EFFECT OF STILL'S DISEASE ON THE HAEMOPOIETIC SYSTEM*

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Recent discoveries of a possible endocrine dysfunction in rheumatoid arthritis have opened up a new line of approach and may eventually provide the key to its cause and to certain hitherto unexplained clinical features.

Rheumatoid disease in childhood has often such a dramatic onset and acute course that for a time the diagnosis may be in considerable doubt. The term "rheumatoid disease" is used advisedly, as polyarthritis may not at first be the most prominent symptom. Fever is the most striking feature at this stage and the child appears to be quite ill with little in the way of physical signs except possibly a macular rash (see Figs 1 and 2).

Blood Picture in Still's Disease

The blood picture, however, is typical: a marked leucocytosis in the region of 17,000 to 30,000 white blood cells per c.mm., and pronounced neutrophilia up to 80 or 90 per cent. Sometimes myelocytes spill over into the peripheral blood field. This leucocytosis may be maintained for some months, but often for a shorter period and in the course of a few weeks the number of white cells returns to normal (see Table, overleaf). Thereafter leucocytosis is seldom repeated, and then only in association with an acute relapse (Schlesinger, 1949).

A polymorphonuclear leucocytosis of this order with high fever naturally suggests an infection of some severity, but repeated and extensive search has never revealed any localized or general infection. Nor have any of the known antibiotics any beneficial effect whatever, and the patient drifts gradually or rapidly into the succeeding and more arthritic form of his disorder. The fever ceases and the leucocytosis disappears. Thereafter the blood picture shows little beyond a persistent moderate degree of anaemia and not infrequently a slight relative lymphocytosis.

On rare occasions the disease takes what can only be described as a rapidly malignant and fatal course. This usually occurs after the malady has become well established and is associated with a severe leucopenia with the white cells in the region of 1,500 to 3,000 per c.mm. Both neutrophils and lymphocytes are equally

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FIGS 1 and 2.—Widespread raised macular rash also involving the face, in a case of Still's disease in a girl of $5\frac{1}{2}$ years.

TABLE

MAIN POINTS OF INTEREST INCLUDING INITIAL LEUCOCYTOSIS IN NINETEEN CASES OF STILL'S DISEASE

Case No.	Sex	Age at Onset	Rash	Spleen	Liver	Jaundice	Initial Leucocytosis W.B.C. per c.mm.	Later Leucopenia	Pericarditis	Fever		Result
										Irregularly continuous	Periodic	
1	M	10/12	+	±	++	Slight	18,000 *P.67	1,500 *P.15 †L.85	Post mortem	+	±	Death
2	M	2 $\frac{1}{2}$	-	±	-	-	24,000 P.84	-	-	+	-	Arthritis ambulant
3	F	6 $\frac{1}{2}$	+	+	-	-	31,000 P.92	-	-		+	Complete recovery
4	M	10 $\frac{1}{2}$	-	-	-	-	17,000 P.72	-	-	+	±	Arthritis
5	M	5 $\frac{1}{2}$	+	-	-	-	22,000 P.78	-	-		+	Recovery
6	M	3	-	-	-	-	14,400 P.66	2,900 P.53 L.44	Post mortem	Terminal		Death
7	M	6	+	-	-	-	22,800 P.77	-	+		+	Arthritis
8	M	7 $\frac{1}{2}$	+	-	-	-	20,000 P.80	-	-	+	+	Migratory arthritis
9	M	2	+	-	-	-	29,000 P.82	-	-		+	Death (gold)
10	M	4 $\frac{3}{4}$	+	+	+	-	12,700 P.84	-	-	+	+	Migratory arthritis
11	M	2 $\frac{7}{12}$	+	++	+++	Slight	19,200 P.57	-	-	+	+	No arthritis Hepatic cirrhosis
12	M	6	+	+	later	+	21,200 P.82	-	-		+	Slight arthritis dementia
13	F	3 $\frac{1}{2}$	+ later	+	+	-	Normal	-	? (Pleurisy)	+	+	Arthritis
14	M	9/12	-	+ later	+ later	-	19,900 P.75	-	? (Pleurisy)	+	+	Severe arthritis
15	F	2 $\frac{1}{2}$	+	+ later	+ later	+	28,200	3,400 P.71 L.24	+		+	Slight arthritis. Recovery from leucopenia
16	F	9	-	±	+	-	17,500 P.72	-	-	+	+	Severe arthritis
17	M	4	+	+ later	-	-	22,600 P.87	-	+	+	+	Arthritis ambulant
18	M	5	+	+	+ later	-	16,500		+	+	+	Recovery
19	F	3	+	-	-	-	13,900 P.76	-	-	±		Arthritis

* Polymorphs per cent.

† Lymphocytes per cent.

involved, but agranulocytosis with a relative lymphocytosis has been observed. These cases are exceptional, but nevertheless do occur and have to be explained.

Leucopenia in rheumatoid arthritis does not necessarily follow this dramatic course; it may, in fact, last for only a short time and be followed by a return of the blood picture to normal. Collins (1937) has reported two instances in adults

with hepatosplenomegaly where the leucopenia persisted for some months without great deterioration of the patient, and the picture is, of course, typical of Felty's syndrome.

Bone Marrow

Lymphadenopathy is by no means constant during the period of leucocytosis, although it may appear later, and the state of the bone marrow is the next obvious matter for investigation.

We have made this examination by puncture in 32 children suffering from Still's disease at various phases and repeatedly in a number of them. The picture was one of general hyperplasia, particularly of the granulocyte series, which were found to be less than 45 per cent. in only three of the 32, and comprised 60 per cent. or more of the total in all the others. A left shift in the whole series was noted, with premyelocyte counts up to 20 per cent. and myelocytes up to 30 per cent. of the total marrow cells. Stimulation of the precursors of other cells was also seen, an over abundance of megakaryocytes, for instance, being not an unusual observation.

Bearing in mind the young age group of the patients, the granulocyte proportions were interpreted as hyperplasia, and the relative percentages of the more primitive of the series represent a clear left shift.

It is interesting to note that where we have been able to see the marrow during the episodes of peripheral depression (we have not yet had the opportunity of examining it in the rare extreme cases described), it has shown no change from the granulocytic hyperplasia with left shift so characteristic of Still's disease.

In fact, when trying to correlate the marrow and peripheral blood findings in the leucopenic stage it is clear that the peripheral blood is not a mirror of the marrow. One wonders if there could be some inhibiting factor present which prevents the escape of the cells formed in the marrow into the circulation.

Hormonal Effect on Blood Formation

A comparative study of the effects of stimulation and failure of the pituitary-adreno-cortical system on blood formation is interesting. The number and relative proportion of the various circulating leucocytes seem to follow a definite pattern according to changes in hormonal control. For example, adrenalectomy in certain animals and Addison's disease in man cause a fall in the total number of leucocytes and neutrophils and a relative increase in lymphocytes (Corey and Britton, 1932). Exactly the opposite happens when the adrenals are stimulated by ACTH injections or by the production of an "alarm reaction" in certain laboratory animals. Leucocytosis results, with a rise of neutrophils and a fall of lymphocytes (Harlow and Selye, 1937; Dougherty and White, 1943; Reinhardt and Li, 1945).

Somewhat similar reactions are seen in man after a single injection of ACTH: provided adrenal function is unimpaired there is an increase in neutrophils and a decrease in eosinophils and lymphocytes. Prolonged administration of ACTH provokes a more sustained and striking change, although there is an escape of

the lymphocytes after the initial depression, no doubt due to their much larger reserve depots compared to those of the eosinophils (Hills and others, 1948). But the degree of leucocytosis produced by these experiments in normal human subjects is far below that seen in the early stages of Still's disease.

How then could this be explained? With the present belief that rheumatoid arthritis is associated with a seriously deranged endocrine system, could the leucocytosis in acute Still's disease be a desperate stimulation of a damaged organ prior to exhaustion? The subsequent leucopenia and relative lymphocytosis, slight in most instances but extreme on rare occasions, might then be interpreted as the result of varying degrees of ultimate failure of the adreno-cortical system.

Relationship to Leukaemia

With these dramatic blood changes in mind a possible relationship between Still's disease and leukaemia is not an unreasonable suggestion, particularly as the two diseases may be indistinguishable in their early clinical course. Can, in fact, rheumatoid arthritis with leucopenia finally develop an agranulocytosis and terminate in leukaemia? We have studied a few cases of this nature and the literature contains rare examples (Conybeare, 1936; Türk, 1938), but confirmatory evidence in our series of bone marrow punctures covering this transformation is lacking. For the moment the matter must rest there, and we agree with most authorities who believe that these unusual forms are leukaemia from the onset, their arthritic symptoms arising from subperiosteal deposits in the vicinity of joints (Taylor, 1926; Karelitz, 1927; Hunter, 1929; Poynton and Moncrieff, 1929; Seward, 1939; Smith, 1933; Sutton and Bosworth, 1934; Poynton and Lightwood, 1932).

Summary

Blood changes in Still's disease have been observed both in the peripheral blood stream and in the bone marrow, and these have been compared to those occurring with hypophyseal-adreno-cortical disturbances.

Tentative theories are advanced to explain how pronounced and sometimes serious haemopoietic derangement might be brought about in Still's disease through hormonal defect. No proof has been found that this disease can ultimately be transformed into leukaemia.

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L'effet de la maladie de still sur le système hémopoïétique

RÉSUMÉ

Les altérations sanguines dans la maladie de Still furent observées aussi bien dans le courant sanguin périphérique que dans la moelle osseuse. Ces altérations furent comparées à celles survenant au cours des troubles hypophyso-corticosurrénaux.

On avance des théories tendant à expliquer comment un trouble hémopoïétique prononcé et souvent grave dans la maladie de Still peut se produire à la suite d'un dérangement hormonal. On n'a pas trouvé de preuve montrant que cette maladie puisse se transformer en leucémie.

El efecto de la enfermedad de still sobre el sistema hematopoyético

SUMARIO

Alteraciones hemáticas en la enfermedad de Still fueron observadas tanto en el torrente sanguíneo periférico como en la médula ósea y fueron comparadas con las que ocurren en la disfunción hipofiso-suprarrenal-cortical.

Se adelanta teorías tentativas para explicar como en la enfermedad de Still un defecto hormonal puede producir una alteración hematopoyética pronunciada y a veces grave. No se hallaron pruebas de que esta enfermedad pueda transformarse últimamente en leucemia.