in underfunction than on normally controlled subjects or in hormone overfunction. Probably when the thyroid function is already above normal range the amount of thyrotrophic hormone mobilized by the action of E.C.T. is not able to increase thyroid function much further, and is perhaps inhibited from doing so by the simultaneous mobilization of A.C.T.H. There appears to be an antagonism between thyrotrophic hormone and A.C.T.H., and A.C.T.H. may inhibit the thyroid. Reiss and Peter (1938) described reduction in blood iodine and atrophy of the thyroid in dogs after treatment with A.C.T.H., and an antagonistic action between thyrotrophic hormone and A.C.T.H. on the blood iodine level. At the same time they noted a decrease in blood iodine in six human cases treated with A.C.T.H., of whom three suffered from Graves's disease. Recent evidence of the antithyrotic action of A.C.T.H. has been reported by R. S. Reiss, Riggs, Thorn, and Forsham (1950).

Probably in many cases E.C.T. operates therapeutically on the anterior lobe/thyroid or anterior lobe/gonadal relationship. It is known that sex hormones in small doses stimulate the anterior pituitary, but large doses inhibit the production of gonadotrophic hormone. The physiological effect of treatment with sex hormones described in this paper may be due to suppression of the production as well as of the function of thyrotrophic hormone by sex hormones acting on the anterior pituitary.

Normal thyroid activity depends on an equilibrium in the production of stimulating and antagonistic hormones. E.C.T. can interfere with the mobilization of pituitary anterior lobe hormones and so influence the total hormone equilibrium. Changes in thyroid activity after E.C.T. are only an indicator for changes in the total hormone equilibrium, irrespective of whether these changes take place inside the normal range only or whether increased or decreased thyroid function is being normalized by E.C.T.

It is not possible at this stage to correlate the therapeutic result of E.C.T. with its physiological effect on one gland. To assume that where the thyroid has been influenced this has been responsible for mental improvement is to imply that a disturbance of thyroid function was originally the cause of the psychiatric illness—an implication not justified without further study. It would be logical to test the supposition by treating psychiatric patients who show a thyroid disturbance from the point of view of this disturbance only. Another way consists in trying to copy the action of the E.C.T. by treating patients with gland concentrates containing all the pituitary anterior lobe hormones.

This is now being attempted in our hospital. Nevertheless, apart from the question of appropriate dosage and the problem of over- and under-sensitivity to hormones, the difficulties are considerable, and deterioration in the progress of the disease and spontaneous remission have to be reckoned with. Our experience shows that thyroid physiology will have to be studied in any further research on the action of E.C.T., and for this the tracer method is convenient and reasonably simple.

Summary

The effect of E.C.T. on thyroid activity has been studied by radioactive tracer technique.

E.C.T. reduces pre-shock hyperactivity and raises pre-shock hypoactivity. Normal pre-shock values are influenced only within the normal range.

This is due to the effect of E.C.T. on the total endocrine equilibrium and especially to the way it influences the antagonism between adrenal cortex and thyroid function.

Relevant problems are discussed and the action of E.C.T. is compared with that of applied hormone therapy.

REFERENCES

- Haigh, C. P., and Reiss, M. (1950). *Brit. J. Radiol.*, **23**, 534.
 Hemphill, R. E. (1946). *Bristol med.-chir. J.*, **63**, 116.
 ———, Macleod, L. D., and Reiss, M. (1942). *J. ment. Sci.*, **88**, 554.
 ——— and Reiss, M. (1942). *Ibid.*, **88**, 559.
 ——— (1944). *British Medical Journal*, **2**, 211.
 Hoagland, H., Callaway, E., Elmadjian, F., and Pincus, G. (1950). *Psychosom. Med.*, **12**, 73.
 ———, Malamud, W., Kaufman, I. C. and Pincus, S. (1946). *Ibid.*, **8**, 246.
 Mikkelsen, W. P., and Hutchens, T. T. (1948). *Endocrinology*, **42**, 394.
 Parsons, E. H., Gildea, E. F., Ronzoni, E., and Hulbert, S. Z. (1949). *Amer. J. Psychiat.*, **105**, 573.
 Reiss, M., Haigh, C. P., Hemphill, R. E., Maggs, R., Reiss, J. M., and Smith, S. (1951). *J. Endocrinol.* In press.
 ———, Hemphill, R. E., Maggs, R., Smith, S., Haigh, C. P., and Reiss, J. M. (1951). *British Medical Journal*, **1**, 1181.
 ———, Murphy, B. M., Halkerston, J. M., and Badrick, R. E. (1949). *J. Endocrinol.*, **6**, 235.
 ——— and Peter, F. (1938). *Z. ges. exp. Med.*, **104**, 49.
 Reiss, R. S., Riggs, D. S., Thorn, G. W., and Forsham, P. H. (1950). *Proceedings of the First Clin. A.C.T.H. Conf.* Philadelphia, p. 193.

THE ANAEMIA OF RHEUMATIC FEVER

BY

J. B. COCHRAN, M.B., B.Sc., F.R.F.P.S., M.R.C.P.

(From the Clinical Chemotherapeutic Research Unit of the Medical Research Council in the Gardiner Institute of Medicine, University of Glasgow)

Anaemia is one of the well-recognized features of rheumatic fever. It is of sudden onset: it may be severe, and it regresses as the acute attack subsides. It is usually classified as an anaemia of secondary type and is described as microcytic or microcytic and hypochromic. Anaemia is a common finding in many acute and chronic infective processes, and the anaemia of acute rheumatism has usually been studied from this aetiological aspect.

Investigations to determine whether it is of haemolytic origin or due to suppression of erythropoiesis have been reported. Douglas and Tannenbaum (1930) consider that infection retards erythropoiesis. In their series, which included three cases of acute rheumatism, they found no evidence of an increase in circulating reticulocytes or of a raised icteric index. Kapp and Coburn (1936) studied the excretion of urinary porphyrin in rheumatic fever and found that the urine of their patients contained abnormally large amounts of coproporphyrin. They state that this does not necessarily indicate increased blood destruction, as it may arise partly or wholly from disturbed liver function. Hubbard and McKee (1939), from a study of recrudescences of rheumatic fever in 17 patients, favour the view that the anaemia is due to suppression of erythropoiesis when the disease is most active, followed by increased red-cell formation as evidenced by a slight but significant increase in reticulocytes as the acute stage regresses. From studies of icteric index, serum bilirubin, and urobilinogen excretion they found little or no evidence of increased blood destruction.

Bradley (1938) introduced an entirely new conception of the problem. He studied a patient with signs of mitral

disease who developed a streptococcal nasopharyngitis and in whom an attack of acute rheumatism was correctly forecast. From haematological data and blood-volume estimations obtained at frequent intervals before and after the onset of the acute attack Bradley concludes that the major part of the apparent anaemia of acute rheumatism results from increased plasma volume, and that the anaemia, as measured by haematocrit or haemoglobinometry, is relative only.

Reid, Watson, and Sproull (1950) have shown that relief of acute rheumatic manifestations is associated first with a fluid shift from intracellular to extracellular fluid compartments, and at this stage the erythrocyte sedimentation rate (E.S.R.) shows no signs of falling. Later, the excess water is removed from the extracellular fluid space mainly by diuresis, and the E.S.R. returns to normal.

In this paper further evidence is presented that the anaemia of acute rheumatism is largely due to haemodilution, and that its severity and relationship to the disease process are governed mainly by fluid shifts within the body.

Methods

Detailed haematological studies were made of 10 patients admitted to hospital with acute rheumatic fever. They were given a standard diet, and the daily fluid intake and urine output were measured. No treatment was prescribed which is known to have a direct effect on erythropoiesis. About every third day at 10 a.m. blood was withdrawn by venepuncture from an elbow vein, using a constant technique. A syringe containing 0.4 ml. of 3.8% sodium citrate was filled to the 2-ml. mark, detached from the needle which remained in the vein, and a small test-tube containing Wintrobe's oxalate mixture was filled to the 5-ml. mark. The citrated sample was used to determine the E.S.R. (Westergren), and haematological data were obtained from the second sample.

Haemoglobin was estimated by the oxyhaemoglobin method of Bell, Chambers, and Waddell (1945), using a photoelectric colorimeter. To test the accuracy of our technique five consecutive readings were made from the same blood sample. The maximum variation was 0.2 g.%. Each patient was allocated a separate haematocrit tube. Red cells were counted, using the same pipette and counting-chamber throughout.

To obtain normal haematological standards for the methods in use blood samples were examined from 16 healthy male and female young adult subjects who had no previous history of blood loss, anaemia, or serious illness. Blood was taken from the female subjects at the intermenstrual phase of the cycle. The same technique was used throughout in subjects and patients.

Results

The values for haemoglobin (Hb), mean corpuscular haemoglobin concentration (M.C.H.C.), and mean corpuscular volume (M.C.V.) in the series of healthy young adult subjects are shown in Table I. In the males the Hb ranged from 12.3 to 14.1 g.%, with a mean value of 13.4 g.%. In the females the corresponding range was 10.3 to 12.8 g.%, with a mean value of 11.9 g.%. In the two groups the values for M.C.H.C. and M.C.V. differed only by 0.1% and $1 \mu^3$ respectively, suggesting that the lower haemoglobin value in the female subject is due to a relatively greater plasma volume compared with

TABLE I.—*Haematological Data in Eight Male and Eight Female Healthy Young Adult Subjects*

Males				Females			
No.	Hb. (g.%)	M.C.H.C. (%)	M.C.V. (μ^3)	No.	Hb. (g.%)	M.C.H.C. (%)	M.C.V. (μ^3)
1	13.5	30.7	87	1	11.8	29.6	77
2	14.1	29.7	80	2	12.4	29.7	77
3	12.3	29.3	85	3	12.4	29.5	84
4	14.0	30.4	80	4	11.6	30.4	85
5	13.6	29.6	90	5	11.9	29.8	87
6	13.7	30.0	84	6	12.4	28.8	88
7	12.4	28.2	77	7	12.8	30.5	83
8	13.8	29.7	93	8	10.3	28.6	88
Means	13.4	29.7	85	Means	11.9	29.6	84

Total means: Hb, 12.7 g.%; M.C.H.C., 29.7%; M.C.V., $85 \mu^3$

total red cells than in the male subject. In the investigations which follow an M.C.H.C. of 29–30% and an M.C.V. of about $80 \mu^3$ are considered to be within normal limits.

Haematological data in a series of five male and five female patients at three stages in the course of acute rheumatic fever are shown in Table II. On admission all patients had fever, tachycardia, evidence of active carditis, and acute joint involvement. At this stage the mean Hb value was 9.8 g.%, M.C.H.C. 28.2%, and M.C.V. $86 \mu^3$. In comparison with the group of normal

TABLE II.—*Haematological Data in Ten Patients at Three Stages in the Course of Acute Rheumatic Fever*

		Acutely Ill				Clinical Improvement				Convalescent			
No.	Sex	Hb (g.%)	M.C.H.C. (%)	M.C.V. (μ^3)	E.S.R. (mm./hr.)	Hb	M.C.H.C.	M.C.V.	E.S.R.	Hb	M.C.H.C.	M.C.V.	E.S.R.
1	F	8.5	26.6	86	85	8.4	27.1	98	85	11.6	27.8	88	10
2	F	9.7	28.2	79	90	27.3	86	105	105	12.4	29.5	87	6
3	F	9.5	31.0	86	124	9.7	30.3	101	105	12.0	30.0	81	8
4	F	11.3	29.7	87	111	9.2	28.6	77	101	11.1	28.3	—	45
5	F	8.5	27.4	90	95	7.7	26.6	—	125	11.6	28.3	85	10
6	M	9.1	27.6	84	100	8.1	26.1	—	92	11.6	27.9	83	8
7	M	10.0	29.0	90	104	9.5	28.8	—	123	11.1	28.8	78	7
8	M	9.8	28.0	90	121	8.8	26.7	—	128	10.9	26.6	73	21
9	M	9.6	27.0	80	60	9.0	28.0	78	54	11.4	27.0	87	16
10	M	12.1	27.5	80	71	9.9	27.5	93	106	12.5	28.4	86	20
Means		9.8	28.2	86	96	9.0	27.7	—	103	11.6	28.3	83	15

subjects there is a Hb mean difference of 2.9 g. associated with M.C.H.C. and M.C.V. differences of 1.5% and $1 \mu^3$ respectively. This would indicate that in the acute stage of rheumatic fever the anaemia is normocytic and normochromic or slightly hypochromic. During the investigation it was noticed that the haemoglobin level often fell further as the acute stage regressed, and this was usually associated with a rise in E.S.R. The blood findings shown under "clinical improvement" in Table II were obtained as soon as there was definite clinical evidence of improvement in the patient's condition. This improvement varied from case to case in detail, but in the main consisted of a fall in temperature, definite relief of arthritis, and obvious subjective improvement. As is shown at this stage, there was a further fall in mean Hb and M.C.H.C. levels of 0.8 g.% and 0.5% respectively, associated with a mean rise in E.S.R. of 7 mm./hr. In the convalescent stage the mean values for M.C.V. and M.C.H.C. showed very little change from those in the acute stage, though the mean Hb value had risen by 1.8 g.%.

FIG. 1.—The close direct relationship of haemoglobin and packed cell volume in a patient during the course of acute rheumatic fever.

In all cases haemoglobin levels and haematocrit values ran parallel both in the development and in the regression of the anaemia. In about 200 observations there was practically no instance in which a fall or rise in Hb of at least 0.2 g. % was unaccompanied by a corresponding fall or rise in packed red cell volume (P.C.V.), which was not always equivalent and which accounted for the minor changes in M.C.H.C. that occurred. The close direct relationship of Hb and P.C.V. throughout the course of rheumatic fever is shown in Fig. 1.

The results so far can be interpreted as indicating haemodilution in the acute stage of rheumatic fever. A fluid shift from intracellular to extracellular compartments is consistent with the observed fall in haemoglobin level which occurs as the acute stage of the disease regresses. Further support for this hypothesis is given by the rapidity of development of the anaemia. This was very noticeable when blood examination was done at intervals of two to three days. Falls in haemoglobin

FIG. 2.—The changes in haemoglobin, packed cell volume, and E.S.R. in a patient who had a relapse of acute rheumatic fever.

concentration of 1 g. % during a three-days interval occurred commonly. Usually such a fall was accompanied by a reduction in M.C.H.C. of 0.5–1 %. One patient who had made a good recovery and whose blood findings had returned to normal levels relapsed while in hospital. A fall in Hb of 1.7 g. % in two days was observed. This was accompanied by an equivalent fall in P.C.V., and the M.C.H.C. showed a reduction of only 0.4 %. The blood data and the changes in E.S.R. in this patient are shown in Fig. 2. A rise in E.S.R. is accompanied by a fall in Hb and P.C.V., and later, as the E.S.R. returns to normal, there is a rise in Hb and P.C.V.

As a further test of haemodilution, fluid-balance studies were carried out on each patient. Daily fluid intake and urine output were carefully measured and the totals subtracted. No account was taken of fluid lost by sweating, respiration, or in the faeces, owing to the technical difficulties of such a complete balance study. Marked sweating in rheumatic fever occurs as the temperature is subsiding, and would affect the fluid balance to any great extent only during the first two to three days of observation. As an example of the changes observed, the fluid balance chart is plotted with haemoglobin and E.S.R. levels in one patient throughout an attack of acute rheumatic fever (Fig. 3). There is an

FIG. 3.—The relationship of fluid balance, haemoglobin, and E.S.R. in a patient throughout the course of acute rheumatic fever.

inverse relationship between the haemoglobin and E.S.R. curves, and a rise in haemoglobin is associated with a relative increase in fluid output over intake. Fig. 3 shows definite negative fluid balance over a period of five to eight days while the haemoglobin level is rising steeply. As no account is taken of fluid lost by other channels than urine it is assumed that, in this patient, fluid previously retained in excess by the body is being excreted. The inverse relationship between haemoglobin and E.S.R. was very striking in all patients studied, and the haemoglobin level at any one point in the illness served as a good indication of rheumatic activity.

In one patient frequent plasma-volume determinations (Gregersen and Stewart, 1939) were made throughout the course of an attack of rheumatic fever. The results were plotted against haemoglobin levels obtained just before each volume estimation (Fig. 4). The curves for haemoglobin and plasma volume showed an inverse relationship, indicating that variations in haemoglobin level were due to variations in plasma volume.

FIG. 4.—The inverse relationship of haemoglobin and plasma volume in a patient throughout the course of rheumatic fever.

Discussion

Previous reports have failed to show any evidence of a haemolytic process in acute rheumatism. In this investigation no special studies were made to detect haemolysis, but no patient ever showed clinical evidence of icterus, and the blood plasma remained pale and watery during the rapid falls in haemoglobin level described and throughout the course of the disease. From a consideration of the haemoglobin, haematocrit, and red-cell measurements obtained, the anaemia can be explained by one of two processes: (a) a relative increase in plasma volume—that is, hydraemia—or (b) a suppression of erythropoiesis resulting in a relative reduction in red-cell mass without any change in total blood volume. The speed of development of the anaemia weighs against the latter possibility; also a raised blood volume in rheumatic fever has been observed in this and in other investigations, and it would seem that the anaemia is largely due to a relative increase in plasma volume without coincident increase in red-cell mass. The anaemia is normocytic and normochromic or slightly hypochromic.

The blood findings throughout the illness support the view that cure of acute rheumatism is associated, first, with a fluid shift from the intracellular to the extracellular fluid compartments, followed by a reduction in the latter by diuresis. It has been shown that the haemoglobin level reaches a lower value after clinical signs of improvement have occurred, and this is compatible with the fluid shift described. Later, as the haemoglobin level returns to normal, fluid-balance studies indicate that this is associated with a relative increase in urine output compared with fluid intake. At the same time the E.S.R. returns to normal.

The ease of obtaining a blood sample by venepuncture in the acute stage of rheumatic fever compared with the convalescent stage is perhaps further evidence of increased blood volume. In the acute stage the blood

usually spurts from the needle, compared with the slow drip in late convalescence.

An increase in reticulocyte level, small but significant, has been shown to occur in rheumatic fever shortly after the stage of greatest disease activity (Hubbard and McKee, 1939). This may be caused by the stimulus of relative anoxia due to a further increase in plasma volume rather than be the result of release of the bone marrow from the influence of a metabolic or other toxin.

The minor changes in M.C.H.C. which occurred are considered to be real, but further investigation is required. Changes in the osmotic pressure of the plasma may cause variations in red-cell size with resultant alterations in M.C.H.C. The latter showed a tendency to fall and rise with the haemoglobin level. While the haemoglobin level falls there is haemodilution and reversal of the albumin/globulin ratio, and both these factors would tend to reduce osmotic pressure, increase red-cell size, and lower M.C.H.C. The reverse would occur as the disease regresses. The reticulocyte increase described above may also play a part in the small reduction of the M.C.H.C. in the early stages of the illness. As estimation of mean cell volume depends on the relatively inaccurate red-cell count, it is intended to carry out direct osmotic pressure measurements to test this theory.

The role of hydraemia and changes in the osmotic pressure of the plasma in anaemia have in the past perhaps not received adequate consideration. Further investigation of these factors may prove of value, especially in anaemias associated with infection. The anaemia of rheumatic fever in particular may have a complete explanation in quantitative and qualitative alterations in the plasma as opposed to functional derangement of the red bone marrow.

Summary

The anaemia of rheumatic fever has been investigated by a detailed haematological study of 10 patients.

Evidence is presented that the anaemia is normocytic and normochromic or slightly hypochromic, and is largely due to hydraemia without alteration in total cell mass.

The anaemia is related to fluid shifts occurring during the rheumatic attack.

It is suggested that hydraemia and changes in the osmotic pressure of the plasma may be important factors in this and other anaemias associated with infection.

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REFERENCES

- Bell, G. H., Chambers, J. W., and Waddell, M. B. R. (1945). *Biochem. J.*, **39**, 60.
- Bradley, W. H. (1938). *Proc. int. Congr. Rheum.*, p. 86. London.
- Douglas, A. H., and Tannenbaum, H. (1930). *Arch. intern. Med.*, **45**, 248.
- Gregersen, M. I., and Stewart, J. D. (1939). *Amer. J. Physiol.*, **125**, 142.
- Hubbard, J. P., and McKee, M. H. (1939). *J. Pediatr.*, **14**, 66.
- Kapp, E. M., and Coburn, A. F. (1936). *Brit. J. exp. Path.*, **17**, 255.
- Reid, J., Watson, R. D., and Sproull, D. H. (1950). *Quart. J. Med.*, **19**, 1.

According to the *Manchester Guardian* (August 22) Mr. R. S. McLaughlin, a Canadian businessman, has given over \$1,000,000 to start a medical foundation which will be for the most part devoted to fellowships enabling their holders to maintain a family if they are living abroad; it will also be used to support clinical and medical research in Canada. Dr. W. E. Gallie, formerly Professor of Surgery and Dean of the medical school at Toronto, is one of the three trustees.