheumatoid arthritis.

At the same time an increasing awareness of the importance of changes in the connective tissue ground substance, termed collagen disease, in such diverse conditions as rheumatic fever, rheumatoid arthritis, polyarteritis nodosa, disseminated lupus erythematosus and scleroderma, is opening up new fields of study, both histological and biochemical. These two approaches, coupled with the finding of widespread lesions in muscles, nerves and heart, have led to the view that rheumatoid arthritis may be the result of biochemical and endocrine changes produced by a variety of traumata, rather than the single result of bacterial infection, bacterial 'toxins' or focal sepsis.

Compound E. Hench conjectured that the 'antirheumatic substance X', the substance presumed to be common to pregnancy and jaundice, might be an adrenal hormone because of the temporary remissions produced in rheumatoid arthritis by anaesthesia and surgical operation, procedures known to stimulate the adrenal cortex. His attention was drawn to 17-hydroxy-11-dehydrocorticosterone, isolated by Kendall. Compound E differs from desoxycorticosterone in that it induces a negative sodium balance and an increased urinary excretion of the ion; it has a marked effect on carbohydrate metabolism, causing an increase in the blood sugar and storage of glycogen in the liver.

In September, 1948, the first patient of the series was treated, a twenty-nine year old woman with rheumatoid arthritis of four and a half years duration, who was practically confined to bed by painful, swollen joints. At this time the blood sedimentation rate was 108 (Westergren).

After a period of preliminary bed rest during which time the joint condition deteriorated, Compound E was started in a daily intramuscular dose of 100 mgm. Within forty-eight hours the patient noticed subjective improvement and was able to move more easily in bed. On the fourth day, scarcely able to walk at all three days previously, she now walked with only a slight limp.

After a week of administration, articular and muscular stiffness had almost completely disappeared, and even the joint swellings were markedly lessened. On the eighth day of treatment 'she shopped down town for three hours, feeling tired thereafter, but not sore or stiff'. At this point the dosage was reduced to 50 mgm. daily for four days, then 25 mgm. daily for ten days. But these doses were inadequate. Rheumatic symptoms increased, and the sedimentation rate rose from 86 to 118. The subsequent course of this first patient has been the least satisfactory of all the patients treated. Although her arthritis has abated, it has never been completely controlled, and arthritic flare-ups have occurred. Hirsuties, acne and amenorrhoea have developed.

To date a further sixteen patients are under treatment. All are reported to have shown marked or very marked improvement and there has been a corresponding fall in sedimentation rate, in many cases promptly and rapidly. Other changes have been a return to normal of the plasma proteins and the albumen-globulin ratio in patients showing high globulin levels, and an improvement of anaemia. Latterly Compound E acetate has been found to be more satisfactory and is now being used instead. In order to check results, unknown to the patients and for one period even to the three physicians treating the patients, a solution of cholesterol identical with Compound E in appearance was substituted. Whenever this happened there was a rapid relapse with return of joint pain and swelling, and increase in the sedimentation rate; these changes were promptly reversed when Compound E was continued.

ACTH and Other Hormones. Two female patients with severe rheumatoid arthritis received 100 mg. of pituitary adrenocorticotrophic hormone intramuscularly for twelve days. Marked clinical improvement, essentially similar to that resulting from Compound E was observed; and the sedimentation rates fell even more promptly and steadily. One patient who had responded to Compound E and ACTH was treated with Compound A (Dehydrocorticosterone) without effect.

Comment. Although the number of patients

treated is small, the rapid and uniform response obtained gives Compound E the unmistakable stamp of specific therapy. The definition of a specific is that it works, and works almost invariably. Hench's results leave little doubt that whatever the nature of rheumatoid arthritis, Compound E will reverse its changes. Reference to encouraging results in the treatment of disseminated lupus and rheumatic fever, though no data are as yet presented, suggests that a therapeutic agent of wide application has been discovered. It seems unlikely that Compound E will be the disappointment that many vaunted methods of treatment have proved to be in the past, but caution is needed as the workers of the Mayo Clinic would be the first to admit. The prompt reversion to activity which occurs when cholesterol injections are substituted not only testifies to the efficacy of the hormone, but indicates that no 'quick cure' is to be expected. As with hormonal therapy in other conditions, Compound E or ACTH may have to be administered over long periods, perhaps throughout the natural length of the disease which may take many years before it burns itself out. If this should be so, side effects such as those which developed in the first patient treated may present inconveniently or even dangerously. It is not, however, improbable that further work will reveal measures or dosage capable of combating side effects, or produce purer preparations. What is certain, however, is that Compound E can be produced only in limited supply for some time to come, and will not be available for extended therapeutic trials until 1950. Supplies of ACTH are also extremely limited. It will be unfortunate if the inevitable publicity results in the uncritical and uncontrolled use of other available steroids for patients suffering from rheumatoid arthritis.

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