NEUROSYPHILITIC CONDITIONS

General Paralysis, General Paresis, Dementia Paralytica

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American Handbook of Psychiatry

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Haslam, an apothecary at Bethlem Hospital in London, is usually credited with having given the first description of general paralysis in 1798. In 1793, however, Chiarugi, the "Italian Pinel," had described some presumably genuine cases.

Haslam's thesis consisted of a report of twenty-nine consecutive cases of insanity which came to autopsy. Of the twenty-nine patients, four may conceivably have been cases of dementia paralytica. The credit for having described this disease is based chiefly on one report—that of a man, forty-two years of age. The mental illness had come on suddenly, while he was working in a garden. He believed himself to be the king of Denmark and at other times the king of France. He also professed to be the master of all dead and living languages and claimed that he had come to England with William the Conqueror. Later, he developed apoplectic phenomena. His speech was inarticulate. He became demented, bedridden, and emaciated, and his buttocks ulcerated. Eighteen months after the onset, he died. Postmortem examination revealed opaque and thickened meninges and enlarged ventricles. It is fair to say that Haslam unknowingly described in this report a typical case of general paralysis.

In the upsurge of syphilis during the Napoleonic wars, many former soldiers developed general paralysis, and French psychiatrists deserve credit for the elucidation of the disorder. Esquirol, in 1814, directed attention to the slurred speech accompanying it. In 1822 Bayle, a young physician at the insane asylum of Charenton in the suburbs of Paris, was the first to recognize general paralysis as a disease entity with characteristic symptoms and distinctive brain changes. The importance of this contribution lies in the fact that, for the first time, a group of patients whose disease could be recognized both clinically and anatomically as a distinct entity had been separated from the general run of mental cases.

In 1826 the French psychiatrist Calmeil referred to the disease as *paralysie generate des alienes* (the general paralysis of the insane). To this day, the term has been retained with slight variations in most countries. Calmeil explained why he coined this term: The French clinicians were impressed by the fact that no other mental disease culminated so frequently in “general paralysis” of all the mental and physical faculties. In the advanced stage, the patients developed a generalized weakness of the entire muscular system. They became unable to move about and finally became bedfast. On the other hand, in the institutions there were many other cases of insanity with similar abnormal behavior and dementia, yet in spite of being there for twenty and more years, the patients did not develop this kind of general weakness.

Etiology

There was much speculation as to the etiology of the disease. Calmeil only once referred to syphilis in the anamnesis of a known debauchee, saying only that he did not know whether this patient had a venereal disease and whether he had been treated with mercury. For many years, it did not enter the minds of psychiatrists that a "skin disease" could also be responsible for a mental disease. Most earlier authors believed that occupations in life which involved hardships, both mental and physical, favored the onset of the illness. As late as 1877, von Krafft-Ebing gave the following etiologic possibilities: heredity, dissipation (Bacchus and Venus), smoking of ten to twenty Virginia cigars, excessive heat and cold, trauma to the head, exhaustive efforts to make a living, weak nerves, and fright. Among women the menopause was given as the most important factor because the onset of general paralysis was frequent between the ages of forty and fifty. Strikingly, von Krafft-Ebing in 1877 did not mention syphilis among the possible causes, although Esmarch and Jessen had published their now famous paper on syphilis and insanity in 1857.

At about the same time, 1860, the Danish physician Steenberg also saw such a connection. In his doctoral thesis entitled, "Syphilitic Brain Disease," Steenberg reviewed the hitherto assumed causes of dementia paralytica, such as heredity, psychic causes, overwork, and alcoholism. He showed that separately and collectively they were insufficient to explain dementia

paralytica, but that, by assuming syphilis as the etiologic factor, a solution as to the cause of this disease was at hand. In 1874 Jespersen, among others, on the basis of a large amount of data, furnished the evidence that general paralysis resulted from syphilis.

At the International Medical Congress in Copenhagen in 1884, where the question of syphilis in dementia paralytica was discussed, there occurred one of the last important disputes concerning the etiology of general paralysis. The Danish physicians were outspoken in their assertion that dementia paralytica was a result of syphilis. Mobius (Leipzig) shared this view. Bajenoff (Moscow) discussed Maudsley's (London) absolute rejection of the theory of the syphilogenic origin of the condition. He himself was skeptical. Magnan (Paris) mentioned that at the mental hospital of St. Anne in Paris, where 300 general paralytics were admitted annually, only thirty to forty syphilitics were found among the cases of dementia paralytica. He again emphasized the role of alcohol. In France almost no one, with the exception of Fournier, believed at that time that there was a connection between general paralysis and syphilis. Shortly before the turn of the century, in 1898, no less an authority than Virchow, in a discussion before the Berlin Medical Society, vehemently denied the syphilitic etiology of general paralysis, tabes dorsalis, tabetic optic atrophy, and aortic aneurysm.

At this stage, the trend of investigation shifted from the clinic to the

laboratory. With the introduction of the newer methods of staining, histopathologic studies on the brain cortex of the mentally ill received a new impetus. In 1904 Nissl and Alzheimer gave a detailed description of the microscopic changes in the brain of general paralytic patients, which were uniform in all instances, including those without a history of syphilis. Furthermore, the Wassermann test, which had been devised about this time (1906), gave a positive reaction in blood and spinal fluid. Schaudinn, in 1905, had discovered the organism of syphilis, but, owing to technical difficulties, it was not until 1913 that Noguchi and Moore were able to demonstrate spirochetes in the brain of general paralytics. The demonstration of *Treponema pallidum* in the cerebral cortex closed the chain of evidence concerning the syphilitic nature of the disease.

Frequency

Throughout the world, until the advent of penicillin, general paralysis was responsible for a high proportion of the admissions to mental institutions. Of the patients admitted to state hospitals for mental disease in the United States, between 5 and 15 percent were so afflicted. In the mental hospital Dalldorf, in Berlin, the admission rate of both men and women paralytics in the period from 1892 to 1902 varied between 22 and 32 percent of the total admissions. In 1930 the number of general paralytics admitted to the Tokyo Insane Hospital constituted 30.7 percent. In Batavia (former Dutch

East Indies), one third of all Asiatic patients admitted to the psychiatric pision of the General Hospital suffered from neurosyphilis. At the Central State Hospital of Indianapolis, from 1927 to 1931, the admission rate due to general paralysis varied between 20.5 and 24.7 percent. By 1947 the figure had dropped to 12.2 percent, and in 1970 it had dwindled to less than 1 percent.

Most general paralytic patients now in mental institutions of the United States are carryovers from the previous decades of high-admission rates. They are patients who were treated with malaria or penicillin but in whom residual organic defects prevented a return to the community.

In a group of 241 patients with various types of neurosyphilis, there were twelve cases of general paralysis.

Clinical Features

The clinical picture of general paralysis consists of a progressive deterioration, leading to a complete undermining of the whole mental and physical personality. It always terminates fatally if not properly treated.

The symptomatology is varied, and general paralysis may produce any psychiatric syndrome, such as manic-like phases, severe depressions, schizophrenic symptoms, and, in the initial stage, a psychoneurosis.

The incubation period averages fifteen years, the lower limit being three years and the upper range approximately forty years.

Mental Symptoms

The most outstanding feature of general paralysis is the progressive destruction of all mental functions. The central symptom of the disease is the dementia, around which are grouped a variety of accessory psychiatric and neurologic manifestations.

The onset of the mental disorder is often difficult to ascertain. The history, as given by the patient, concerning the earliest symptoms is usually worthless. Of greater importance are the observations of close relatives, but even the patient's wife may fail to see the significance of the earliest changes, such as misplacing various articles and repeating the same story several times. One patient, an ardent card player, would sit up all night playing cards, and at other times would shuffle a deck of cards endlessly without playing.

Memory soon becomes affected. Recent events cannot be remembered, while remote happenings may still be recounted with accuracy. The patient forgets that he has just eaten his dinner, and he is confused about the time of day. Although the patient may do some minor erratic things, his personality may remain intact for a considerable length of time, and routine duties may be carried out remarkably well.

A disturbance of affect may set in relatively early. The patients become apathetic and dull, and remain unimpressed by tragedies that may strike their

families. Sometimes, the incipient stage is characterized by anxiety and emotional instability. The appearance of euphoria is most characteristic. This feeling of well-being is difficult to differentiate from the peculiar stage of happiness in the manic phase of a manic-depressive psychosis. It may be a component of the loss of judgment.

With the advance of the illness, irritability, loss of memory, and slovenliness become more obvious. At this stage, gross mental abnormalities may suddenly appear. I knew a patient who drove at high speed through a red light, killing a pedestrian. When he was arrested, he did not comprehend the seriousness of the charge and told police in an excited manner that he was King Herod. Some patients commit sudden acts of violence. One patient at a public health center, where he was receiving weekly injections of tryparsamide, took the door of the waiting room off the hinges and tore the linoleum from the floor. A bartender entered his competitor's business place and, with an ax, hacked the furniture to pieces. Sometimes patients will do odd and silly things, such as going to the grocery store and walking away without paying the bill. One patient tried to buy a Buick automobile in a five-and-ten-cent store. A merchant created confusion in a bank, where he insisted on cashing a check for $25,000 without having funds on deposit. One patient forced his wife into the car and drove her to the local mental hospital, saying that she was insane. Another patient came home with a six-foot maple tree and tried to plant it on the windowsill.

Such acts are the result of gross loss of judgment, which is one of the basic symptoms of the disease and from which some of the delusions originate. Delusions, however, are not always present in the clinical picture. Some patients live merely in childlike contentment, manifesting boastful tendencies throughout the course of the disease. The content of the delusions is usually related to the educational background and to the news of the day. In the 1920s, when Henry Ford was in the limelight, many patients imagined themselves to be Henry Ford. At about the same time, the Prince of Wales, then a bachelor, visited the United States. An unmarried woman with general paralysis told me that she was engaged to marry the Prince. In 1933, when prohibition ended, one patient boasted of drinking several gallons of whisky a day. During World War II, a grandiose paralytic told medical students during a lecture that he was a pe-bomber pilot and that he had just returned from the battle of the Coral Sea, during which he had sunk several Japanese battleships and a dozen cruisers. His plane had had both wings shot off, but he returned safely to his base. Other patients during the war period claimed to own aircraft carriers and battleships. The records of the grandiose delusions often give a panorama of the historic and social background of a nation. In France the patients used to be Napoleon, in Germany they were the Kaiser, in Czarist Russia they were czars and grand dukes. But in Soviet Russia they are great engineers or inventors. Grandiose delusions, as a rule, are transitory and disappear easily, even without treatment. On the other hand, in a few malaria-

treated patients, exalted delusions persisted for years, although the serology had reverted to normal.

As the psychosis progresses, the mental deterioration becomes the outstanding symptom, and the original symptomatology recedes to the background. In the terminal stage the deterioration is profound. There is no other mental disease in which dementia is so complete. At this time there are often wild outbursts of destructiveness, and the strongest sedation is necessary to control the patient. The most absurd things may happen. One patient drove a pencil deep into the root of his tongue, “trying to dig out a bug which was under his molar teeth.” Frequently, one observes prolonged grinding of the teeth which is almost pathognomonic of the disease. Finally, the patients become bedridden and develop a “general paralysis” of all the intellectual and physical functions. Bedsores over hips and buttocks may develop, which even the utmost care cannot prevent. In other instances, spasticity sets in, causing flexed extremities, and subsequent contractures of legs and arms. Following penicillin treatment, the physical condition of the patient is better maintained despite dementia, and distressing states such as these here described are now rarely seen.

Psychiatric Syndromes

How frequently the various syndromes occur is difficult to estimate, because they cannot be sharply differentiated and often merge into one another. Bostroem's figures, listed in Table 5-1, are possibly the most reliable.

Table 5-1

SYNDROME	PERCENT
Simple dementia	34.0
Euphoric dementia	29.0
Expansive type	10.0
Hypomanic form	0.5
Depressive form	7.0
Delirious and confusional state	11.0
Motor excitement	5.5
Schizophrenic syndrome	3.0

The Simple and Euphoric Dementias

The most common type of general paralysis is the gradually deteriorating form. A slowly advancing dementia occurs without delusions and excitement. Impairment of judgment, memory defects, and lack of insight are the principal symptoms. In half of the cases, the dementia is colored by a euphoric state.

The Expansive and Depressed Forms

The usual textbook picture of general paralysis represents the expansive type with delusions of grandeur. The exalted mood, the absurd delusions of wealth and power, and the happy, cheerful frame of mind make the diagnosis easy.

The depressed type may start with an attack of extreme worry lasting for months before other symptoms appear. The picture may resemble an agitated depression in middle life or an involutional melancholia. One of my patients believed that he was going to die and prayed in a loud voice for long periods of time. A fifty-year-old preacher threatened to chop off his head as a sacrifice for the sins which he had committed. Occasionally there are successful suicide attempts. The taking of poison was the first symptom of disease in one instance; in another, a patient jumped out of a third-floor hospital window.

The Schizophrenic Syndrome

About 3 percent of the cases of general paralysis present the schizophrenic form. From South America a much higher rate has been reported. Some patients in this group present paranoid delusions as the only outstanding clinical manifestation. One patient told me that people were reading her thoughts; another accused relatives and physicians of trying to poison him to collect his insurance. A laborer brought a revolver to the factory and shot a fellow worker, imagining that the latter held a grudge against him. Paranoid delusions occurring in general paralysis may be as fleeting and temporary as the grandiose delusions, and often disappear following therapy. Instances with the psychopathology characteristic of schizophrenia have been reported by the most experienced psychiatrists. Bumke tells of a case with negativism from the pre-Wasserman days. For one year this patient was considered a catatonic schizophrenic, until he suddenly died of paralytic convulsions.

Hallucinations occur in about 6 percent of cases. Auditory and visual hallucinations are most common, but olfactory hallucinations have also been observed. At times, it is difficult to say whether one is dealing with true hallucinations or with confabulation. Hechst, in a histologic study of the schizophrenic type of general paralysis, came to the conclusion that schizophrenic symptoms are not associated with any particular localization of the paralytic brain process.

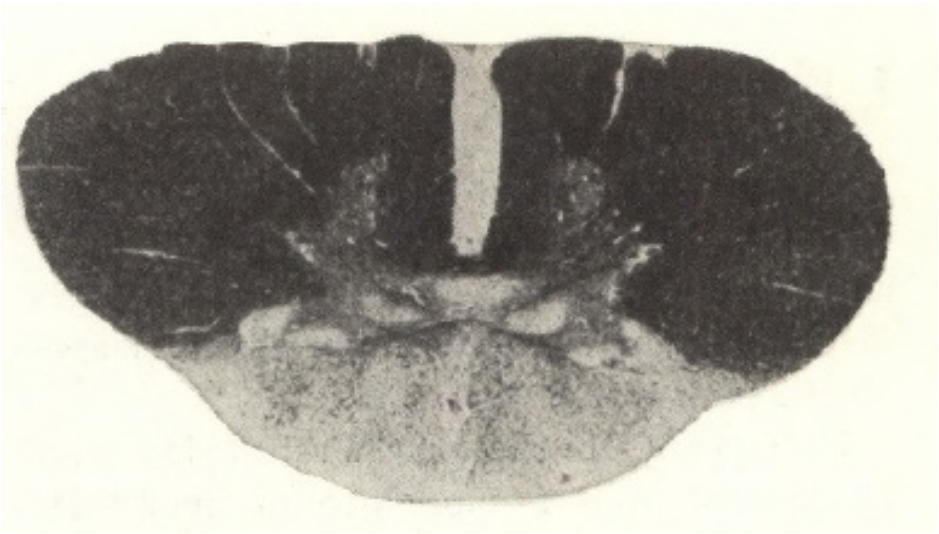
The Senile Form

Until Nissl's and Alzheimer's histopathologic studies, senile general paralysis was in the main unrecognized, being diagnosed as senile or arteriosclerotic psychosis. In the aged, the disease is particularly difficult to diagnose without a spinal fluid examination. In most cases, argyrophil plaques in the brain are absent, but senile alterations are occasionally added to the paralytic process. Contrary to prevailing opinion, excellent therapeutic successes have been obtained in old age.

The Taboparalytic Form

In the taboparalytic form there is a combination of general paralysis and tabes dorsalis (Figure 5-1). Some clinicians are willing to make a diagnosis of taboparalysis only if, in addition to the absent patellar reflexes, there is an ataxic gait or other tabetic symptoms, such as root pains, crises, etc. Absent knee jerks without other symptoms of tabes are common, and these cases are not different from those of the usual general paralytic patient.

Figure 5-1.



Spinal cord in taboparalysis. There is a degeneration of the posterior columns. Weil's myelin sheath stain.

Lissauer's General Paralysis

In 1901, Lissauer called attention to an atypical type of general paralysis, characterized by epileptiform and apoplectiform attacks, followed by signs of a localizing nature, such as hemiplegia, aphasia, apraxia, or hemianopsia. Lissauer's general paralysis is rare. At autopsy, there is extreme atrophy of an entire cerebral region, or of a group of convolutions, which far exceeds the generalized cortical atrophy of the brain in the average case.

Prepsychotic Personality

Most authors agree that, in general paralysis, the premorbid personality influences the clinical picture. The cerebral process seems to serve as a release for personality trends, intensifying innate tendencies. If an inpidual with a cyclothymic constitution develops general paralysis, he will frequently show a manic or depressive reaction. If he has euphoric tendencies, he will become expansive and excited. Likewise, schizoid personalities are prone to show schizophrenic states. This relation, however, is not an absolute one. In some instances the clinical picture corresponds only slightly to the premorbid personality, and in others not at all.

Physical Signs

The important neurologic symptoms of general paralysis are the speech defect, pupillary abnormalities, handwriting disorders, changes in the tendon reflexes, convulsions, and apoplectic phenomena.

In the incipient stage no physical signs may be present, and a most careful neurologic examination, including psychologic testing and electroencephalogram, may give no clue as to the organic nature of the illness. But an examination of the cerebrospinal fluid will, even at this early stage, reveal a typical "paretic" formula. In some instances, the nervous manifestations were attributed to stressful life experiences until, weeks later, more obvious symptoms became manifest or the spinal fluid was examined. On the other hand, the disease may begin with a sudden convulsion, a transient hemiplegia, or an aphasia preceding mental changes by several months.

The disorder of speech is so typical that a correct diagnosis can often be made as the patient talks. The disturbed articulation is manifested as hesitation and later as slurring. The speech defect used to be the main symptom on which the psychiatrists of the nineteenth century depended for diagnosis. If this particular speech involvement was present in an insane patient, he was considered incurable. It can often be recognized during conversation. Otherwise, test phrases such as "Methodist Episcopal Church,"

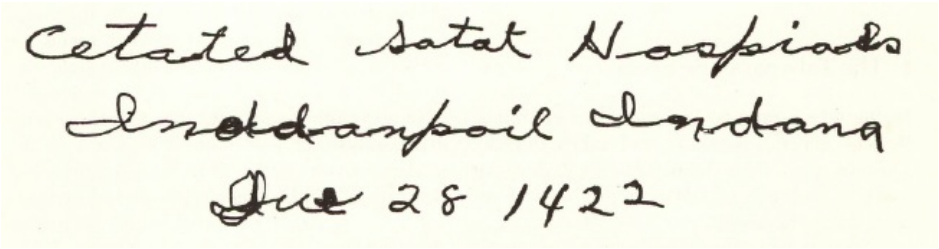
"army reorganization," "national hospital for the epileptics," and others have to be employed to reveal the disturbance. Later, the patient is unable to form sentences, and in the terminal stage, the speech is completely unintelligible. It should be added that cerebral arteriosclerosis with bulbar symptoms may cause a similar speech impediment.

The pupillary changes consist of irregularity of outline, inequality of size, and impairment (diminution or absence) of the light and convergence reflexes. Normal pupils are present in 5-10 percent of cases, but toward the end of the illness almost all untreated paralytics have pupillary abnormalities. Following penicillin treatment, there is, at times, an improvement in the pupillary reactions. Of greatest importance is the Argyll Robertson pupil. The frequency of this sign depends on the stage of the disease. It is infrequent in incipient general paralysis; in the advanced stage, it is present in about 50 percent of cases. Pupils which are fixed to both light and accommodation are less frequent. The diagnostic value of absolute fixation of the pupils is not as great as that of the Argyll Robertson sign; the former may be observed in various other diseases, for example, cerebral arteriosclerosis, multiple sclerosis, or alcoholism.

Handwriting disturbance is manifested by misspelled words, omissions, misplacements, and repetitions of letters and syllables (Figure 5-2). Almost never does the patient recognize the mistakes. Occasionally, the outstanding

feature of the handwriting disorder is the tremor. In the advanced stage, there is agraphia, the patient being unable to draw more than a few wavering lines. The handwriting is normal in 10 percent of patients.

Figure 5-2.



Sample of handwriting in general paralysis. The patient was asked to write Central State Hospital, Indianapolis, Indiana, and the date, which was June 28, 1952.

Junius and Arndt reported on knee jerks in 992 untreated cases; patellar reflexes were normal in 16 percent, increased in 54 percent, and diminished or absent in 30 percent. The abdominal reflexes are occasionally absent; less frequently, the cremasteric reflexes are wanting.

A fine or coarse rapid tremor particularly of the extended fingers, tongue, and labial muscles is often present. The face becomes expressionless and devoid of normal mimic motions. There is flattening and smoothing out of the nasolabial folds.

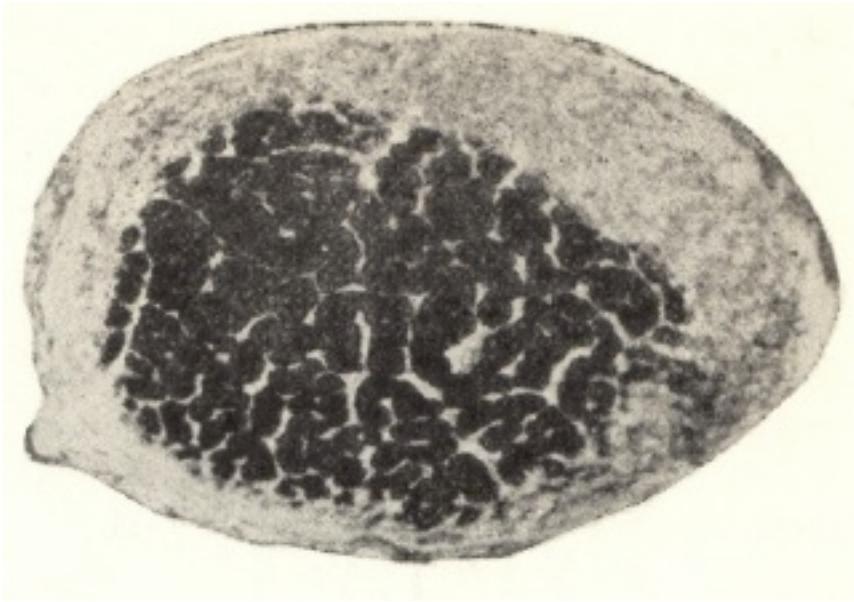
The most important motor disturbances are convulsions and apoplectic phenomena. They appear in any stage of the disease and are present in 35-65 percent of cases. Psychomotor attacks or epileptic equivalents occur, manifested by sudden periods of excitement, extreme violence, and impulsive shouting, sodes. In successfully treated patients, the Some patients have died during these epi-convulsions, as a rule, cease entirely. Occasionally, however, the seizures persist indefinitely, despite disappearance of all other symptoms. In a few otherwise completely recovered cases, convulsions made their appearance for the first time a few months or several years after malaria or penicillin therapy.

Syphilitic Optic Atrophy

In about 2 percent of general paralysis there is complete or nearly complete blindness owing to optic atrophy. If special attention is paid to the early stages of this complication, partial optic atrophy can be recognized in about one third of the cases (Figure 5-3). The early signs consist of field defects, and somewhat later of pallor of the optic disks, reduction of visual acuity, and difficulties in distinguishing colors.

Syphilitic optic atrophy is due to a chronic inflammatory process, followed by a slow degeneration of the nerve fibers. Infiltrations, composed of plasma cells and lymphocytes, extend from the periphery along the septa toward the interior of the optic nerves, first producing marginal degeneration. This manifests itself in a concentric and slowly advancing narrowing of the visual fields.

Figure 5-3.



Partial syphilitic optic atrophy in general paralysis. The optic nerve reveals a large marginal area of demyelination. There was two-grade paleness of the optic disk and an irregular contraction of the visual field. (Courtesy of Charles C. Thomas, Publisher.)

Involvement of the Aorta

The most important and frequent extracerebral lesion of general paralysis is syphilitic aortitis, having been observed at autopsy in 33-56 percent of cases. Most instances are clinically asymptomatic, with the exception of the aortic aneurysm and aortic valve incompetency. In the author's own findings, a slight or moderate widening of the aortic arch, as revealed in X-rays, was present in 7 per cent. An insufficiency of the aortic valve was diagnosed by auscultation in 2 percent.

Laboratory Findings[1]

Cerebrospinal Fluid

The abnormalities of cerebrospinal fluid consist of an increase of cells, elevation of the total protein, increase in globulin, a first-zone colloidal gold curve (paretic curve), and a strongly positive Wassermann reaction. The blood Wassermann and Kahn tests are positive in 95 percent.

There are patients in whom only a complete spinal fluid examination permits a differential diagnosis between general paralysis and other psychiatric conditions. Negative spinal fluid in an untreated (but not in a treated) patient precludes the diagnosis of general paralysis.

Electroencephalogram

In untreated patients, abnormal or borderline tracings are observed in from 55-81 percent. In general paralysis or in any other type of neurosyphilis, there is no characteristic electroencephalographic pattern. The more abnormal the electroencephalogram, the greater is the likelihood of a history of convulsions. The incidence of abnormal electroencephalograms, in cases of general paralysis with seizures, is 91 percent, as compared to 44 percent in those without convulsions.

Following successful therapy, an improvement in the electroencephalographic tracings has been reported in most instances. In the interpretation of an electroencephalogram the existence of organic alterations may be revealed, but an occasional absence of electroencephalographic abnormality does not exclude the presence of a cerebral lesion.

Pneumoencephalogram

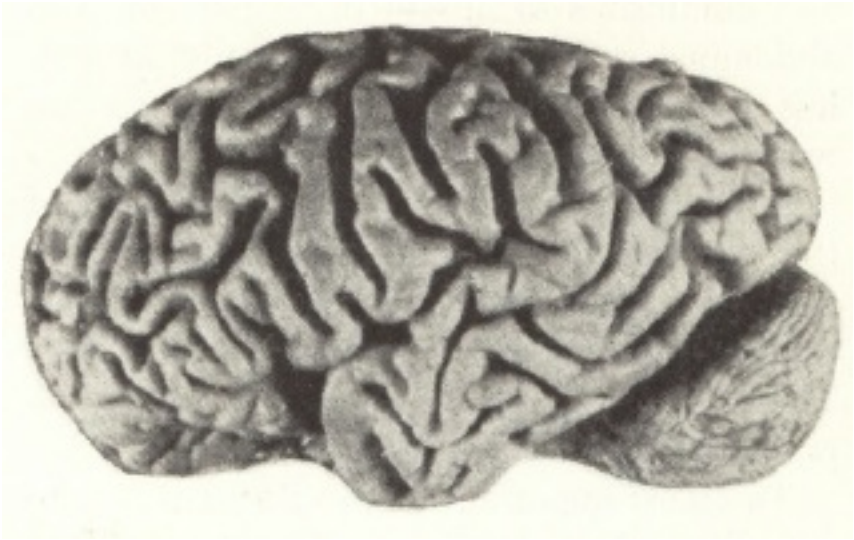
Pneumoencephalography is not a delicate diagnostic method because of the limitations in the recognition of minor cortical atrophies. It is of little auxiliary value in the diagnosis of early general paralysis. In advanced cases there is dilatation of the ventricular system and of the subarachnoid spaces.

Pathology

Gross Changes

The macroscopic findings in general paralysis consist of cloudy and thickened meninges, atrophy of the cerebral convolutions (Figure 5-4), enlargement of the ventricles, and granular ependymitis. In incipient cases there may be almost no gross changes in the brain. The turbidity of the meninges is the result of a chronic syphilitic meningitis. Minor degrees of atrophy of the cerebral convolutions are difficult to discern. The decrease of weight due to the atrophic process may amount to 100 g., or more, although it is not rare to find brains with normal or even increased weight.

Figure 5-4.



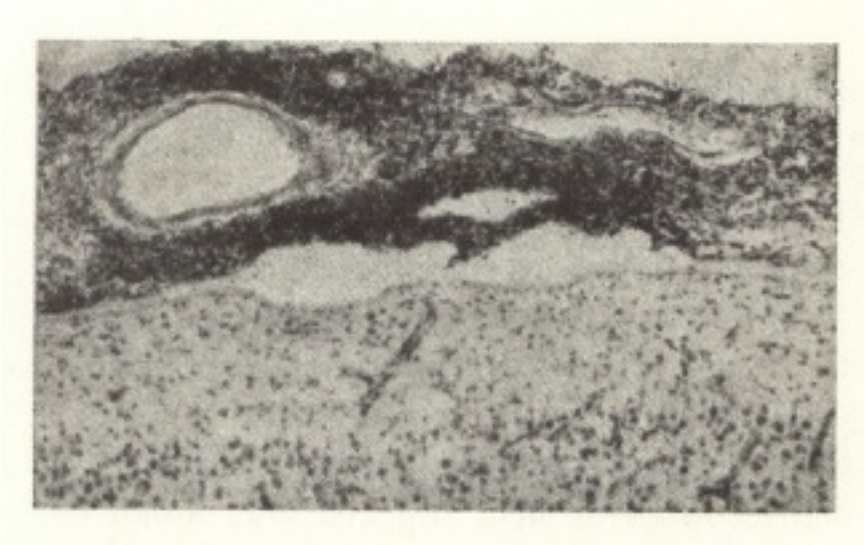
Brain in general paralysis. Marked atrophy of the cerebral convolutions. The sulci are gaping.

Microscopic Changes

The main histologic feature of general paralysis is a syphilitic meningoencephalitis. The meninges are infiltrated with plasma cells and lymphocytes (Figure 5-5). In the cortex, and to a lesser degree in the white matter, there is perivascular infiltration (Figure 5-6). Some of the infiltrating cells in the vessel walls and the rod cells of Nissl, when stained by the Turnbull blue method, reveal blue pigment granules. This pigment represents the so-called "iron of general paralysis." In the capillaries, multiplication of endothelial cells takes place, causing capillary obstruction. Moreover, there is

new formation of capillary buds and of small blood vessels, most of which never become normally functional blood channels. These newly formed vessels pierce the parenchymatous tissue. They contribute to the subtle disorganization of the cortex and thus become an important factor in the causation of the ensuing dementia. Another alteration of the mesodermal tissue is the formation of rod cells, the *Stabchenzellen* of Nissl. The rod cells are derivatives of Hortega's microglial cells, which assume the form of enlarged rod-shaped cellular elements. And finally, there is a diminution of the perivascular clasmatocytes (histiocytes), only seen on supravital study.

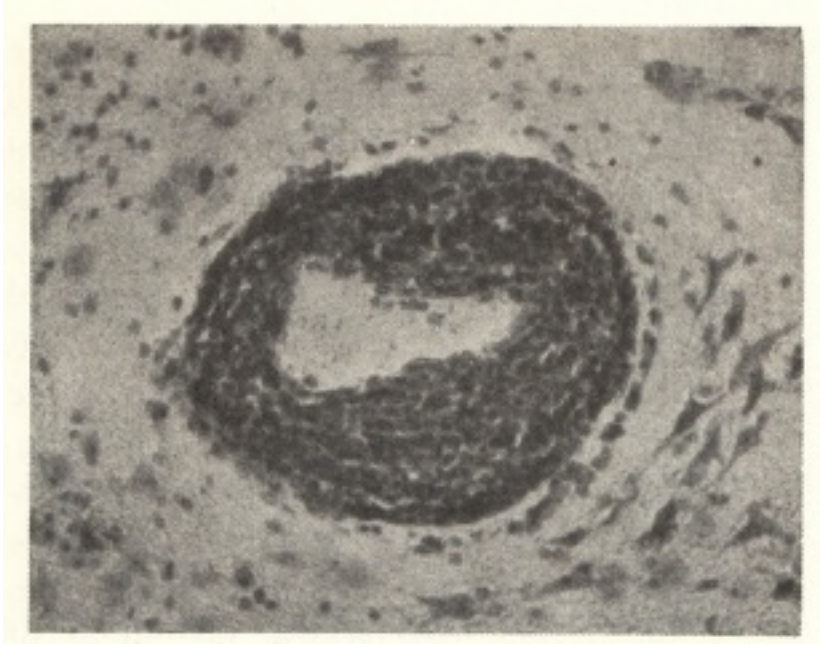
Figure 5-5.



General paralysis. Syphilitic meningitis. The meninges are infiltrated with

plasma cells and lymphocytes. Toluidine blue stain

Figure 5-6.



Perivascular infiltration of a cortical vessel in general paralysis. Toluidine blue stain.

The scarcity of the phagocytic elements in the general paralytic brain is linked to the question as to why only a small number (3-5 percent) of all untreated syphilitics develop general paralysis. Clasmatocytes are generally identified with antibody formation and with local tissue immunity.

The ganglion cells show all degrees of changes, the majority of diseased

nerve cells exhibiting the chronic type of cell degeneration. But normal-appearing neurons are found lying next to markedly degenerated forms. The myelin sheaths and the axis cylinders, as well as the neuroglia reveal minor alterations. Cajal gave an excellent review of the glial changes in general paralysis.

The summation of the histopathologic changes in both the mesodermal and the ectodermal tissue leads to a disturbed cytoarchitecture of the cortex, in which the normal arrangement of the cell layers is lost (Figure 5-7).

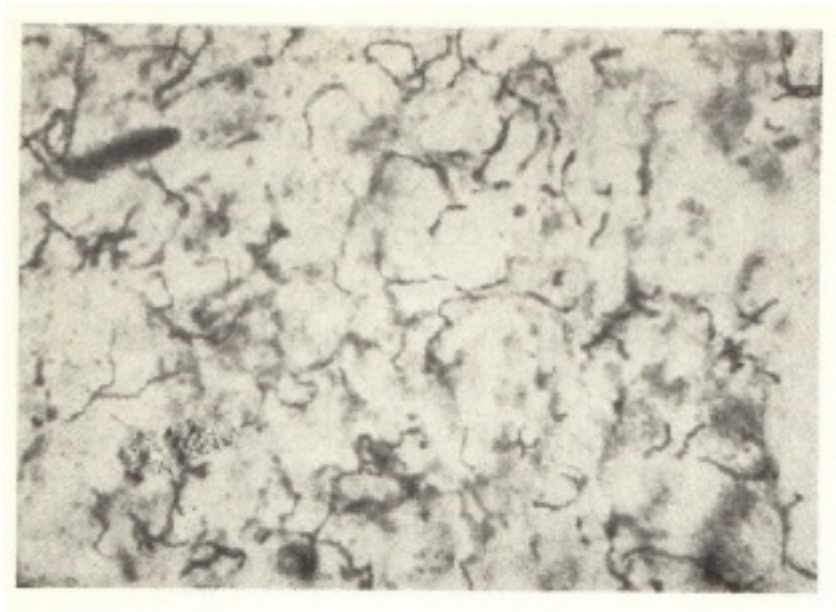
Figure 5-7.

Disturbed cytoarchitecture of brain cortex in general paralysis. The normal arrangement of cell layers is lost, and the ganglion cells show all degrees of degeneration. Perivascular infiltration is pronounced. Toluidine blue stain.

Spirochetes in the Brain

In brains of untreated patients, spirochetes in great numbers may be present (Figure 8). In other brains a few or no organisms can be found, despite time-consuming search in many tissue blocks. In his famous 1913 studies, Noguchi, and all others after him, succeeded in finding *Treponema pallidum* in approximately one fourth of the cases. The high percentage of negative results is explained by a possible cyclic decrease, and by an increase in the number of organisms. During the phasic decrease, spirochetes rarely attain such numbers as to put themselves within easy reach of microscopic search. *Treponema pallidum* has a preference for the gray matter. In the white matter and in the meninges they are rare, if not completely absent.

Figure 5-8.



General paralysis. Spirochetes in cerebral cortex. Dieterle stain.

Treatment

After the syphilitic etiology of general paralysis had been established, antisyphilitic treatment with arsphenamine (salvarsan), bismuth, and mercury compounds was tried, but without success.

Malaria Therapy

For many years it had been recognized that mental patients improved occasionally after an intercurrent febrile disease, such as typhoid fever, malaria, erysipelas, and tuberculosis. In 1887, Wagner-Jauregg proposed the idea of intentionally inducing a febrile disease for therapeutic purposes. He selected first the streptococcus of erysipelas, but this proved unsatisfactory. A simple fever-producing agent became available in 1890 with Koch's tuberculin. Wagner-Jauregg used tuberculin at first in all types of psychiatric patients. After observing improvement mainly among general paralytics, he concentrated on that mental disorder. Later, he used typhoid vaccines.

During World War I, a soldier who had contracted malaria on the Balkan Front was admitted by mistake to the psychiatric clinic of the University of Vienna. Wagner-Jauregg, then head of the clinic, seized this opportunity, and on June 14, 1917, inoculated three general paralytic patients with the blood from this soldier. This marked the beginning of malaria therapy. The first favorable reports of this mode of treatment were received with skepticism,

but psychiatrists in Europe soon hailed the discovery. In 1927 Wagner-Jauregg was awarded the Nobel prize for this achievement.

Malaria therapy consisted of inoculating a general paralytic patient with 1-3 cc. of *Plasmodium vivax* (tertian) malaria blood, obtained from another patient who was undergoing this treatment. The patient was permitted to have eight to twelve malarial paroxysms with daily temperature elevations ranging from 103 to 105° F. Malaria fever was then terminated with quinine.

Penicillin Therapy

In 1943, when Mahoney and co-workers suggested that penicillin had treponemicidal action, the National Research Council furnished the expensive new drug to a few psychiatrists (Dattner, Ebaugh, Solomon, and Bruetsch) for evaluation in the treatment of general paralysis. It soon became apparent that penicillin in the amount of 10 million units was equal to malaria therapy and would surpass it if given in still higher total dosage. Although *Treponema pallidum* was extraordinarily sensitive to penicillin, it was possible to show that 10 million units were not sufficient because spirochetes persisted in some brains. A minimum of 15-20 million units was recommended for maximal results in general paralysis.

Malaria therapy produced full recoveries in 35 percent of unselected patients. Penicillin, in the total dosage of 10 million units, raised the recovery

figure to 50 percent.

Latin-American investigators by using a combination of penicillins which maintain various levels of blood concentration, raised the recovery rate to 83 percent. The schedule consists of three injections of 2.4 million units of benzathine penicillin G (1.2 million units into each buttock) on the first, fifth, and ninth days, plus twenty injections of 500,000 units of procaine penicillin, administered every twelve hours. The total dosage is 17,200,000 units, given within ten days.

The disappearance of mental symptoms may begin during therapy, or it may be delayed for several weeks or months. Within six to twelve months there will be an improvement in the nonspecific tests of the spinal fluid (cell count, globulin, total protein, and the colloidal gold reaction). But the Wassermann tests of blood and spinal fluid may not become negative for ten years or longer. Persistence of positive serologic tests for syphilis, or progression of clinical symptoms, does not necessarily mean a continuation of infection. Treatment for the sole purpose of obtaining seronegativity is usually futile.

The favorable effect of penicillin is also reflected in the brain tissue. There is a reduction and final disappearance of the round cell infiltrations, of Nissl's rod cells, and of the iron pigment.

The action of penicillin is on the syphilitic organisms themselves. Malaria therapy, on the other hand, stimulates the defensive powers of the host by activation of the reticuloendothelial cells (clasmatocytes, histiocytes).

There is convincing evidence that penicillin alone is capable of curing general paralysis. Where it fails, malaria therapy will also probably fail.

To sum up, penicillin in the treatment of general paralysis is highly efficacious in large dosage. It is inexpensive and practically without risk, and the treatment is of short duration.

Retreatment

If the patient has received a minimum of 15 million units of penicillin, retreatment is usually not necessary. If there is no improvement after three months, another course of penicillin may be given, for the penicillin might have been absorbed poorly from the muscle depots.

Penicillin Sensitivity[2]

Penicillin allergy is now the most common of all drug allergies and the most frequent cause of anaphylactic shock in man. In cases with a clear-cut penicillin allergy, penicillin should not be used. When the history of penicillin allergy is less clear-cut, consideration may be given to penicillin skin testing

or hemagglutination tests. Skin tests using nanogram amounts of penicilloyl polylysine and penicillin from the vial detect many, but not all, cases of penicillin allergy. Fatalities due to intradermal testing are extremely rare, but have been reported. Intradermal tests should be followed by intramuscular tests using minute amounts of penicillin. All penicillin allergy testing should be done in the hospital with resuscitation equipment at the bedside, experienced medical personnel, and a large-bore intravenous drip running.

Symptoms of anaphylaxis to penicillin include vertigo, nausea, flushing, pruritis, dyspnea, and abdominal pain. At the first sign, 0.5 cc. at 1/1000 epinephrine and 50 mg. Benadryl should be given IM, and an intravenous drip with large needle started. If severe dyspnea or hypotension occurs, intravenous vasopressors, air way, and assisted respiration will be necessary.

One complication of antibiotic treatment of syphilis is the Jarisch-Herxheimer reaction. The reaction is presumed to be a response to antigens released from killed spirochetes. Fever appears within twelve hours of the onset of treatment and lasts up to 48 hours. Temperatures of 102° F are not rare and 104° F has been recorded. Aspirin and skin cooling measures may be used for treatment. In neurosyphilis, convulsions and increased agitation may appear. The patient must be sedated and restrained if necessary. Treatment should be continued with no change in the original schedule.

If penicillin cannot be used, tetracycline is the drug of choice. The drug should be given orally in pided doses of 2 g. per day for thirty to forty days for neurosyphilis. Follow-up spinal fluid analysis should be performed more frequently (at 1, 3, 6, and 24 months after treatment would be adequate for the usual case). Erythromycin is the drug of third choice. It should be given orally in the estolate form (Ilosone) in the same doses as tetracycline. Liver function must be monitored as hepatotoxicity has been reported with erythromycin estolate. Other forms of erythromycin are not absorbed from the gastrointestinal tract well enough to be used. Cephalothin is probably a good alternative to penicillin in the treatment of neurosyphilis. However, a significant number of people allergic to penicillin are also allergic to cephalothin, and treatment schedules for neurosyphilis have not been clinically evaluated.

Psychotherapy

After successful treatment with penicillin, the patient becomes a well-adjusted personality without any psychotherapy whatsoever. If treatment with antibiotics should fail, psychotherapy will not benefit the patient either.

After the patient has gained insight, the problem should be frankly discussed with him and his relatives. Specific instructions as to medical checkups and the avoidance of hazardous occupations should be provided. Work around dangerous machines and the driving of trucks and buses should be prohibited, because a former general paralytic patient is never entirely safe from a seizure, although he may have been free of mental symptoms for years.

The Fully Recovered Patient

The intelligence in this group shows no deviation from previous levels, and full working capacity is restored. This is true not only of the simpler occupations, such as farming, but also of the professions. Kauders reported a general paralytic patient who was treated in 1920 with therapeutic malaria and, twenty-seven years later, at the age of eighty, enjoyed full mental and physical health, being active as the manager of a circus.

The Partially Recovered Patient

In some cases the premorbid intellectual and emotional status cannot be restored. These patients require permanent institutional care. They constitute the bulk of the general paralytic patients who are at present in mental institutions. For example, hospitalization for approximately 5000 veterans of World War I, who developed insanity due to syphilis, has now been provided by the Veterans Administration. In most of these patients, the delusions and the bizarre behavior have disappeared; they now represent all stages of mental deterioration. In some instances, cyclothymic manifestations have come into prominence, and others exhibit a schizophrenic picture with mannerisms and oddities which in no way can be differentiated from the classical type of schizophrenia. Since in some of these cases the spinal fluid abnormalities have reverted to normal and the pupillary reactions also have become normal, there are no longer clinical signs in the conventional sense of an organic psychosis.

Some authors attributed the new clinical picture to a concomitant affective or schizophrenic disorder. The post-treatment psychiatric syndromes in general paralysis are complex exogenous reactions resulting from residual alterations of the brain cortex, which are so subtle that they do not reveal themselves with present methods of neurohistology.

Patients with residual brain damage at times have periods of acute agitation and require treatment with tranquilizing drugs.

A paranoid-hallucinatory syndrome develops in a few patients during or after malaria or penicillin treatment. Electroshock therapy is of benefit in this condition.

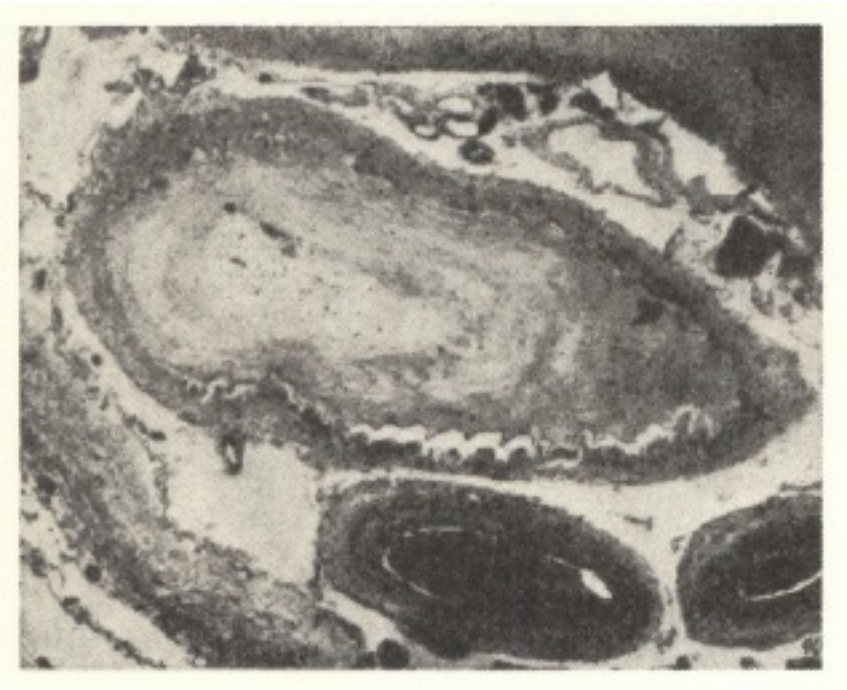
Psychosis with Meningovascular Neurosyphilis

The term “meningovascular neurosyphilis” embraces syphilitic processes in the meninges and vessels of the brain. In contrast to general paralysis, which is always fatal if not treated, meningovascular syphilis frequently shows clinical and serologic improvement even without treatment.

The important anatomic feature is cerebral softening due to endarteritic occlusion of cerebral arteries. The common clinical manifestation is apoplexy resulting in a hemiplegia, which at times is associated with an aphasia. The hemiplegia often improves rapidly, without any therapy, and to a far greater degree than might be expected from the initial symptoms.

The focal lesions are sometimes associated with acute psychic disturbances, in which periods of confusion and delirious states are conspicuous. Clouding of consciousness develops in some patients, with complete disorientation of several months’ duration. This may be followed by a rather sudden return to an almost normal mentality. In other instances, various degrees of emotional apathy or dementia may follow the stroke. Slight pupillary changes are frequently the only residual neurological signs.

Figure 5-9.

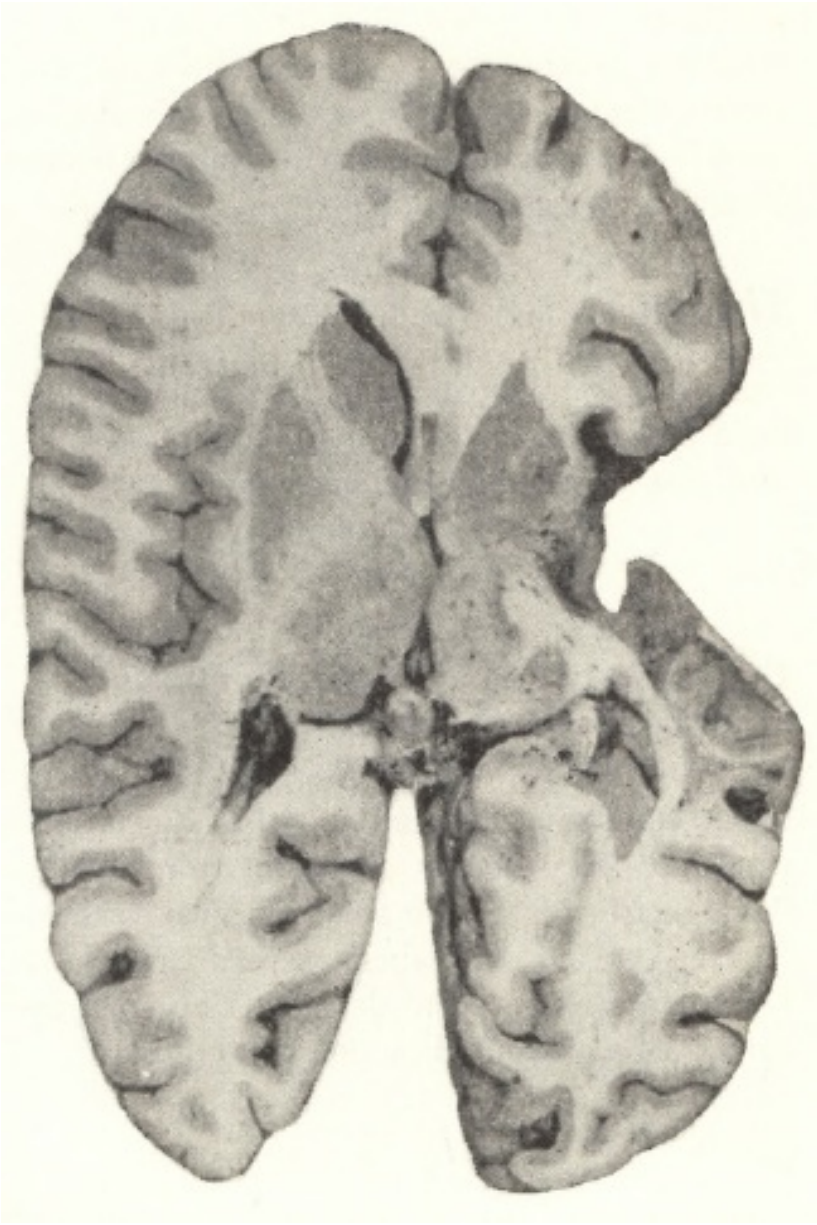


Syphilitic occlusion of artery in brain of patient with meningovascular neurosyphilis. Hematoxylin-eosin stain.

The chronic mental disorders with meningovascular syphilis do not show any characteristic content and may resemble any psychotic state.

Patients with gumma of the brain usually present mental symptoms, but a gummatous new growth is now a great rarity.

Figure 5-10.



Meningovascular neurosyphilis. Large area of softening involving right internal capsule. Stroke at age of forty-one. The patient was hemiplegic and aphasic for the remainder of his life.

Laboratory Findings

Cerebrospinal Fluid Reactions

In the fluid, the cell count may vary between 5 and 500 cells per cubic mm. In half of the cases, the cell count is normal. The protein content ranges from normal values to 500 mg. per 100 cc. In a typical case, the colloidal gold reaction shows a mid-zone curve, but a first-zone (paretic) curve is occasionally present. The Wassermann reaction in the spinal fluid is positive in two thirds of the cases, and in the blood in 80 percent. Occasionally, a positive Wassermann reaction of the blood or of the spinal fluid is the only abnormality.

Electroencephalogram

Patients with recent vascular accidents have a higher percentage of abnormalities in the electroencephalogram than those with old lesions. In some patients with an old hemiplegia, the electroencephalogram is normal.

Therapy

In the treatment of meningovascular syphilis, a course of penicillin

consisting of 10 million units is usually sufficient.

The So-called “Tabetic Psychosis” Other Than Taboparalysis

In an occasional instance of tabes dorsalis, a psychotic state occurs, resulting from syphilitic endarteritis of the small cortical vessels. In 10 percent of tabes, general paralysis (taboparalysis) used to develop. This tragedy can now be prevented by penicillin therapy.

Psychosis with Congenital Neurosyphilis

Juvenile General Paralysis

This form of general paralysis constituted 1.6-1.8 percent of all cases admitted to mental institutions. In the great majority of cases, the illness begins around the age of fourteen or fifteen. In 10 percent the onset is before the sixth year of life, and in 3.6 percent mental symptoms begin after the twentieth year.

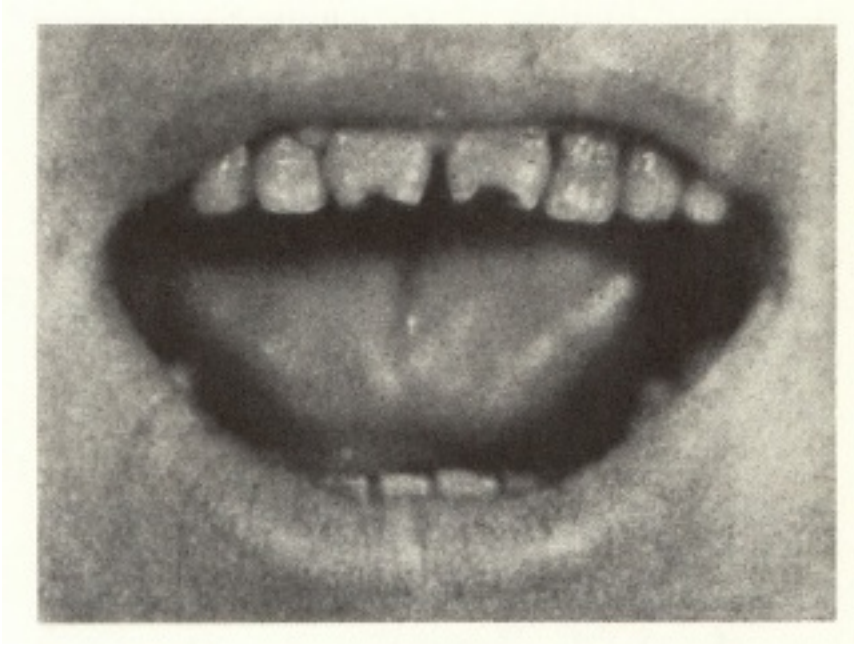
There are minor clinical variations from the adult form. Mental retardation, which is present in about 40 percent, becomes apparent soon after birth and is often associated with retarded physical development. Convulsions prior to the onset of juvenile general paralysis occur in one third of the cases, simulating idiopathic epilepsy. Optic atrophy is more frequent than in the adult form.

The psychiatric syndromes are less clear-cut, with the exception of the dementing type. A schizophrenic picture with mutism, catatonic behavior, and negativism has been observed. One of my patients, a well-developed and intelligent seventeen-year-old Negro girl, without the physical stigmata of congenital syphilis and with normal pupillary reactions, was considered a catatonic schizophrenic, until a routine spinal fluid examination revealed findings characteristic of general paralysis. Following penicillin therapy there

was complete recovery.

Stigmata of congenital syphilis are present in 75 percent and consist of Hutchinson's teeth (Figure 5-11), residue of previous interstitial keratitis, and nerve deafness, listed according to their importance.

Figure 5-11.



Juvenile (congenital) general paralysis. Hutchinson's teeth. Note notching of median incisors.

The anatomic changes in the brain are generally the same as in the adult

type.

Juvenile Meningovascular Neurosyphilis

This type of congenital neurosyphilis is more frequent than juvenile general paralysis, but its diagnosis is infinitely more difficult because of the uncharacteristic clinical and serologic findings. Symptoms may be present at the time of birth or may make their appearance in infancy, puberty, or even later in life.

Whenever congenital syphilis involves the central nervous system, it may cause arrest or deterioration of the intellectual development of the child. Behavior disorders are occasionally observed in this type of cerebral involvement, which is usually stationary in nature. The abnormal behavior ranges from lying, stealing, and attacks of rage to impulsive acts. Irritability, restlessness, and depressive phases are often present. Two thirds of these problem children rate below average in intelligence, some being feeble-minded and others are borderline cases of mental deficiency. The remaining children possess normal intelligence. Psychotic episodes may occur, associated with temporary confusion, periodic hallucinations, and pseudodementia.

Penicillin treatment shows particularly favorable results in progressive cases. In stationary cases with positive serologic reactions, therapy has a

prophylactic effect in forestalling a new flare-up of the disease in later years.

Bibliography

Alexander, M. and J. Titeca. "L'Épilepsie post-malariathérapique," *J. Beige Neurol. Psychiatr*., 36 (1936), 354.

Alpers, B. J. "Gumma of the Brain," *Am. J. Syph*., 23 (1939), 233.

Alzheimer, A. "Histologische Studien zur Differentialdiagnose der Progressiven Paralyse," in A. Alzheimer, and F. Nissl, eds., *Histologische und Histopathologische Arheiten über die Grosshirnrinde, mit Besonderer Berücksichtigung der Pathologischen Anatomie der Geisteskrankheiten*, Vol. 1, p. 18. Jena: Fischer, 1905-1913.

Arieti, S. "General Paresis in Senility; Critical Review of the Literature and Clinico-Pathologic Report of Six Cases," *Am. J. Psychiatry*, 101 (1945), 585.

Bayle, A. L. J. *Recherches sur l'arachnitis chronique, la gastrite et la gastro-entérite chronique, et la goutte, considérées comme causes de l'alienation mentale*. Paris: Didot le Jeune, 1822.

Benda, C. E. "Syphilis in Serum Negative Feebleminded Children; A Histologic Study in Meningoencephalitis Syphilitica and in the Nissl-Alzheimer Endarteritis," *Am. J. Psychiatry*, 96 (1940), 1295.

Borges Fortes, A. "Tratamento da Paralisia General pela Penicilina, *Arq. Bras. Neuriat. Psiquiatr.*, 51 (1956), 23. Penicilina e demência paralítica, O Hospital, Rio de Janeiro, November, 1956, pp. 645-673.

Bostroem, A. "Die Luespsychosen," in O. Bumke, ed., *Handbuch der Geisteskrankheiten*, Vol. 8, Spez. Teil 4, pp. 70-146. Berlin: Springer, 1930.

____. "Die progressive Paralyse (Klinik)," in O. Bumke, ed., *Handbuch der Geisteskrankheiten*, Vol. 8, Spez. Teil 4, p. 248. Berlin: Springer, 1930.

Bruetsch, W. L. "Activation of the Mesenchyme with Therapeutic Malaria," *J. Nerv. Ment. Dis.*, 76 (1932), 209.

_____. "The Histopathology of Therapeutic (Tertian) Malaria," *Am. J. Psychiatry*, 12, (1949) 19.

_____. "Penicillin or Malaria Therapy in the Treatment of General Paralysis? (A Clinico-Anatomic Study)," *Dis. Nerv. Syst.*, 10 (1949), 368.

_____. "Why Malaria Cures General Paralysis," *J. Indiana State Med. Assoc.*, 42 (1949), 211.

_____. "Penicillin Therapy of Cardiovascular Syphilis with Large Total Dosage; Its Rationale Based on Histologic Studies," *Am. J. Syph.*, 35 (1951), 252.

_____. *Syphilitic Optic Atrophy*, pp. 6, 57, 78. Springfield, Ill.: Charles C. Thomas, 1953.

_____. "Neurosyphilis: Symptomatology and Pathology," in A. B. Baker, ed., *Clinical Neurology*, Vol. 2, pp. 799-845. New York: Hoeber, 1955.

Bumke, O. *Lehrhuch der Geisteskrankheiten*, p. 386. München: Bergmann, 1936.

Cajal, S. R. "Neuroglia of the Cerebrum and Cerebellum in Progressive Paralysis with Technical Observations on the Silver Impregnation of Pathologic Nervous Tissue," *Z. Ges. Neurol. Psychiatr.*, 100 (1926), 738.

Callaway, J. L., H. Löwenbach, R. O. Noojin et al. "Electroencephalographic Findings in Central Nervous System Syphilis Before and After Treatment with Penicillin," *JAMA*, 129 (1945), 938.

Calmeil, L. F. *De la Paralysie considérée chez les aliénés*. Paris: Bailliere, 1826.

Dattner, B. "Zur Frage der Paranoid-Halluzinatorischen Paralysen," *Wien. Med. Wochnschr.*, 87 (1937), 278.

_____. "Treatment of Neurosyphilis with Penicillin Alone at Bellevue Hospital," *Am. J. Syph. Gonor. Ven. Dis.*, 32 (1948), 399.

Dayton, N. A. “Degree of Mental Deficiency Resulting from Congenital Syphilis,” *JAMA*, 87 (1926), 907.

DeWeck, A. L. in M. Samter et al., eds., *Immunological Diseases*, 2nd ed., p. 433. Boston: Little Brown, 1971.

Ebaugh, F. G., H. H. Dixon, H. E. Kiene et al. “Encephalographic Studies in General Paresis,” *Am. J. Psychiatry*, 10 (1931), 737.

Epstein, S. H. and H. C. Solomon. “The Effect of Treatment on the Mental Level of Patients with General Paresis,” *Am. J. Psychiatry*, 95 (1939), 1181.

Esmarch, F. and W. Jessen. “Syphilis und Geistesstörung,” *Allg. Ztschr. Psychiatr.,* 14 (1857), 20.

Esquirol, E. “Démence,” in Dictionaire des sciences médicales, Vol. 8, p. 283. Paris: Panckoucke, 1814.

Ferguson, F. R. and M. Critchley. “A Clinical Study of Congenital Neurosyphilis,” *Br. J. Child. Dis*., 26 (1929), 163.

_____. “A Clinical Study of Congenital Neurosyphilis. Part II. Congenital Tabes, Tabo-paresis and General Paralysis,” *Br. J. Child. Dis*., 27 (1930), 1.

Finley, K. H., A. S. Rose, and H. C. Solomon. “Electroencephalographic Studies on Neurosyphilis,” *Arch. Neurol. Psychiatry*, 47 (1942), 718.

Forster, E. and E. Tomasczewski. “Nachweis von Lebenden Spirochäten im Gehirm von Paralytikem,” *Dtsch. Med. Wochnschr*., 39 (1913), 1237.

Gianascol, A. J., G. D. Weickhardt, and M. A. Neumann. “Penicillin Treatment of General Paresis; A Clinicoanatomic Study,” *Am. J. Syph*., 38 (1954), 251.

Gjestland, T. “The Oslo Study of Untreated Syphilis; An Epidemiologic Investigation of the Natural Course of the Syphilitic Infection Based upon a Re-study of the Boeck-Bruusgaard Material,” *Acta Derm. Venereal*., Suppl. 34, 35 (1955), 1.

Gougerot, H. “Les Reliquats cicatriciels de la syphilis viscérale. Épilepsie résiduelle après guérison de la paralysie générale progressive,” *Paris Med*., 1 (1929), 209.

Grant, A. R. and H. T. Kirkland. “Spirochaetes in the Brain in General Paralysis,” *J. Ment. Sci*., 73 (1927), 595.

Greenblatt, M. and S. Levin. “Factors Affecting the Electroencephalogram of Patients with Neurosyphilis,” *Am. J. Psychiatry*, 102 (1945), 40.

Gross, S. W., A. Stein, and P. G. Myerson. “Surgical Treatment of Gummas of the Brain,” *Am. J. Surg*., 58 (1942), 78.

Haslam, J. *Observations on Insanity: with Practical Remarks on the Disease and an Account of the Morbid Appearances on Dissection*. London: Rivington, 1798.

Hayes, R. H. and I. Werbner. “Chlorpromazine in the Treatment of Symptomatically Refractory Conditions in General Paretics,” *Dis. Nerv. Syst*., 17 (1956), 48.

Hechst, B. “Histopathologische Untersuchungen bei der Schizophrenen Form der Progressiven Paralyse,” *Arch. Psychiatr*., 102 (1934), 25.

Hooshmand, H., M. R. Escobar, and S. W. Kopf. “Neurosyphilis: A Study of 241 Patients,” *JAMA*, 219 (1972), 726-729.

Idsoe, O., T. Guthe, R. P. Willcox et al. “Nature and Extent of Penicillin Side Reactions with Particular References to 151 Fatalities from Anaphylactic Shock,” *Bull. WHO*., 38 (1968), 159.

Jahnel, F. “Die Spirochaeten bei der Paralyse,” in O. Bumke, ed., *Handbuch der Geisteskrankheiten*, Vol. 11, pp. 498-538. Berlin: Springer, 1930.

Junius, P. and M. Arndt. “Beiträge zur Statistik, Aetiologie, Symptomatologie und pathologischen Anatomie der progressiven Paralyse,” *Arch. Psychiatr*., 44 (1908), 249.

Kauders, O. “Zur Klinik, Theorie und Geschichte der Malariabehandlung,” *Wien. Z. Nervenheilkd*., 1 (1947), 47.

Kraepelin, E. “General Paresis,” Nerv. & Ment. Dis. Monogr., No. 14. New York: Nerv. & Ment. Dis. Publ. Co., 1913.

Krafft-Ebing, von, R. “Zur Kenntnis des Paralytischen Irreseins beim Weiblichen Geschlecht,” *Arch. Psychiatr*., 7 (1877), 182.

Lissauer, H., and E. Storch. “Uber einige Fälle Atypischer Progressiver Paralyse,” *Monatsschr. Psychiatr. Neurol.*, 9 (1901), 401.

Löwenberg, K. “Syphilis of the Central Nervous System and of the Aorta,” *Klin. Wochnschr*., 3 (1924), 531.

Lucas and Price. “Cooperative Evaluation and Treatment for Early Syphilis,” *Br. J. Vener. Dis*., 43 (1967), 244-248.

Lurie, L. A., J. V. Greenbaum, and E. B. Brandes. “Syphilis as a Factor in Behavior Disorders of Children,” *Urol. Cutan. Rev*., 45 (1941), 108.

McCartney, J. L. “The Psychopathic Hospitals of Japan,” *J. Nerv. Ment. Dis*., 71 (1930), 640.

Mahoney, J. F., R. C. Arnold, and A. Harris. “Penicillin Treatment of Early Syphilis; Preliminary Report,” *Ven. Dis. Inform*., 24 (1943), 355; *Am. J. Public Health*, 33 (1943), 1387.

Menninger, W. C. *Juvenile Paresis*. Baltimore: Williams & Wilkins, 1936.

Merritt, H. H., M. Moore, and H. C. Solomon. “The Iron Reaction in Paretic Neurosyphilis,” *Am. J. Syph*., 17 (1933), 387.

Merritt, H. H. and M. Springlova. “Lissauer’s Dementia Paralytica; A Clinical and Pathologic Study,” *Arch. Neurol. if Psychiatry*, 27 (1932), 987.

Neel, A. V. and I. Ostenfeld. “Contribution to History of Dementia Paralytica with Special Reference to Contributions of Scandinavian, Particularly Danish Scientists,” *Acta Psychiatr. Neurol.*, 21 (1946), 605.

Nicol, W. D. “General Paralysis of the Insane,” Br. J. Vener. Dis., 32 (1956), 9.

Nissl, F. “Zur Histopathologie der Paralytischen Rindenerkrankung,” in A. Alzheimer, and F. Nissl, eds., *Histologische und Histopathologische Arheiten über die Grosshirnrinde, mit Besonderer Berücksichtigung der Pathologischen Anatomie der Geisteskrankheiten*, Vol. 1, p. 315. Jena: Fischer, 1905-1913.

Noguchi, H. “Additional Studies on the Presence of Spirochaeta Pallida in General Paralysis and Tabes Dorsalis,” *J. Cutan. Dis*., 31 (1913), 543.

Noguchi, H. and J. W. Moore. “A Demonstration of Treponema Pallidum in the Brain in Cases of General Paralysis,” *J. Exp. Med*., 17 (1913), 232.

Orlando, R. and M. Arndt. *Paralisis General. Estado Actual y Problemas*, pp. 101, 179. Buenos Aires: Lopez & Etchegoyen, 1945.

_____. “La atrofia óptica en la neurosífilis,” Neuropsiquiatría, 1 (1950), 110.

Page, J. “Mental Disease in Russia,” *Am. J. Psychiatry*, 94 (1938), 859.

Rothschild, D. “Dementia Paralytica Accompanied by Manic-Depressive and Schizophrenic Psychoses; the Significance of Their Co-existence,” *Am. J. Psychiatry*, 96 (1940), 1043.

Schulte, H. “Klinischer Beitrag zur Kenntnis der Kongenitalluischen Störungen des Zentralnervensystems,” *Z. Ges. Neurol. Psychiatr*., 169 (1940), 250.

Sparling, F. “Diagnosis and Treatment of Syphilis,” *N. Engl. J. Med*., 284 (1971), 642-657.

Taggart, S. R., S. B. Russell, and E. V. Price. “Report of Syphilis Follow-up Program Among Veterans After World War II,”*J. Chron. Dis*., 4 (1956), 579.

Thomas, E. W. “Current Status of Therapy in Syphilis,” *JAMA*, 162 (1956), 1536.

Van Wulfften Palthe, P. M. “Syphilis des Nervensystems bei Asiaten in Niederländisch-Indien (Java und Sumatra),” *Acta Psychiatr. Neurol*., 12 (1937), 207.

Virchow, R. “In Discussion of: Tabische Sehnerven Atrophie, Tabes, Progressive Paralyse und

Aneurysma der Aorta," *Berl. Klin. Wochnschr.*, 35 (1898), 691.

Volland, W. "Ueber das 'Paralyseeisen' und die Eisenablagerungen bei Mesaortitis Syphilitica unter Besonderer Berücksichtigung ihrer Herkunft und Spezifität (Histopathologische und Humoralpathologische Untersuchungen)," *Arch. Path. Anat.*, 309 (1942), 145.

Wagner-Jauregg, J. and W. L. Bruetsch. "The History of the Malaria Treatment of General Paralysis," *Am. J. Psychiatry*, 102 (1946), 577.

Warrell, D. A. "Physiologic Changes during the Jarisch-Herxheimer Reaction in Early Syphilis," *Am. J. Med.*, 284 (1971), 642-657.

Wong, Y. T. and H. Packer. "Penicillin Versus Penicillin-Malaria in the Treatment of Dementia Paralytica," *Am. J. Syph., Gonor. Ven. Dis.*, 32 (1948), 212.

Notes

1 Sparling's article can be consulted for further details of laboratory findings in the diagnosis and treatment of syphilis.

2 We are indebted to William T. Bachmann for editorial advice and help in revising this section on penicillin sensitivity.