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# MENTAL DISTURBANCES IN TUBERCULOUS MENINGITIS*

BY

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Ever since tuberculous meningitis was first defined as a specific disease (Whytt, 1768) it has been recognized that disturbances of the mind form an integral part of the clinical picture. As the disease progresses, so these disturbances increase until the illness closes in coma and death. Thus the classical descriptions of the disease insist on apathy, irritability, and insidious changes in personality as among the chief characteristics of the early stages of the illness. Whytt himself, writing of children, says : " Their spirits being low they incline mostly to lie in bed, although they are more often disposed to watching than sleep ". Trousseau (1868) says : " Sadness setting in unaccountably is a premonitory sign of great value in a child " ; while Osler (1892) states specifically that " the personality may completely change ".

Towards the end of the prodromal phase the mental changes deepen to semi-stupor or frank delirium, usually described as either hysterical (Gowers, 1893) or as delirium tremens (Barlow, 1899). The prominence of the mental symptoms is reflected in the discussions of the differential diagnosis. Two conditions often confused with tuberculous meningitis were hysteria and typhoid fever. Both typhoid fever and tuberculous meningitis are characterized by headache, fever, and delirium, and the likeness between the two is still acknowledged by the use of the term " the typhoid state " in modern accounts of general tuberculosis (Gow and Bodley Scott, 1950).

In doubtful cases the point at issue was whether the delirium should be ascribed simply to general toxaemia or to direct cerebral insult. Wilson (1844), writing of acute rheumatic fever, had urged that " it be remembered in the treatment of ' head symptoms ' incidental to this as to other forms of acute disease, that the brain may be unsettled by many influences that do not originate within the brain itself ".

Gowers (1893) recognized both general and local causes for mental disturbances but suggested that they could be distinguished clinically. When discussing the differential diagnosis between tuberculous meningitis and typhoid fever, he says :

" The error always arises from ascribing initial headache and subsequent delirium to cerebral disease in the presence of sufficient pyrexia to account for the symptoms and from disregarding the relation between the two. When they are the result of general disease, as Sir William Jenner long ago pointed out, the headache ceases when the delirium begins."

Today there is good reason to believe that the mental disturbances of tuberculous meningitis are the direct result of the infection of the brain. But the problem of whether these disturbances differ in kind from those encountered in other organic confusional states has not been resolved ; still less the question of whether these mental changes can be attributed to injury of any particular part of the brain.

Organic confusional states are commonly classified as the acute—which are characterized by delirium, disorientation, hallucinations and, sometimes, coma-vigil—or as chronic—characterized by mental dulling, amnesia, and disorder of the emotions. In the first, recovery is said to be sudden and complete except for amnesia for the actual period of confusion. We have not found any detailed account in the literature of the pattern of recovery in the chronic group, though a few cases are reported in which recovery, or at least improvement, took place (Korsakoff, 1889 ; Jolliffe, Wortis, and Fein, 1941). Tuberculous meningitis is now a treatable disease, and recovery can be expected in over two-thirds of all cases, but not infrequently this takes place after periods of confusion lasting for months. Cases of tuberculous meningitis under treatment therefore provide a new field for the study of organic confusional states since, on the one hand, these cases cannot conveniently be classified as either acute or chronic, while, on the other, they afford ample opportunity for observations on the pattern of recovery.

* This study was begun by one of us (M. W.) in conjunction with the late Sir Hugh Cairns. Since that time additional material has come to hand which has allowed the work to be completed.

The results of such a study are reported here in the hope that they may help to elucidate the pattern of recovery from organic confusional states in general, and may also help to determine the degree of recovery and the nature of the residual disturbance after long periods of semi-consciousness and dementia.

### Material and Methods

Our material was drawn from cases of tuberculous meningitis treated at the United Oxford Hospitals and the Military Hospital for Head Injuries, Wheatley. This particular study was largely confined to those adults who, though drowsy and irrational, were yet alert enough to answer questions and permit of some form of psychological assessment.

Whenever possible, the patient's intellectual capacity was assessed by intelligence tests adapted from the Wechsler and Terman-Merrill scales. Memory span was assessed by digit repetition and by repetition of sentences from the Babcock scale. Learning was measured by the Rey-Davis Test; by ability to learn a set of digits or a sentence slightly longer than the immediate memory span; and by learning of the paired-associates from Wechsler's Memory Scale. Delayed recall was measured by the ability to recall pictures or numbers a short time after they had been presented; by reproduction of the Babcock designs from memory test; and by the progressive prompting technique (Williams, 1953).

It will be appreciated that the tests had to be chosen to suit each individual and that few patients were subjected to the full battery.

### The Prodromal Phase

We have little to add to existing descriptions of the mental changes in the prodromal phase, though it is worth noting that in one case the presenting symptom was a subjective impairment of memory. Typically, the earliest mental changes are so insidious that they may be imperceptible to one who did not know the patient before his illness. Sometimes, however, when the patient is convalescent it becomes obvious in retrospect that personality changes were in fact present during the active stage of the disease. Thus, a child under treatment may for weeks seem fully conscious and alert, spending his time sitting up in bed playing with his toys, yet he may remain sullen, uncooperative, and withdrawn. In view of his apparent well-being he is probably judged to be spoilt or shy, or his attitude is attributed to a justifiable dislike of doctors. And then, quite suddenly, he becomes friendly and smiling and anxious to be talked to and played with. When such case records are studied in retrospect it is found that this improvement has coincided with some other favourable change, such as a fall in the protein content of the cerebrospinal fluid (C.S.F.), or the beginning of a persistent gain in weight, that is in itself evidence that the meningeal infection is obsolescent.

There is one negative finding of considerable diagnostic value that should be mentioned. These patients, even in the early stages of the disease, lack the over-alert, apprehensive expression so often seen in pre- or non-paralytic poliomyelitis (Russell, 1952). Irritable as they are, when undisturbed they lie on one side with their eyes closed, and the first perceptible mental change is a faint clouding of awareness.

### The Fully-developed Disease

In our experience the mental disturbances seen once the full clinical picture of tuberculous meningitis has developed may vary in degree from case to case, but in kind are remarkably constant. The characteristic picture is well shown by the following case.

*Case* 1.—M. C., aged 19 years, was admitted to hospital on November 16, 1950. The history and physical findings were strongly suggestive of tuberculous meningitis. Treatment with streptomycin was begun within 24 hours and the diagnosis later confirmed by identification of *M. tuberculosis* in the C.S.F.

On admission he was drowsy, confused, disorientated, and incontinent of urine and faeces. The degree of drowsiness fluctuated, but he never became deeply unconscious.

He remained in this state for the first five days, and then, on November 22, he began to improve. He still slept most of the time but woke as soon as he was spoken to and was very cheerful, indeed euphoric. He was now orientated in place and time, could describe pictures accurately, and showed a fair ability on intelligence tests. For example, his performance on the Wechsler similarities was equivalent to an I.Q. of 110. Immediate rote memory and learning were up to average. On Babcock's sentence repetition test he repeated the sixteenth sentence correctly at the first trial, and the twenty-third correctly at the third trial.

In spite of this good performance, he was totally unable to retain memories for any length of time and when pressed would confabulate freely. For example, even after half an hour he had little recollection either of the tests he had done or of the pictures he had been shown. On one occasion he tried hard to remember the examiner's name, but when seen by the same examiner a week later denied ever having seen her before. His memory for the eight months before his illness was also extremely vague. He could name the camps he had been

in, but could not say for how long, or in what order, he had been in each. He talked a great deal about his girl-friend, but had no idea where they had first met. He also had several vivid recollections of football matches, but did not know when he had played them. By contrast, his memory for events preceding his entering the Army, three months before the onset of his illness, seemed to be intact: he gave a good account of his childhood and the work he had done before he was called up.

During the next five to six weeks he showed sustained improvement in spontaneous activity and intellectual ability, and grew less euphoric. But although his retrograde amnesia steadily shortened, improvement in memorizing was very slow. Thus, although about this time he became able to remember the names of his doctors, he could not remember the contexts of their visits. He read many books each week, but shortly after they had been removed from his bedside he was unable to give their titles or recount any of their contents. Formal test material was also poorly retained. His performance on the Wechsler Similarities Test was equivalent to an I.Q. of 120 (i.e., it showed a gain of 10 points), but his answers to some of the questions on the Wechsler Comprehension Test were poor and lacking in insight. (For example, to the question, "Why should we keep away from bad company?" he answered, "You don't want to get into it".)

By January 5, 1951, two months after the onset of his illness, his behaviour was quiet and responsible. The defect of memorizing had recovered, and he had no longer any difficulty in retaining the names of his attendants or the test material. He was no longer incontinent. The Wechsler Comprehension Test indicated some slight further improvement in thought processes. The retrograde amnesia had largely disappeared, though his memory for events of the week immediately preceding the onset of his illness was still very hazy.

At this stage the onset of deafness due to the streptomycin made conversation difficult, but it was apparent from those tests that could be applied that intellectual ability and memorizing were well up to average. He reproduced the "Designs" from the Stanford-Binet test, Form I, correctly two weeks after seeing them at a single presentation. On the Rorschach test he gave many well-integrated responses indicating a high level of intelligence. By contrast with this excellent recovery of his intellectual faculties he still had a complete amnesia for the first six weeks of his illness and a retrograde amnesia for one week preceding its onset.

When he was discharged from hospital in July, 1951, his parents considered that his previous ability, personality and interests were fully restored; and subsequent follow-up studies confirmed that physical and mental recovery were complete except for the deafness and the amnesia for the first weeks of his illness.

In this and similar cases analysis of the illness, according to the defects exhibited at different times, allows three successive mental states to be distinguished. We have called these the confusional state, the amnesic state, and the post-recovery state.

**The Confusional State.**—During the early days of the illness patients are apathetic and lack initiative. Although when roused they may appear fairly alert, they are grossly disorientated in space and time. There is great poverty of speech, and they are quite incapable of sustaining any rational conversation. Thus in many respects the picture resembles that described in other acute organic confusional states (see e.g., Henderson and Gillespie, 1936).

**The Amnesic State.**—This more or less coincides in time with the period during which patients remain critically ill: it corresponds in fact with what has been called "the period of deadlock" (Cairns and Smith, 1952; Smith, 1953). Though patients may be sufficiently alert and rational to occupy themselves and to cope adequately (though not yet quite normally) with intellectual problems, they have the greatest difficulty in retaining any new impression for more than a few minutes. Memory for remote personal events is commonly intact, but for the events of the illness and for those that have preceded it by anything up to several months it is hazy and poorly integrated. Euphoria or depression and total lack of insight are the rule, as is incontinence of urine and faeces. Patients thus exhibit all the major symptoms of the chronic organic confusional state.

**The Post-recovery State.**—Once the amnesic state has passed mental recovery, as assessed from the observations of relatives, from performance at work, and from psychological tests, is sustained and complete except for the residual amnesia.

Nineteen adult patients, all of whom had been confused and amnesic, were examined at various intervals up to four years after the onset of the illness in an attempt to assess the frequency and nature of any residual mental disability. Such a disability can only be assessed in relation to the patient's original personality and abilities. In point of fact, many of our patients had very humble backgrounds, and, as a whole, their scholastic standards were low. Thus not only were three of our adult patients virtually illiterate, but from a total of 31 Service men there was only one officer, while among the adolescents there was only one public-school boy. In this respect these patients differed markedly from those composing a series of 50 unselected cases of pneumococcal meningitis treated at Oxford.

The findings in these 19 cases are summarized in

TABLE I

RESIDUAL MENTAL DISTURBANCE IN 19 ADULT PATIENTS CONFUSED DURING THE ILLNESS

| Nature of Disturbance | Present | Absent |
|---|---|---|
| Defects of intellect .. .. .. .. | 0 | 19 |
| Defects of memorizing .. .. .. | 4* | 15 |
| Defects of personality .. .. .. | 3* | 16 |
| Amnesia for time of illness .. .. .. | 19 | 0 |
| Retrograde amnesia .. .. .. .. | 6 | 13 |

* Subjective disability not confirmed by objective tests.

Table I. No measurable disturbance of intellect, personality, or memorizing was found in any case; and although four patients complained of forgetfulness for minor day-to-day events, this was not confirmed by the memory and learning tests. Three other patients complained of, or were said by their relatives to show, slight defects in concentration and sense of responsibility. There was, however, in each some indication that the past illness was being used as an excuse to cover a fundamental difficulty in personality or social situation.

The residual amnesia was in marked contrast to these trivial changes. None of the 19 patients had any recollection of the first few weeks or months of the illness, and six had in addition a considerable retrograde amnesia. In four cases this retrograde amnesia extended backward for more than a year—in one case for at least four years—before the onset of the illness. As a whole this retrograde amnesia was seldom uniform or global but consisted rather of an inability to organize past events in correct temporal sequence, of memory gaps, and of haziness of memory, as in the following case.

*Case* 2.—E. C. (Cairns and Taylor, 1949; Case 4), aged 22, developed tuberculous meningitis early in March, 1947. His scholastic career was exceptional in this series. He had matriculated at 15, had passed top of a book-keeping class at night school, and again passed out first from the clerical course he took while serving in Germany. Early in 1946 he had been posted to Germany, and in September, 1946, six months before the onset of his illness, he had taken a clerk's course and had received a fresh posting to a regiment stationed in the Ruhr.

He had a long and difficult illness, with a typical amnesic state and period of deadlock lasting in all about four months, and complicated by severe hypertension of central origin. He was discharged cured at the end of January, 1948.

He was seen in December, 1950, almost four years after the onset of his illness. He was then extremely well; he was working full-time as a clerk, had been promoted and had recently become engaged to be married. On questioning it was found that his amnesia for the first four months of his illness was still complete. Moreover, he was aware of profound defects in his memory for the whole of the time he had spent in Germany. He said: "For this period I have no consecutive stream of memory. When I try to think back, I am very hazy. Some events stand out but I can't chronicle them with clarity. One incident I remember very clearly. I can place it about the spring of 1946 because of world events which I remember were going on at that time."

For the six months spent in Germany which immediately preceded his illness his loss of memory was virtually complete. During that time he had learnt typewriting and had apparently become quite proficient; but on recovery he had no recollection of the course except for a large sheet of letters hanging on the wall, of which the first were Q W E R T. Recently he had been sent a photograph of the men on his course. He found he could name them all without difficulty, although he had no idea whatever of when or where he had met them.

After the course he appears to have gone to Berlin, where he has an undated recollection of visiting the Berlin Zoo and of his horror at the emaciation of the animals.

For his life before he went to Germany and after recovery from the active phase of his illness his memory was intact.

He was last seen in February, 1953, when he was still in the best of health and the amnesia was unchanged.

This patient was sufficiently intelligent to give an excellent account of his amnesia and also to allow an accurate comparison to be made between his mental capabilities before and after his illness. He provides an excellent example of the compatibility of a profound and extensive retrograde amnesia with full intellectual recovery.

### Variations from the Typical Picture

Variations from this typical picture have been seen at all its stages and are most commonly those of degree. The acute confusional period may be absent, or intensified to the point where the patient is hallucinated and so wildly delirious that he is almost or completely inaccessible from the outside world. In two relapsing cases the patients at the onset of the relapse were not only hallucinated but terror-stricken, a condition reminiscent of the "delirium tremens" well described by the older authors (Barlow, 1899).

During the amnesic period some patients, instead of being euphoric, were withdrawn and negativistic, or even acutely depressed. Thus certain patients would refuse to eat and when compelled to do so would keep mouthfuls of food tucked into their cheeks for hours at a time. In two cases this refusal to eat persisted as a kind of anorexia nervosa well into convalescence: one patient who had to be fed by means of a constant intragastric milk drip would lean out of bed and turn off the drip whenever the nurses were not watching him.

The greatest variation in the amnesic period was

in its duration. Although in some successful cases it lasted for only two or three weeks, in others it was prolonged for months, and some patients were still unable to retain recent impressions long after their physical recovery was assured.

In fatal cases in which death was due to uncontrolled meningitis the mental confusion persisted and increased in intensity until stupor and coma supervened. In three fatal cases, and three only, the patients seemed to remain fully conscious until shortly before death. Two of these patients were small children and detailed studies were therefore impossible. The third was a girl of 14 years who was undoubtedly lucid for weeks in spite of her uncontrolled infection. These cases will be referred to again.

As might be expected, the permanent loss of memory for the illness itself, like the retrograde amnesia (Table II), tended to vary in extent with the

TABLE II
RELATIONSHIP BETWEEN RETROGRADE AMNESIA AND LENGTH OF CONFUSIONAL PERIOD

| Confusional Period | No. of Patients | Duration of Retrograde Amnesia | |
|---|---|---|---|
| | | Under One Week | Over One Week |
| None .. .. .. | 14 | — | — |
| Under 1 week .. .. | 7 | 2 | — |
| Over 1 week .. .. | 13 | 2 | 7 |
| Total .. .. | 34 | 4 | 7 |

duration of the period of confusion, but was often longer than the course of the illness suggested. Thus, although residual mental disturbances were not anticipated, and accordingly were not systematically sought, in those who had remained lucid throughout their illness a surprising number were found after recovery to be quite unable to recall the early days of their treatment. Although they had always appeared alert, rational, and well able to keep track of their experiences, their impression on looking back was that they must have been unconscious for several weeks.

### The Pattern of Recovery

By dividing the mental disturbances seen during the illness into three states, it is not implied that the changes between them were abrupt and measurable. On the contrary, in every case the transition was gradual. For example, the passing of the confusional stage might first show itself by the patient's becoming able to feed himself and then, a day or two later, by his asking for a cigarette or looking at the comic strips in the newspaper. Similarly with the offset of the amnesic stage : a patient who for weeks has denied ever having seen his doctor before will begin to realize that his memory is faulty and say in response to questioning, " I should know your name. I've seen you often enough ". And, a little later, " Oh dear, I've forgotten. And they told me just before you came. It's not X, is it ? " (giving the name correctly). Similarly the patient in Case 4, while still disorientated, would attempt to reconcile his belief that he was still at home with his perception of the hospital environment : " They can make a hospital out of your home nowadays ". The same sequence is shown in regaining sphincter control. The patient is at first incontinent of urine and faeces ; later he regains control over his bowel ; later still he is only incontinent of urine during the night ; and finally he is horrified to be told that he ever wet his bed. The transition from one stage to another is well exemplified by the following case :—

*Case* 3.—E. G., aged 19, had suffered from idiopathic epilepsy from childhood and was admitted to hospital from an epileptic colony. For the first week in hospital he remained drowsy, confused, and unable to feed himself. During the second week the acute confusional state lightened. He began to sit up in bed and gradually learnt to feed himself until by the end of 12 days he was alert, friendly, and cooperative, but with a gross amnesia for all recent events. Thus he never could remember having seen the ward sister before in spite of the devoted care she gave him. When the trolley was brought for his daily lumbar puncture he would obediently roll over on his side, but as soon as the needle was withdrawn he would deny that he had ever had anything done to his back. He was fully awake all day and occupied himself with handwork or reading the comic strips in the papers, but the moment he was distracted from his occupation he would have no recollection of what he had been doing at the moment of distraction. Many attempts were made to teach him to weave. He would copy the instructor's demonstration correctly, but as soon as his attention was withdrawn from the loom he would deny that he had ever been shown what to do. On several occasions he played a fully competent game of noughts and crosses with the examiner, but when a few minutes later he was shown the sheet of paper on which the game had been played he denied that he had ever seen it before. He maintained that the possessions and letters on his bedside locker belonged to other people.

His orientation in place and time were equally bad. Thus, although he knew that he was not in the Colony, he always maintained that he was somewhere near it. For four months there was little change. He then slowly began to show signs of improvement in memorizing and in orientation. Although on formal testing he would still deny any recognition of test material, he would correctly " guess " what pictures he had been shown a few minutes before. If interrupted in the middle of a task, he would be able to remember what he had been doing, and go on with it. He admitted that the possessions on the locker were his, although unable to describe them

from memory. He realized that he was in a hospital at some distance from his Colony.

Five months after the onset of the illness great improvement was noted. He could repeat a short story correctly and describe pictures several days after they were presented to him. He had great difficulty, however, in learning by rote and was unable to master the Rey-Davis board at the first position, even after five trials. Shortly after this the frequency of his fits increased, and his memorizing ability consequently became difficult to assess.

Although this patient's fits were reasonably well controlled throughout most of his illness, it is possible that the unusual depth and duration of the amnesia was related to the epileptic tendency and that this allowed the recovery phase to be studied, as it were, in slow motion. We have seen a similar delay in mental recovery in elderly patients.

### The Specificity of the Mental Changes for Tuberculous Meningitis

The question arises of whether the mental changes described here are specific for the tuberculous intracranial infection or whether they are simply the expression of general toxaemia. There can be no reasonable doubt that they are directly related to the meningeal infection. In the first place, they are not exhibited by patients dying of other forms of tuberculosis, nor are they seen in miliary tuberculosis until the meninges become involved. Secondly, and conversely, we have had several cases in which there was unequivocal evidence that the miliary tuberculosis had healed but in which the meningitis, and with it the mental changes, persisted. Thirdly, an exact correlation can often be established between the intensity of the mental changes and that of the meningeal inflammation. Quite commonly patients under treatment with streptomycin show a sudden spontaneous increase in the cell count and protein content of the cerebrospinal fluid, accompanied by a temporary worsening in their mental and physical state. These phenomena probably represent spontaneous intrathecal tuberculin reactions. Certainly they can be reproduced at will by injecting small amounts of tuberculin directly into the cerebrospinal fluid (Smith and Vollum, 1950).

There is good evidence that these injections are of therapeutic value (Smith, 1953), and it is now our practice when treating tuberculous meningitis to supplement the daily systemic and intrathecal chemotherapy with intrathecal injections of tuberculin. The tuberculin is given about once every four to eight days, and in sufficient amounts to provoke a reaction. This reaction consists of an acute exacerbation of all the signs and symptoms of the meningitis, mental as well as physical. Physically, the patient is feverish, vomits, and complains of headache. The neck stiffness increases or returns, the intracranial pressure rises, and focal neurological signs become more obvious. Mentally, the patient tends during the reaction to fall back temporarily to the level from which he has just recovered. Thus, one who has recently been stuporous and is still very confused will relapse into stupor; while one who has recovered from his confusion but is still amnesic will again become confused. The following is a typical case :—

*Case* 4.—J. M., an Irish labourer of 21, was admitted to hospital on June 1, 1950. On admission he was drowsy, confused, and disorientated, and totally uninterested in his surroundings. Focal neurological signs were limited to nystagmus and mild ataxia. Unless disturbed he lay curled up on his side with his eyes closed, and though he could be roused sufficiently to take part in a limited neurological examination it was impossible to hold his attention for more than a few minutes before he would sigh, turn over, and go to sleep again. He was incontinent of urine and faeces. Treatment was begun immediately with intrathecal and intramuscular streptomycin, supplemented by intrathecal injections of tuberculin given about once every four days.

For the next 12 days the patient remained drowsy but could usually be roused to take part in a limited conversation. But for the day after each tuberculin injection he was almost unrousable, and speech, if present at all, was restricted to a few monosyllables.

During the next six weeks he became progressively easier to rouse during the intervals between the tuberculin reactions, and soon was alert enough to cooperate in a fairly extensive psychological examination. This showed him to be grossly disorientated in place and time, and inconsistent in his accounts of himself and his past. He was almost completely amnesic for all day-to-day and moment-to-moment events. For example, on several occasions attempts were made to teach him a simple wire puzzle. Although he struggled to solve it, he could never do so except immediately after each demonstration. He was also frequently shown a series of inkblots which changed from a black circle into the silhouette of a rabbit (Williams, 1953). He never remembered having seen the end of the series when the first was shown to him again. Intellectual ability was very restricted. He gave correct answers to only three questions on the Wechsler Similarities Test, and only five on the Wechsler Picture-Completion Test, a score roughly equivalent to an I.Q. of 55. He treated nurses and staff as old friends, calling them by the Christian names of former acquaintances.

During the 24 hours following each tuberculin injection the patient was much more lethargic, and, though easily roused, was unable to cooperate in any of the above tests.

During the next two weeks the patient's intellectual ability and general attitude showed considerable improvement. For example, by this time he was able to beat

every other patient in the ward at draughts. He would attempt to rationalize the inconsistencies in his orientation, and although he still had difficulty in retaining day-to-day information, he began to show signs of recognizing the pictures that he had seen repeatedly. However, during his tuberculin reactions he would again become as confused and disorientated as ever.

Nine weeks after the onset of his illness he was correctly orientated, could recognize the hospital personnel, and was no longer incontinent. Intellectual ability was greatly improved. He could solve the wire puzzle alone, and his performance on the Wechsler tests indicated an I.Q. of about 97. He took an interest in the affairs of the ward and could give the gist of the daily news. However, during his tuberculin reactions he would again become amnesic and was inclined to be confused. Thus on one occasion he was shown a number of pictures before receiving tuberculin later that evening. The following day he had a typical reaction, and was vomiting and complaining of headache. His orientation remained correct, but he was unable to recall any of the pictures he had been shown the previous evening. Two days later, without any further prompting, these pictures were readily recalled.

To what extent these mental changes are specific for tuberculous meningitis, as opposed to other diseases of the brain, is harder to answer. There is no doubt that their quality is sufficiently constant to be a very considerable help in diagnosis. The lack of anxiety and apprehension in the prodromal phase has already been noted. This is a useful point in the differentiation of tuberculous meningitis from pre- or non-paralytic poliomyelitis. In the latter condition the patient looks ill and flushed and shows a very considerable degree of meningism, but in spite of this he is usually over-alert and obviously apprehensive (*Lancet*, 1953). By contrast, by the time the patient with tuberculous meningitis is showing a comparable degree of meningism and general toxicity, he is, as a rule, already becoming clouded and sleepy.

How useful the characteristic picture of the amnesic stage may be is shown by the following case :—

*Case* 5.—G. S., a man of 32, came under our care on September 1, 1952. Two years before, bilateral apical pulmonary tuberculosis had been diagnosed but regarded as obsolete. However, during 1952 he began complaining of night sweats and general malaise and was accordingly admitted to hospital elsewhere, when radiography of his chest showed recent extension of the pulmonary lesion. At the end of August he began to complain of headache and became irrational and aggressive, and on August 30 he had a generalized convulsion. Lumbar puncture the next day yielded a fluid under normal pressure and containing 70 cells per c.mm. (90% lymphocytes), 100 mg. protein per 100 ml., sugar 73 mg. per 100 ml., and chlorides 680 mg. per 100 ml. The following day he was transferred to the Military Hospital for Head Injuries, Wheatley.

On admission there he was feverish but there was no stiffness of the neck. Three discrete oval or circular patches of choroiditis were seen in the right eye, he was a little tremulous, and had a mild degree of slurring dysarthria, but no other abnormal physical signs. Mentally, he was aggressive, suspicious, and confused. At night he became very irrational and noisy and was incontinent of faeces. Nevertheless, he was correctly orientated in time and space, his memory for past events was good, and he was able to retain seven digits forward and four backward without difficulty. Radiography of the chest confirmed the presence of bilateral pulmonary tuberculosis, and lumbar puncture yielded a fluid containing 163 cells per c.mm. (94% lymphocytes), 150 mg. protein, 40 mg. sugar, and 710 mg. chlorides per 100 ml. Examination of smears of the cerebrospinal fluid showed fragments of acid-fast material which were thought to be tubercle bacilli. A bromide blood-cerebrospinal fluid permeability test was set up (Taylor, Smith, and Hunter, 1954).

A provisional diagnosis of tuberculous meningitis was made and treatment begun with intrathecal and intramuscular injections of streptomycin. After the bacteriological report was received intrathecal tuberculin was also given. In spite of this, he grew worse. He developed retention of urine and the dysarthria and tremor grew more marked. Mentally he also deteriorated. He became euphoric and fatuous and would chatter to himself for hours, while psychological testing revealed gross defects of intellect and concentration. In spite of this, he remained correctly orientated and no serious defect in his powers of memorizing could be demonstrated.

It was by now apparent that the mental picture was very different from that usually seen in established cases of tuberculous meningitis ; moreover, the lack of response to specific chemotherapy, the results of serial bromide tests, and of pneumoencephalography, were all against this diagnosis. The original smears of the cerebrospinal fluid were therefore restained and re-examined, and it was established that the acid-fast fragments were artefacts. At the same time the Wassermann and Kahn tests were found to be strongly positive in blood and cerebrospinal fluid. The diagnosis of tuberculous meningitis was accordingly rejected in favour of general paresis. Subsequent events left no doubt that this was the correct diagnosis.

In this case the finding of a predominantly lymphocytic meningitis accompanied by choroiditis and mental changes in a man with established pulmonary tuberculosis strongly favoured a diagnosis of tuberculous meningitis. This diagnosis was first seriously questioned when it was appreciated that the pattern of the mental disorders was an exact reversal of the characteristic pattern of tuberculous meningitis in that orientation and memory were relatively well preserved in the face of gross disorders of intellect.

The fact that the mental picture in tuberculous meningitis is sufficiently constant to have diagnostic importance does not imply that it is unique. On the contrary, it is in many respects very similar to that seen in a variety of conditions. In particular, the sequence of events as described here bears an obvious resemblance to that following blunt head injuries of moderate and severe degree. An analogy can be drawn between what we have called the " confusional state " and the state of " traumatic delirium " ; and between the " amnesic state " of tuberculous meningitis and the " traumatic confusional state " (Symonds, 1949). Moreover, in both conditions the patient is left with a permanent amnesia for the period of confusion and with some degree of retrograde amnesia (Russell, 1935 ; Russell and Nathan, 1946).

But on closer comparison the differences appear only less striking than the resemblances. Thus, during the confusional state of tuberculous meningitis the patient shows none of the agitation, overactivity, and aggression seen in traumatic delirium and, for that matter, in many other acute organic confusional states. The severe mental confusion is accompanied and to some extent masked by profound somnolence—indeed, the depth of sleep exhibited by the patient at one moment, compared with the intensity of his reaction when stimulated the next, is a striking characteristic of tuberculous meningitis. In this respect the typical delirium also contrasts strongly with the perpetual, silent, struggling delirium, " le mutism furieux " (Rilliet and Barthez, 1884) of acute purulent meningitis.

The amnesic state of tuberculous meningitis resembles the traumatic confusional state in that disorientation in time and space, gross defects in memorizing, and a tendency to confabulation are common to both, as are the stages by which the patient recovers his memory (Martin, 1937) and orientation (Paterson and Zangwill, 1944). But whereas in the traumatic confusional state the defect in memorizing is accompanied by severe impairment of other intellectual functions—by " a basic confusion of thought " (Symonds, 1949)—in tuberculous meningitis the defect in memorizing is out of proportion to the intellectual loss as a whole. A patient may thus be capable of doing complex problems in mental arithmetic quickly and accurately (Case 3), or be the acknowledged draughts champion of his ward (Case 4) at a time when he is still incontinent and totally unable to recognize his doctors or to remember the time of year or the whereabouts of his hospital. There appears also to be a difference in quality between the amnesic state of tuberculous meningitis and such organic dementias as acute alcoholic intoxication, and the acute confusional stage of typhus and general paresis. The difference between the mental picture of tuberculous meningitis and that of general paresis has already been exemplified (Case 4). In tuberculous meningitis patients are seldom, if ever, grossly deluded or grandiose. They may fabricate stories of their past, but the incidents they recount are associated with actual past events and lack the " ego-inflating " quality noted by von Stockert (1943) in typhus. Though they lack insight and are commonly either slightly euphoric or sullen in their attitude, they are not elated or unduly talkative, nor over-emotional and subject to rapid changes in mood.

The difference between the mental disturbances consequent on tuberculous meningitis and those that follow a serious head injury become most striking when the permanent residua are considered. In both conditions amnesia for the period of confusion coupled with some degree of retrograde amnesia is the rule. But after head injury the relationship between the length of the post-traumatic amnesia and the permanent loss of intellectual acumen is so close that the duration of the post-traumatic amnesia has proved a valuable guide to the ultimate prognosis (Symonds and Russell, 1943 ; Russell and Nathan, 1946). In tuberculous meningitis, on the other hand, an amnesic period lasting for months has proved perfectly compatible with full intellectual recovery. So, too, with the permanent retrograde amnesia. After recovery from tuberculous meningitis the permanent retrograde amnesia is usually measured in days and often in weeks or months, and, together with amnesia for the active stage of the illness, forms the only detectable mental deficit in an otherwise perfect recovery. By contrast, the retrograde amnesia following head injury is commonly measured in seconds or minutes (Russell, 1935), while retrograde amnesias of more than a few hours' duration are not only exceptional, but are probably always associated with some permanent defect in mental function other than the amnesia (Symonds, 1949).

Finally, we have never seen the syndrome of post-traumatic dementia (Symonds, 1949) or traumatic psychasthenia (Mapother, 1937). One patient complained for some months of a tendency to undue fatigue, and the Service patients, who receive pensions, have, as a whole, been slower to return to full-time work than have the civilians. But the great majority of our patients have ultimately not only returned to work but have done so with all their old efficiency, while measurable defects in intelligence,

personality changes and temper tantrums, post-meningitic headaches, and epilepsy are conspicuous by their absence. The quality of recovery is, in fact, as good as that seen after successful treatment of pneumococcal meningitis (Smith, Cairns, and Duthie, 1946). This is the more remarkable when it is remembered that some patients suffered from severe systemic tuberculosis in addition to the meningitis, and that others became totally and permanently deaf from the streptomycin.

One other condition that must be considered is Wernicke's encephalopathy. The main features of this syndrome have been summarized as " loss of appetite, vomiting, nystagmus, diplopia, palsy of external ocular muscles, apathy or apprehension, loss of memory, disorientation, confabulation, and coma " (*Lancet*, 1952). If severe generalized wasting is added, it becomes an accurate outline of the clinical picture seen in any moderately severe case of tuberculous meningitis. Fuller descriptions of the mental changes in Wernicke's encephalopathy only emphasize the likeness (Phillips, Victor, Adams, and Davidson, 1952). Moreover, mental recovery, when it occurs, appears to follow much the same pattern as in tuberculous meningitis and to be complete except for amnesia for the period of confusion (De Wardener and Lennox, 1947). It thus appears that in quality, pattern of recovery, and concomitant physical findings the mental disturbances of tuberculous meningitis bear a closer resemblance to those of Wernicke's encephalopathy than to those of head injury, of acute intoxications, or of other intracranial infections.

### Discussion and Conclusions

In brief, it may be said that the chief characteristic of the mental disturbances in tuberculous meningitis is a disproportion between the disorder of memory and that of other intellectual faculties. Early in treatment—that is, during the confusional state—this disproportion is not obvious because the gross failure of retentive memory is masked by semi-stupor or, more rarely, by frank delirium with hallucinations. But as the illness runs its slow course it becomes apparent that recovery of the memory defect lags farther and farther behind that of other intellectual functions until, in the end, the patient is left with a profound amnesia for much of his illness, and for the weeks or months preceding it, as his only permanent deficit.

It is tempting to try to correlate these mental changes with the pathological findings. It is notorious that in tuberculous meningitis the brunt of the disease falls on the base of the brain and particularly on the more anterior of the basal cisterns, the cisternae chiasmatica, interpeduncularis, et ambiens. In untreated cases the pathological changes are not limited to this site : the vessels over the convexity of the hemispheres are studded with tubercles, the brain itself may be oedematous, and some degree of infarction of brain tissue is the rule. In such cases the patients have usually been in profound coma for many days before they died.

But just as the stupor and general confusion of the moderately advanced, untreated case yields under treatment and is succeeded by the amnesic state, so, too, the pathological picture changes. In many of those cases that come to necropsy after a period of deadlock lasting for weeks, the inflammatory process is found to be virtually limited to the more anterior of the basal cisterns : the cisternae chiasmatica, interpeduncularis, et ambiens are choked with dense tuberculous exudate, while the cisternae pontis et magna show nothing more than a little thickening of the meninges. It is undoubtedly this exudate that, by virtue of its anatomical distribution, gives rise to many of the characteristic clinical findings ; for example, the communicating hydrocephalus, the optic atrophy, and, probably, the common sixth and third cranial nerve palsies (Cairns and Smith, 1952, figs. 117 and 118). This inflammatory process directly involves the floor of the third ventricle, and well marked hypothalamic disturbances complete the syndrome. In the Oxford series these disturbances have included hypertension (e.g., Case 2), glycosuria, anorexia or bulimia, hypo- or hyper-thermia, disturbances of sleep rhythm, diabetes insipidus, and Fröhlich's syndrome.

The correlation between the physical and pathological findings is thus unequivocal, and the question must be faced of whether or not there is any justification for attributing the mental picture to the same pathological changes.

There is a certain amount of circumstantial evidence to support this hypothesis. In the first place, the typical mental picture is not seen in other intracranial infections, such as general paresis, where the chief pathological changes are found in the substance of the cerebral hemispheres rather than in the hypothalamus and at the base of the brain (e.g., Case 5). Secondly, in those three cases already referred to that differed so markedly from our other fatal cases in that consciousness was fully preserved until shortly before death, the pathological findings showed an almost exact reversal of the typical pattern. In these three cases, and in these three only, the cisterna magna was obliterated by tuberculous exudate while the anterior basal cisterns were virtually clear.

Thirdly, there is the unmistakable correspondence between the intensity of the mental changes and that of the inflammatory process. This is best seen when intrathecal tuberculin is used in treatment (e.g., Case 4). During the tuberculin reaction the tuberculous lesion becomes hyperaemic and oedematous. This access of inflammation reaches its height about 24 hours after the injection and then subsides. The exacerbation of the mental disturbances follows exactly the same course, and this has been seen in cases where necropsy showed that active tuberculous disease was limited to the anterior basal cisterns.

Finally, there is an obvious analogy between tuberculous meningitis and Wernicke's encephalopathy. Not only are the physical and mental pictures in the two conditions remarkably alike, but in both the main pathological process is characteristically situated in, or in immediate relation to, the floor of the third ventricle and midbrain. Campbell and Russell (1941), when discussing the correlation between the clinical and pathological abnormalities of Wernicke's encephalopathy, comment on " the apparent fact that lesions situated as in Wernicke's disease can disorganize mental function ". Recently renewed interest has been shown in the part played by the diencephalon and brain-stem in the maintenance of consciousness (Cairns, 1952), and circumscribed lesions of the diencephalon have been shown to produce mental changes in man (Gillingham, 1953) and in animals (Sherwood, 1953).

Such evidence as we have that the mental changes in tuberculous meningitis are directly related to the characteristic anatomical lesion is, at the best, no more than suggestive. Nor is this any place to attempt to discuss the inter-relationship of different parts of the brain in regard to mental function. Nevertheless, we venture to present these observations on the mental changes in tuberculous meningitis in the hope that they may form a small contribution towards the delineation of the various patterns of mental disturbance associated with relatively clear-cut pathological lesions.

## Summary

The mental disorders seen in tuberculous meningitis have been studied in adult patients both during the illness and after recovery.

The characteristic pattern of mental disorders seen once the full clinical picture has developed is described, together with variations in this pattern.

Three separate mental states are distinguished : the confusional state, the amnesic state, and the post-recovery state.

The chief characteristic of the mental changes is the predominance of the disorder of memory over the other intellectual deficits. This is seen most clearly in the amnesic and post-recovery states.

The pattern of recovery from the confusional and amnesic states is described.

The pattern of the mental disorders in tuberculous meningitis is compared with that seen in other organic dementias, notably that following head injury. It is pointed out that the picture in tuberculous meningitis is sufficiently characteristic to have diagnostic importance.

The possible relation between the mental disturbances of tuberculous meningitis and the characteristic pathological lesion is briefly discussed.

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