TORULOSIS OF THE CENTRAL NERVOUS SYSTEM.

By DONALD BLAIR, M.A., M.D.Cantab., D.P.M.Lond.,

Assistant Medical Officer, L.C.C. Mental Hospital Service.

[Received October 22, 1942.]

IN March, 1939. there was admitted under my care at the St. Pancras Hospital Mental Observation Unit a case of torulosis of the nervous system. This is a very rare disease in this country and the present case is only the third recorded in British medical history (Greenfield *et al.*, 1938 ; Smith and Crawford, 1930), and the first one to have come under mental hospital supervision. Although such a rarity here, torulosis is more common in the United States, and cases have been reported from nearly every part of the world.

A thorough search into the literature on this subject led me to believe that cases may sometimes be missed through ignorance of the clinical and pathological features of this infection. This paper is written with the object of presenting a picture of the outstanding characteristics of torulosis of the nervous system in the hope that if these are more generally appreciated, cases will be diagnosed which might otherwise have been missed.

HISTORY AND NOMENCLATURE.

Fungus diseases of the nervous system have been described since the early days of bacteriology and pathology. Originally, however, pathologists attributed to fungi many infections really due to cocci ; consequently fungus infections fell into such disrepute as to be considered almost non-existent. It is quite likely that cases of fungus infection are more frequent than we think.

The first indisputable case of infection of the human central nervous system by a higher fungus was demonstrated by Zenker in 1861. Since then sporadic and infrequent cases of invasion of the nervous system by several different forms of fungus have been described. In 1916 Stoddard and Cutler first differentiated the characteristics of torulosis, which was subsequently found to be the commonest form of fungoid infection of the central nervous system.

Various names have been appended to the organism producing this disease. Stoddard and Cutler correctly realized that it was related to examples of torula occurring elsewhere in nature (Fotheringham, 1902 ; Henrici, 1930), and christened it *Torula histolytica*. Greenfield (1924), on the other hand, refers to it as *Cryptococcus hominis*, and such synonyms as *Torulopsis hominis* and *Saccharomyces tumefaciens* have also been used. I propose in this article to retain the original name "Torula," but since Freeman (1931) has shown that " histolytica " describes the characteristic of the organism erroneously, we shall refrain from the use of doubtful adjectives.

GENERAL PATHOLOGY.

The organism is a pseudo-yeast, several species of which have been known for many years to infect animals. Although it is said frequently to inhabit the human nasopharynx (Jones, E. L., 1920), and intestinal canal (Anderson, 1917) saprophytically, it is fortunately seldom pathogenic to man. It is, broadly speaking, differentiated from other infectious fungi by the absence of mycelation and sporulation, the process of budding as a means of reproduction and its poor fermentative powers.

Torula may infect the central nervous system (*a*) specifically and alone, (*b*) in combination with systemic lesions elsewhere, (*c*) combined with pulmonary lesions

https://doi.org/10.1192/bjp.89.374.42 Published online by Cambridge University Press

only. Reporting on the 60 cases of torulosis described in the literature up to that date, Levin (1937) found that 30 (50 per cent.) cases had been confined to the central nervous system alone, 9 (15 per cent.) of the others were associated with lesions of the lungs only, and 8 (13 per cent.) with a generalized systemic infection. Other organs involved in association with the central nervous system were : Kidney (2), spleen (1), adrenal glands (1), abdominal lymph glands (1), peribronchial lymph glands (1), tonsils (1), subcutaneous tissue (1) and skin (5). Others have described involvement of the thyroid, bone marrow and prostate.

The occurrence of skin lesions in this series is interesting, since other authors (Freeman, 1931 ; Stoddard and Cutler, 1916) have claimed non-involvement of the skin as a primary lesion to be one of the differentiating distinctions of torula infection from other fungus infections. Mitchell (1936) has drawn attention to the association of torula infection and Hodgkin's disease in certain patients, even going as far as to point out the similarity of the clinical appearance and histological reaction in the two diseases. In certain cases, tuberculosis of the lungs has co-existed with a torula infection of these organs (Freeman, 1931).

The organisms vary very considerably in their size from one case to another. At one end there are minute rounded bodies scarcely one micron in diameter, and at the other large bodies 40 to 50 microns across. Their shape under the microscope is round or oval. They all have a capsule, but here again their characteristics differ. Some have a well-marked capsule which may be as thick as twice the diameter of the body itself, so that the organism has the appearance of being surrounded by a halo of clear space. At the other extreme it is only with a very careful search under the high-power microscope that any capsule at all is found. Any intermediate grade may occur.

Staining Reactions.

Haematoxylin and eosin usually stains the organisms a bright blue, but sometimes pink, and not infrequently fails to stain them at all.

The aniline dyes (thionin and methylene blue) stain most of these organisms darkly, but some of them remain unstained.

Gram's stain.—The organism reacts in an amphophilic manner, many organisms staining darkly, but others becoming pink. The capsule stains in a characteristic manner which reveals multiple radiations traversing it.

Cultivation.

The organisms will grow on almost any medium at room temperature of 37° C., but thrive best on blood-agar, Loeffler's medium and Sabouraud's medium (maltose agar). In all three they grow at the bottom of the tube and do not turn it turbid. The appearance of the colonies may be likened to elevated and piled-up droplets of boiled starch.

Animal Inoculation.

Transference of the infection to animals is frequently the only reliable way to effect a diagnosis. The most susceptible animals are mice and rats. In guinea-pigs the localization of the infection specifically to the brain and testicle is practically pathognomonic. Rabbits are comparatively resistant and usually infection has no effect on them at all. An important practical point is that the organism in a few instances takes as long as six months to cause illness in its victim, so that diagnosis must not be considered negative in infected animals until at least that period has elapsed without symptoms. The animals must be injected intra-peritoneally or intra-cerebrally. Intranasal application does not affect the central nervous system if the nasal mucous membrane is uninjured or free from disease.

Post-mortem Appearances.

(a) *Macroscopical.*

The Central Nervous System.

The infection is almost invariably confined to the leptomeninges and the brain and spinal cord. It has been known to involve the Gasserian ganglion, however, and even to perforate the dura mater and involve the skull.

The degree to which the meninges are involved varies. Sometimes nothing is noted beyond a few nodules of approximately 1 to 3 mm. diameter scattered over the following positions singly, or in any possible combination : (*a*) the cerebral cortex, (*b*) the Sylvian fissure, (*c*) the junction of fissures about the optic chiasma. In others basal meningitis is the outstanding feature, while universal thickening of

https://doi.org/10.1192/bjp.89.374.42 Published online by Cambridge University Press

the meninges over the convexity of the brain may occur in others still. The resemblance to miliary tuberculosis or tuberculous meningitis is often quite marked.

The meningeal and superficial cerebral vessels are frequently markedly engorged, but thickening of the pia and arachnoid themselves often obscures this to a large extent.

The cerebral meninges are the most commonly involved, but the cerebellar and spinal ones are also frequently affected. Greenfield (1938) has shown how certain cases have been diagnosed antemortem by removal of a portion of cerebellar meninges for biopsy. These cases were, previously to operation, diagnosed as cerebral tumour of the posterior fossa, but on exposure nothing beyond a suspicious-looking cerebellar meningitis was found.

The subarachnoid and intraventricular spaces are frequently filled with a gelatinous, starchy fluid, usually turbid in appearance and grey in coloration, but sometimes translucent and of a yellow coloration.

The brain itself usually shows a varying number of cysts of the grey matter. Sometimes the whole of the cortex is riddled with small cysts, giving it the so-called " soap-sud " appearance ; sometimes they are less numerous and more discrete, and very occasionally only a single large cyst occurs. Minute cysts may also be seen in the basal ganglia, and occasionally in the cerebellar cortex and spinal cord. The cysts are filled with a gelatinous starchy fluid similar to that in the subarachnoid spaces. No caseation or abscess formation takes place.

White, rather hard, trabeculated bodies of varying numbers and sizes (up to 2 cm. diameter) can sometimes be seen in the grey and white matter of the cerebrum and cerebellum. These are due to conglomerations of the granulomatous material.

The Lungs.

The lungs may be permeated with granulomatous masses varying in number and size. These may take the form of minute yellow or brownish tubercles (called by Hirsch and Coleman (1929) " acute torulosis ") and looking to all intents and purposes like the condition seen in miliary tuberculosis ; they may have more extensive limits and appear rather like patches of tubercular broncho-pneumonia ; or they may be very large and occupy the greater part of a whole lobe. When of a large size, these masses have a soft, necrotic centre composed of a characteristic pinkish gelatinous material which when evacuated leaves a rugged cavity. There is seldom any visible caseation and never any gangrene or putrefaction.

Other Organs.

Similar types of lesion occur in other organs. On the one hand one may have numerous embolic tubercles, or on the other, large granulomatous masses whose centres tend to soften and necrose. Caseation and true abscess formation are unknown, unless secondary infection takes place.

(b) *Microscopical.*

The histo-pathology of this disease reveals in all cases a specific type of granulomatous lesion. This consists of the following formation : At the centre of the lesion, endothelial cells and fibroblasts react by marked proliferation. More peripherally some small round cells and plasma cells may be present. Polymorphs of all types are conspicuous by their almost total absence from the lesion. Giant cells with centrally placed nuclei occur towards the innermost parts of the lesion. These are usually of a foreign body type, but occasionally of a tuberculous one. Scattered throughout the lesion are rounded, poorly staining, hyaline bodies, usually extracellular, but sometimes intracellular, which are recognized under the microscope as the organisms themselves.

The Central Nervous System.

The microscopic pictures are of a typical nature, but resemble syphilis in that they are sometimes of an intense, localized, granulomatous nature resembling a gumma, and at others of a more diffuse and less granulomatous nature. The more diffuse the meningitis, the less the proportionate number of giant cells and the greater the number of endothelial ones.

The picture seen in the cerebral substance explains the already described

https://doi.org/10.1192/bjp.89.374.42 Published online by Cambridge University Press

macroscopical characteristics seen there. The so-called diffuse cysts are found to be due to direct invasion of the brain substance by the organisms themselves, and this usually takes place along the perivascular spaces, producing bottle-neck cystic enlargements. The deeper cysts (so-called) are found to be due to masses of the organism also. The nerve cells around the cysts are deformed and misshapen, due to pressure on them of the manifold organisms, but they exhibit very little abnormality of Nissl granules or general structure when stained appropriately. Moreover, very little of the lipoid substance characteristic of nerve degeneration is ever found. This shows that the destructive action of the organisms is attained by pressure and not directly by histolysis. Neuroglia exhibits very little proliferative reaction in these lesions. Granulomatous masses (as opposed to cysts) may be seen in the cortex, the basal ganglia and white matter of the brain. They form white, rather hard, trabeculated bodies which may reach a diameter of 2 cm. or more.

The Lungs.

In the lesions here, more fibrosis and inflammatory reaction is discernible than in those of the brain. The organisms are nearly always recognizable if sufficient care is taken.

Other Organs.

Similar granulomatous reactions (to those in the lungs) may occur.

The Cerebro-spinal Fluid.

1. Changes in the cerebro-spinal fluid are almost invariably present, but like other signs of this disease, their degree of variation from one base to another is considerable, and if the disease is not to be missed, one must be fully acquainted with the picture as a whole.

1. *Pressure.*—This is usually raised, commonly to around 300 mm. of water and occasionally higher, having reached in one case to 700 mm. of water. It has been stated that sometimes the pressure is not raised, but Freeman (1931) says that if a manometer is used, failure to register an increase would be found to be an outside rarity.

2. *Specific gravity* is usually about 1008.

3. *Colour consistency*, clear, xanthochromic, or turbid; often throws down a heavy sediment. In many cases a pellicle forms on standing.

4. *The cell count* varies within the extreme limits of 3 and 1,000 cells per c.c., usually between 300 and 700 cells. These are for the greater part lymphocytes, but occasionally polymorphs reach as high as 30 per cent. Red blood cells may be present. If a very high cell count is recorded it must be regarded with suspicion, since it is probable that many of the so-called cells are really unidentified torulae.

5. *The albumen and globulin* content is usually increased.

6. *The sugar content* varies, but is sometimes considerably decreased.

7. *The colloidal gold curve* is sometimes of a luetic and occasionally of a paretic type.

8. *The Wassermann reaction* is negative.

9. *The torulae organisms* are nearly always present and may be cultured from the fluid.

Examination of the Cerebro-spinal Fluid.

Several points of importance are to be noted. (1) In order to exclude the presence of the organisms, the pathologist should never fail to examine the cell deposit under the higher powers. (2) Smears made from centrifugal deposits are liable to destroy these fungi in the process.

Therefore a hanging drop preparation of this sediment on examination in an official "blood count" chamber are the most likely means of detecting the organisms. A useful help is to mix a drop of Indian ink with a loopful of the sediment on a slide, place a cover slip over it, and examine under the microscope. The organisms will be surrounded by a "halo" owing to the failure of the ink to stain the capsules.

Finally, it has to be remembered that microscopic examination is frequently inconclusive, and cultivation and animal inoculation are essential for a definite diagnosis.

Aetiology.

Very little is known of the aetiology of the disease. The organisms are widely spread in nature and have been found in plants, insects, butter and milk. Fortunately they are very seldom pathogenic to man, although they are claimed to have been isolated in saphrophytic forms from the human skin, throat and gastro-intestinal tract. When this is so, the way in which the organism gains access to the body is not understood. Most authorities agree with Freeman that it is seldom

https://doi.org/10.1192/bjp.89.374.42 Published online by Cambridge University Press

a primary infection of the skin. The question of entry by the tonsils, nasal mucous membrane, respiratory tract or alimentary tract has not been settled. Freeman and Weidman (Freeman, 1931) produced a meningeal invasion by use of intranasal swabs. In all cases a requisite amount of trauma was necessary.

The disease, as far as is known, is mainly one of adult life. Up to date its incidence has been higher in the male than in the female sex. It is more common in the U.S.A. than elsewhere, but its distribution is universal and it may attack persons of any occupation or race.

Symptomatology.

From what has been said of the varying pathological manifestations of these organisms, it is not surprising that they produce symptoms which can mimic several different diseases of the central nervous system.

Levin (1937), summarizing the reports on the 60 cases reported up to that time, found that their diagnosis prior to the results of culture of the cerebro-spinal fluid or autopsy were as follows:

Tuberculous meningitis	10
Meningitis, unqualified	5
Encephalitis	7
Tumour of the brain	6
Abscess of the brain	4
Dementia psychosis	5
Dementia paralytica	2
Miscellaneous	2
Unstated	19

We see from this that although the majority of cases tend to present themselves primarily to the neurologist, a certain number will come for diagnosis to the psychiatrist. Moreover, some of the former group may, as in the present case, terminate in a mental hospital ward.

Certain clinical tendencies in this disease are worthy of special note. The disease tends to take a chronic, but almost invariably fatal course (only one case up to date is reported to have recovered). More often than not, it commences with headache. This gradually becomes more persistent and more severe and is usually localized in the frontal region. It is followed sooner or later by the onset of other symptoms, usually of a meningo-encephalitic nature, e.g. faintness, vertigo and vomiting, etc. Stiffness and rigidity and pain of the neck are frequent, and are often associated with positive Kernig's and Brudzinski's signs. Staggering gait, ataxia and hemiplegia have been noted. Paralysis of the higher cranial nerves may give rise to such symptoms as amblyopia, diplopia, strabismus, nystagmus and ptosis, and extensive basal meningitis may produce all forms and degrees of irritation and paralysis of the lower cranial nerves.

Sometimes organic disease of the brain may be simulated, and this occurs especially in older persons. In this respect it is worth quoting Meyer's case recorded by Freeman (1931):

> "The patient was a white female, aged 59 years, who lived in Easton, Maryland. She came of a family in which there were several psychoses, and, herself, had always betrayed anxiety. For many years also she had suffered from haemorrhoids. In March, 1925, she became more than usually querulous, complaining, suspicious, and in August complained of marked weakness and distress upon any exertion. The onset of the real illness, however, was in September, with headache and pains in the limbs, which condition was associated with great apprehension, agitation and depression. She complained constantly, and was very fearful. To this was later added confusion, and she was admitted to Phipps Clinic on December 12, 1925, with a diagnosis of agitated depression. Examination showed considerable emaciation. The temperature rose occasionally to 100·4° F., the pulse was 95, the blood pressure 110·70. The pupils were normal, speech was thick, there were tremors of the tongue, eyelids and hands, the patellar reflex was greater on the right than on the left, but the Babinski sign was negative.

https://doi.org/10.1192/bjp.89.374.42 Published online by Cambridge University Press

" The blood Wassermann reaction was negative, the haemoglobin 66 per cent., W.B.C. 8,760, N.P.N. 50 mgm. The urine showed a trace of albumin but nothing else. The spinal fluid contained a moderate amount of globulin, with 27 cells; the Wassermann reaction was negative, the colloidal gold curve 123421000, mastic 555554321000.

" The patient became semicomatose shortly after admission, with stiffness of the neck and a positive Kernig sign. Examination of the fundus showed choking of both discs. The tongue became dry. Cheyne-Stokes respiration developed and death resulted on December 27, 1925, after an illness of three months. The final diagnosis was agitated depression with superimposed organic disease of the brain.

" Necropsy showed little except chronic nephritis and thickening of the meninges. The brain in this case was considered normal, and was released for anatomical study until examination of the hypophysis revealed characteristic thickening of the meninges in the neighbourhood, with fibrosis, cellular infiltration, and the presence of large pale rounded bodies with narrow capsules, evidently torulae. Some lay free in the meshes of the meninges, others were enclosed in multinucleated giant cells. This finding led to more detailed examination of the brain, and there was found a patchy thickening of the leptomeninges, especially about the chiasma and floor of the third ventricle, and in places over the convexity. On microscopical section, abundant evidence of torulae was revealed."

The headache may be associated with insomnia, restlessness, irritability, confusion, delusions and hallucinations, or alternatively with somnolence, apathy, amnesia, lethargy and coma.

The disease is usually afebrile and very rarely has a temperature of over 101° F. The blood pressure is normal and there is no abnormality of the urine. The blood count is usually normal, but variations of the leucocyte count of a non-determinant nature have been described. Eosinophilia does not occur.

Enlargement of the lymph glands is frequent, and may lead to erroneous diagnosis of tuberculosis or even Hodgkin's disease. Signs of involvement of the lungs may mislead one to a diagnosis of tuberculosis of the lungs and meninges.

Differential Diagnosis.

From the above discussion on symptomatology, it is obvious that diagnosis must be made from: Meningitis (tuberculous and other forms); encephalitis; tumour of the brain; abscess of the brain; general paralysis of the insane, and the senile psychoses. Clinically, the diagnosis from other fungi and yeast infections may be difficult. A point of importance is said to be the rarity with which the skin is involved in torulosis of the nervous system, especially in the early stages of the disease. Fortunately, pathological details leave little doubt as to the organisms responsible, and make it easy to differentiate torulosis, provided the details are known. It is not proposed here to give a long discussion on the matter, but the following Table I synthesized from the findings of many authors demonstrates the main features and may be useful for reference in doubtful cases.

Treatment.

The biological characteristics of the organism, such as its resistance to temperature, drying, changes in hydrogen ion, concentration, roentgen rays, aniline dyes, etc., its thick capsule and the poor reaction it produces in the tissue of its host render it particularly difficult to influence, and up to date no medicinal treatment has proved of any noteworthy effect in stemming the dread and relentless progress it pursues.

The following treatments have been tried with no effect: Massive doses of iodides; mercury preparations; tartar emetic intravenously; intra-spinal injections of iodides, colloidal silver, gentian violet and merchurochrome.

Shapiro and Neal (1925) tried out the effect of various drugs on cultures of this organism—sodium iodide 1/500, quinine sulphate saturated, sodium salicylate 1/500, colloidal silver 1/600 and magnesium sulphate 1/500 had no affect on the organism, but acriflavine 1/10,000 was found to have important inhibiting powers

https://doi.org/10.1192/bjp.89.374.42 Published online by Cambridge University Press

TABLE I.—*Showing the Main Pathological Characteristics of Various Fungoid Infections in Man.*

	Saccharomyces.	Monilia.	Torula.	Blastomyces.	Coccidiodesis.
Synonyms	1. True yeast	1. *Oidium albicans*	1. *Torula histolytica* 2. *Cryptococcus hominis*. 3. *Torulopsis hominis*	1. Gilchrist's disease 2. Chicago disease	1. Californian disease. 2. Coccidioidal granuloma.
Size in microns	5 to 15	3 to 30	1 to 50	8 to 20	5 to 75
Mycelium	—	±	—	—	—
Hyphae	—	—	—	—	+
Endospores	?	—	—	—	+
Budding	+	+	+	+	—
"*Halo*" *appearance*	+	—	—	—	—
In culture:					
(*a*) Mycelium	—	+	—	+	+
(*b*) Spores	+	—	—	+	+
(*c*) Colour of colonies	Cream	Cream	Cream, yellow, brown	Grey	Grey to white.
(*d*) Contour of colonies	Round, smooth	Round, smooth	Smooth, moist, muscoid	Radial folds, concentric rings and spines	Fluffy, spiny.
Animal inoculation	None	Rabbits, I.L.*	Mice, rats, guinea-pigs, I.P.* or I.C.*	Mice, rats, I.P.* or I.T.*	Guinea-pigs, I.P.*
Human lesions:					
(*a*) Skin	+	+ + +	+	+ + + +	+ + +
(*b*) Systemic	+	+ +	+ +	+ +	+ + +
(*c*) C.N.S.	+	+	+ + + +	+ +	+ +
Characteristic pathological changes	Abscesses, necrosis, polymorphs, giant cells, epithelial growth	Chronic ulceration	Gelatinous tumours, very little inflammatory reaction, marked epithelial hyperplasia, no abscess, no caseation, few polymorphs, giant cells	Miliary abscesses, necrosis, caseation, polymorphs, epithelial cells, hyperplasia	Chronic granuloma, abscess formation, chronic ulceration, giant cells.

* I.C. = intracerebral; I.L. = intrapulmonary; I.P. = intraperitoneal; I.T. = intratesticular.

https://doi.org/10.1192/bjp.89.374.42 Published online by Cambridge University Press

on its growth. There are no records, however, of this drug's having been employed therapeutically.

Apart from drugs, repeated lumbar puncture is undoubtedly a beneficial and life-prolonging procedure. It aids in alleviation of the intense headache, reduces the symptoms due to increased intracranial pressure and prolongs life considerably in certain cases.

Case History.

On April 26, 1939, the patient, a male, aged 45, was admitted to St. Pancras Hospital Mental Observation Unit.

He was restless, resistive and difficult to examine, but the following physical signs were made out. He had a mouth containing much sordes, numerous carious teeth, and a dry and heavily furred tongue. His throat was inflamed and parched, and his cervical lymph glands on either side were enlarged. He had cyanosis of the lips and cheeks; some clubbing of the fingers; heart sounds of a very poor quality and an enlargement of the heart to the left. At this stage there were no definite signs of involvement of the respiratory system. A dry scaly desquamation of the hands and feet was noted.

Mentally the patient was in a state of delirious confusion. He was virtually out of touch with reality and inaccessible to any questioning. He was extremely restless, noisy, and over-active, and required constant nursing restraint to keep him in bed. Observation showed him to be hallucinated for all senses. He frequently conversed with visionary personages and sometimes appeared terrified at unpleasant hallucinations. He mumbled and chattered to himself all the time and was so confused that he did not know his relatives when they came to see him.

History prior to admission.—This commenced on February 2, 1939, with the onset of a persistent severe and intractable headache. It was localized particularly across the forehead, and was accompanied a few days later by a pain across the back of the neck and behind the ears, and also an increasing pyrexia and general malaise.

On February 13, 1939, the patient was admitted to the Royal Free Hospital. The physical signs present were similar to those already mentioned as present when I first saw the case, but of a less marked degree. In the central nervous system the only abnormal signs present were some pain on flexion of the head forwards accompanied by a slight rigidity of the posterior neck muscles.

The swinging temperature gradually diminished and after several days disappeared altogether. The headache persisted for a fortnight, but then gradually lessened and eventually ceased altogether. The patient was discharged on March 8, 1939.

Unfortunately the headache returned within a few days and the patient was readmitted to the Royal Free Hospital on March 20, 1939. The following positive nervous symptoms had developed: Kernig's sign and Brudzinski's sign; all tendon jerks excessively brisk; left pupil irregular, but both pupils reacting normally to light and accommodation. At this time nothing abnormal about his mentality had been noticed.

The patient's general condition deteriorated and he lost weight. He was gradually noticed to become restless and overactive and about a month after readmission the earliest psychotic symptoms appeared. He became irrational and deluded and started to refuse his food. His condition became steadily worse, and he was soon so restless, noisy and confused that he was impossible to look after in a general hospital and had to be removed to the mental observation ward.

Subsequent History.

The patient's restlessness continued in the face of large doses of paraldehyde and other sedatives, and he was soon perpetually picking at the bedclothes and himself.

April 29, 1939: Blistering of the internal aspect of both knees was noted. This was the result of self-inflicted friction during restlessness.

April 30, 1939: Despite sedatives, lumbar puncture, etc., the patient continued to become progressively more and more confused and over-active.

May 1, 1939: The patient passed suddenly from delirium to coma and died an hour later.

https://doi.org/10.1192/bjp.89.374.42 Published online by Cambridge University Press

Post-mortem Examination.

This revealed the typical picture of a torulosis of the nervous system and elsewhere.

The body was one of a well-built middle-aged man. He had obviously lost weight recently. He had dryness and desquamation of the skin of the feet and legs and large bilateral blood blisters of the knees, due to self-inflicted chafing. Some superficial bruises bore witness to his recent restlessness.

Central Nervous System.

The blood vessels of the meninges and brain were congested and their surroundings injected. The subarachnoid space over the surface of each hemisphere was filled with a diffuse yellow-brown gelatinous material (characteristic of the infection), which was also present to a lesser degree in the ventricles. No cysts were obvious, and slicing up of the whole central nervous system revealed no further macroscopic changes.

The Lungs.

These showed signs of a broncho-pneumonia characteristic of the disease. The lungs appeared normal apart from terminal congestion, and pinkish patches of consolidation with minute yellowish pin-point spots dotted throughout them, reminiscent of miliary tuberculosis.

The only other organic change due to torulosis was the appearance of small pinpoint dots in the kidneys which proved to be embolic colonies of torulae.

The diagnosis of this case, originally made during life by Dr. Joan Taylor of the Royal Free Hospital, who isolated the torulae from the cerebro-spinal fluid, was confirmed by Dr. Margaret Gillespie, of the L.C.C. Laboratories, Hampstead. The post-mortem examination was performed by Dr. Joan Ross of the Royal Free Hospital (the Coroner's pathologist).

In addition to the pathologist named above I am indebted to Dr. Feldman, Medical Superintendent of St. Pancras Hospital, for permission to publish this case; to Dr. Ball, Medical Registrar, for details of the case history while in the Royal Free Hospital; and to Dr. Lilly, Medical Superintendent of Cane Hill Hospital, for his interest and encouragement.

References.

Anderson, H. W. (1917), "Yeast-like Fungi of the Human Intestinal Tract," *J. Infect. Dis.*, **21**, 341.

Benham, Rhoda W. (1935), "Cryptococci," *ibid.*, **57**, 255.

Idem and Hopkins, A. M. (1933), "Yeast-like Fungi Found on the Skin and in the Intestines of Normal Subjects," *Arch. Dermat. and Syph.*, **28**, 532.

Brandt, R., and Zach, F. (1937), "Mycoses of the Scalp due to *Torula histolytica*," *Dermat. Wchnschr.*, **105**, 1180.

De Busscher, S., Scherer, H. J., and Thomas, F. (1938), "Meningitis due to Torula: Localization of Yeast Infection of the Nervous System," *Rev. Neurol.*, **70**, 149.

Caldwell, G. T. (1937), "Systemic Cryptococcus Infection with a Report of Case of So-called *Torula histolytica* Infection," *Texas State J. of Med.*, **33**, 310.

Crone, J. T., de Groat, A. F., and Wahler, J. C. (1937), "Torula Infection," *Am. J. Path.*, **13**, 863.

Cudmore, J. H., and Lisa, S. R. (1938), "Torula Meningo-encephalitis Case," *Ann. Int. Med.*, **11**, 1747.

Dienst, R. B. (1938), "*Cryptococcus histolyticus* Isolated from Subcutaneous Tumor," *Arch. Dermat. and Syph.*, **37**, 461.

Ducumin, Ç. J., Bassal, L., and Militzsky, O. (1937), "Osseous Tumour of the Orbit with Aspect of Cancer due to *Torulopsis neoformans*," *Bull. Assoc. Franç. pour l'étude du Cancer*, **26**, 580.

Evans, W. (1922), "Torula Infection," *Californian State J. Med.*, **20**, 383.

Fitchett, M. S., and Weidman (1934), "Generalized Torulosis Associated with Hodgkin's Disease," *Arch. Path.*, **18**, 225.

Flu, P. C., and Woendregt, M. M. G. (1918), "A Case of Blastomycosis of the Central Nervous System," *Meded. v. d. Gencesk. dienst in Nederl. Indie*, **6**, 1.

https://doi.org/10.1192/bjp.89.374.42 Published online by Cambridge University Press

FREEMAN, W. (1931), "Torula Infection of the Central Nervous System," *J.f. Psychol. u. Neurol.*, **43**, 236.
FROTHINGHAM, LANGDON (1902), "A Terminal-like Lesion in the Lung of a Horse caused by a Blastomyces (Torula)," *J. M. Research*, **9**, 31.
GILL, W. D. (1934), "Torula Mycosis in Man with Special Reference to Involvement of the Upper Respiratory Tract," *Tr. Am. Laryng. Rhin. and Otol. Soc.*, **40**, 247.
GREENFIELD, J. G. (1924), "Blastomycotic Infection of the Nervous System," *Med. Science*, **10**, 267.
Idem, MARTIN, J. P., and MOORE, M. T. (1938), "Meningo-encephalitis Due to *Cryptococcus meningitis* (*Torula histolytica*) with Report of a Case," *Lancet*, **2**, 1154.
HARDAWAY, A. M., and CRAWFORD, P. M. (1935), "Pulmonary Torulosis," *Ann. Int. Med.*, **9**, 334.
HENRICI, A. T. (1930), "Moulds, Yeasts and Actinomycetes." New York: John Wiley & Son.
HIRSCH, E. F., and COLEMAN, G. H. (1929), "Acute Miliary Torulosis of Lungs," *J.A.M.A.*, **92**, 437.
JOHNS, F. M., and ATTWAY, C. L. (1933), "Torula Meningitis," *Am. J. Cl. Path.*, **3**, 459.
JONES, E. L. (1920), "Torula Infection of the Naso-Pharynx," *South. M. J.*, **20**, 120.
LEVIN, E. A. (1939), "Torula Infection of the C.N.S.," *Arch. Int. Med.*, **59**, 667.
LYNCH, F. B., and ROSE, E. (1936), "Torula Meningitis," *Ann. Clin. Med.*, **4**, 755.
MCGHEE, J. L., and MICHELSON, I. D. (1936), "Torula Infection in Man," *J. Surg. Gynaec. and Obst.*, **42**, 803.
MCKENDREE, C. A., and CORNWELL, L. H. (1936), "Meningo-encephalitis Due to Torula," *Arch. Neurol. and Psychiat.*, **16**, 167.
MAGRUDER, GREGORY (1939), "A Report of 3 Cases of Torula Infection of the C.N.S.," *J. Lab. Clin. Med.* (February), **24**, 495.
MASSAC, J. C., and ROONEY, J. S.(1930), "Meningitis Due to Torula," *Arch. Neurol. and Psychiat.*, **16**, 167.
MITCHELL, L. A. (1936), "Torulosis," *J.A.M.A.*, **106**, 450.
MOOK, H. W., and MOORE, M. (1936), "Cutaneous Torulosis," *Arch. Dermat. and Syph.*, **33**, 951.
ROGERS and JELSMA, F. (1933), "Torula Meningo-encephalitis," *J.A.M.A.*, **100**, 1030.
SAWERS, W. C., and THOMSON, E. F. (1935), "Torulosis," *M. J. Aust.*, **2**, 581.
SHAPIRO, LOUIS L., and NEAL, J. B. (1925), "Torula Meningitis," *Arch. Neurol. and Psychiat.*, **13**, 174.
SMITH, F. B., and CRAWFORD, J. S. (1930), "Fatal Granulomatosis of the C.N.S. Due to a Yeast-Torula," *J. Path. and Bact.*, **32**, 291.
STODDARD, JAMES L., and CUTTER, E. C. (1936), *Torula Infection in Man*, Monograph 6, Rockefeller Inst. for Med. Research.
STONE, W. J., and STURDIVANT, B. F. (1929), "Meningo-encephalitis Due to *Torula histolytica*," *Arch. Int. Med.*, **44**, 560.
TANNER, F. W., and LAMPORT, M. (1924), "A Study of Yeasts from Sore Throats," *Centralb. f. Bakt.*, **91**, 282.
TANNER, F. W., LAMPORT, E. N., and LAMPORT, M. (1927), "On the Presence of Yeast-like Fungi in Normal Throats," *ibid.*, **103**, 94.
TÜRK, W. (1907), "Ein Fall von Hefeinfektion (Saccharomykose) der Meningen," *Arch. f. Rhin. Med.*, **99**, 335.
WATTS, J. W. (1932), "Torula Infection," *Am. J. Path.*, **8**, 167.
WEIDMAN, F. D. (1933), "Cutaneous Torulosis," *South. M. N.*, **26**, 851.
Idem and FREEMAN (1924), "Indian Ink in the Microscopic Study of Yeast Cells," *J.A.M.A.*, **83**, 1163.
Idem and RATCLIFFE, H. L. (1934), "Extensive Generalized Torulosis in a Cheetah or Hunting Leopard," *Arch. Path.*, **16**, 362.
WHITE, E. C. (1930), "A Case of Meningo-encephalitis Due to Torula," *U.S. Nav. M. Bull.*, **28**, 615.
WILE, V. J. (1935), "Cutaneous Torulosis," *Arch. Dermat. and Syph.*, **31**, 58.
WILHELM, C. M. (1914), "The Primary Meningeal Form of Systemic Blastomycosis," *Am. J. M. Sc.*, **169**, 212.
WORTIS, S. B., and WHITEMANN, H. B. (1928), "A Case Report of Torula Meningitis," *Bull. New York Acad. Med.*, **4**, 531.
ZENKER (1861), "Encephalitis mit Pilzentwickelung im M. Gehirn," *Jahr. v. d. Gesellsch. f. Natur. u. Heilk. i. Dresden*, 1861–62.

https://doi.org/10.1192/bjp.89.374.42 Published online by Cambridge University Press