less, normal and raised values occurring in all groups. The raised values always became normal after iron therapy, however, even in the absence of a material rise in haemoglobin level.

Conclusions

In 50 cases of rheumatoid arthritis, failure of their anaemia to respond to intravenous iron could not be predicted from the results of any of the investigations examined.

Return of the haemoglobin to normality occurred regularly when one or more of the following were present: sedimentation rate below 30 mm. in one hour, microcytosis, gross hypochromasia, and raised total iron-binding capacity of the serum.

The haemoglobin, however, returned to normal or improved greatly in many cases which showed none of the above criteria.

It appears that intravenous iron is always worth trying in the anaemia of rheumatoid arthritis, except when severe constitutional disturbance or the imminence of surgery makes preferable the rapid rise in haemoglobin which follows blood transfusion.

My thanks are due to Dr. G. D. Kersley for his helpful criticism and advice, and for allowing the investigation of patients in his care. I am indebted to Professor C. Rimington for providing some pure protoporphyrin and to the Empire Rheumatism Council, whose grant for the purchase of a fluorimeter made the porphyrin part of this work possible.

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ACTINOMYCOTIC PYAEMIA

BY

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Human infection with filamentous organisms of the group *Actinomyces* is an uncommon but well-recognized condition. In most cases the anaerobic species *Actinomyces israeli* is the causal organism, and infection with it usually results in localized lesions in the neck or abdomen (Cope, 1938), although on rare occasions generalized pyaemic spread occurs with multiple abscesses throughout the body (Israël, 1878; Harbitz and Grondahl, 1911; Shrewsbury, 1928). In a much smaller number of cases infection is due to aerobic filamentous organisms, most commonly *Nocardia asteroides*, which usually cause pulmonary lesions and are often associated with systemic spread (Biggart, 1934; Benbow *et al.*, 1944; Kirby and McNaught, 1946). The relative frequency of infection with the different organisms is difficult to determine, since few detailed bacteriological studies are reported and diagnosis has often been based upon the appearance of a filamentous organism in a stained film or on the presence of "granules" in pus.

Systemic spread was equally fatal in both types of infection until the use of antibiotics in treatment, and precise bacteriological diagnosis was therefore not important. Since the behaviour of the two species

towards antibiotics is different, cultural identification of the organism has become imperative, particularly in view of the possibility of complete recovery even after prolonged illness and in the presence of pyaemic dissemination as in the following case.

Case Report

The patient, a 50-year-old director, first noticed vague malaise, with loss of appetite and weight, in March, 1950. In August he had a mild fever for several days, which subsided without treatment. In October he developed left-sided chest pain, and on admission to hospital two weeks later was pyrexial and ill, but, apart from some loss of weight, there were no abnormal physical signs. A chest x-ray film showed some loss of translucency at the left costo-phrenic angle. A blood examination showed: red cells, 4,100,000 per c.mm.; Hb, 84% (12 g. per 100 ml.); white cells, 6,400 per c.mm.; blood urea, 36 mg. per 100 ml.; erythrocyte sedimentation rate (E.S.R.), 24 mm. per hour (Wintrobe). The pyrexia subsided without treatment after a week in hospital and the patient was discharged.

He remained unwell and continued to lose weight. In April, 1951, he had a further attack of chest pain, which improved after several days' treatment with penicillin. On May 24 he suddenly developed a fluctuant painful swelling in the left arm, and at about this time developed several painful whitlows. The swelling in the arm was aspirated, but the contents were sterile on culture; it continued to discharge for about two months. A chest x-ray film showed no change since October, 1950. On July 5 a painful swelling appeared in the left calf, and smaller swellings occurred on his feet and left arm before readmission to hospital on July 26. He was then febrile, ill, and wasted, and had lost 3 stone (19 kg.) in weight. There was a productive cough, with abundant purulent sputum; numerous rales and crepitations were audible at both lung bases. The liver and spleen were not palpable, and the abdomen appeared normal. The cardiovascular system was normal. A very tender, fluctuant swelling (5 by 2 by 2 cm.) was present in the left gastrocnemius; and a smaller nodule (about 2 by 1 by 1 cm.) was felt in the muscles of the left forearm. There were two flat greyish lesions about 0.2 cm. diameter in the skin at the margin of the nail bed on the left hand, and larger bluish grey lesions in the skin over the right tibia, on the medial surface of the right foot, and on the right heel. These lesions consisted of a central zone of necrotic skin (the largest was 2 by 1 cm.) surrounded by a thin, slightly raised red area and a wider diffuse zone of induration tender to touch.

A blood count showed: red cells, 4,200,000 per c.mm.; Hb, 88% (12.2 g. per 100 ml.); white cells, 7,400 per c.mm. (89.3% polymorphonuclear leucocytes). The E.S.R. was 129 mm. per hour (Westergren), and the chest x-ray film now showed diffuse miliary shadowing throughout both lung fields. The urine was normal. Aspiration of the calf abscess produced about 0.5 ml. of thick blood-stained material, containing numerous pus cells, and a Gram-positive filamentous branching organism with many smaller Gram-negative bacilli. Similar filamentous organisms were seen in the pus from all the superficial lesions, and were also present in the sputum, which contained yellowish granules. Exploration of the calf showed a thick-walled abscess cavity, containing about 40 ml. of viscous blood-stained pus in which were numerous yellow granules, which showed typical "ray fungus" on microscopical examination. The patient was first treated with intramuscular streptomycin, 2 g. a day, since infection with *N. asteroides* seemed probable. He remained pyrexial, several new lesions appeared in the extremities, and after one week 2 mega units of penicillin daily were given together with the streptomycin. The latter was replaced after 14 days' treatment by "sulphatriad," 3 g. daily, in view of the isolation of *A. israeli* from the pus and sputum, and the penicillin was increased to 4 mega units daily.

The pyrexia continued for a further two weeks and then subsided slowly. Several painless nodules appeared in the subcutaneous tissues on the arm and leg, but resolved without causing abscesses. No fresh lesions appeared after three weeks' treatment, and those that were already present healed; the sputum diminished greatly. There was no change in the radiological appearances of the chest, and the E.S.R. remained raised for several months. After about five weeks' treatment the patient had improved and had gained weight for the first time for two years. On discharge from hospital on October 17 his weight was 8 st. 10 lb. (55.3 kg.), there was neither cough nor sputum, and no abnormal physical signs were present. The chest x-ray film was unchanged and the serum proteins and sedimentation rate were still abnormal.

Daily injections of 1 mega unit of penicillin together with 2 g. of sulphatriad by mouth were continued for a further three months at home, and these were finally stopped after six months' treatment. The serum proteins and liver-function tests were still abnormal, but thereafter improved steadily. The patient returned to work in April, 1952, and has since remained well. The chest film still showed some miliary shadowing in September, 1952, although this was less pronounced.

Bacteriology and Serology

A filamentous organism was isolated from the pus from the abscesses in the gastrocnemius and on the feet and from the sputum. On primary culture in Brewer's medium it grew well in anaerobic conditions in 10% CO₂ at 37° C. The organism also grew aerobically in 10% CO₂ when it dissociated to give a rough and a smooth strain. The latter was stable, but the rough strain continued to dissociate in repeated subculture.

The primary strain, under anaerobic conditions, always gave a heavy growth of rhizoid, adherent colonies, which were just visible to the naked eye at 24 hours' incubation. After six days the colonies were 1–1.5 mm. in diameter. This strain, grown aerobically, gave a less luxuriant growth, the colonies after six days being only 0.3–0.5 mm. in diameter. The smooth dissociated strain, under aerobic conditions, gave a much more luxuriant growth than did the rough strain.

Impression colonies of both strains showed the typical appearance of actinomycetes. The rough strain was a filamentous organism which showed a typical branch formation, while the smooth strain consisted almost entirely of rod-shaped organisms. Both strains passed through the life cycle described in the case of *A. israeli* (syn. *bovis*) (Morris, 1951).

The fermentation reactions of the organisms with carbohydrates are shown in Table I, and are compared with a summary of the widely differing reactions of *A. israeli* (*bovis*) previously reported. These are listed in detail by

TABLE I.—Biochemical Reactions of the Organism

	Dextrin	Rhamnose	Dulcitol	Xylose	Starch	Aesculin	Sorbitol	Inulin	Raffinose	Arabinose	Maltose	Saltin	Mannitol	Sucrose	Lactose	Glucose	G. γ. ogen
Summarized results (Sullivan <i>et al.</i> , 1940)	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Strain under investigation	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

+ = Acid production. — = No reaction. v = Variable reaction. * = Human strains only.

Sullivan and Goldsworthy (1940). Phosphatase was produced (Morris, 1952). Acid but no gas was produced in litmus milk. Catalase was not demonstrated in the presence of hydrogen peroxide. Hydrogen sulphide was not produced, and nitrates were not reduced. No growth was obtained in 10% bile broth, in broth at pH 9.6 or pH 5, or in 6.5% NaCl broth. The organism failed to grow at

room temperature or at 45° C. Indole and Voges-Proskauer tests were negative, and the methyl-red test was weakly positive.

Complement-fixation tests have been shown to be satisfactory in the study of the *Actinomyces* (Morris, 1952). The following titres were obtained with the organism: human-strain antiserum, 1 in 1,280; bovine-strain antiserum, 1 in 640; and patient's serum, 1 in 1,280.

Discussion

There was no definite evidence to indicate the time of first infection in the present case, although it was clear that localized pulmonary infection preceded the pyaemic abscesses, which were accompanied by miliary spread throughout both lungs. Disseminated actinomycosis seems to arise from pulmonary infections, since in the more common type of abdominal and cervical lesions localization with extensive fibrosis is the characteristic feature. The nature of the primary pulmonary changes in the present case was not known, but may have been insignificant, since *A. israeli* has been isolated from the sputum in cases of chronic bronchitis (Kay, 1948).

The peripheral lesions in the present case seem to have been confined to muscle, subcutaneous tissue, and skin, for no evidence was found of spread to internal organs. This curious localization has been noted in several necropsy reports in the literature. The small necrotic subcutaneous lesions were strikingly painless, and were similar to those described in nocardial infections by Kirby and McNaught (1946). The organism showed the typical cultural and life-cycle appearances of *A. israeli*, although it was unusual in that it grew freely in aerobic culture in CO₂. This may have determined the mode of spread, since it has been claimed that systemic infection rarely, if ever, occurs with anaerobic organisms (Weed and Baggenstoss, 1949). The filaments were accompanied by a small Gram-negative bacillus in the stained film which on anaerobic culture was shown to be *Bact. actinomycetem comitans*. This organism has been claimed to be invariably associated with anaerobic actinomycetes, even in peripheral closed abscess (Holm, 1950), and to distinguish these lesions from those produced by nocardia, in which it is not found.

Serial analyses of the serum proteins were performed by Dr. J. Hardwicke. Total serum protein was estimated by the biuret method (Weichselbaum, 1946), fibrinogen by nitrogen estimation on fibrin clot (Peters and Van Slyke, 1932), and differential serum proteins by a modified technique of electrophoresis on filter paper (Kunkel and Tiselius, 1951).

TABLE II.—Plasma Protein Estimations

Date	Total Protein (g./100 ml.)	Albumin (g./100 ml.)	Globulin (g./100 ml.)				Fibrinogen (g./100 ml.)
			α ₁	α ₂	β	γ	
31/6/51	5.7	1.0	0.3	0.6	0.6	3.2	0.47
8/10/51	8.0	1.9	0.3	0.7	0.6	4.5	0.55
30/11/51	9.0	2.5	0.4	1.0	1.6	3.5	0.58
22/1/52	8.6	2.4	0.3	1.1	1.2	3.6	0.69
21/3/52	8.2	4.4	0.4	0.9	0.7	1.7	0.52
4/9/52	7.5	5.0	0.2	0.5	0.6	1.2	0.43
Mean normal values by method		4.5	0.2	0.6	0.6	0.8	0.34

On admission the total protein was low (Table II), the fibrinogen slightly raised, and the γ-globulin greatly raised. During treatment the total protein rose, with an increase in all fractions, but the high γ-globulin concentration did not fall appreciably until penicillin was discontinued, several months after clinical recovery. The serum albumin remained low until the γ-globulin fell, suggesting a possible inverse relationship between these fractions.

Similar changes in the serum proteins in chronic infections have been reported (Marrack and Hoch, 1949), and high total globulins associated with abnormal liver-function tests were described in a case of actinomycosis by Torrens and

Wood (1949). This high γ -globulin, which may be a reflection of antibody formation, probably accounts for the abnormal liver-function tests. γ -globulin has also been shown to increase the E.S.R. (Hardwicke and Squire, 1952), which in this case remained high long after clinical recovery, and made it, therefore, an unsatisfactory index of progress.

The successful treatment of localized actinomycosis with antibiotics has been widely reported, but recovery after pyaemic dissemination seems to be extremely rare. *A. israeli* is sensitive to penicillin and rarely develops resistance (Boand and Novak, 1949); streptomycin resistance usually develops rapidly. Sulphonamides are usually given with penicillin, although there is no direct evidence of synergistic action between these substances. In the present case penicillin and sulphatriad were used in combination for six months; the streptomycin given in the seven days before the identity of the organism was established had little effect. Several cases have been reported, however, of the successful use of streptomycin in those rare instances in which the strain is penicillin-resistant (Torrens and Wood, 1949; Pemberton and Hunter, 1949). The majority of strains of *Nocardia* are penicillin-resistant (Drake, 1946), but have been shown to be highly sensitive to sulphonamides and moderately sensitive to streptomycin (Glover *et al.*, 1948).

Summary

A case of generalized pyaemia with miliary pulmonary infiltration due to *Actinomyces israeli* is described.

The organism, described in detail, was unusual in showing free growth in aerobic culture in CO_2 .

During the illness gross abnormalities of the serum proteins were observed by electrophoresis on paper strips.

The patient was treated with penicillin and sulphonamides for six months and made a full recovery.

We wish to acknowledge our gratitude to Dr. Ernest Bulmer for permission to publish this case, to Mr. V. Brookes for the surgical details, and to Dr. J. Hardwicke, in receipt of a Medical Research Council grant in the Department of Experimental Pathology, University of Birmingham, for the detailed protein studies.

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At the official opening of the 38th Nurses and Midwives Conference and Exhibition in London on October 12, Mrs. Iain Macleod said that, although there were more nurses in the Health Service than ever before (147,000 full-time and 27,500 part-time, as compared with 118,000 and 17,000 respectively in June, 1948), there was still a great need for more nurses in mental hospitals and tuberculosis wards. This difficulty was being partly overcome, as more nurses were now being trained in sanatoria, but there was still a shortage in mental institutions.

ACTION OF THIOURACIL AND THYROXINE ADMINISTRATION ON ADRENAL FUNCTION

BY

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Many recent studies have shown a relation between adrenal and thyroid functions, though its nature has not yet been defined. Depression of thyroid has been found when the adrenal is stimulated by A.C.T.H., by stress, or by adrenaline, or when cortisone is given; a few authors have reported benefit to the exophthalmos of Graves's disease from cortisone administration,^{1 2} which others deny.^{27 28 29} On the other hand, in Addison's disease thyroid function is apparently also low, as shown by basal metabolic rate (B.M.R.), by plasma-protein-bound iodine (P.B.I.), and by radio-iodine uptake^{1 25}; when such patients are given cortisone there is initially thyroid stimulation, but later thyroid depression.²⁵ In myxoedema are usually found low indices of adrenal function, low urinary 17-ketosteroids, low urinary reducing and formaldehydrogenic steroids, and impaired eosinophil response to A.C.T.H.^{1 4 5 6 24}; and partial correction of these abnormalities has sometimes been reported after treatment.^{1 7} In thyrotoxicosis, involvement of the adrenal function has been long suspected, but its nature and its degree are still ill defined: 17-ketosteroid excretion is usually below normal in that condition^{4 5 7}; the excretion of reducing steroids is said to be raised,^{5 6} but low formaldehydrogenic steroid output has been reported.⁸ In animals, thyroxine administration has been found to induce a hypertrophy of the adrenal cortex.^{9 10 12 13 17} Thiouracil or thyroidectomy is said by most authors to cause an atrophy of the adrenal cortex,^{9 10 11 12 13 14 16 18 19 20} though a few have observed no change.^{15 21 22}

This paper reports some measurements of adrenal function in thyrotoxic patients, both when untreated and after control by thiouracil. To assist in differentiating any effects due solely to the thiouracil, and not dependent on its effect on thyroid function, similar measurements have also been made in patients with primary myxoedema and in one normal subject at two or more levels of thyroid dosage.

Procedure

The thyrotoxic patients were first tested in hospital untreated, and then again when the thyrotoxic features had subsided—that is, after three to six weeks' treatment and while still receiving methylthiouracil. Five out of 10 patients received methylthiouracil, 200 mg. thrice daily; the remaining five had this dosage plus L-thyroxine, 0.45 mg. daily, and 10 mg. of potassium iodide daily. The pre- and post-treatment test procedures were planned to be an identical sequence, and were performed as follows: the patients were kept in hospital for two to three days; on the first morning, after a night's rest in hospital, the first 24 hours' collection of urine was started and the eosinophil depression test with A.C.T.H. carried out. The next morning the second 24 hours' collection of urine was started, and the eosinophil depression test with adrenaline performed.

The treated myxoedematous patients under full thyroid treatment were tested in the same way on what had been