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SARCOIDOSIS IN IDENTICAL TWINS

WITH TORULOSIS AS A COMPLICATION IN ONE CASE*

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[WITH SPECIAL PLATE]

The identical twins whose histories are recorded in this paper were found to have sarcoidosis. While under observation because of sarcoidosis one of them developed torulosis (cryptococcal infection). The presenting manifestation of this infection was osteitis of one scapula, and as this resolved there was at first some hope that the infection might run a benign course—recovery from localized torulosis has been recorded several times (see Gendel *et al.*, 1950); eventually, however, the patient died of cryptococcal meningitis.

CASE REPORTS

The twins were born in 1921. They had no brothers or sisters. Their father died of asthma and pneumonia at the age of 36, their mother of coronary thrombosis when 62. Except during the war, and from 1948 to 1952, the twins lived together in Kent. Both served in North Africa during the war, and the first twin also spent some time in India.

First Twin—Sarcoidosis Complicated by Torulosis

This man, who was employed in an estate agency, married in 1946. In January, 1952, his wife had a small haemoptysis: radiography showed small, partly calcified lesions in the apical part of each lung; tubercle bacilli were found in films of one specimen of sputum, and once subsequently in gastric washings. She was treated conservatively in a sanatorium, made a good recovery, and remains in good health. A radiograph of her husband's chest in February, 1952, showed some mottling of both lung fields. He was advised to come into hospital for investigation; as he had no symptoms he delayed doing so until January, 1954.

First Admission (January 7 to February 13, 1954)

The only clinical abnormalities were two small, soft, mobile lymph nodes in the right supraclavicular fossa and one in the right axilla, very large but clean tonsils, and a nodule, about 0.5 cm. in diameter, in the skin over the fifth left costochondral junction. The scar of an inguinal herniorrhaphy, which had been performed in childhood, was healthy.

Investigations.—Chest radiograph (Special Plate, Fig. 1): extensive infiltration in lungs, predominantly in middle and lower zones; no obvious hilar enlargement. Mantoux reaction negative (0.2 ml. of 1:10 old tuberculin). Serum albumin 5.5 g., globulin 3.7 g. per 100 ml. Hb 14.9 g.

*These patients were mentioned briefly by Littman and Zimmerman (1956) on p. 37 of their monograph on torulosis.

per 100 ml. Leucocytes 7,000 per c.mm. (neutrophils 4,865, eosinophils 35, lymphocytes 700, monocytes 1,400). Erythrocyte sedimentation rate 11 mm. in one hour (Westergren). Wassermann reaction negative. Biopsy of a cervical lymph node (January 13) showed histological changes which were consistent with the clinical diagnosis of sarcoidosis (plate, Fig. 2).

Treatment.—A course of cortisone (100 mg. by mouth daily), streptomycin (1.0 g. intramuscularly three times a week), and sodium *p*-aminosalicylate (12 g. by mouth daily) was started on January 15. On February 2 the dose of cortisone was raised to 150 mg. daily.

Progress.—During the first week in hospital he had occasional slight fever in the evening; subsequently he was afebrile. After he left hospital the dose of cortisone was reduced—on February 26 to 100 mg. a day, and on March 5 to 75 mg. a day. His tonsils had become appreciably smaller by this time; there was no radiological change in his chest. On March 8 he had a rigor (temperature 101° F.=38.3° C.); he therefore stopped taking cortisone (total dose 6,400 mg. over 53 days). Rigors occurred again on the next two days and his left shoulder became swollen and painful. Examination on March 12 showed an ill-defined, fluctuant swelling, about 6 cm. across, over the left acromion; the nodule on the chest wall was also noticed to have become larger and fluctuant. The patient said that the tip of the left shoulder had become sore during his first week in hospital, a few days before starting the course of cortisone, and that the soreness had passed off after two or three days; later it recurred periodically until the sudden onset of the painful swelling at the same site. The swelling was aspirated (March 12), yielding about 50 ml. of pink fluid which was noted to be remarkably mucoid. No organisms were seen in films of the fluid, some of which was therefore inoculated into a guinea-pig; aerobic and anaerobic cultures on blood-agar were sterile after 72 hours' incubation at 37° C. A Löwenstein medium was also inoculated.

Second Admission (March 15 to May 21, 1954)

Radiological examination on admission showed irregular areas of destruction in the acromion and neck of the left scapula (Special Plate, Fig. 3). The findings in chest radiographs were unchanged. Between March 16 and 30 he received 40,500,000 units of penicillin by intramuscular injection. The swelling on the shoulder was aspirated several times at intervals of a few days, yielding mucoid, bloody fluid in amounts ranging from 10 to 50 ml.; 5 ml. of 10% sodium *p*-aminosalicylate was instilled through the needle after each aspiration. At first the fluid

reaccumulated rapidly, but by April 23 the swelling was getting smaller. The swelling on the chest wall was aspirated once (March 27), yielding 2 ml. of fluid like that from the shoulder; it then gradually disappeared. The patient's temperature was usually normal during this stay in hospital, and it never exceeded 99.6° F. (37.6° C.). Early in May the guinea-pig which on March 12 had been inoculated with fluid from the shoulder lesion was killed: the only noteworthy finding at necropsy was enlargement of a lymph node draining the inoculation site, and histological examination of this node showed suppurative lymphadenitis with morphologically typical cryptococci in the abscesses (Special Plate, Fig. 4).

Further Investigations.—May 6: Re-examination of fluid which had been kept in a refrigerator at 4° C. since it was aspirated from the shoulder on March 22 showed cryptococci in wet films. *Cryptococcus neoformans* was isolated in cultures from this stored specimen, and also from a freshly aspirated specimen and from the Löwenstein culture inoculated on March 12. No fungi or tubercle bacilli were found in gastric washings (films, cultures, and guinea-pig inoculation). Cryptococci were not isolated from sternal marrow or from 24-hour specimens of urine. The cytology of the sternal marrow was normal. The erythrocyte sedimentation rate fell from 58 mm. (March 16) to 18 mm. (May 4) in one hour (Westergren). Serum albumin 4.3 g., globulin 2.2 g. per 100 ml. Electroencephalography normal. The patient went home on May 21.*

Third Admission (July 7 to August 19, 1954)

The patient's general condition was good. The swelling on his shoulder had gradually disappeared while he was at home. His skin was healthy, and there was no trace of the lesion in the skin of the chest. Three soft, mobile lymph nodes were felt above the clavicles, and four in the right axilla. His tonsils had enlarged again. On July 21 tonsillectomy, bronchoscopy (normal), and excision of an axillary lymph node were performed; the operation wounds healed uneventfully. Cultures of both tonsils and of bronchial washings yielded *Streptococcus viridans*, *Neisseria catarrhalis*, and an unencapsulated yeast-like organism which was not studied further; cultures of the lymph node were sterile. The specimens yielded no growth on Löwenstein's medium; material from each of them was injected into mice, which remained healthy and showed no abnormality when killed 138 days later. Histological examination of the tonsils and lymph node showed sarcoid lesions identical with those in the lymph-node biopsy of January 13; no organisms were found in the sections.

Further Investigations.—Radiographs of the chest and left shoulder showed no material change since the previous admission. Radiographs of the spine were normal; calcified mesenteric lymph nodes were present. Hb 14.8 g. per 100 ml. Leucocytes 5,500 per c.mm. (neutrophils 4,345, eosinophils 165, lymphocytes 770, monocytes 220). Erythrocyte sedimentation rate ranged between 17 and 10 mm. in one hour (Westergren). As is usual in torulosis, no agglutinins to cryptococci could be demonstrated, and a cryptococcal complement-fixation test was negative.

Treatment.—Although the swelling over the shoulder had already subsided, a course of 2.575 g. of 2-hydroxystilbamidine was given by injection (July 26 to August 19). Thrombophlebitis developed in the veins used for the injections; there were no other reactions.

Progress.—The patient returned to work in September, 1954. In October he mentioned a feeling of tightness in both parietal regions; clinically there was no other change. In February, 1955, he felt well, apart from a feeling of tightness across the forehead; the only clinical abnormality was a single palpable lymph node in the right axilla; radiographs of the skull were normal, those of the chest showed

no change, and the scapular lesion had regressed considerably. By November the scapular lesion had regressed still further; the patient felt well and had no fever. In April, 1956, he began to complain of losing energy and weight. Although he looked well his temperature was 99.8° F. (37.7° C.), the tip of his spleen was palpable, and the erythrocyte sedimentation rate was 31 mm. in one hour (Westergren). He stayed at home under observation; slight fever persisted. After a month he was admitted to hospital with two weeks' history of pain above and between the eyes, stiffness of the neck and slight photophobia, with occasional vomiting. Up to this time cerebrospinal-fluid examination had always been avoided so that there might be no possibility of precipitating cryptococcal meningitis by needling the theca.

Fourth Admission (May 25, 1956)

On admission he looked ill; his temperature was 99.4° F. (37.4° C.) and his spleen reached half-way to the umbilicus. Radiography showed considerable diminution in the extent of the osteolytic lesion in the left acromion, with some restoration of the normal structure; the appearances in the chest were unchanged, and the skull and cranial air sinuses were radiologically normal. Lumbar tap: cerebrospinal fluid under normal pressure; 12 leucocytes per c.mm.; protein 50 mg. per 100 ml.; *Cryptococcus neoformans* isolated on cultivation. His temperature ranged between normal and 102° F. (38.9° C.) during the fortnight after admission.

Treatment and Progress.—"Nystatin" ("mycostatin")† was given in doses of 200,000 units in 2 ml. of 2% procaine solution twice daily by intramuscular injection between June 8 and 21 (total 4,800,000 units), and in doses of 1,000,000 units three times a day by mouth between June 8 and July 12 (total 101,000,000 units by mouth). Although the cryptococcus from the C.S.F. was sensitive *in vitro* to nystatin, the antibiotic had no clinical effect. The patient's temperature ranged between 97° and 103.8° F. (36.1° and 39.9° C.), and was seldom less than 100° F. (37.8° C.); he was troubled by frontal or occipital headache on some days, but otherwise felt well, apart from a rigor (temperature 104.6° F.=40.3° C.) on June 20. A course of 2-hydroxystilbamidine, to which the cryptococcus was sensitive *in vitro*, was started on June 20; an intravenous injection of 250 mg. was given on alternate days until July 19 (total 3,375 g.). During July the fever continued and his general condition gradually worsened; nausea and vomiting were troublesome at times and were not lessened by chlorpromazine. Mild papilloedema developed and he had periods of drowsiness and coma. Sulphadiazine was given in doses of 1.0 g. four times a day between July 7 and August 3 (total 61 g.). A second course of 2-hydroxystilbamidine was begun on August 2, 250 mg. being given intravenously every second day until August 20 (total 2 g.). There was no local or systemic reaction of any sort to this treatment. Lumbar tap on July 31: pressure 180 mm. of C.S.F., with no sign of obstruction; fluid slightly yellow; 40 leucocytes per c.mm.; protein 380 mg. per 100 ml.; chloride (as NaCl) 575 mg. per 100 ml.; large numbers of cryptococci in centrifugate; *C. neoformans* grown on culture. Lumbar tap on August 14: pressure 180 mg., with little rise with Queckenstedt's test; 20 leucocytes per c.mm.; protein 500 mg. per 100 ml.; *C. neoformans* isolated. Paper-strip electrophoresis of C.S.F. showed that most of the protein was albumin; the total globulin content was so small that it was impossible to get well-defined staining of the separate fractions; mucopolysaccharides could not be demonstrated by the method of applying toluidin blue to the paper.

The patient's condition deteriorated more rapidly after the first week in August; his temperature became subnormal and coma deepened. He died quietly on August 21, 1956, about 32 months after the first symptom of cryptococcal infection and 15 weeks after the onset of meningitic symptoms.

*Studies of the blood groups of both brothers by Dr. S. Shaw gave identical results: Group A₁; rhesus phenotype CcDee, probable genotype CDe/cde; NsNs; P+, Lu+, K-, Lea-, Leb+, Fy^a+

†We are indebted to Messrs. E. R. Squibb and Sons for supplies of this antibiotic.

Biopsy Histology

The lesions in the cervical lymph node (January 13, 1954, before treatment with cortisone) and in the axillary lymph node and tonsils (July 21, 1954) were identical (Special Plate, Fig. 2). Rounded aggregates of epithelioid histiocytes had replaced most of the lymphoid tissue. Some of the aggregates were confluent, but their individuality was readily appreciated, particularly in preparations silvered to show reticulin. Giant cells were rare. No organisms were found on examination of over 200 serial sections of each specimen (among the staining methods used were Ziehl-Neelsen, Gram, Gridley, periodic-acid-Schiff, mucicarmine, and silver impregnation), including examination by fluorescence microscopy (auramine-O preparations), dark field illumination, phase-contrast microscopy, and polarized light—all methods which may from time to time prove valuable in searching for fungi when these are scanty. There was no caseation; a few of the larger aggregates showed central fibrinoid necrosis. There was a little hyaline sclerosis around some aggregates. No Schaumann bodies or asteroides were found. The appearances were fully consistent with sarcoidosis.

Necropsy

The main findings *post mortem* were: cachectic emaciation; cryptococcal meningitis, affecting particularly the base of the brain and the cauda equina; an ill-defined pseudocyst in the acromion of the left scapula, with no detectable abnormality in the overlying soft tissues; sclerotic sarcoidosis affecting all groups of lymph nodes, the lungs, and the spleen; and heavily calcified, caseous lymph nodes in the mediastinum and in the mesentery of the small intestine. Cryptococci were demonstrated microscopically in the meningeal exudate (Special Plate, Fig. 5), and *C. neoformans* was cultivated from this exudate and from the liver, but not from the spleen, lymph nodes, lungs, or left scapula. Histological study showed that the tissue reaction in the cryptococcal meningeal lesions was predominantly of the granulomatous type, although the picture was obscured by extensive necrosis of the granulomatous tissue, particularly in the cerebral sulci and the adjacent part of the cortex; in places the picture was merely that of widespread colonization of the meninges by cryptococci, with little or no reaction to their presence. No cryptococci were demonstrated in sections of any other part of the body, although over 100 blocks of tissue were examined. The acromial lesion showed old necrosis of adipose marrow, with patchy fibrosis but no specific features; apart from a little fibrosis no abnormality was found in the soft tissues around the scapula or at the site of the former fluctuant lesion of the skin of the chest wall. The lesions of sarcoidosis were histologically typical of that condition, although predominantly in an advanced stage of sclerosis; active lesions were present in association with the sclerotic ones wherever the latter were found. The calcified, fibrocaseous mediastinal and mesenteric lymph nodes were devoid of features diagnostic of their nature, although their appearances were quite consistent with effete tuberculosis; no micro-organisms of any sort were found in them.

Mycology

The organism isolated from the patient's shoulder in 1954 showed the characteristics of a *Cryptococcus neoformans* of moderate virulence as defined by Benham (1956). On primary isolation it possessed a well-defined capsule; it grew well on peptone-maltose agar and blood agar at 37° C., but not at room temperature: it fermented glucose, saccharose, and maltose, but not lactose. The guinea-pig which was inoculated on March 12, 1954, with the first aspirate was killed 41 days later when still apparently well; cryptococci were found only in the lymph node draining the inoculation site, and sections of the spleen, liver, lungs, heart, and kidneys were normal. The findings were similar in a guinea-pig which was killed 41 days after inoculation with aspirate on May 6.

Cultures of the cryptococcus which was isolated from the aspirate of May 6 were inoculated into the peritoneal cavity of three mice on May 17. Torulosis was subsequently confirmed in two of these mice, with typical cerebral involvement in one. In subsequent experiments the organism gave rise to a variant form which caused rapidly fatal disseminated torulosis in mice.

The cryptococcus isolated from the cerebrospinal fluid during the final stages of the patient's illness, and from the tissues at necropsy, showed the same features as the original strain in this case. An india-ink preparation of the cerebrospinal fluid, showing *C. neoformans* with typical halo-like capsules, is illustrated in Fig. 5 of the Special Plate.

Unencapsulated yeasts which were isolated from a 24-hour specimen of urine on May 21, 1954, and from the tonsils and bronchoscopic washings on July 21, 1954, were thought to be commensals, of no pathological significance.

Blood-agar plates which had been planted with fluid aspirated on March 27, 1954, from the lesion on the chest wall yielded a very scanty growth of yeasts. As no yeasts were seen in films of this specimen the organisms which were grown were considered to be contaminants; they were not investigated further.

The cryptococcus isolated from the scapular lesion in 1954 was sensitive *in vitro* (plate test) to 2-hydroxystilbamidine isethionate, bis-(2-hydroxy-3,5-dichlorophenyl) methane, methyl *p*-hydroxybenzoate, undecylenic acid, chlorphenesin, diamidinodiphenylamine dihydrochloride, mersalyl, anemonin, and mercaptomerin. It was resistant to sulphadimidine, penicillin, streptomycin, chloramphenicol, chlortetracycline, oxytetracycline, sodium propionate, and *p*-aminosalicylic acid.

The cryptococcus isolated from the C.S.F. in 1956 was sensitive *in vitro* to nystatin, 2-hydroxystilbamidine isethionate, and "novex"; it was resistant to sulphadiazine and *p*-aminosalicylic acid. There was no evidence of synergism or of antagonism between nystatin and the stilbamidine preparation.

Second Twin—Sarcoidosis

This patient, who is a clerk, was the identical twin of the first patient. When his sister-in-law was found to have tuberculosis he was advised to have his chest radiographed. He delayed taking this advice until February, 1954. The picture showed mottled shadowing in both lungs, mainly in the middle zones, with collapse of the basal part of the right upper lobe; there was no evident enlargement of the hilar lymph nodes. He was admitted to hospital for investigation.

First Admission (April 20 to May 18, 1954)

He had no symptoms other than mild, vague "indigestion." His health had always been good; he broke a rib at games in 1951, and radiography at that time showed no evidence of lung disease. The only clinical abnormalities on admission were a large mobile lymph node above each clavicle, a smaller node behind the left sternomastoid and one in the right axilla, and a few rales high in each axilla. His tonsils were normal. There was a healthy scar where a meibomian cyst had been excised some years earlier. He had no fever.

Investigations—Mantoux reaction negative (0.2 ml. of 1:10 old tuberculin). Hb 16.3 g. per 100 ml. Leucocytes 5,200 per c.mm. (neutrophils 3,925, eosinophils 25, basophils 50, lymphocytes 700, monocytes 500). Erythrocyte sedimentation rate 6 mm. in one hour (Westergren). Serum albumin 5.1 g., globulin 2.2 g. per 100 ml. Biopsy of a supraclavicular lymph node (April 23) showed a picture of sarcoidosis, indistinguishable from that in the biopsy specimens from his brother; no organisms could be demonstrated in sections examined by the methods used in the case of the brother's biopsies; no specimen was available for culture. Gastric washings: no tubercle bacilli or yeasts found (films, cultures, and guinea-pig inoculation). No organisms in films or cultures of bone marrow and of 24-hour specimens of

urine. Cytology of sternal marrow normal. Wassermann reaction negative. Radiographs of shoulders, spine, and pelvis normal.

Treatment.—Streptomycin (1 g. intramuscularly daily, April 29 to May 14; thereafter, thrice weekly until June 14) and sodium *p*-aminosalicylate (18 g. daily, April 29 to June 14) were given.

Progress.—He was seen regularly as an out-patient after leaving hospital. At the end of 1954 he had a short neuritic episode, with pain in the left shoulder on moving his head, "pins-and-needles" and numbness in the left thumb, and loss of sensation to pin-prick on the medial aspect of the back of the left hand and forearm. Radiographs showed no abnormality of the cervical spine and shoulders. His general condition remained good, although there was no change in the radiological findings in the lungs; lymph nodes in the neck, axillae, and groins were transiently enlarged, and in June, 1955, the spleen was just palpable. Throughout these months he had periodic bouts of aching in the right iliac fossa after meals.

Second Admission (November 4 to December 3, 1955)

He was readmitted because of the persisting complaint of abdominal pain, which culminated in a severer attack than usual a fortnight before admission. This attack was associated with malaise and shivering, and he took to bed. For some days he vomited often, and was able to keep only fluids down. He had no fever while in hospital; there was slight tenderness in the lower part of the abdomen, particularly in the right iliac fossa, and slight enlargement of the seminal vesicles. Moderately enlarged, mobile lymph nodes were present in the neck and axillae.

Investigations.—Radiological examination after a barium meal showed that the terminal loop of the ileum, while mobile, had a fixed S-shape, which suggested the possibility of adhesions to a mass of lymph nodes or to the mesentery. Chest radiographs showed no definite change since April, 1954. Hb 14.7 g. per 100 ml. Leucocytes 8,200 per c.mm. (neutrophils 6,070, eosinophils 165, lymphocytes 1,640, monocytes 325). Erythrocyte sedimentation rate ranged between 13 and 18 mm. in one hour (Westergren). Repeated examination of vomitus, faeces, and urine (including mid-stream specimens of urine obtained after massage of the seminal vesicles and prostate) showed no tubercle bacilli, fungi, or other pathogens (films and cultures). Intravenous pyelography revealed no abnormality of the renal outlines or of the calices and pelves. Urine normal.

Progress.—His symptoms gradually subsided without special treatment. It was thought that they were due to sarcoidosis affecting the abdominal lymph nodes. He felt well and had no symptoms when he left hospital. In March, 1956, the spleen was palpable, but the superficial lymph nodes were considerably smaller than on any previous examination; the wall of the caecum was readily felt and was thought to be thickened; the chest radiographs were unchanged, and he felt well. In April, 1957, his condition was reported as unchanged.

Comment on the Cases

These identical twins were found to have sarcoidosis at about the same time. It is conjectural whether the tuberculous infection from which the wife of the married twin suffered was related to their illness. It is interesting that calcified lymph nodes, suggestive of past tuberculous lymphadenitis, were found radiologically and at necropsy in the first case. Sarcoidosis has been observed in at least three other pairs of identical twins (Sherer and Kelley, 1949; Gilg, 1952; Rogers and Netherton, 1954); sarcoidosis in other siblings has been reported by several authors, whose cases are referred to by van Zwanenberg and Barry (1955) and by Swirsky and Lowman (1955).

The original diagnosis of cryptococcal osteitis in the first case was established, in our view, beyond any reasonable doubt, although at necropsy no specific evidence of infection

of the bone remained demonstrable. The radiological findings were remarkably similar to those of cryptococcal acromial osteitis illustrated by Collins (1950). Cryptococcal osteitis is not uncommon in cases of torulosis (see Gosling and Gilmer, 1956). No other evidence of torulosis was found in our case at first, with the possible exception of the lesion on the chest wall, the nature of which was unproved. The clinical history suggested that the cryptococcal bone infection was already manifest before the course of cortisone was started. It is debatable whether cortisone in any way affected the progress of the infection, although the liability of infective conditions to advance rapidly in patients taking cortisone makes it possible that resistance to the cryptococcal infection was lessened in this case. Israel *et al.* (1954) drew attention to the risk of aggravating fungal infections by giving cortisone, and their observations have been repeated by others. The hormone was given to our patient with the hope that the sarcoidosis might be favourably influenced and the risk of pulmonary fibrosis reduced. There have been many reports indicating that treatment with corticotrophin or cortisone may be beneficial, particularly in cases of extra-pulmonary sarcoidosis with symptoms of short duration (Israel *et al.*, 1954). Substantial improvement in certain cases of pulmonary sarcoidosis treated with streptomycin, *p*-aminosalicylic acid, and cortisone was observed by Hoyle *et al.* (1955). The only evidence that treatment influenced the lesions of sarcoidosis in either of our twin patients was the temporary, but striking, shrinkage of the tonsils in the one who received cortisone. In view of the manifestation of cryptococcal infection during treatment of his brother with cortisone this drug has not been given to the second twin.

There is no evidence that any of the antibiotics or other drugs affected our patient's cryptococcal infection in any way. The organism was resistant *in vitro* to *p*-aminosalicylic acid, streptomycin, and penicillin, of each of which the patient had received full courses before the cryptococcal infection was recognized; it was sensitive *in vitro* to 2-hydroxystilbamidine, but clinical manifestations of the bone infection had already subsided before this drug was first given, and neither it nor nystatin had any effect on the meningitis. The ineffectiveness of treatment conforms with the published experience of others (see Littman and Zimmerman, 1956), although Leithold *et al.* (1957) have suggested that 2-hydroxystilbamidine was responsible for the "apparent cure" (15½ months' observation without evidence of recurrence) of the cryptococcal infection in their patient with sarcoidosis.

This is the nineteenth case of torulosis in this country. References to the first ten cases have been given elsewhere (Symmers, 1953); one of these cases (Galton and Whittick, 1950) has now been described in detail (Lumb, 1954). Eight further cases are on record (Cruikshank and Harrison, 1952; Pierce, 1953; Spencer, 1954; Caldwell and Raphael, 1955; Beck *et al.*—2 cases; Levene and Michaels, 1955; Misch, 1955), and several unpublished cases are known to us.

As is usual with torulosis, the source and portal of entry of the infection are unknown in our case. The natural environment of *C. neoformans* is not known; pathogenic strains have been isolated from soil (Emmons, 1951) and from pigeon nests and droppings (Emmons, 1955). Spontaneous infections occur in animals, but seem to be uncommon (literature: Skulski and Symmers, 1954); the only animal infection so far reported in Britain was in a pet ferret (Skulski and Symmers, 1954), although Carter and Young (1950) isolated pathogenic cryptococci from cow's milk in Scotland.

DISCUSSION

The occurrence of cryptococcal infection in a patient with sarcoidosis is of particular interest in view of the occasional association between other diseases of the lymphoreticular system and torulosis. Torulosis and sarcoidosis have been associated in only a small number of published cases—a case mentioned briefly by both Collins (1950, Case 3) and

N. S. PLUMMER *ET AL.*: SARCOIDOSIS IN IDENTICAL TWINS

FIG. 1.—Extensive infiltration in lungs, predominantly in middle and lower zones (January, 1954).

FIG. 2.—Lymph-node biopsy (January, 1954): sarcoidosis. (Haematoxylin and eosin. $\times 133$.)

FIG. 3.—Irregular areas of destruction in acromion and neck of left scapula (March, 1954).

FIG. 4.—Lymph node from guinea-pig: suppurative lymphadenitis following inoculation with aspirate from patient's shoulder. Five cryptococci seen; the clear space around each organism represents its mucoid capsule. (H. and E. $\times 625$.)

FIG. 5.—India-ink preparation of cerebrospinal fluid, showing cryptococci with their typical capsular halo. ($\times 680$.)
(All illustrations refer to first twin.)

T. J. MILLS: FRACTURES OF RADIUS

FIG. 1a.—Smith's fracture of radius.

FIG. 2a.—Anterior marginal fracture of radius.

FIG. 1b.—End-result of treatment of Smith's fracture.

FIG. 2b.—End-result in anterior marginal fracture.

Fisher (1950, Case 2), a case described by Gandy (1950), two cases illustrated by Littman and Zimmerman (1956), a case described by Lepow *et al.* (1957), that reported by Leithold *et al.* (1957), and a further case which Littman and Zimmerman (1956) mentioned and which they said would be reported by Heller, McLean, Campbell, and Jones (1957). Torulosis has repeatedly been observed in cases of Hodgkin's disease and other malignant diseases arising in the lymphoreticular system; Zimmerman and Rappaport (1954) reviewed this association, and from their study of the cases filed in the Armed Forces Institute of Pathology at Washington D.C. presented evidence which strongly supports the belief that the mycotic infection in such cases is a complication of the primary disease of the lymphoreticular system and not its cause. This evidence has recently been briefly summarized (Symmers, 1957). A comparable association between histoplasmosis infection and the malignant diseases of the lymphoreticular system has been described (Cawley and Curtis, 1948; Murray and Brandt, 1951; Zimmerman, 1955; Nelson *et al.*, 1957). To our knowledge the occurrence of histoplasmosis in association with true active sarcoidosis has not been recorded, although histoplasmosis has been known to mimic sarcoidosis and has been reported in the case of a patient who had developed sarcoidosis previously (Symmers, 1956).

It was noted by Zimmerman (1955) that patients with malignant diseases of the lymphoreticular system, like patients with other debilitating diseases, are liable to develop aspergillosis, moniliasis, and mucormycosis. He suggested that an increased incidence of these three mycoses, and in particular of their disseminated forms, might be related to the increased use of antibiotics, chemotherapy, and hormone therapy; these therapeutic factors do not seem to have altered the incidence of torulosis and histoplasmosis. One of us (N. S. P.) has under observation two patients who have sarcoidosis with advanced pulmonary fibrosis and from whose sputum *Aspergillus fumigatus* has been isolated repeatedly. The diagnosis of sarcoidosis has been well substantiated in one of these cases, but in the other there has been no biopsy; it is likely that the fungus is saprophytic in these cases. At the London Chest Hospital Dr. K. F. W. Hinson has shown us preparations from another case of sclerosing pulmonary sarcoidosis in which a bronchiectatic cavity contained a "mycetoma" formed of masses of fungus with the typical morphology of *Aspergillus* (see Hinson *et al.*, 1952).

It is pertinent to the finding of fungi in cases of sarcoidosis that the supposed fungal nature of the structures described by Hallberg (1943) in lesions of sarcoidosis is very doubtful. Similarly, Törnelli's (1946) interpretation of the pathogenetic significance of *Candida*, which he found in the respiratory tract of patients with sarcoidosis, is questionable. Unless specifically sought, the presence of a complicating fungal infection in any case of sarcoidosis might easily be overlooked. It is possible that appropriate investigation of all biopsy and necropsy material from cases of sarcoidosis—and, indeed, of any disease affecting a considerable part of the lymphoreticular system—would reveal more instances of associated infection, including fungal infections: we would urge that all such material should be investigated bacteriologically and mycologically as well as histologically.

Summary

The occurrence of sarcoidosis in identical twins is recorded. The wife of one of them had pulmonary tuberculosis. One twin developed osteitis of the scapula, symptoms of which appeared to antedate a course of cortisone, although the latter may have aggravated the infection: *Cryptococcus neoformans* was isolated from a subcutaneous pseudo-abscess which formed over the bone. The patient died of cryptococcal meningitis 32 months later. Treatment, including administration of nystatin (mycostatin) and 2-hydroxystilbamidine, was unavailing.

We should like to thank Dr. C. R. H. Weekes, Tunbridge Wells, for referring these two patients to us, Dr. A. P. Barter for help with the clinical study, and Dr. S. Shaw for some of the laboratory investigations.

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SMITH'S FRACTURE AND ANTERIOR MARGINAL FRACTURE OF RADIUS

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[WITH SPECIAL PLATE]

Smith's fracture and the anterior marginal (or reversed Barton's) fracture are relatively rare, and it is because of their rarity that their treatment needs to be discussed.

The former fracture was first described by R. W. Smith (1847), a Dublin surgeon, as "a fracture of the lower end of the radius—from half an inch to an inch above the articulation—with displacement of the lower fragment along with the carpus forwards" (Special Plate, Fig. 1). The inferior radio-ulnar joint is disrupted and the triangular fibrocartilage torn, or the ulnar styloid is avulsed. The deformity has been likened to a garden spade, there being a dorsal prominence over the distal end of the upper fragment and a fullness of the wrist on the volar aspect due to the displaced distal fragment. The head of the ulna is prominent on the dorsum of the wrist (Fig. A). The injury is caused by a fall on the back of the wrist.