modifying the response of the organ to the sympathetic transmitter seems to be finally established. It is pleasant to point out that these observations are in full agreement with the evidence and views of Blaschko and his colleagues put forward in 1937 and of Gaddum in the following year. The action of cocaine seems to be similar to that of ephedrine and to consist also in an inhibition of amine oxidase.

The effect of thyroid feeding in diminishing the amine oxidase in the liver furnishes an explanation for old observations not only on the physiological but also on the clinical side. In the thyroid-fed animal adrenaline produces a greater hyperglycaemia than in the normal animal, and the work of Marks (1925) brought this fact into relation with the diminished sugar tolerance of hyperthyroid patients. Because of the fall of amine oxidase in the liver, the extent of the glycogenolysis which occurs as a result of a given sympathetic stimulus is supernormal.

Perhaps of greater import is the evidence that thyroid feeding causes a fall in the amine oxidase in the blood vessels, and that this fall is accompanied by a raised blood pressure and a raised sensitivity to the pressor action of adrenaline. These observations implicate amine oxidase in the control of blood pressure in the clearest manner, and show that changes in the amount of this enzyme or in the factors which modify its activity must be carefully considered in relation to hypertension.

Summary

At the vagus nerve endings and at motor nerve endings in skeletal muscle the enzyme cholinesterase is present. Evidence is shown that there is a corresponding enzyme, amine oxidase, around the sympathetic nerve endings in the blood vessels, the nictitating membrane, and the iris of the cat. This enzyme destroys the sympathetic transmitter, *noradrenaline*, more rapidly than it destroys *adrenaline*. The enzyme declines in amount after denervation, and in the nictitating membrane during the first ten days the decline is proportional to the increase in sensitivity to *noradrenaline*. Later the amount of enzyme is restored both in nictitating membrane and in the blood vessels.

The amount of amine oxidase in the liver is reduced by thyroid feeding and increased by thyroidectomy. These changes probably explain the greater hyperglycaemia which adrenaline produces in the thyroid-fed animal.

The amount of amine oxidase in the blood vessels is reduced by thyroid feeding. This is correlated with a rise in the blood pressure and an increase in the pressor effect of adrenaline.

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THE ANAEMIA OF HYPOPITUITARISM

BY

V. K. SUMMERS, M.D., M.R.C.P.

Consultant Physician, Walton Hospital, Liverpool

The purpose of this paper is to present observations on some of the haematological changes which occur in hypopituitarism. A normochromic anaemia of moderate severity and refractory to treatment is usual in this syndrome (Sheehan and Summers, 1949), but examples of both hypochromic and hyperchromic anaemia are also recorded. In few of the recorded cases are details of absolute values given, and accurate classification of the anaemia is therefore impossible. One case of aplastic anaemia has been reported (Bloom and Bryson, 1948), and Addisonian pernicious anaemia has also been described (Witts, 1932). The diagnosis of severe hypopituitarism in these cases is, however, doubtful.

All the cases in the present study, with one exception, were typical examples of hypopituitarism due to post-partum necrosis of the anterior lobe, and had had amenorrhoea since their last delivery, absent pubic and axillary hair, cold-sensitivity, lowered basal metabolism, low 17-ketosteroid excretion, and typical responses to the insulin-sensitivity test. The exception was a case occurring in a man who had typical clinical and biochemical changes, but in whom the aetiology of the hypopituitarism was uncertain. Subsequent necropsy in one of these cases confirmed the clinical diagnosis.

Methods

The observations presented were made on 10 patients. All were observed as in-patients in the early stages, and the subsequent follow-up was done as out-patients. All the haematological investigations were made by me.

Blood for red-cell counts was obtained by venepuncture from an antecubital vein, using a dry sterilized syringe and needle. The blood was collected into a 5-ml. bottle containing Wintrobe's anticoagulant mixture (1.2 g. ammonium oxalate and 0.8 g. potassium oxalate dissolved in 100 ml. neutral distilled water). To prevent deterioration 1 ml. of 40% formalin was added to this mixture; 0.5 ml. was run into each bottle from a burette and allowed to dry. The blood was diluted in a Thoma haemocytometer pipette using Hayem's fluid (sodium chloride 1 g., sodium sulphate 5 g., corrosive sublimate 0.5 g., and distilled water 200 ml.).

The haemoglobin was estimated by means of a Spekker photo-electric absorptiometer, using a yellow-green filter with an optical density of 0.475; 100% by this method corresponds to 14.8 g. of haemoglobin per 100 ml.

Reticulocyte counts were made using equal parts of blood and a brilliant cresyl blue solution (consisting of one part of a saturated alcoholic solution of brilliant cresyl blue to five parts of a normal saline solution to which 0.4 g. of sodium citrate was added). After mixing of the blood and cresyl blue, smears were made, dried, and counterstained with Leishman's stain. The number of reticulocytes in 1,000 red cells was counted.

The mean corpuscular volume (M.C.V.), the mean corpuscular haemoglobin (M.C.H.), and the mean corpuscular haemoglobin concentration (M.C.H.C.) were determined by the methods of Price-Jones, Vaughan, and Goddard (1935).

The methods available for determination of the red-cell diameter are open to many inaccuracies. The value of the diffraction method of Pijper (1919, 1947) in the determination of red-cell diameter has recently been assessed by Hird (1949), who thought the method unreliable in esti-

inating macrocytosis except in the extreme upper range, greater than 8.5μ , and of no value in assessing microcytosis.

The method of Price-Jones (1910), although considerably more accurate than diffraction methods, is extremely laborious and technically difficult. For these reasons no direct measurement of red-cell diameter was made. It was also considered that the cubic measurement of cell volume was a more accurate indication of cell size, providing spherocytosis was absent.

The usual gruel meal was given for assessing gastric acidity, specimens of gastric juice being collected at 15-minute intervals for three hours. At the end of 90 minutes 0.5 mg. of histamine acid phosphate was given.

Haematological Data

The haematological data in these cases are recorded in Table I, together with details of the duration of the disease, the basal metabolism, and the state of gastric secretion.

TABLE I.—Blood Counts in Cases of Hypopituitarism

Case No.	Time Since Onset (Years)	B.M.R. %	Cholesterol mg./100 ml.	R.B.C. mil./c.mm.	Hb g./100 ml.	M.C.V. μ^3	M.C.H.C. %	Achlorhydria
Macrocytic Hypochromic Anaemia								
1	6			4.1	11.9	102	30	+
2	6	-40	190	3.2	9.6	104	30	+
3	17	-38	370	3.3	9.7	109	27	+
4	17	-42	360	3.5	9.4	110	30	+
5	31	-29	125	3.0	8.5	94	28	+
6	35		120	3.5	11.6	114	29	+
Normocytic Hypochromic Anaemia								
7	7	-45	380	3.8	9.1	92	26	+
8	15	-25	150	4.1	11.7	90	32	+
9	20	-44	80	4.7	10.6	85	27	Free acid
10	20	-46	191	4.2	12.0	88	32	+

For the purpose of classification an anaemia was regarded as macrocytic if the M.C.V. was greater than $94 \mu^3$, normocytic if between 78 and $94 \mu^3$, and microcytic if less than $78 \mu^3$. If the M.C.H.C. was less than 32% the anaemia was regarded as hypochromic (Wintrobe, 1946).

Macrocytic Hypochromic Anaemia.—In six cases the anaemia was macrocytic and hypochromic, the red-cell count ranging between 3 and 4.1 millions per c.mm. and the haemoglobin between 8.5 and 11.9 g. per 100 ml. The M.C.V. ranged between 94.3 and $113.6 \mu^3$. No polychromatic cells, no cells showing basophilic stippling, and no immature cells were seen in the stained films. Few anisocytes and poikilocytes were observed. Clinically three patients had marked myxoedematous features, and three moderate. Histamine-fast achlorhydria was present in all the cases in which this test was performed. The bone marrow was normoblastic in all cases.

Normocytic Hypochromic Anaemia.—There were four cases in this group, the red-cell count ranging between 3.8 and 4.7 millions per c.mm. and the haemoglobin between 9.1 and 12 g. per 100 ml. The M.C.V. ranged between 85 and $92.1 \mu^3$, and was in all cases near the upper limit of the normocytic range. No immature or polychromatic cells were seen in the stained films. Free hydrochloric acid was present in one case. The bone marrow was normoblastic in all cases. Clinically, two patients had myxoedematous features.

Achlorhydria.—Achlorhydria occurred in nine cases of hyperchromic anaemia recorded in the literature, but in four such cases normal gastric acidity was found; similarly, in cases of hypochromic anaemia occurring in hypopituitarism and recorded there were five instances of achlorhydria and four of normal gastric acidity. Achlorhydria was found in all but one of the cases studied in the present series.

Glossitis, Perlèche, Koilonychia.—Atrophy of the mucous membrane of the tongue with perlèche was observed only in Case 7, in which the anaemia was of normocytic type. There are very few reports in the literature of glossitis

occurring in hypopituitarism, but cases are recorded by Means, Hertz, and Lerman (1940, Case 4), Fraser and Smith (1941, Case 2), and Caughey (1946). All these patients had a hyperchromic anaemia, but no details of cell size are given in the reports. There are no reports in the literature of either perlèche or koilonychia occurring in cases of hypopituitarism associated with anaemia.

Therapy

Various methods of treatment were tried in these cases, and the results of such therapy on the blood counts and haemoglobin are discussed.

Thyroid

All patients who had a macrocytic hypochromic anaemia had appearances resembling myxoedema. The basal metabolic rate in those cases in which the estimation was made was similar to the rate seen in myxoedema, and severe thyroid atrophy is one of the constant post-mortem findings in severe hypopituitarism. Thyroid deficiency might reasonably be deduced to cause part of the syndrome of hypopituitarism, and therefore thyroid extract was given to Cases 3, 4, and 6. The dose administered was 0.5 g. twice daily. This small dose of thyroid was given because of the possible risk of inducing an adrenal crisis, examples of which have been reported. The results of treatment are shown in Table II.

TABLE II

Case No.	Before Treatment				After Treatment			
	R.B.C. mil./c.mm.	Hb g./100 ml.	M.C.V. μ^3	B.M.R. %	R.B.C. mil./c.mm.	Hb g./100 ml.	M.C.V. μ^3	B.M.R. %
4	3.5	9.4	110	-42	3.6	9.6	90	-8
6	3.5	11.6	114		3.6	11.8	93	
3	3.3	9.7	109	-38	3.4	9.7	94.2	+4

The duration of treatment in Cases 4 and 6 was six months and in Case 3 ten months. No reticulocytosis was observed during the treatment. Although the changes in the red-cell count and the haemoglobin were not marked, there was a reduction in the size of the red cells as manifested by the M.C.V., and this was associated with a rise in the B.M.R. in the two cases in which observations on this were made. No investigations of the effect of thyroid was made in patients with a normocytic anaemia.

The effects of thyroid therapy in hypopituitarism have been reported frequently, but no constant pattern of response by the blood-forming tissues can be detected. Thus a fall in the red-cell count and haemoglobin was noticed by Boller and Goedel (1935, Case 1), Robertson (1945), and Daughaday *et al.* (1948, Case A. A.). On the other hand, van Balen (1939, Case 1) observed an initial rise in both the red-cell count and haemoglobin, but this was followed by a return to the starting levels within a month. Mallory (1940) noticed no change in the blood after thyroid had been given; Darley *et al.* (1944) also observed no improvement after administering thyroid, iron, and liver. A reduction in the mean corpuscular diameter from 8.7 to 8μ was found by de Langen (1937, Case 1), but there was no change in the haemoglobin.

However much the clinical appearances, the basal metabolism, and the blood picture in hypopituitarism resemble those in myxoedema, thyroid extract does not seem to produce improvement in the blood in the macrocytic anaemia of hypopituitarism.

Testosterone

Testosterone propionate administered intramuscularly or implanted subcutaneously produces clinical improvement in most cases of hypopituitarism. Four patients have been treated in this way: in Case 4, 400 mg. of testosterone propionate was implanted subcutaneously in the abdominal

wall, and in Cases 1 and 5, 100 mg. of testosterone propionate was given intramuscularly each week for one month, when four 100-mg. pellets were implanted in the subcutaneous tissue of the abdominal wall. Neither of these patients had received any other form of treatment. Case 10 had previously received 1,250 mg. of "ferrivenin"; in this case also four 100-mg. pellets of testosterone propionate were implanted subcutaneously, and subsequently at three-monthly intervals. Treatment with thyroid extract had been given in Case 4; but none had been given for eight months before implanting testosterone. The results of treatment are shown in Table III.

TABLE III

Case No.	Before Treatment				After Treatment				Duration of Treatment, Months
	R.B.C. mil./c.mm.	Hb g./100 ml.	M.C.V. μ^3	M.C.H.C. %	R.B.C. mil./c.mm.	Hb g./100 ml.	M.C.V. μ^3	M.C.H.C. %	
4	3.5	9.4	111	30.0	3.7 4.9 4.8	9.6 13.6 13.6	105 87 88	30 33	1 2 3
10	4.2	12.0	88	32	5.0 4.9 4.1	13.8 13.8 11.9	88 88 101	30 30 90.0	6 9 4
1	4.1	11.9	102	29.7	3.7 3.4	10.3 9.4	90.7 90.0	30 30	1 2
5	3.0	8.5	90.3	29.3					

In Case 10 there was a small rise in both the red-cell count and haemoglobin, which had almost reached its maximum at the end of two months. In Case 5 there was a rise in the red-cell count and haemoglobin at the end of the first month, but a fall in both these values occurred at the end of the second month, although both the haemoglobin and the red-cell count were above the initial levels. No change was observed in the other two cases. No reticulocytosis was observed in any case.

Experimental evidence suggests that androgenic hormones may influence blood formation. Vollmer and Gordon (1941) noted an increase in the red-cell count after testosterone was given in rats, and Finkelstein *et al.* (1944) found that testosterone accelerated the rate of recovery from post-haemorrhagic anaemia in male rats. Korenchevsky and Hall (1945) also reported that androgens increased the red-cell count and haemoglobin in both normal and castrated male rats; Crafts (1946), however, found that, although testosterone prevented a fall in the red-cell count in hypophysectomized rats, the haemoglobin level fell.

There are few reports in the literature of the effects of androgens on the blood in cases of human hypopituitarism, and the evidence of these is inconclusive. Williams and Whittenberger (1942), using a blunderbuss therapy which included testosterone, reported a slight increase in both the red-cell count and the haemoglobin. Daughaday *et al.* (1948) found varying effects from testosterone in their cases. Thus, in their Case H. O. there was little change in cells or haemoglobin after one month's treatment with testosterone, but at the end of seven months there was a rise of nearly 30% in the red-cell count and 10% in the haemoglobin. These changes were accompanied by a small increase in the M.C.V. A similar response was recorded in their Case H. O. N. after several months' treatment, but in Cases T. R. and M. T. no significant change in cells or haemoglobin occurred.

In the present series the results following testosterone therapy are variable, and this, together with the evidence in the literature, suggests that the androgenic hormones have no specific effect on the anaemia of human hypopituitarism.

Iron

Iron, both orally and intravenously, was tried on Cases 2, 4, and 10, all of whom subsequently had other treatment. No significant change in either the red-cell count or haemoglobin was observed. The details are given in Table IV.

TABLE IV

Case No.	Before Treatment		After Treatment (1,000 mg. Ferrivenin)	
	R.B.C. mil./c.mm.	Hb g./100 ml.	R.B.C. mil./c.mm.	Hb g./100 ml.
2	3.2	9.6	3.4	9.4
4	3.5	9.4	3.6	9.3
10	4.2	12.0	4.1	12.0

Beneficial effects from the administration of iron in these cases have rarely been reported, although Jersild and Iversen (1943) did report one case in which iron salts appeared to have a beneficial effect on the anaemia. Crafts (1946) has also shown that iron does not prevent the development of anaemia in hypophysectomized rats, although the rate of development was slowed; he also demonstrated that the haemoglobin levels continued to fall in these animals, although iron was being administered continuously.

Liver

Normoblastic marrow was obtained in all these cases, and therefore the anaemia was considered to be unresponsive to liver, folic acid, or vitamin B₁₂, which are of such value in treating the megaloblastic anaemias.

Cortisone and A.C.T.H.

When supplies of cortisone and A.C.T.H. became available for experimental treatment, the opportunity was taken to treat two cases of hypopituitarism with cortisone and two with A.C.T.H.

Cortisone.—Case 2 had previously been treated with iron, progesterone, testosterone, and chorionic gonadotrophin. No treatment of any sort had been given for eight months before cortisone therapy; the second patient (Case 8), who was treated with cortisone, had also been treated with testosterone before she came under observation, but had had no treatment for five months before the beginning of cortisone therapy. Cortisone acetate, 100 mg. daily intramuscularly, was given to Case 2 for 20 days, when she refused to have any further injections. She was observed for one month before treatment was begun, during which time frequent blood examinations were made. She returned to hospital 44 days after the cessation of treatment, when her condition had relapsed to what it had been before treatment was started. It was possible to treat Case 8 for only 11 days before the supplies of cortisone were exhausted. The effects of cortisone treatment are shown in Table V. In

TABLE V

Case No.	Hb g./100 ml.	R.B.C. mil./c.mm.	M.C.V. μ^3	M.C.H.C. g./100 ml.	Retic. %	Treatment Day
2	9.5	3.2	100	30	0.1	Before treatment
	9.4	3.5	91	30	1.7	7
	10.8	3.9	90	31	3.6	14
	10.5	3.8	90	31		16
8	11.7	4.1	90	32	0.02	Before treatment
	12.1	4.1	90	33	0.02	7
	12.5	4.0	90	33		12

Case 2 cortisone caused an improvement in the red-cell count and haemoglobin, produced a reticulocytosis, and caused a fall in the M.C.V.; in Case 8, although the duration of treatment was limited to 11 days, there was a slight increase in the haemoglobin concentration.

A.C.T.H.—The effects of A.C.T.H. on the blood in two cases are shown in Table VI; the dose given was 75 mg. daily in three injections. Case 3 had previously been treated with thyroid but had had no treatment for two years prior to receiving A.C.T.H.; Case 10 had also been treated with testosterone and iron, but had had no treatment for several months before having A.C.T.H. Unfortu-

TABLE VI

Case No.	Hb g./100 ml.	R.B.C. mil./c.mm.	M.C.V. μ^3	M.C.H.C. %	Retic. %	Treatment Day
10	{ 12.0 11.8	{ 4.2 4.4	88	32	0.1	Before treatment
3	{ 9.7 9.7	{ 3.3 3.4	109 109	27 27		14

nately, treatment in Case 10 had to be interrupted owing to the development of a cerebrovascular crisis after 10 days; treatment in Case 3 was continued for 15 days.

Hench *et al.* (1950), reviewing the effects of cortisone and A.C.T.H. in rheumatoid arthritis, noted that the concentration of haemoglobin and also the red blood count improved. Moreover, in Cushing's syndrome, in which there is an increased secretion of the gluco-corticoid hormones of the adrenal cortex, a polycythaemia is constantly found. The prompt response in Case 2 of both the haemoglobin and the red-cell count, and the presence of a reticulocytosis, suggest that cortisone may be capable of curing the anaemia of hypopituitarism. In view of this improvement it was particularly unfortunate that the patient terminated treatment prematurely. The response of the haemoglobin in Case 8 was again suggestive of the potency of cortisone in relieving the anaemia: the duration of treatment in this case is unfortunately too short to allow conclusions to be drawn.

The response of both the cases in which A.C.T.H. was given was disappointing; in neither case, however, was it possible to continue the administration for a very long time, and little change was observed clinically. The occurrence of cerebrovascular episodes in these patients makes it necessary to proceed cautiously with this substance, and in future it might be better to give small doses for a prolonged time.

Summary

Two types of anaemia are found in hypopituitarism—macrocytic hypochromic and normocytic hypochromic. The anaemia is usually of moderate severity.

The response to treatment with thyroid, testosterone, and iron is unsatisfactory, but cortisone seems to produce a prompt increase in the red-cell count and the haemoglobin concentration.

The cortisone and A.C.T.H. used in this work were a gift from Merck and Co. through the Medical Research Council. These substances were made available for this work through Professor H. L. Sheehan, to whom I am also indebted for much helpful advice.

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A SURVEY OF PULMONARY EMBOLISM IN A GENERAL HOSPITAL

BY

D. S. SHORT, M.D., M.R.C.P.

Senior Registrar, National Heart Hospital
 (formerly Senior Registrar, Southmead General Hospital)

A careful watch for pulmonary embolism in all departments of a general hospital combined with the free use of radiography showed thrombo-embolic disease of the lung to be the commonest of all serious acute pulmonary diseases. The radiological appearances having been discussed elsewhere (Short, 1951), the object of this communication is to present the clinical aspects of the condition and to stress its frequency.

Pulmonary embolism or pulmonary infarction was diagnosed in 113 patients admitted to Southmead General Hospital during the two and a half years ending March 31, 1950, and seven cases were seen elsewhere by me during the same period. I examined 85 of the 120 cases personally. The remainder were either rapidly fatal cases, or cases in which the diagnosis was not made before death or discharge from hospital. Necropsy revealed a certain number of unsuspected infarcts, and eight cases were diagnosed in retrospect by looking up the notes of all patients from the surgical and obstetrical wards who had chest radiographs taken post-operatively or in the puerperium. Besides the 120 definite cases presented here, a further 30 were seen in which the diagnosis of pulmonary infarction seemed probable but which are omitted because the evidence was inadequate or because it was impossible to exclude an alternative diagnosis.

Incidence

Table I analyses the cases according to the underlying disease. One-quarter were surgical (post-operative), one-sixth obstetrical, and the remainder (58%) medical. Of the medical cases, four-fifths were suffering from heart disease.

TABLE I.—Analysis of Cases According to Underlying Disease

	No.	Pulmonary Infarction	Pulmonary Embolism	Death	Necropsy
Medical ..	70	65	6*	45	41
Surgical ..	30	22	8	10	9
Obstetrical ..	20	19	2*	2	2
Total ..	120	106	16	57	52

* In two instances, pulmonary infarction was followed by massive pulmonary embolism.

Pulmonary embolism or infarction was diagnosed in 2.5% of all medical cases, 0.5% of all surgical cases, and 0.17% of all obstetrical cases. The incidence of pulmonary thrombo-embolism exceeded that of all other serious acute pulmonary diseases during this period, including lobar pneumonia (Table II).

TABLE II.—Hospital Admissions over Two and a Half Years of the Major Pulmonary Diseases (Excluding Tuberculosis)

Disease	No.
Primary pleural effusion ..	33
Primary carcinoma of lung ..	50
Lobar pneumonia ..	100*
Pulmonary embolism and infarction ..	113

* This figure from the hospital records may include some cases of bronchopneumonia and virus pneumonitis; it is probably too high.