CRYPTOCOCCAL MENINGO-ENCEPHALITIS

BY

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Busse (1894, 1895, 1896) and Buschke (1895) reported the presence of yeast-like organisms in a 31-year-old woman with a "gumma-like" or sarcoma-like affection of the tibia. She also had lymphadenopathy and secondary skin lesions followed by involvement of the knee-joint; after death multiple lesions in the bones, skin, lungs, spleen, and kidney were found. Vuillemin (1901) differentiated this organism from the true yeasts and named it *Cryptococcus hominis*. Versé (1914) reported what was believed to be the first human case of cryptococcosis of the nervous system diagnosed before death. He recorded an extensive leptomeningitis in a woman of 29 years.

The consensus of opinion of medical mycologists is that the most suitable name for the pathogen is *Cryptococcus neoformans*. *C. neoformans* is the organism most often present in mycotic meningitis cases in man. It is found in milk and milk products, in fruit, on the skin, and in the mouth. The disease is thought to be rare; most cases are reported from America and Africa. The recorded cases do not represent the true incidence, for many have been misdiagnosed as lymphocytic, tuberculous, or syphilitic meningitis.

Because of the infrequency with which these cases are reported and the greater use of antibiotics, which is likely to increase the incidence of fungal diseases, the following case is put on record.

Case Report

The patient, a boy aged 4 years, was born of West African parents. His mother, a qualified nurse, had him immunized against all the common conditions, including poliomyelitis and tuberculosis. In March, 1960, she noticed a rash on his face which she thought was a fungal infection, and treated it with local applications of nystatin.

On September 1 he had a fall and sustained a head injury. That evening he complained of frontal headache and vomited. Subsequently he remained well until September 7, when there was a recurrence of frontal headache and vomiting, and he had vague abdominal pain. This persisted until September 10 and culminated in a convulsion, followed by pyrexia.

On admission to a general hospital his temperature was 100° F. (37.8° C.), but no localizing signs in the central nervous system, apart from abnormal irritability. A tentative diagnosis of subdural haematoma was made and he was kept under observation. Investigations showed: E.S.R., 15 mm./1st hour (Wintrobe); Hb, 12.1 g./100 ml. (82%); W.B.C., 14,100 (P.74%, L.21%, M.5%); Mantoux test 1/1,000 was negative in spite of B.C.G. inoculation.

By September 12 he had marked signs of meningeal irritation, screaming episodes, and continued pyrexia. A lumbar puncture produced fluid at normal pressure which contained R.B.C. 42/c.mm., W.B.C. 64/c.mm. (all lympho-

cytes), protein 10 mg./100 ml., sugar 84 mg./100 ml., and chlorides 680 mg./100 ml. Next day his symptoms became worse. Examination of the fundi revealed nothing abnormal. Lumbar puncture was repeated, the findings being: R.B.C. 635/c.mm., W.B.C. 112/c.mm. (all lymphocytes, protein 10 mg./100 ml., sugar 75 mg./100 ml. At this stage a diagnosis of "non-specific lymphocytic meningitis" was made and he was treated symptomatically. Virological studies were undertaken, with negative results.

On September 14 his speech became slurred. He was drowsy and incontinent of urine. Generalized muscular weakness and flaccidity of limbs developed. The fundi remained normal, but pupillary reaction to light became very sluggish, and there was well-marked ptosis of the left eye. He then developed difficulty in swallowing, with accumulation of saliva in the throat. Meningo-encephalitis with bulbar palsy was suspected, and as his condition continued to deteriorate steroid therapy was begun. On September 15 he was transferred to Neasden Hospital, the regional centre that dealt with bulbar palsies.

On examination at Neasden Hospital the patient was found to be fully conscious but irritable. The skin was clear, his rectal temperature 98.6° F. (37° C.), and his throat intensely congested, with enlarged tonsils showing a fair amount of exudate. He asked for ice-cream, which was immediately offered to him. He swallowed quite well, and as he had gained confidence examination of the central nervous system was not difficult. The fundi were normal; there was marked ptosis of the left eye; the left pupil was much larger than the right and its reaction to light was impaired; and conjugate eye movements were normal. The

FIG. 1.—Photomicrograph of a nigrosin film, showing budding cryptococci.

FIG. 2.—Photomicrograph of a section of cortex. Arrows point to capsulated spheroidal cryptococci.

palate moved well on phonation, and his speech, though slow, had no nasal element. All sensations seemed normal, but he had a complete areflexia. Although there was generalized flaccidity of limbs, voluntary movements were possible. The diaphragm and intercostal muscles acted well. There were no other physical signs of any significance.

The chest x-ray picture was within normal limits. Hb was 9.9 g./100 ml. (67%); the blood group B, rhesus-positive; and there was no evidence of sickle-cell trait. Urine showed a trace of albumin only, porphyrins were not detected. Throat culture did not grow *Corynebacterium diphtheriae* or haemolytic streptococci. A direct smear from the throat was negative for organisms of Vincent's angina, candida, and yeast cells. A lumbar puncture was not performed immediately as he had had one so recently.

His condition remained unchanged until September 17, when he gradually lapsed into coma—that is, about 36 hours after admission. At this stage a lumbar puncture yielded a slightly turbid fluid that was at first reported to contain R.B.C. 88/c.mm., lymphocytes 72/c.mm., and 322 other cells per c.mm., which were thought to be “endothelial cells.” All other constituents of the cerebrospinal fluid were normal. This sounded very suspicious, and on request a smear was made and stained with indian ink. This revealed that the so-called “endothelial cells” were in fact cryptococci (later identified as *C. neoformans* by the London School of Hygiene and Tropical Medicine). A photomicrograph of a nigrosin film is shown (Fig. 1).

Treatment.—Until the diagnosis was made the child was treated symptomatically. Steroid therapy had started before admission. He had two 5-mg. doses of prednisolone while under our care, and tetracycline 250 mg. six-hourly. At first he was taking “complan” well by mouth, with added vitamins. When he became drowsy, feeding was continued via a plastic naso-gastric tube. Thus his water-and-salt balance was kept within normal limits, and, as soon as the diagnosis was made, specific therapy was instituted. He was given amphotericin B, 0.5 mg. in 5 ml. of water intrathecally, and 20 mg. in 250 ml. of 5% dextrose by intravenous drip. Unfortunately he died on the evening of September 17.

Necropsy Findings.—The C.S.F. was turbid, and, apart from a slight oedema of the brain tissue, there was no macroscopic evidence of any inflammatory reaction. Microscopically there was slight swelling of the pia-arachnoid, a few scattered leucocytes and plasma cells, but a large number of capsulated spheroidal cryptococci (Fig. 2). Other findings were a terminal bronchopneumonia, early pericarditis, and peritonitis. The suprarenals were healthy.

Discussion

Fungal infections are perhaps more common since the introduction of antibiotics. Unless blastomycotic skin lesions are present the possibility of visceral fungal invasion is apt to be overlooked. We did not think of it until a verbal report was received on the C.S.F. from a lumbar puncture performed 36 hours after admission to Neasden Hospital. The fact that protein, sugar, and chlorides were found to be within normal limits points to an inherent inability of the cryptococcus to give rise to any immediate acute inflammatory reaction. This apparent failure of the primary defence mechanism appears to be associated with low antigenicity of a number of fungi. Cryptococci may invade tissues and multiply by budding without giving rise to an inflammatory reaction, because they do not seem to produce an exotoxin. After a varying length of time their mere presence in larger numbers comes to be regarded as foreign bodies which lead to an infiltration with round cells and macrophages (usually with giant-cell formation), and so a granulomatous lesion is produced. In cryptococcal meningo-encephalitis, granulomata are

usually found at the base of the brain, but these were not present in our patient. Therefore the spinal fluid is not likely to show much alteration other than a marked pleocytosis, as in our case, and consequently the diagnosis depends on the detection of the yeast-like cells.

There are conflicting reports that complement-fixing antibodies are present in the serum of patients suffering from cryptococcosis. Neill *et al.* (1949, 1951) claim to have demonstrated precipitins in the spinal fluid, urine, and blood of patients, and a specific capsular reaction in immune rabbit serum. Diagnostic hypersensitivity skin tests have also been described, but are unreliable (Evans and Theriault, 1953).

It will be recalled that there was a vague history of fungal infection of the face which was treated locally with nystatin. It is possible that this may have been the site of the original infection, and presumably dissemination was either embolic or through the respiratory or the intestinal tract. Approximately 80–90% of patients with cryptococcal meningo-encephalitis die within the first year, many within six months, of the onset of neurological manifestations (Littman and Zimmerman, 1956). Some, however, live a considerable time in spite of the presence of viable cryptococci in the C.S.F.

In assessing the efficacy of new fungicidal drugs, the fact that natural remissions occur must be remembered, and these necessitate a prolonged period of observation. Many antibiotics and other drugs have been used without great success, including streptothricin and actidione. Recently amphotericin B (“fungizone”) has given more encouraging results, especially when the nervous system is not involved. Martin *et al.* (1959) described five cases of cryptococcal meningo-encephalitis which were given 50–100 mg. of the drug dissolved in 250–500 ml. of 5% dextrose solution intravenously daily for six weeks. In three cases the condition appeared to be arrested, but relapse occurred in the remaining two. Pimstone and Saunders (1959) note that intrathecal administration of the drug in a dose of 0.5–1 mg. in 5 ml. of distilled water may be used when the central nervous system is involved, and is said to produce a C.S.F. fungicidal level for 24–48 hours.

Summary

A case of cryptococcal meningo-encephalitis with post-mortem findings is described.

The known low antigenicity of *Cryptococcus neoformans* is correlated to the pathological findings—namely (a) in the central nervous system there were only a few scattered leucocytes and plasma cells in spite of the presence of a large number of cryptococci; and (b) during life the cerebrospinal fluid showed red blood cells, lymphocytes, and cryptococci, but protein, sugar, and chlorides were normal. This suggests a host-parasite armed neutrality with unpredictable dissemination at any time.

Ultimate prognosis seems to be uniformly bad, and one must admit that, at present, specific treatment is far from satisfactory.

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RAPID SELECTION OF GROUP A RECIPIENTS AMONG MASS CASUALTIES

BY

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One of the major advances in medicine in the 1939-45 war was the development of an efficient blood transfusion service which was able to provide an adequate supply of group O blood for the emergency treatment of casualties. In the event of another major conflict, the use of atomic and nuclear weapons is likely to result in much heavier civilian and military casualties with consequently a much increased demand for blood.

The use of suitable group O blood only for the emergency transfusion of casualties has one great advantage—namely, that the blood can be given without knowledge of the patient's blood group and without prior cross-matching. In the 1939-45 war disasters from incompatible blood transfusion were almost unknown (Whitby, 1953), and in Korea most of the recorded transfusion reactions followed the use of locally procured blood instead of the doubly checked group O blood which was normally supplied (Crosby, 1955). A major criticism of restricting blood used for casualties to group O only is that it results in an unbalanced utilization of the donor panel; for, in the United Kingdom, only some 47% of the population belong to group O and 42% are group A, 8% group B, and 3% group AB (Dobson and Ikin, 1946).

From the distribution of the ABO groups, it can be seen that if group A blood could be used, it would be possible nearly to double the supply of blood available for the emergency treatment of mass casualties. The essential requirement for such a scheme is a rapid yet reliable method of distinguishing group A and AB casualties, who could receive group A blood (A recipients), from group O and B casualties, who would still require group O blood (O recipients).

Zeitlin (1954) described a method of selecting group A recipients by a simple test which consisted of adding one drop of tap-water and one drop of patient's blood to a slide coated with potent anti-A serum and watching for microscopic agglutination, which occurred within one minute with groups A and AB. For urgent cases,

especially obstetrical emergencies, Zeitlin suggested the use of O and A rhesus-negative blood for O and A recipients respectively. He also suggested that the method of dividing emergency cases into two major groups according to the reaction obtained with a single test serum had an obvious practical application in large-scale emergency work—for example, in dealing with civilian or military casualties, rail accidents, and the like. Akeroyd and Crosby (1955) have discussed the advantages of using Zeitlin's method to increase the supply of blood in the event of war or a major disaster.

This paper describes three trials which were carried out to test the feasibility of rapidly selecting A recipients under field conditions. Similar trials have been conducted by J. H. Akeroyd (1958, personal communication) in America, and by H. C. Jeffrey (1960, personal communication) with British troops in Germany.

The Trials

Trials 1 and 2.—These trials were carried out in 1957 with the co-operation of a field ambulance which organized two night exercises involving the admission and documentation of "casualties" at the rate of approximately one a minute. Blackout conditions were observed. The reception tent was lit by pressure lamps and hurricane lamps only. Blood-grouping was carried out by two teams, each consisting of two laboratory technicians with considerable experience in blood-grouping. Blood was obtained from each "casualty" by finger-prick. One drop was placed on a Zeitlin slide together with one drop of water and the slide examined for agglutination after one minute. In addition, a few drops of blood were added to a tube containing normal saline. The cell suspensions were ABO blood-grouped next day in the laboratory by the tube method.

In the first trial the personnel reading the slide tests often experienced difficulty in deciding whether or not agglutination was present, and this difficulty was greatest in those parts of the reception tent where the lighting was poorest. For the second trial electric head-lamps were used; these gave satisfactory illumination, making agglutination, if present, obvious.

Trial 3.—This was carried out in 1960 at a Territorial Army training camp. On this occasion liquid anti-A serum was used. Fingers were swabbed with iodine in 70% alcohol and a separate sterile disposable needle ("seralet") was used for each individual. A drop of blood was collected on to a clean slide and one drop of anti-A serum added. The blood and serum were mixed by means of the disposable needle and the slide was examined for agglutination after one minute. An electric head-lamp was used for illumination when the tests were carried out after dark. At the same time a few drops of blood were collected into glucose-citrate solution. The slide groupings were performed by day and by night under a variety of conditions—that is, in tents, huts, vehicles, and in the open. The first few tests were read by me, but most were carried out by a nursing orderly and an infantry private soldier, neither of whom had had any previous experience in blood-grouping. The only instruction these two men received was a short explanation at the beginning of the trial and a demonstration on the first few groupings carried out. The cell suspensions were forwarded to the East of