blood. There was a single small haemorrhage adjacent to the optic disk in each fundus. The urine and the blood pressure were normal.

Case 2.—A 25-year-old woman was found to have an iron-deficiency anaemia nine days after a normal confinement at home. On admission her Hb was 4.2 g./100 ml. and M.C.H.C. 25%. Platelets were reported to be normal in the film. She had a single small haemorrhage in the right fundus.

Case 3.—This was a case of idiopathic thrombocytopenic purpura with iron-deficiency anaemia in a woman aged 40. Her Hb level on admission was 7.3 g./100 ml. and M.C.H.C. 29%. Platelets varied from 9,000 to 21,000 per c.mm. Bone marrow examinations showed an iron-deficiency anaemia with "deficient platelet formation." She had multiple large coalescing flame-shaped haemorrhages adjacent to the disks in both eyes, with numerous smaller haemorrhages in the peripheral areas of the retinae.

Case 4.—A man aged 70 complained of bleeding gums. After investigations, which included two bone-marrow examinations, a diagnosis of aplastic anaemia was made. The Hb on admission was 8.4 g./100 ml., the white cell count 3,000/c.mm., and the platelet count 21,000/c.mm. The fundi showed several large haemorrhages near the disks with smaller peripheral haemorrhages.

Patients in the megaloblastic group tended to present with more severe anaemias than those in the normoblastic group. The two most severe anaemias of all were, however, of the iron-deficiency type associated with hookworm infestation. These patients had Hb levels of 1.5 and 1.6 g./100 ml. Neither showed any retinal change apart from pallor.

Discussion

Retinal changes in severe anaemias have usually been ascribed to deficient oxygenation consequent on low haemoglobin. Few authors have ventured to suggest that they might be significant in the differential diagnosis of anaemia. The report which is in closest accord with our findings is that of Foster Moore (1925), who wrote: "It is believed that there is a considerable reduction of the platelets in the blood in such diseases as pernicious anaemia and acute lymphatic leukaemia, conditions in which [retinal] haemorrhages are common; in chlorosis, on the other hand, there seems to be no diminution of the platelets and haemorrhages do not occur."

Our evidence suggests that retinal haemorrhages are much more frequent and extensive in megaloblastic anaemias and thrombocytopenic conditions than in anaemias due to blood loss or iron deficiency. It appears that retinal changes are not solely dependent on deficient oxygenation or low Hb levels. Among the factors which may contribute to these changes is thrombocytopenia. In two-thirds (15) of our cases of megaloblastic anaemia the pathologists gave an unsolicited report that "platelets were decreased in the peripheral blood," or words to that effect. Recent experience has, however, shown us that some patients with megaloblastic anaemias and retinal haemorrhages may have platelet counts of over 90,000 per c.mm. Reports of deficient platelets appear only twice in the other group of patients. In both these patients (Cases 3 and 4) the thrombocytopenia was definitely established and retinal changes were marked.

Some of the haemorrhages in megaloblastic anaemias have pale yellow centres very similar to those which occur characteristically in leukaemia. In leukaemia this is said to be due to central aggregation of leucocytes within the haemorrhagic area. It is difficult to see why

a similar change should occur in megaloblastic anaemias unless it depends on the proportion of white cells to red cells. In megaloblastic anaemia due to the low red-cell count this proportion is usually greater than normal, though not as great as in leukaemia.

Summary

During an analysis of 74 cases of severe anaemia among Indians the retinal appearances were studied in relation to the type and severity of the anaemia. It was found that retinal haemorrhages occur almost universally in severe megaloblastic anaemia and in anaemia associated with thrombocytopenia. Retinal changes occur rarely in cases of iron-deficiency anaemia or anaemia due to blood loss.

Though this sign has been mentioned previously, it is felt that its value has not been sufficiently emphasized. It is diagnostically useful in communities where severe anaemias of these types are prevalent.

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Preliminary Communications

A Sodium-excreting Steroid ?

As soon as the sodium-retaining properties of the highly potent steroid aldosterone were discovered in 1952 by Simpson and Tait, it at once became a possibility that there was also formed in the body a steroid with the reverse action—that is, with sodium-excreting properties. Indeed, the suggestion that such a substance might exist had already been made by Wilkins and Lewis (1948) to explain the excessive salt-losing condition seen in some patients with congenital adrenal hyperplasia.

Other early observations pointed to the existence of such a compound. Thus the patient with Addison's disease is much more sensitive to the sodium-retaining effects of D.C.A. than is the normal subject. This suggests the production in the normal of a substance antagonizing the sodium-retaining action of D.C.A. Then, again, difficulty has been experienced in carrying out a satisfactory bioassay of the sodium-retaining factor present in urine extracts. For instance, Luetscher, Demin, and Johnson (1952), Singer and Venning (1953), and Cope and Garcia-Llaurado (1954) all encountered urine samples in which the sodium-retaining activity was not increased by using a much larger dose of extract in the test animals, so that a proper dose-response curve could not be obtained. Indeed, it was for this reason that Cope and Garcia-Llaurado (1954) carefully refrained from drawing any quantitative conclusions from their assays. They stated that their results did not

provide enough evidence on which to base any useful estimate of the quantity of aldosterone present in urine.

Many complicating substances might have been present in the early crude extracts, and preliminary purification by paper chromatography often led to better bioassay results of the sodium-retaining factor. But this was not always so, and Dyrenfurth and Venning (1959) have recently published their own circumstantial evidence for the existence of an interfering and sodium-excreting factor. They found that extracts freed of most of their cortisol, cortisone, and corticosterone sometimes showed less aldosterone when assayed at a high dose-level than at a lower, and suspected, therefore, that an antagonizing substance was present which could be diluted out. Indeed, they found some urine extracts which actually increased sodium output.

There is good reason to believe, therefore, in the existence of a sodium-excreting factor in man and to believe that this occurs at least sometimes in the urine. Search for such a sodium-excreting factor (S.E.F.) is being pursued vigorously in several research centres.

One such search has been carried out by a Ciba group in Basle (Neher *et al.*, 1958). These workers were able to isolate from hog adrenals a fraction which appeared to have sodium-excreting properties. This they identified as $3\beta,16\alpha$ -dihydroxy-allopregnan-20-one, and this compound has been synthesized by the same group. They believe that this steroid has sodium-excreting properties (S.E.F.), though they admit that its activity is inhibited or enhanced by conditions which have not yet been fully elucidated.

Since a naturally occurring steroid with sodium-excreting properties would clearly be of the highest physiological and therapeutic importance, we have tested this steroid for possible sodium-excreting activity in man under favourable clinical conditions.

Five patients have been used for the tests, all representing, so far as possible, the same clinical state of convalescence from moderate congestive failure with recent oedema. None had received any diuretic during the preceding 10 days or more, and they might therefore have been expected to be very responsive to a sodium diuretic. This particular clinical situation was chosen for the tests because it was one in which a sodium diuretic might prove useful, and one, moreover, likely to be favourable to the revelation of any sodium-excreting activity possessed by the compound.

The first subject was on a normal salt intake, the remaining four being on a low-sodium intake of 22 mEq daily. Baseline urinary excretions of sodium and potassium were measured for four to seven days. The steroid was then given as a daily intravenous injection for three successive days. After two or three further days, in which any effect of the steroid could subside, a single dose of 1 g. of chlorothiazide was given to four of the subjects. The results obtained are summarized in the Table.

Mean Daily Urinary Excretion mEq

Case No.	Daily Dose Steroid (mg.)	4 Days Control		3 Days Steroid		1 g. Chlorothiazide	
		Na	K	Na	K	Na	K
1	40	71	70	68	67	—	—
2	60	10	75	8.6	70	87	79
3	80	6.5	42	10	40	131	65
4	100	7	102	12	87	80	75
5	100	8	37	7	28	58	50
Mean ..		20	65	21	58	89	67

From these experiments it is clear that, under the clinical conditions chosen, the steroid (S.E.F.) caused no significant change in urinary sodium excretion, though chlorothiazide provoked a sharp sodium diuresis. The mean effect in the five cases is an increase of only 5% in sodium excretion, and this may be compared with the mean increase of 330% produced by a single dose of chlorothiazide.

No conclusions can safely be drawn about any effects on potassium excretion because the intake was not fully controlled, but it cannot be large.

Whether this steroid will prove to have sodium-excreting properties under other clinical conditions remains to be seen. This seems unlikely, because the steroid possesses a saturated ring A, and this is not usually associated with physiological activity.

Summary

Evidence suggesting the existence of a sodium-excreting factor in the human subject is briefly reviewed.

A new steroid, $3\beta,16\alpha$ -dihydroxy-allopregnan-20-one, said to have sodium-excreting properties, has failed to show any such activity in a clinical situation in which it could have provided useful therapy.

We are greatly indebted to Dr. Neher and to Dr. Gross, of Basle, for a generous sample of this steroid in a form suitable for intravenous injection.

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Phenethyldiguanide: A Dangerous Side-effect

Phenethyldiguanide (D.B.I.) is the most recent of the hypoglycaemic drugs to become available to clinics in this country. Early work has suggested that D.B.I. has a place in the treatment of adult diabetics, in whom it has an advantage over the arylsulphonylureas by reason of the absence of secondary failures and a wider spectrum of action (Williams *et al.*, 1958; Krall and Camerini-Davalos, 1958; Walker, 1959). In addition, it may in conjunction with insulin improve the control of unstable diabetics (Pomerance, 1957; Odell *et al.*, 1958; Krall and Bradley, 1959).

The action of D.B.I. has not yet been elucidated—it produces hypoglycaemia in the absence of endogenous insulin, thereby differing from the arylsulphonylureas. It has been suggested that it acts by promoting anaerobic glycolysis, which is less efficient than normal aerobic metabolism in that more glucose is required per unit of energy produced (Williams *et al.*, 1958). The