bled during this period. In summary, 3 out of 4 patients with H.H.T. experienced the appearance, enlargement, or aggravation of bleeding of lesions during oral contraceptive therapy.

The appearance of telangiectasias in H.H.T. at puberty, and the correlation of epistaxes with the menstrual cycle, give weight to a possible causal relationship between œstrogens and the aggravation of H.H.T. Paradoxically, oral œstrogens have been recommended to counteract epistaxes in this condition.[1,2] We hope that our experience will stimulate the prospective study of additional patients to determine whether in fact women with H.H.T. represent a group genetically predisposed to increased morbidity from oral contraceptives.

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MITOCHONDRIAL ASPARTATE TRANSAMINASE

SIR,—It has recently become possible to determine the isoenzymes of aspartate transaminase (G.O.T.) by a sensitive semiquantitative method,[3] and this technique has now been applied to a series of African patients, mostly from the wards of Mulago Hospital. As well as seeking out patients suffering from various individual diseases, we have obtained samples from a wide variety of cases—as nearly as possible a whole medical-ward population over a period of several days.

It is known that serum levels of both isoenzymes, but predominantly of the cytoplasmic form, are raised in infective hepatitis [4]; and following myocardial infarction it is the mitochondrial form which shows a greater relative increase.[5] A striking feature of the present cases is that many show a considerable rise in the level of mitochondrial isoenzyme alone, or have only a slight change in the level of cytoplasmic isoenzyme. Of nine with grade D or E mitochondrial isoenzyme (over 15 I.U. per litre) and not more than 23 I.U. per litre total aspartate transaminase,[6] three have cirrhosis of the liver, three have schistosomiasis, one has hepatitis, one has primary hepatoma, and one has had treatment for malignant melanoma but was admitted on this occasion with an inflammatory mass in the right iliac fossa which had almost resolved when the blood-sample was taken. All four confirmed cases of primary hepatoma (including the one noted above) and several suspected cases, show a considerable rise in the level of mitochondrial enzyme (grade C or above), with not more than 21 I.U. per litre total aspartate transaminase. So far, only two cases of endomyocardial fibrosis have been tested: both show distinct elevation of the mitochondrial enzyme. It has been reported [7] that the total-aspartate-transaminase level is usually normal in this condition, but the method used [6] is very insensitive to the mitochondrial isoenzyme.[5] A large number of other cases show modest increases of the mitochondrial isoenzyme alone, or increases of both together, but we will not discuss these further here.

We do not wish any premature conclusions to be drawn—for example, in cases of endomyocardial fibrosis it will be difficult to ascertain whether excess serum enzymes arise from the heart or the liver, and even more difficult to determine the mechanism of release. It seems clear, however, that study of mitochondrial enzymes in the serum will add a new dimension to clinical enzymology, by allowing an approach to the study of intracellular events through observations on the blood.

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OSCILLATION DURING THE IMMUNE RESPONSE

SIR,—The report by Dr. Dwyer and Dr. Mackay (Jan. 24, p. 164), that the number of antigen-binding lymphocytes in blood shows rapid fluctuation after antigenic stimulation, adds to the evidence that oscillation may occur during the immune response.[1–3] The factors responsible for oscillation in the production of red-cells, granulocytes, and platelets have lately been reviewed,[4] and, in view of the close similarity between the production of differentiated blood-cells and antibody-producing cells, it may be questioned whether similar factors operate during the response to antigenic stimulation.

Two principal mechanisms may give rise to oscillation in biological systems—negative feedback and interaction between populations. There is now much evidence that antibody controls its own production by some form of negative feedback.[5] Britton and Moller [1] have reported that the number of 19*S*-antibody-forming cells in mice showed oscillation following the administration of endotoxin. Since these workers were able to prevent a rise in the number of these cells by administering antibody beforehand, their observations provide strong evidence that negative feedback was responsible for the oscillation. The point raised by Dr. Dwyer and Dr. Mackay, that the fluctuations observed in their own study were too rapid to be accounted for by negative feedback, is not necessarily valid, since rapidity of oscillation in a feedback system may merely indicate that the time-delay in or time-characteristic of the system is brief.

The possible role of interaction between populations is difficult to assess and quite speculative. In their classic early work Lotka [6] and Volterra [7] pointed out the oscillatory nature of the equilibrium which results from one type of interaction between populations—that between two animal species, one of which is the predator and one of which is the prey. This type of Lotka-Volterra equilibrium may be involved in the interaction between replicating antigen (the prey) and immune cells (the predators). Similar types of interaction, however, may also be involved in the competition for stem-cells or for an antigen between different antibody-producing cell-lines, or in the interaction between a stem-cell compartment and a more differentiated compartment.

Oscillation is more than a phenomenon of visual interest. Its presence may point to the existence of hitherto unsuspected feedback loops or population interactions. Conversely, the ubiquity of feedback loops and population interactions makes it possible that many physiological

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