Papers and Originals**ACUTE TUBERCULOSIS AND GRANULOCYTIC DISORDERS***

BY

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During the past 60 years the possibility that a special relation exists between tuberculosis and haematological abnormalities has occupied the thoughts of many investigators. Most of the early observations were made in German-speaking countries and were summarized in 1939 by Siegmund. Among the original descriptions were instances of a particularly acute form of tuberculous miliary necrosis with depressed blood formation which varied from a simple leucopenia affecting mainly the granulocytes to agranulocytosis and pancytopenia. Other authors noted the development of acute tuberculosis in patients with myeloid leukaemia. Later writers have confirmed these findings but have failed to agree upon the extent to which the tuberculosis may influence the behaviour of the bone-marrow. For example, the haematological changes that occasionally accompany acute tuberculosis may resemble acute leukaemia in that primitive white cells appear in the blood and marrow, but at post-mortem examination no conclusive evidence of leukaemia can be found, there being no leukaemic infiltration of the tissues. Sometimes, when the blast cells are particularly numerous, an underlying acute leukaemia is presumed, and indeed would probably be diagnosed as such were it not for the tuberculosis. At other times the abnormal white cells are less primitive and a so-called leukaemoid reaction is suspected.

Pathogenesis

Patients having tuberculosis and haematological defects are encountered only rarely, and the experience of single investigators is necessarily limited. Partly for this reason the prevalence, type, and distribution of tuberculosis in the various blood disorders have never been satisfactorily determined. Lowther (1959) examined some 27,000 post-mortem reports in the Glasgow area for the years 1925 to 1952 for instances of leukaemia and tuberculosis. These are compared in Table I with the findings in 6,420 necropsy

TABLE I.—*Association Between Leukaemia and Tuberculosis. Post-mortem Case Reports, St. Bartholomew's Hospital, London, and Hospitals in the Glasgow Area (Lowther, 1959)*

Leukaemia	St. Bart's, 1930-61			Glasgow, 1925-52		
	No.	With Tuberculosis		No.	With Tuberculosis	
		No.	%		No.	%
Acute myeloid ..	71	3	4	68	2	3
Chronic ..	63	6	10	63	8	13
Acute lymphatic ..	45	6	13	75	3	4
Chronic ..	50	5	10	43	2	5
Monocytic ..	13	1	8	17	1	6
Total ..	242	21	8.7	266	16	6.4

reports at St. Bartholomew's Hospital during the period 1930 to 1961.

In view of the highly selective nature of the material and the smallness of the numbers with tuberculosis, no absolute conclusions can be drawn. The trends in the two series are similar, with rather more tuberculosis associated with

lymphatic leukaemia in the Bart's series. Acute myeloid leukaemia was less often associated with tuberculosis than the chronic variety. The overall figure for tuberculosis in leukaemia would seem to be about 7% in Britain.

The morbid anatomical features of the tuberculosis may be classified into healed or well-encapsulated scars in the lungs or lymph nodes, active pulmonary tuberculosis, and miliary tuberculosis. The distribution of the Bart's material is shown in Table II. The tuberculosis was healed in 16, active in the lungs in 3, and acute miliary in 10—that is, the tuberculosis was healed in about one-half of the cases, leaving 3-4% of patients with leukaemia having

TABLE II.—*Type of Tuberculosis Associated With Various Blood Disorders. (St. Bart's Post-mortem Reports, 1930-61)*

	Total	Healed	Active Pulm.	Acute Miliary
Myeloid leukaemia ..	134	5	1	3
Lymphatic ..	95	9	2	
Monocytic ..	13	1		
Polycythaemia vera ..	5	1		3
Granulocytopenia ..	13			2
Leukaemoid ..	2			2
Total ..	262	16	3	10

active tuberculosis. The occurrence of pulmonary tuberculosis in 3 out of 262 necropsy reports is unremarkable, but the figure of 10 instances of acute miliary tuberculosis is clearly excessive: seven occurred in conjunction with defective granulopoiesis and three rather fortuitously with polycythaemia vera. In this context the term "leukaemoid reaction" is used to describe a leucocytosis with primitive white cells but no primitive red cells in the blood and without leukaemic infiltrations in the tissues; in essence, it is a leucocytosis with overactivity of the granulocyte precursors in the marrow.

These tables suggest that the various diseases and reactions listed have no particular association with active pulmonary tuberculosis, but that they are unusually likely to be accompanied by acute miliary tuberculosis. Indeed, the relation between haematological defects and acute miliary tuberculosis is the most important aspect of the subject under discussion.

Microscopy shows the usual range of pathological changes, which vary from well-differentiated nodules having caseation, cellular infiltration, giant cells, fibrosis, and scanty bacilli to acellular necrosis and abundant bacilli. Undoubtedly the most remarkable feature is the frequency with which a particularly violent infection develops, one that has been recorded much more often in association with haematological abnormalities than with any others. In its fully developed form it is usually termed "non-reactive tuberculosis," to indicate its three main characteristics—namely, necrosis surrounded by normal tissue, little or no cellular reaction, and very large numbers of bacilli. Table III shows the 10 cases of miliary tuberculosis in the Bart's material according to diagnosis and the type of tuberculous reaction. Three cases of chronic myeloid leukaemia, two of granulocytopenia, and one of polycythaemia vera were judged to have had non-reactive tuberculosis. The other

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four cases were normally reactive. These figures are in keeping with published cases, of which about one-half have been described as non-reactive with no particular variation between the various haematological diagnoses.

TABLE III.—*Reactive and Non-reactive Tuberculosis in Various Disorders. (St. Bart's Post-mortem Reports, 1930-61)*

	Reactive	Non-reactive
Myeloid leukaemia ..		3
Polycythaemia vera ..	2	1
Granulocytopenia ..		2
Leukaemoid ..	2	
Total ..	4	6

O'Brien (1954) found 66 cases of non-reactive tuberculosis in the literature up to 1950, the haematological findings being as follows: agranulocytosis 22, leukaemia 13, leukaemoid reactions 7, normal count 6, panmyelophthisis 5, myelosclerosis 5, polycythaemia 2, Hodgkin's disease 1, no record of count 5. Similar cases which have been published since conform to the same pattern. The conclusions would seem to be that non-reactive tuberculosis is usually associated with an abnormal blood picture, that the number of white cells mainly of the granular series is reduced in about one-half, but that other abnormalities may coexist, including leukaemia.

Cases Without Haematological Defects

The occasional occurrence of non-reactive tuberculosis in patients without haematological defects prompted a review of the remaining 118 cases of acute miliary tuberculosis which came to necropsy at Bart's during the period under review. Only two of them were non-reactive. One had advanced chronic pulmonary and renal tuberculosis with a terminal miliary dissemination. The other was admitted in 1947, before anti-tuberculosis drugs became generally available.

Case 1.—A man aged 41 had had a course of radiotherapy a year previously for an anterior mediastinal tumour which at necropsy was found to be a simple dermoid cyst. On admission he complained of a continuous and moderately severe pain in the right lower abdominal quadrant of four days' duration. On examination he was afebrile and had tenderness in the right iliac fossa; a mass was suspected. A blood count showed 10,900 white cells per c.mm., with a normal differential. The pain and tenderness increased, and at laparotomy five days later a mass of induration, adhesions, and enlarged nodes was found in the region of an ulcer in the terminal ileum. Biopsy of a node showed discrete tubercles containing epithelioid cells, giant cells, fibrosis, and an excess of acid-fast bacilli. His general health subsequently deteriorated, with increasing fever, and he died a month later, the total length of his illness from the onset of symptoms being rather less than six weeks. Further white-cell counts varied from 3,300 to 22,900/c.mm., no abnormal cells being noted. The sternal marrow was not aspirated. Vast numbers of tubercle bacilli were seen in the sputum and stools. Post-mortem examination revealed an acute tuberculous ulcer of the terminal ileum with gross enlargement and caseation of the abdominal nodes, one of which was calcified. The mediastinal nodes were also enlarged and caseous. There was limited fibro-caseous tuberculosis below the apices of both lungs. The lungs, liver, spleen, peritoneum, and kidneys showed advanced miliary tuberculosis. Tuberculous foci throughout were non-reactive and showed masses of acid-fast bacilli (see Fig.). No leukaemia infiltration of the tissues was seen.

Why this patient should have developed so overwhelming an infection is uncertain. No blood dyscrasia was evident. The form which the tuberculosis took seems to have been a reactivation of a primary abdominal infection, because

calcification was seen in an abdominal node, followed by a haematogenous dissemination. Limited fibrocaseous tuberculosis existed near the apices of both lungs and could account for a bronchogenic spread in the lungs.

This is an extreme example of non-reactive tuberculosis, in which bacillary multiplication seems to have been completely uninhibited wherever the disease struck. It resembles a variant of tuberculosis which has interested Pagel and his colleagues (Blair and Pagel, 1947; Pagel and Woolf, 1949; Ball *et al.*, 1951). They found eight cases in the literature and added three of their own in which a rapidly fatal infection developed without any antecedent clinical tuberculosis or haematological abnormality. The average age was 44, the total white-cell count was less than 1,000/c.mm. in 8 of the 11, and tubercle bacilli were very abundant in the tissues. The distribution of the disease strongly suggested the acquisition of a fresh primary infection, often in the intestine, with massive enlargement of the lymph nodes and a spread of bacilli to the liver, spleen, and bone-marrow. The leucopenia seemed sometimes to develop after the tuberculosis had set in, and was accounted for by tuberculous involvement of the marrow. Perhaps its most remarkable characteristics are the apparent primary complex in the abdomen in the majority and the vast numbers of bacilli. Similar infections may involve the thorax, where a primary focus in the lungs is less easily identified. Case 1 has many of the features of Pagel's cases, such as the ulcer in the terminal ileum, the massive abdominal nodes, and the profusion of bacilli. On the other hand, the finding of a calcified abdominal node suggests a reactivated primary infection.

Diagnosis of Non-reactivity

While spectacular examples of non-reactive tuberculosis have been recorded from time to time (Marzullo and De Veer, 1931; Leibowitz, 1938), a study of the literature soon reveals that the pathological criteria of diagnosis have often been perfunctory. Ziehl-Neelsen staining has often been limited to one or two sites, and bacilli have sometimes been

Case 1. Massive bacillary multiplication in alveolar exudate. ($\times 500$.)

scanty or absent, the diagnosis of non-reactivity being based on acellular necrosis. Clearly, no specific dividing line exists between reactive and non-reactive tuberculosis, but an abundance of bacilli would seem to be essential.

In order to determine the distribution and numbers of bacilli the Bart's post-mortem material was reassessed, fresh sections being cut from all relevant paraffin blocks and stained by the haematoxylin-eosin and Ziehl-Neelsen techniques. A further 13 reports of patients having acute tuberculosis and defective granulopoiesis were available, 10 of which were generously contributed by colleagues from other hospitals; with one exception, pathological material was available for microscopical examination from those who died.

Table IV shows the numbers of bacilli in various sites in patients in this series dying with acute tuberculosis and granulocytic disorders. None had received anti-tuber-

TABLE IV.—Numbers of Tubercle Bacilli in Various Sites in Patients Dying from Acute Tuberculosis and Granulocytic Disorders

	Lung	Media- stinal Nodes	Abdominal Nodes	Liver	Spleen	Marrow
Myeloid leukaemia (6 cases)	0 ++ + 0	+++ +++ — ++	+++ 0 +++ +++	++ — ++ ++	++ 0 + +++	+ 0 — —
Polycythaemia vera (3 cases)	+++ +++ ++	— ++ +++	— ++ +++	— + ++	— ++ +++	— — ++
Leucopenia Leukaemoid (2 cases)	— —	— —	— —	++ —	++ —	0 —

Note: None of the above had anti-tuberculosis drugs.

culosis drugs. The three pluses indicate a Gaffky 10, or more than 100 bacilli to a field viewed with the 1/12-in. objective. The minuses indicate tubercles without visible bacilli, and the noughts no evidence of tuberculosis.

Abundant bacilli were seen most often in the mediastinal and abdominal nodes. The lungs, liver, and spleen were also heavily infected at times. Bacilli were visible in only four of the marrows and were never very numerous. The two patients with leukaemoid reactions, who both had disseminated tuberculosis, had few bacilli.

In no instance did the bacillary count reach a Gaffky 10 in all the tissues in which tubercles were visible; indeed, the paucity of bacilli in the marrow alone precluded this. Yet seven of them showed all the features of non-reactive tuberculosis in places, principally the lymph nodes, and these have been accepted as instances of non-reactive tuberculosis.

Clinical Features

The clinical features are much as would be expected in patients with acute disseminated tuberculosis. They include prostration, loss of weight, fever, and tachycardia. If anti-tuberculosis drugs are not given, a terminal illness lasting one to three months can often be identified.

Table V indicates the methods of clinical diagnosis. Of the 20 shown, tuberculosis was undiagnosed during life in 10; all had acute disseminated disease, the existence of which came as a surprise at necropsy. Mistakes are inevitable in the circumstances, for the tuberculosis mainly involves lymph nodes which are comparatively inaccessible to clinical and radiological examination, and the liver and spleen may already be enlarged by the blood dyscrasia. Also the clinical features resemble those of other complications of serious blood disorders such as broncho-

pneumonia, septicaemia, staphylococcal and streptococcal infections, and fungus disease. Since only about 3 to 4% of patients with leukaemia develop acute tuberculosis, tuberculosis is merely one of many causes of an acute febrile episode. Of the remaining 10 patients, tuberculosis was diagnosed positively in seven during life and strongly suspected in the other three.

TABLE V.—Methods of Clinical Diagnosis of Acute Tuberculosis in Granulocytic Disorders

	Undiagnosed	Diagnosed
Myeloid leukaemia	5	1. Ascites (presumed Tb) 2. Sp. Tb +. X-ray miliary 3. Tb node of neck 4. Laparotomy (intestinal obstruction)
Polycythaemia ..	3	1. Previous Tb node of neck 2. Sp. Tb +. Hilar nodes, pleural effusion 3. Polyserositis
Leukaemoid ..	1	1. Sp. Tb +. X-ray opacities 2. Tb node of neck. Marrow 3. Liver biopsy
Leucopenia ..	1	
Total ..	10	10

An abnormal radiograph of the chest existed in only 4 of the 20 patients, one showing unusual opacities, another miliary mottling, and the other two pleural effusions.

A liver biopsy was performed on only two patients. One revealed miliary tuberculosis which could not be diagnosed by other means. Several authors have stressed the importance of this investigation (Medd and Hayhoe, 1955), and it might have been performed more often in the present series, in which 15 of the 17 patients with acute tuberculosis who came to necropsy had tubercles in the liver.

Aspiration of the sternal marrow is probably the simplest method of diagnosing disseminated tuberculosis when obvious signs of the infection are lacking—for example, enlarged superficial nodes, pulmonary infiltrations, and serous effusions. How often it is likely to yield a positive result is questionable (Schleicher, 1946). Emery and Gibbs (1954) found histological tubercles at necropsy in 13 out of 44 children who died from miliary tuberculosis; they found them in a volume of bone-marrow which they estimated could have been obtained by aspiration during life. In the present series, post-mortem examination of the marrow in 16 cases showed tubercles in 10, bacilli being visible in 5. Various bones were used for this purpose, principally the humerus, and the sections were undoubtedly more satisfactory than sternal aspirates, but it seems certain that marrow tubercles exist in the majority and that bacilli are visible in a fair proportion—in the present series in one-third. The only occasion on which a sternal puncture was specifically used for the purpose of diagnosing tuberculosis in the 20 patients under review was one of extreme illness in a man with severe leucopenia. A solitary enlarged node in the neck had shown tuberculosis at biopsy, but no culture had been made. A sternal aspirate grew bacilli which were resistant to isoniazid and P.A.S. and which subsequently responded partially to streptomycin and second-line drugs.

The alkaline phosphatase stain may be useful in differentiating a leukaemoid reaction from a chronic or subacute myeloid leukaemia. The staining is confined to fairly mature neutrophil leucocytes. In a leukaemoid reaction, over 80% of the juvenile and band forms are likely to show the brownish-black granules of phosphatase, whereas in normal or leukaemic blood the figure is unlikely to exceed 10%. Unfortunately it has no application in myeloblastic reactions, in which the differential diagnosis is most difficult when tuberculosis coexists.

Haematological Patterns

In considering a possible pathogenetic relation between tuberculosis and haematological disorders, we may be fairly certain that tuberculous infection as such does not seem to predispose to grossly abnormal peripheral blood counts. For example, Muller (1943) found no striking changes in 1,000 patients suffering from pulmonary tuberculosis upon whom 6,000 blood films were made. Perhaps the commonest abnormality is a mild neutropenia, but a transient *leucocytosis* sometimes occurs which can often be accounted for by a secondary bacterial infection. Rarely a brisk polymorph leucocytosis develops in acute or sub-acute pulmonary tuberculosis; the blood count reverts to normal with the subsidence of the infection so that the full extent of the tuberculosis cannot always be determined.

The more serious haematological defects may be divided into two groups. First there are the primary blood diseases in which the diagnosis can be firmly established—for example, acute and chronic myeloid leukaemia and polycythaemia vera. Second, and more difficult, are the various reactions which appear in peripheral blood films from time to time and include neutropenia, agranulocytosis, pancytopenia, and leukaemoid reactions.

So far as the first group is concerned, the present series included 10 cases of *myeloid leukaemia* and three of *polycythaemia vera* in association with acute tuberculosis. In all but one the diagnosis of the blood disease preceded the onset of symptoms and signs attributable to tuberculosis, and this is the pattern of cases recorded in the literature (Paulley and Lintott, 1953; Rothstein and Jarrold, 1954; Rosenthal, 1956).

Case 2.—A man aged 54 was admitted to hospital extremely ill with high fever and thrush of the mouth and throat. A diagnosis of myeloid leukaemia had been firmly established in Greece four months previously and he had been treated with six injections of nitrogen mustard. A radiograph of his chest showed miliary mottling. Acid-fast bacilli were found in the sputum and treatment with anti-tuberculosis drugs led to a considerable clinical improvement. Four months later he suddenly relapsed and his white blood count, which had varied from 4,100 to 14,000/c.mm. in hospital rose to 364,000/c.mm., of which the majority were immature granulocytes. He died four days later.

At necropsy the cervical, mediastinal, and abdominal nodes were considerably enlarged. All were infiltrated with leukaemic cells and some in each group were also caseous. The liver and spleen showed miliary tubercles and leukaemic deposits. The miliary shadows in the lungs, the nature of which had given rise to some speculation during life because they failed to resolve with anti-tuberculosis therapy, consisted of a mixture of healing tubercles and leukaemic deposits.

The following case illustrates the uncertainty which attends the diagnosis of acute leukaemia when post-mortem examination reveals no leukaemic infiltration of the tissues.

Case 3.—In October, 1957, a woman aged 31, when in good health, passed some segments of tapeworm. On examination her liver and spleen were just palpable and a blood count showed Hb 13.6 g./100 ml., white blood cells 5,800/c.mm., of which 1,450 were neutrophils and 800 immature myeloid cells. The sternal marrow was almost completely replaced by blast cells, probably myeloblasts. A diagnosis of acute myeloid leukaemia was made and treatment with mercaptopurine 125 mg. daily was started.

During the next six months her health gradually deteriorated until her death in April, 1958. The spleen became impalpable after a month, but she developed bruising and diarrhoea. The mercaptopurine was continued and she had 40 mg. of prednisolone daily in addition during the final month. Courses of penicillin and chloramphenicol were followed terminally by

oropharyngeal thrush. Abnormal white cells had disappeared from her peripheral blood by January, 1958, by which time she developed a leucopenia with totals varying from 2,400 to a terminal 400/c.mm. Her sternal marrow in March showed an excess of immature myeloid cells and about 50% "blasts."

Histological examination of post-mortem material showed gross non-reactive tuberculosis with enormous numbers of bacilli in an ulcer in the terminal ileum and abdominal nodes, and miliary tuberculosis of similar type in the liver and spleen. The marrow showed a general reduction of cellularity with groups of "blast" cells and some tiny necrotic foci in which tubercle bacilli were not demonstrated. No leukaemic infiltrations were visible in the liver, spleen, nodes, or other tissues.

The fact that the original sternal aspirate showed the marrow to be almost completely replaced by blast cells renders the diagnosis of acute myeloid leukaemia beyond reasonable doubt. Subsequent treatment with mercaptopurine ridded the peripheral blood of immature cells, but 50% of blasts persisted in the marrow. Perhaps this is sufficient explanation of the lack of leukaemic deposits in the tissues, but the possibility that the tuberculosis played a part cannot be excluded. Indeed, this failure of the tissues to show leukaemic deposits when leukaemia and acute tuberculosis coexist has been noted on many occasions, and at times has caused some doubt to be thrown upon the nature of the blood disease (Jaffé, 1933; Ryan and Medlar, 1937; Betz and Liègeois, 1953; Zylberszac *et al.*, 1953). Obviously the alternative diagnosis is a leukaemoid reaction. Often, as in the present instance, the cellular pattern at the onset is sufficiently characteristic for myeloid leukaemia to be diagnosed with reasonable confidence. When the haematological evidence is less obvious the diagnosis of a leukaemoid reaction should be avoided in patients who have had radiotherapy or cytotoxic drugs.

Leukaemoid Reaction

The following case illustrates most of the features ordinarily regarded as being typical of a *leukaemoid reaction* (Heck and Hall, 1939; Emery and Lorber, 1950; Fountain, 1954; Hughes *et al.*, 1959).

Case 4.—The patient was a man aged 25. In September, 1945, four months after the death of his wife from pulmonary tuberculosis, he suddenly became ill with a cough, pain in the chest, and fever. On admission to hospital in October he had a large left serous pleural effusion. His sputum contained scanty tubercle bacilli on smear and culture. Serial blood counts showed a leucocytosis, mainly of the granular series, with immature forms of which a few were myeloblasts (Table VI). The cells in the sternal marrow were almost all of the myeloid series, with a slight excess of immature forms. He became progressively more ill in hospital with continued fever, and died on December 1, 1945.

TABLE VI.—Case 4. *Acute Tuberculosis and Leukaemoid Reaction*

	Oct. 17	Oct. 29	Nov. 5	Nov. 12	Nov. 17	Nov. 23	Dec. 1
Total W.B.C.	32,000	68,000	82,000	36,000	17,000	8,000	15,000
Myeloblasts (%)	2.5	2	1	3	1	1	1
Myelocytes (%)	32.5	28	42	10	12	7	13
Polymorphs (%)	46	58	50	65	75	81	77
Eosinophils (%)			1	12			
Lymphocytes (%)	12.5	5	5	7	10	9	8
Mononuclears (%)	6.5	7	1	3	2	3	1

Post-mortem examination showed a mass of caseous nodes at the left hilum in association with the pleural effusion. There were miliary tubercles in the lungs, liver, spleen, and marrow. Bacilli were not visible in sections, nor were there any leukaemic infiltrations in the tissues.

The diagnosis of a leukaemoid reaction, as opposed to acute leukaemia, is based upon the lack of leukaemic

infiltrations in the tissues and the variety of granulocytic precursors, the intermediate forms being well represented with no gross excess of blast cells; a similar distribution was noted in the marrow. The first blood count showed immature forms, but the illness during the previous month and his wife's death from tuberculosis earlier in the year strongly suggest* that the tuberculosis preceded the leukaemoid changes.

For a tuberculous aetiology to be completely convincing, there should be evidence of active infection together with a normal blood picture before the immature cells appear, and these should then disappear with anti-tuberculosis therapy. So far as is known, no patient has been observed who has satisfied all these criteria, including the necessary sternal aspirates at each stage, one reason being that leukaemoid reactions are most likely to accompany acute tuberculosis of the lymph nodes and serous cavities, and the haematological abnormalities already exist when the first observations are made.

Miliary Tuberculosis with Neutropenia

The coexistence of acute tuberculosis and *neutropenia* of one sort or another has been recorded on many occasions (Kernohan, 1950; Evans *et al.*, 1952; Leggat *et al.*, 1953; Cooper, 1959). Almost all case reports refer to patients whose illnesses were fatal within a few months, who received no anti-tuberculosis drugs, and in whom the acute tuberculosis and neutropenia persisted until death.

Partly because of the difficulty in diagnosing miliary tuberculosis in the early stages, the abnormal blood count is usually discovered first. Occasionally the cause of the haematological defect may be strongly suspected. For example, a neutropenia or pancytopenia may be an early feature of a leukaemia, or a suppression of the granulocytes may result from a drug reaction; Arends (1950) cites a patient whose pneumonia was treated with sulphonamides and who subsequently developed agranulocytosis and fatal miliary tuberculosis. But in most cases the original cause of the illness remains in doubt. The introduction of anti-tuberculosis drugs provided a ready means of further clarification, but disappointingly few case reports have been published so far (Medd and Hayhoe, 1955). Those that have suggest that the neutropenia tends to persist despite adequate chemotherapy. The following two cases illustrate the effect of anti-tuberculosis treatment.

Case 5.—A man aged 46 was admitted to hospital in September, 1953, with a week's history of lassitude, headaches, and shivering. On examination he was ill, with a temperature of 100° F. (37.8° C.), the liver was enlarged one fingerbreadth and the spleen one handbreadth below the costal margin; the axillary lymph nodes were palpable. Blood counts are shown in Table VII; the platelets were within normal limits. During the next week he became desperately ill, at the end of which a marrow puncture revealed a myeloid reaction with myelocytes 37% and blast cells 4.5%. A radiograph of the chest showed no abnormality, and a Mantoux skin test was weakly positive at 100 T.U. The temperature rose to 104° F. (40° C.)

TABLE VII.—Case 5. *Leucopenia, Miliary Tuberculosis*

	Hb%	Total W.B.C.	Polymorphs (%)	Lymphocytes (%)	Monocytes (%)
Sept. 1953	81	300	48	48	4
Oct. 1953	88	2,400	76*	17	7
Nov. 1953	88	1,800	51	40	9
Dec. 1953	87	1,800	56*	35	9
Mar. 1954	82	3,100	61	33	6
Sept. 1954	97	1,400	54	39	7
Feb. 1955	90	1,500	45	45	10
Nov. 1955	90	1,900	52	40	8
Mar. 1956	86	1,800	86	10	4

* Occasional myelocyte.

despite penicillin therapy. The possibility of an acute tuberculous infection was then considered and a course of streptomycin and isoniazid started. A dramatic clinical improvement was evident in a few days and the fever resolved in a week. A liver biopsy in October revealed miliary tubercles, no bacilli being visible; the material was not cultured.

On discharge from hospital in April, 1954, he was well, and after a period of convalescence resumed his work as a clerk. He was readmitted for assessment in November, 1955, still feeling well. His liver was enlarged two and his spleen three fingerbreadths; Hb 13.8 g./100 ml., white blood cells 1,900/c.mm., with a normal differential count. The marrow showed somewhat diminished cellularity with normal morphology. Anti-tuberculosis drugs were stopped after a course lasting over two years.

He was again admitted in March, 1956, with further hepatic enlargement. A blood count showed that the leucopenia persisted. Laparotomy revealed an inoperable gastric carcinoma with secondaries in the liver. No miliary tubercles were visible in the liver or spleen. He died at home six months later, no necropsy being performed.

This patient was extremely ill a week after the onset of symptoms, at which time his spleen was considerably enlarged and the white cells in his peripheral blood numbered only 300/c.mm. These features suggest that the leucopenia preceded the onset of symptoms. The prompt clinical response to anti-tuberculosis drugs and the confirmation of the diagnosis by liver biopsy five weeks later must indicate that the acute febrile illness was caused by miliary tuberculosis. The inference would seem to be that the tuberculosis developed after the leucopenia, and this view is confirmed by the persistence of the leucopenia until his death three years later in spite of more than two years of effective chemotherapy.

Case 6.—In March, 1957, a man aged 42 developed a febrile illness without localizing signs which persisted for a month and recurred at intervals subsequently. The details of his blood counts are shown in Table VIII. In November moderate bilateral serous pleural effusions were noted during one of his episodes of fever; they were treated by aspiration only and

TABLE VIII.—Case 6. *Acute Tuberculosis and Leucopenia*

	Hb%	W.B.C.	Polys%
Apr. 1957	74	2,500	45
Nov. 1957	60	950	30
May 1958	82	1,500	15
Nov. 1958	70	1,000	30
Apr. 1959	80	1,150	38
Oct. 1959	52	450	40
Dec. 1959	88	5,000	74
Apr. 1960	60	2,100	28

Note: No abnormal W.B.C. seen. Platelets 33,000-90,000.

did not recur. During the period November, 1957, to October, 1959, he had chronic ill-health, seldom being fit enough to do any work. A sternal aspirate in 1958 showed a relatively acellular marrow, 30% of the nucleated cells being immature forms with 6% myeloblasts. He had blood transfusions at intervals of about three months and was given prednisone 15 mg. daily from August to October, 1959. In October, 1959, he had a sharp febrile illness, and a radiograph of his chest showed rounded masses in his lungs measuring up to 5 cm. in diameter. His sputum contained tubercle bacilli, and a Mantoux skin test was negative at 100 T.U. His total white-cell count fell to 450/c.mm. He was treated with anti-tuberculosis drugs and showed a temporary improvement in his general health, his white blood cells rising to 5,000/c.mm. He then became progressively weaker despite continued drug therapy until his death in August, 1960.

Post-mortem examination showed that the opacities noted in the radiographs were discrete fibro-caseous nodules of tuberculosis, four in the right lower lobe and the other in the left upper lobe. The pleurae were adherent. Scattered miliary

tubercles were seen in the liver and spleen. A few acid-fast bacilli were visible in the lungs, liver, and spleen.

This patient was known to have had a leucopenia for two and a half years before the onset of acute tuberculosis, by which time he was already a sick man. The final febrile illness started after he had had prednisone for two months, and this may well have been significant (Hughes *et al.*, 1959; Forbes, 1961).

Discussion

These case histories and the clinicopathological considerations which preceded them illustrate many of the difficulties in trying to establish a relation between acute tuberculosis and abnormal haematological states. So far as the tuberculosis is concerned, two outstanding problems are apparent: namely, its curious distribution and the tendency to assume a non-reactive form.

The distribution of the tuberculosis, with massive lymph-node involvement and haematogenous dissemination to the liver, spleen, and bone-marrow, is unlike that seen in any other circumstances. Other conditions in which comparable features develop include simple miliary tuberculosis, primitive tuberculosis, and, so far as uninhibited bacillary multiplication is concerned, tuberculosis in various animals. In simple miliary tuberculosis the tubercles occur most commonly in the lungs, liver, and spleen, and the meninges are often involved; lymph-node enlargement from the primary infection may be evident, but is usually not excessive; whereas in acute tuberculosis with haematological defects the lungs are infrequently affected, except by the reactivation of a former focus of tuberculosis, and meningitis is rare. Primitive tuberculosis, which strikes communities with little or no previous experience of the infection, may attack the lymph nodes and serous surfaces predominantly, with subsequent miliary dissemination, but the heaviest infection usually occurs in the lungs in the form of an acute excavating pneumonia; except for this frequent pulmonary involvement the features are very similar to the cases under discussion.

The free multiplication of bacilli is, paradoxically, a characteristic of tuberculosis in some animals which are ordinarily regarded as having a high degree of resistance to tubercle bacilli—namely, rats and mice. After an intravenous injection, bacillary multiplication is tolerated in the lungs, liver, and spleen, but caseation does not occur and tuberculin sensitivity is difficult to demonstrate. Eventually the animals are stifled by a granulomatous process. Clearly the lack of caseation and hypersensitivity differentiates this reaction.

The histological features of non-reactive tuberculosis suggest a fundamental disturbance of the immunological processes. The two types of cell which are most concerned with the evolution of tuberculosis—namely, the monocytes and the lymphocytes—appear to be defective. The monocytes, while retaining their ability to ingest bacilli, have difficulty in destroying them (Lurie, 1955); the lymphocytes are remarkably sparse in the caseous foci. By contrast, the granulocytes are often strikingly abundant in areas where the bacilli are plentiful. A possible explanation of this unusual cellular pattern lies in the distribution of the tuberculosis, with gross involvement of tissues containing elements of the reticulo-endothelial system and consequently impairment of the response to antigenic stimulation. If this is so, the normal monocytic and lymphocytic responses may well be deranged whereas the granulocytes, being less intimately involved, might become relatively more prominent in the reaction.

Important Factors

Of the many factors which determine the form or degree of acuteness of a tuberculous infection, the size of the inoculum and the state of local tuberculous sensitivity and resistance are important. In the present context there is no reason to suppose that the size of the inoculum is in any way unusual, so that the tendency towards non-reactive tubercles must first be explained in terms of hypersensitivity and resistance.

While the sudden introduction of large numbers of bacilli into the blood-stream may temporarily depress hypersensitivity by exhaustion or neutralization of antibody, the rapid development of acellular necrosis in non-reactive tuberculosis must be regarded as a manifestation of hypersensitivity. In this context tuberculin skin tests are misleading. Four patients with acute tuberculosis in the present series had Mantoux tests, three being negative to 100 T.U. and the other weakly positive at this strength; these findings are similar to the few recorded cases which were investigated in this way (Hegler, 1938; Gibson, 1946; Arends, 1950). Some at least of these depressed reactions are likely to have been non-specific. As Pilcher (1930) has pointed out, the cutaneous capillaries of cachectic and debilitated tuberculous patients often fail to respond to a variety of inflammatory irritants, and a depressed tuberculin skin reaction does not necessarily imply diminished sensitivity elsewhere.

The state of resistance in non-reactive tuberculosis is less easily assessed. In general, the ability of the bacilli to multiply is an index of the state of resistance, but free multiplication is most likely when fresh caseous tissue is available. Indeed, a study of the cases in this series shows that the enormous numbers of bacilli which were sometimes encountered were most likely to be found at the perimeter of fresh acellular necrosis, although they sometimes extended into the necrosis and also to the more viable surrounding tissue. These are the changes to be expected in a hypersensitive patient with lowered resistance and the features of non-reactive tuberculosis can hardly be explained in any other way.

Some doubt has been cast from time to time upon the nature of the acid-fast bacilli in non-reactive tuberculosis. Filamentous forms have been demonstrated occasionally and avian strains of tubercle bacilli were suspected in some of the earlier case reports. Latterly these alternatives have not been substantiated, and both human and bovine strains of tubercle bacilli have been isolated repeatedly. Indeed, there is no reason to suppose that the bacilli differ in any way from those found in other types of tuberculosis.

In considering the haematological patterns which may accompany non-reactive tuberculosis, defective granulopoiesis seems to occur in more than one-half of the cases, in the form of myeloid leukaemia, granulocytopenia, and a leukaemoid reaction. Other reactions which have been observed include pancytopenia; occasionally blood formation appears to be unaffected. These findings contrast strangely with the distribution of the tuberculosis, which affects predominantly the lymph nodes and to a less extent the liver and spleen. Although tubercles are nearly always visible in the bone-marrow if they are looked for diligently enough, they are usually scattered and would not at first sight be expected to cause gross haemopoietic dysfunction.

Effect on Blood Formation

From the evidence of experimental work, tuberculous infection seems to have a variable effect upon blood forma-

tion. Myeloid metaplasia, anaemia, pancytopenia, and myelosclerosis have all been induced in laboratory animals by tubercle bacilli and their products. For example, Feldman and Stasney (1937) obtained a leucocytosis of 125,000/c.mm. by injecting tuberculin into sensitized rabbits. Perhaps the most significant experiment was conducted by Doan and Sabin in 1927. They injected a large number of rabbits with bovine bacilli. Those surviving the initial infection regularly developed tubercles in the bone marrow which spread for about three months and then tended to heal spontaneously, the marrow eventually returning to normal despite progressively fatal tuberculosis elsewhere. Serial blood counts showed anaemia and a fall in the granulocytes and platelets during the period of invasion of the marrow with a subsequent gradual return to normal. This depression of haemopoiesis during acute tuberculosis was often seen in patients in this series and has been recorded by others, and must be regarded as characteristic of tuberculosis of the marrow in man, but the range of blood dyscrasias that have been observed in laboratory animals is such as to suggest that tuberculous implants in the reticulo-endothelial system are variable in their effects and could conceivably act as a trigger mechanism in the development of several types of blood picture.

In non-reactive tuberculosis in man the state of tuberculin sensitivity is quite abnormal, and the marrow may be more extensively affected than the paucity of tubercles suggests. In these circumstances, as O'Brien (1954) has pointed out, the difference between stimulation and inhibition of the marrow cells may be slight, and the paradox of granulocytopenia and leukaemoid changes resulting from similar processes can be explained in this way.

Over the years, much thought has been given to the likely sequence of events when patients have acute tuberculosis and an abnormal blood picture. It is generally agreed that acute tuberculosis may complicate myeloid leukaemia and polycythaemia vera, the initial diagnosis of the primary blood disease having been firmly established first, so that the question of the blood changes being secondary does not arise. The difficulties occur in the various haematological reactions for which no adequate cause can be found other than the tuberculosis.

If the tuberculosis is to be considered as the primary defect, then the infection must reach at least some components of the haemopoietic system, particularly the lymph nodes and the bone-marrow, before the blood changes take place. It has been suggested that relics of a primary infection may sometimes be retained in these structures and induce fibrotic and proliferative reactions. If the blood-forming elements are then further damaged by chemicals or irradiation, or the state of tuberculous hypersensitivity and resistance is suitable, one or other type of blood disorder might result (André *et al.*, 1961). This argument is difficult to substantiate. From both experimental and morbid anatomical evidence, normal blood-forming tissues seem to be particularly well equipped to withstand tuberculous infection, and the marrow is rarely if ever the site of demonstrable chronic tuberculosis.

The other possibility is that the blood disorder comes first. Here the sequence of events would be that a lymph node of the primary infection becomes active as a result of the haematological defect and discharges bacilli into the general circulation. Some of the bacilli then lodge in other damaged parts of the reticulo-endothelial system where they find that they are able to initiate fresh foci of disease. Clinical observation suggests that this is the commoner mode of development. The onset of symptoms referable

to the tuberculosis is usually acute and in keeping with the distribution and microscopical features of the tubercles. In contrast, the haematological changes are sometimes evident before the acute symptoms. The spleen and to a less extent the liver are often much larger than would be expected in uncomplicated miliary tuberculosis, and the effect of anti-tuberculosis drugs upon the blood disorder is usually most disappointing.

Summary and Conclusions

Acute tuberculosis, usually with miliary dissemination, seems to develop in about 3-4% of patients with myeloid leukaemia. Evidence of healed tuberculosis exists at necropsy in a further 3-4%.

Miliary tuberculosis may be seen in association with a variety of haematological reactions—for example, leucopenia, agranulocytosis, pancytopenia, and leukaemoid reactions.

The histological features of the tuberculosis in these cases often assume a non-reactive form—that is, the tubercles show discrete necrosis with little or no cellular reaction and very large numbers of bacilli.

Occasionally the features of non-reactive tuberculosis are demonstrable throughout the extent of the miliary tuberculosis. More often they are of limited extent and are most likely to be seen in the lymph nodes and rather less frequently in the lungs, liver, and spleen. When miliary tuberculosis develops in association with a blood disorder the non-reactive form can be seen in at least some of the tissues in about one-half of the cases.

The relation between acute tuberculosis and abnormal blood pictures, particularly in so far as they refer to the granulocytes, is by no means clear. Experimental work suggests that tuberculosis may stimulate or depress marrow function, but the factors which determine the form the reaction takes are not understood. Clinical experience confirms the range of reactions that occur from time to time.

Some clarification of the difficulties in interpretation was anticipated when anti-tuberculosis drugs were introduced. Their effect upon acute tuberculosis in patients with myeloid leukaemia is similar to that in patients without a blood disease. In granulocytopenic states the drugs are equally effective against the tuberculosis but the granulocytopenia seems usually to persist.

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CLINICAL SIGNIFICANCE OF SPLINTER HAEMORRHAGES

BY

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Splinter haemorrhages have been recognized as a characteristic physical sign of subacute bacterial endocarditis since Horder (1920) drew attention to their association with this disease. It has been stated by Lewis (1942) and White (1947) that their presence is due to an increased capillary fragility in this condition. Bramwell and King (1942), however, considered that they are embolic in origin.

Wood (1956) stated that they "are in no way diagnostic of bacterial endocarditis" and that they may also be present in septicaemia, rheumatic fever, and severe anaemia. Platts and Greaves (1958) found that they occurred in 44% of patients with uncomplicated mitral stenosis and in 15% of other patients. They also noted that they occurred with some frequency in patients who appeared to be in normal health, and suggested that their presence may be due to factors unconnected with disease.

The aim of this investigation was to determine what factors, other than the above diseases, are associated with this apparently common physical finding, in order to help the clinician assess its clinical significance when he elicits it.

In a pilot study 200 patients (from six wards) in the Whittington Hospital were examined. Details of their age, sex, occupation, duration in hospital, diagnosis, temperature, and blood-pressure were recorded. Hess's test was performed—according to the method suggested by Wood (1956)—and the urine of each patient was examined chemically for blood. The fingers and toes were examined for splinter haemorrhages. Other details which might have been relevant, such as purpura and the results of laboratory investigations, were also recorded.

The pilot study suggested that age, occupation, duration of the patient in hospital at the time of examination, and blood-pressure were factors which might be associated with the presence of splinter haemorrhages. It also showed that examination of the toenails was a fruitless task, because they were very often thick and opaque.

Material and Methods

A group of patients who had all been admitted to 12 of the general medical and surgical wards of the Central Middlesex Hospital from April to July, 1962, were examined.

The age, duration in hospital at the time of examination, occupation, blood-pressure, and presence or absence of splinter haemorrhages were recorded for each patient.

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Each patient was examined for or questioned about the relevant factor in the order stated above, so as to avoid bias in classifying the occupational grade when the presence or absence of splinter haemorrhages was known.

Each patient was placed in one of four groups according to his occupation and activities. The patient was first classified as "manual" or "non-manual" according to the extent to which his hands might be exposed to trauma as a result of his occupation. The patients in each main group were then subdivided into a further two groups depending on the extent to which the patient in fact used his hands either at work or at home. There were thus four grades of occupation (1, 2, 3, and 4) based on increasing exposure to trauma.

For example, a motor mechanic would be classified as grade 4 if he actually wielded the tools himself, but as grade 3 if he had not worked for some weeks prior to admission to hospital, or if he was a foreman who rarely used his hands. Similarly, a housewife would be classified as grade 4 unless she had a servant to perform her heavy duties, in which case she would be grade 3. A clerk would be classified as grade 1 unless he indulged in a moderate amount of gardening or decorating at home, in which case he would be classified as grade 2.

Splinter haemorrhages were defined as longitudinally linear lesions, red, brown, or black in colour, not blanching on pressure, which were visible beneath the nail in the distal third of the vascularized part of the nail-beds of the fingers or thumbs. Any lesion which, by its appearance or from the patient's account, was due to an actual splinter was discounted.

Results

A total of 267 patients were examined, and splinter haemorrhages were found in 51 (19.1%).

To estimate the strength of the association between splinter haemorrhages and each of the other factors, it was decided to calculate product moment correlation coefficients and partial correlation coefficients. It should, however, be appreciated that the data are not "normally" distributed in each of the factors analysed, and so this approach cannot be regarded as providing exact probability levels for the coefficients. The following interpretations have therefore been put upon the probabilities found: (1) 0.10, non-significant; (2) between 0.10 and 0.01, doubtfully significant; (3) less than 0.01, statistically significant.

Correlation coefficients were calculated between the presence or absence of splinter haemorrhages and various