taken that, at the time of gaining such control, new habits of living which cause ill-health should either be prevented or, if they arise, be controlled. Such errors in living are undoubtedly developing at the present time, and it is the duty of medical science to find out their relative disease-producing importance. The chemical manipulation of food may well be the basis of some of these errors, and the problem requires investigation.

Official inquiry—both laboratory and judicial—and control want strengthening. There ought to be a practical counterpart in this country of the Food and Drug Administration of the U.S.A., in the form of either a public institute for such work or an extensive and close liaison with other institutions capable of making the necessary investigations. Official direction and control of, and responsibility for all such matters should ultimately be placed with the Ministry of Health, as this is fundamentally a medical problem. Apart from chemicals long in use, a decision ought to be made on whether any new chemicals should be allowed in food processing and production before they have been adequately tested for their toxicological effects. No use of chemicals based on effective aesthetic or even practical advantages conferred on food by these substances should be countenanced if they have harmful effects on animals; and, apart from questions of toxicity, the present trend of lowering the nutritive value of extensively eaten food such as bread, both by chemicals and by other forms of manipulation, demands attention.

One final suggestion is that if people want bread which has not been chemically treated in any way they ought to be able to purchase it. This is no doubt possible in the case of wholemeal bread, but the same ought to apply to bread made of flour of lower extraction. At least untreated flour of this kind ought to be freely available so that persons can bake their own bread if they wish.

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ACUTE TUBERCULOUS SEPTICAEMIA
WITH LEUCOPENIA

BY

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Acute tuberculous septicaemia presents as an obscure clinical picture, with pyrexia, severe leucopenia, and a rapid downhill course. No case so far recorded has been diagnosed during life, but in view of the possibility of chemotherapy an early diagnosis is very desirable. Three cases will be described. They were observed on the same medical unit within four years, which alone suggests that this form of tuberculosis is commoner than is usually believed.

Case 1

A plasterer aged 54 was admitted on April 17, 1946. He had been well until three weeks previously, when he developed rigors followed by severe sweating. The personal and family histories were not significant. On examination he was very ill. He had herpes labialis, a furred tongue, and petechiae on the chest. There was an impaired note with diminished breath sounds at the right base. No abnormal signs were present in other systems.

White cells numbered 925 per c.mm. (neutrophils 72%, lymphocytes 21%, monocytes 5%, eosinophils 2%). The white cells rose later to 1,100 and 1,450, with 86% neutrophils on each occasion. Haemoglobin, 89%; red cells, 4,400,000; colour index (C.I.), 1.0. Sputum gave a growth of *Staph. aureus* and pneumococci. No tubercle bacilli were seen. X-ray films of chest showed some consolidation at both bases.

His temperature was irregular up to 101° F. (38.3° C.). A diagnosis of pneumonia with leucopenia was made, and he was treated with penicillin and liver extract. He steadily became worse and died on April 24.

Summary of Necropsy and Histological Findings

(For anatomical details, see Blair and Pagel, 1947.) The main feature was the presence of extensive naked-eye changes in the spleen, liver, and mesenteric lymph nodes. There were areas of necrosis full of acid-fast bacilli and devoid of the classical tuberculous cells. The shadowy preservation of the organ structure in the necrotic areas suggested that it was an example of "direct necrosis." (For definition, see Case 3.)

Careful dissection and post-mortem radiography failed to detect any traces of old or fresh tuberculous changes in the lung. Extensive fresh caseation of the mesenteric lymph nodes, however, suggested that the intestinal tract was the portal of entry.

The numerous areas of necrosis full of tubercle bacilli which were present in the marrow of the sternum and the femur were regarded as the cause of the leucopenia.

There was haemorrhagic consolidation of the basal part of both lower lobes. The alveolar exudate was full of cocci, but no acid-fast elements were seen.

Tubercle bacilli of human type were recovered from a mesenteric lymph node.

Case 2

An insurance agent aged 56 was admitted on May 5, 1947. He had been well until one month previously, when he had fainted in the street and bruised himself. He later developed a rash on his face, arms, and legs, and twitching of the face.

On examination he was seriously ill. His tongue was heavily coated and his throat was red, although no exudate was seen. Sonorous rhonchi were present over both lungs. He had a regular tachycardia of 168, which was found to be due to a 2:1 auricular flutter. No abnormal signs were found in the central nervous system or the alimentary system.

White cells numbered 2,050 per c.mm. (neutrophils 46%, lymphocytes 48%, other cells 6%). Haemoglobin, 78%; red cells, 3,100,000; C.I., 1.25. The white cells later fell to 500 and 250, the majority being lymphocytes. An x-ray film of the chest showed patchy consolidation of the right lower lobe. The cells in the cerebrospinal fluid were normal, but the protein was 55 mg. per 100 ml.

A diagnosis of bronchopneumonia with leucopenia was made. There was an intermittent pyrexia up to 101° F. (38.3° C.), and he was treated with penicillin, pyridoxin, and folic acid. Despite full dosage of digitalis the auricular flutter persisted, and he died on May 18, five weeks after the onset of his illness.

Summary of Necropsy and Histological Findings

(For anatomical details see Pagel and Woolf, 1949.). A fresh caseous primary complex was found in the right lower lobe of the lung, consisting of a large wedge-shaped caseous area and enlarged caseous bifurcation lymph nodes.

There was haemorrhagic consolidation of the lower lobes near the base, with many cocci but no acid-fast elements visible in the exudate.

The spleen showed no naked-eye changes other than an anaemic infarct near the upper pole. Histologically, this was due to endophlebitis with innumerable acid-fast bacilli in the swollen and fibrinoid-necrotic intima.

A small anaemic infarct in one kidney was due to an arterial thrombosis, without evidence of a tuberculous origin.

There was no naked-eye evidence of multiple necrotic foci as seen in Case 1, but, histologically, innumerable ill-defined small areas of necrosis, teeming with acid-fast bacilli, were seen in the spleen, liver, suprarenals, and bone marrow (femur and sternum).

Tubercle bacilli of the human type were recovered from a bifurcation lymph node and from the spleen.

Case 3

A housewife aged 47. Apart from an attack of "congestion of the lungs" in 1946, she had been well until three weeks before admission on July 19, 1949. Since then she had been feverish, with anorexia and malaise, and had become much worse on the day of admission. On account of her confused state she was admitted to the mental observation ward.

On examination she was severely toxic, with a temperature of 103° F. (39.4° C.) and a pulse of 128. Her tongue was dry and furred, and there were a few petechiae on her back and abdomen. There were no abnormal signs in the lungs, but her spleen was easily palpable. The general picture strongly suggested typhoid fever.

The white cells totalled 700 per c.mm. (neutrophils 70%, lymphocytes 30%). The count rose to 1,900, but later fell to 400. The proportion of neutrophils was never less than 48%. Haemoglobin, 58%; red cells, 3,200,000; C.I., 0.9; platelets, 30,000. Cerebrospinal fluid was normal. Agglutinations against *Salmonella typhi* and *paratyphi* were negative. Sternal puncture showed reduction in cellularity due to a marked diminution of the granulocytes and their precursors; the van den Bergh test gave a positive delayed direct reaction, with bilirubin 2 units. Serum proteins: albumin 1.8, globulin 3.7 g. per 100 ml.

Typhoid fever was soon excluded, but the cause of the leucopenia remained obscure. It was thought that she might have been taking some drug, but no evidence of

this could be found. Primary agranulocytosis and miliary tuberculosis were also considered. She was treated with penicillin, liver extract, and bone-marrow extract, but steadily deteriorated, became jaundiced, developed ulceration of the fauces, and died eight days after admission.

Necropsy: Summary of Naked-eye Changes

Multiple subpleural petechiae, with basal haemorrhagic consolidation, were present in both lungs. A small subpleural necrotic nodule was found in the left lower lobe, associated with extensive greyish-white necrosis of the enlarged bifurcation and left lower bronchopulmonary lymph nodes. In the mesentery, near the ileocaecal junction, there was a hard calcified lymph node. The liver was jaundiced and enlarged, and showed no focal changes. The spleen weighed 280 g. and also showed no focal changes. The kidneys were normal in size and appearance. The femoral marrow was dark red.

Histological Examination

The left bifurcation lymph node was almost completely replaced by confluent oedematous areas of necrosis containing round chromatin fragments but with no cellular response at the periphery. Round chromatin debris is due to a process of "direct necrosis" of the lymphocytes without previous "tuberculation," and should be distinguished from "caseation," which follows the conversion of the tissue cells into epithelioid and giant cells. Since the nuclei of these cells are spindly or varying in shape, so are their chromatin fragments. Many colonies of long granular acid-fast bacilli were found in the necrotic areas (Fig. 1).

FIG. 1.—Case 3. Hilar lymph node, showing long beaded acid-fast bacilli. ($\times 900$.)

The basal parts of the lung showed a confluent pneumonia. The focus described in the left lower lobe consisted of a number of small ill-defined necrotic foci with a tendency to confluence, some of which seemed to have developed in the intima of a pulmonary vein. In the spleen the Malpighian corpuscles were scanty and were mostly replaced by collections of plasma cells and mononuclear cells. The pulp was very cellular, with many swollen reticulum cells and histiocytes. Some of the large mononuclear cells contained long granular acid-fast bacilli. In the liver small focal collections of swollen histiocytes containing acid-fast bacilli were seen in many sinusoids. The fat marrow had numerous "active" islets, in which large reticulo-endothelial

cells containing acid-fast bacilli predominated. There were also small areas of necrosis containing bacilli (Fig. 2). The adrenals showed no evidence of necrosis. An abdominal lymph node showed a typical calcified primary focus with marginal ossification. There was no evidence of recrudescence.

FIG. 2.—Case 3. Bone marrow (sternum), showing ill-defined areas of necrosis; $\times 100$. Inset: Close-up of central focus; $\times 250$.

Bacteriology

Cultures from the caseous bronchial lymph node were contaminated, but an inoculated guinea-pig developed an enlarged deep inguinal lymph node as the sole lesion. Cultures from the guinea-pig produced a profuse growth of an acid- and alcohol-fast bacterium which was not characteristic of either a human or a bovine tubercle bacillus. Inoculation into a guinea-pig produced a local granuloma only. It is therefore not certain that the organism cultivated was the cause of the disease.

Comments on Case 3

There are the unmistakable traces of healed *primary intestinal infection*. This must have occurred years ago, as the calcified abdominal lymph node is partly ossified.

The present condition is unrelated to primary infection. It presents the features of *genuine reinfection*. By this we understand a renewed infection from without. It causes a caseous focus, to be found at the portal of entry, followed by a caseous change (or, as in the present case, "direct necrosis") in the regional lymph nodes—in other words, a new lesion of the primary complex type. It is supposed to occur when allergy has disappeared as the result of a complete healing of the primary complex. In the present case, gross involvement of the hilar lymph nodes by a widespread and rapid process of direct necrosis was impressive.

There is evidence of extension into a pulmonary vein, although it could not be proved that this was due to

direct communication of the vessel with a lymph node which had ruptured into it.

Generalized spread, notably to the liver, spleen, and bone marrow, followed. The changes found in these organs present a slightly different picture from that seen in most cases described. First of all, there were no naked-eye changes. Secondly, necrotic foci were missing in the sections of the liver, were scarce in those of the spleen, and were small in extent in the bone marrow. Apart from "direct necrosis" of unchanged tissue elements a cellular reaction preceding necrosis is indicated by the small collections of reticulo-endothelial cells, as seen in the liver and spleen. These showed beginning nuclear degeneration and were full of acid-fast bacilli.

Small areas of necrosis were most widespread in the bone marrow, and explain the blood changes.

The pathological changes described must be attributed to the action of acid-fast bacilli which were present in all of them; and, vice versa, wherever acid-fast organisms were seen they were associated with such changes. Thus it can be concluded from the histological picture that these organisms were not secondary invaders.

Discussion

Definition and Frequency

"Acute tuberculous septicaemia" is a rare condition. Altogether about 30 cases can be collected from the literature (von Wyss, 1940; Blair and Pagel, 1947; Pagel and Woolf, 1949). A number of these cases are based on very scanty post-mortem data, and should be ignored, as should those that have been described from clinical evidence alone (so-called "typhobacillosis").

A further reduction will depend upon the strictness of definition. "Acute tuberculous septicaemia" in the strict sense means an independent manifestation of tuberculosis. It is marked by a spread of necrotic foci without the usual tuberculous features other than the presence of acid-fast bacilli. This definition excludes:

(a) Cases mixed with or following on miliary or other clinical tuberculosis.

(b) Those without histological data.

(c) A considerable number of observations representing the terminal states of a blood disease (for example, myeloid leukaemia, pernicious anaemia, Hodgkin's disease, polycythaemia). There were no fewer than 7 such cases out of 18 collected by von Wyss from the literature. In addition, four out of the eight cases collected from necropsy material at Zurich by the same author belonged to this category. Two of the remaining four cases showed a severe leucopenia, and these are included, since, unlike the other blood diseases mentioned, the blood condition appears to be a result rather than a cause of tuberculous septicaemia.

Pathogenesis

Acute tuberculous septicaemia follows fresh primary infection or, as in Case 3 of the present series, reinfection. The portal of entry is not infrequently the gastrointestinal system (9 out of 15 cases with relevant data). This need not necessarily mean bovine infection; for human strains have been recovered in spite of intestinal infection (Jacobowitz, 1934; Siegmund, 1939; Blair and Pagel, 1947). The peculiar character and course of the disease do not therefore seem to be explained by any special characteristics of the bacterial strains involved.

We are ignorant of the causes which enable the tubercle bacillus to set up an overwhelming generalized infection without cellular response. It may be that an age factor is operative, the majority of the cases involving

higher age groups. A special condition of the haemopoietic system may be derived from the occurrence of an acute spread similar to fulminant tuberculous septicaemia in the terminal phases of blood diseases. It should be emphasized, however, that we have no evidence of a primary failure of the body to produce cells, notably polymorphs, to account for the peculiar lack in resistance. Tuberculous septicaemia is observed in leukaemias with superabundant circulating cells, and usually fails to appear in ordinary agranulocytosis. In some cases leucopenia can be shown to set in after the acute illness has developed. Finally, there are no data in the general and experimental pathology of tuberculosis which would support the hypothesis of diminished antituberculous resistance due to a primary damage to the leucocyte-forming systems (Pagel, 1948).

Anatomical Forms

According to post-mortem findings, two categories can be distinguished: (a) cases with naked-eye changes—to wit, a spread of necrotic foci usually twice or three times the size of miliary nodules (these are found in the spleen and liver); (b) those without characteristic naked-eye changes. There may be the simple "septic changes," such as subserous petechiae, or a "septic spleen," or a few simple infarcts. The majority of cases belong to category (a); for example, all but one of the 30 cases reviewed by von Wyss (1940). Apart from the case of Scholz (1918), those reported by Pagel (1927), Pagel and Woolf (1949), and Case 3 of the present series fall under category (b). In other words, these cases seem to be particularly uncommon.

Clinical Features

Only eight other fully recorded cases could be found in which severe leucopenia was associated with post-mortem evidence of acute tuberculous septicaemia, although there are several reports of cases with normal or unrecorded white counts (von Wyss).

Scholz (1918) reported the case of a woman of 56 who died after four weeks' febrile illness. She was jaundiced and her spleen was palpable. The leucocyte count varied from 1,650 to 1,800 per c.mm., with a neutrophil percentage of 11–23. At necropsy, enlarged bronchial lymph nodes, a necrotic laryngitis, and a soft enlarged spleen were found. The liver and spleen contained numerous small necrotic foci with abundant tubercle bacilli.

Nasse's (1931) patient, a man of 53, was ill for six weeks before death with fever, cough, and anorexia. Leucocyte counts of 1,333 and 1,777 per c.mm. were recorded without differential counts. Necrotic foci containing tubercle bacilli were found in the lungs, liver, and spleen at necropsy.

Steinbrinck (1938) recorded the case of a man who died after a febrile illness of two to four weeks. The spleen was palpable. The leucocyte count fell from 1,700 to 400 per c.mm. with 6–8% neutrophils. The haemoglobin was 38%. Sternal puncture showed marked diminution of the neutrophil series. Necropsy revealed small areas of necrosis in many organs, all of which contained tubercle bacilli.

Müller (1938) described the case of a man of 54 who died after six weeks' illness with fever, cough, and malaise. The spleen was palpable. Leucocytes numbered 500–1,000, with 51–75% neutrophils. Haemoglobin was 38–44%, and sternal puncture was normal.

Necropsy revealed caseating mesenteric, retroperitoneal, and inguinal lymph nodes, with large irregular tuberculous lesions of the spleen. Tuberculous lesions of the kidney and liver were also present. The spleen had necrotic foci containing tubercle bacilli; the liver contained tubercles with giant cells and central necrosis.

Von Wyss (1940) recorded two cases of his own. His Case 6 was a man of 35 who died after four to six weeks' illness, characterized by sweats, malaise, and a morbilliform rash. The liver and spleen were enlarged. Leucocytes numbered 370 to 670 per c.mm. with 45–56% neutrophils; haemoglobin 51%. Blood culture grew a non-haemolytic streptococcus. Necropsy showed chronic tuberculosis of the left upper lobe and miliary necroses in the liver, spleen, lungs, kidneys, bone marrow, and lymph nodes containing human tubercle bacilli. His Case 7, a woman of 35, had been taking amidopyrine tablets for headaches for five years. She died after three weeks' illness in which she had a high fever, rigors, and vomiting. Apart from a papular rash on the legs, there were no special clinical findings. The leucocytes fell from 6,000 to 800 per c.mm., with 2.5–11% neutrophils. At necropsy, miliary necroses were found in the lungs, spleen, and bone marrow. The marrow also showed a marked diminution of granulocytes.

Siegmund (1939) reported nine cases of a reactive generalized tuberculosis. Of four cases with a severe leucopenia, only one was reported in detail. A man aged 29 died after three months' illness, during which he complained of tiredness, headaches, and sleeplessness. He ran an intermittent fever, but no cause for it was found. The leucocyte count fell from 3,000 to 425 per c.mm., the neutrophil percentage varying from 52 to 91. Necropsy revealed innumerable small necrotic foci in the lungs, spleen, lymph nodes, bone marrow, and skin. These foci contained tubercle bacilli, which were found to be of human type. An ulcer of the stomach was the site of a recent primary infection, which was associated with enlarged lymph nodes in the region of the pancreas.

Kernohan (1950) recorded the case of a man aged 61 who died 17 days after admission to hospital. He had been unwell for five months. Pyrexia, pallor, and enlargement of the liver and spleen were noticed. He had an aplastic anaemia (haemoglobin 36%) with 1,200 white cells. Sternal marrow examination revealed aplasia. The spleen showed multiple areas of necrosis with a slight mononuclear reaction around the margins. Acid-fast bacilli were found in the lesions. The picture was that of an atypical miliary tuberculosis.

Thus, including our three, 11 cases of acute tuberculous septicaemia with leucopenia have been fully recorded. The ages varied from 22 to 56, with an average of 44 years. Eight were men and three women. The acute illness, which was invariably fatal, lasted between three and twelve weeks. Rigors, anorexia, and malaise were the most frequent symptoms, and all cases ran a high fever of no constant type. The spleen was enlarged in six cases and the liver in three. Jaundice was present twice. In two cases there was a history of widespread skin eruption before admission, and a third case was found to have a papular eruption on the legs. Ulceration of the fauces was noticed only twice during life, just before death, although it was found in two other cases at necropsy. In 8 of the 11 cases the total leucocyte count fell below 1,000 per c.mm., but in only three of the nine cases in which differential counts were made did the neutrophil percentage fall below 40.

The haemoglobin was 60% or below in 6 out of 10 cases in which it was recorded, and the colour index was usually high. The platelets were recorded as being markedly diminished in three cases. Sternal puncture revealed a depression of the granulocytes in two cases, aplasia of the bone marrow in a third case, and a normal marrow in a fourth. Thus it appears that a depression of one or all of the blood-forming elements usually occurs.

Although severe leucopenia has been a striking feature of all the present cases, it is a complication rather than an essential feature of the disease, since it is, in our opinion, caused by the action of the tubercle bacillus on the bone marrow. In only one of the above cases (No. 6) was there evidence of a drug playing a part in the development of the leucopenia. In some of the cases the initial leucocyte count was normal or only slightly depressed, the severe leucopenia developing later. Nevertheless, its importance is stressed because it should prove one of the few helpful diagnostic features in a disease in which a correct diagnosis has apparently never been made during life.

Since the disease runs a rapid downhill course, an early diagnosis would have to be made if chemotherapy were to be given a chance of success. The most important factor in making the diagnosis would be to consider the possibility of acute tuberculous septicaemia in cases of high fever associated with leucopenia. The clinical picture often suggests typhoid fever or miliary tuberculosis. Splenic enlargement, abnormal chest signs, skin eruptions, and jaundice may also be present. A certain diagnosis could be made only by finding the tubercle bacillus. Since large numbers of tubercle bacilli can be found in the bone marrow post mortem, von Wyss has suggested that sternal puncture should be performed in an attempt to find the causal organism. Horowitz and Gorelick (1951) have described a method by which tubercle bacilli were demonstrated in the bone marrow in 14 out of 20 patients with advanced tuberculosis. This would seem to be the most likely way of confirming the diagnosis. Aspiration biopsy of the liver might also prove diagnostic.

It is possible that streptomycin might result in a cure if it were administered before irreversible changes had occurred. A trial of the drug would be fully justifiable in what is otherwise a hopeless condition.

Summary

Three cases of acute tuberculous septicaemia with leucopenia are described, and are compared with eight cases which have previously been recorded in the literature.

Rigors, anorexia, and malaise were common symptoms. A high fever was always present and an enlarged spleen was often felt.

A severe leucopenia without a striking relative neutropenia was the commonest finding in the blood. An aplastic anaemia and a thrombocytopenia were also seen.

A rapid downhill course invariably occurred, with death between three and twelve weeks from the first symptom.

Acute tuberculous septicaemia followed a fresh primary infection or a genuine reinfection in each of the three cases.

At necropsy, multiple necrotic foci were seen in the liver and spleen in Case 1, but in Cases 2 and 3 no characteristic naked-eye changes were visible in any organ.

In all cases histological examination revealed numerous necrotic foci containing acid-fast bacilli in many organs.

It is considered that the occurrence of these organisms in the bone marrow accounts for the leucopenia and anaemia.

The difficulty in diagnosis lies in the absence of characteristic features in this disease. Examination of the bone marrow for tubercle bacilli is recommended. Streptomycin should be given a trial in a suspected case.

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ACROSCLEROSIS

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Scleroderma is a condition which may present in several ways. In its commonest form it appears as localized areas in the skin which show thickening, adhesion to the subcutaneous tissues, a smooth waxy surface, and progression to atrophy. This form—localized scleroderma or morphoea—is a disease of little consequence. The generalized form is a serious disease. The skin changes are similar, but large areas of the body are affected and the disease is steadily progressive. It is usually insidious in onset and runs a chronic course, but rarely may occur in acute form with rapid development of the typical changes. Among patients with generalized scleroderma it is possible to separate a group in whom the skin changes are confined to the hands, forearms, face, and upper chest, and are commonly preceded by Raynaud's phenomena in the hands. There is some dispute whether this form, which has been given the name of acrosclerosis, is a disease *sui generis* or is merely one way in which generalized progressive scleroderma may present.

Hutchinson (1893, 1895, 1896) seems to have been the first to recognize the association of Raynaud's phenomena with sclerodermatous changes. He separated such sclerodermatous changes from those of "diffuse scleriosis," not only because of their intimate association with Raynaud's phenomena but also because the skin changes were confined to the digits and, less often, to the face. He used the terms "acrosclerodermia," "acroteric morphoea," and "acroteric scleriosis" to cover the condition. Sellei (1931, 1934) likewise separated acrosclerosis from chronic progressive scleroderma and strongly supported the view that it is a disease in its own right. O'Leary and Waisman (1943), in an admirable account of the condition, also regarded it as