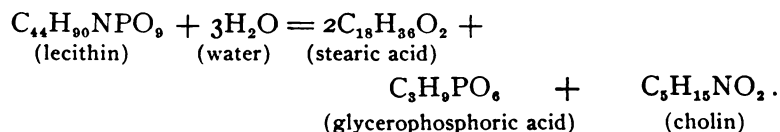


A CONTRIBUTION TO THE CHEMISTRY OF NERVE DEGENERATION IN GENERAL PARALYSIS AND OTHER MENTAL DISORDERS.

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While morphological studies of the central nervous system have created an immense literature since the advent of the neuron concept, it is only within the last few years that the chemical changes involved in cell and fibre degeneration have been the subject of attention. With the advance of neurological technique, it was observed that different morbid changes reacted differently to various stains and this was particularly well illustrated in those cases of myelin-sheath decay that reacted to osmic acid in such a manner as to precipitate the metallic osmium, the microscopic picture of such a reaction being the appearance of a large number of black droplets, arranged in a straight line along the course of the original myelin sheath. This reaction had proven the substance in question to be fat. The chemistry of nerve degeneration, so far as a present knowledge will permit us to state, is limited to katabolic processes in the lecithin, which is the main constituent of the myelin sheath and to decomposition in the axis cylinder. Of the latter we know but little, but certain facts are well established for the former process. The complex phosphorized fat, lecithin, splits up on hydrolysis into glycerophosphoric acid, stearic acid and cholin. The stearic acid unites with the glycerol radicles to form neutral fat and it is on this latter that the Marchi reaction depends. This takes place according to the following formula:



While the synthetized neutral fat collects in droplets along the course of the myelin sheath, the cholin is eliminated in the cerebrospinal fluid and the blood, while the glycerophosphoric acid appears in the urine, serving to augment its organic phosphorus.

Steapsin also splits lecithin into glycerophosphoric acid, free fatty acids and cholin. Hasebrock¹ investigated the action of putrefactive bacteria on lecithin, and found that these same products were formed, but only when the action of atmospheric oxygen was completely shut off. By the continuous action of bacteria, the cholin furthermore splits up into CO_2 , CH_4 and NH_3 . Under these circumstances, poisonous cholin derivatives are not produced, but by the addition of oxygen cholin is readily transformed into the poisonous neurin and muscarin. As the decomposition products of lecithin pass most readily into the cerebrospinal fluid, it is to this that we must turn our chief attention. Even in normal individuals, the amount of the fluid, if we take as a standard that obtained by lumbar puncture, is subject to great variations. According to Nya,² the fluid is most abundant during the first years of life and there is an increase under pathological conditions in certain infectious diseases and always in hydrocephalus and general paralysis. This latter has also been noted by other observers. The normal fluid is usually colorless or light yellow, the pigment being that found in blood serum-lutein. In subdural hemorrhage, from whatever cause, the color is red, while in jaundice it is greenish-yellow and purulent in suppurative meningitis. Abadie³ states that after the ingestion or the subcutaneous injection of potassium iodide or methylene-blue, these substances may appear in the fluid. The reaction of the central nervous system is alkaline during life, but after death or on long continued activity, the reaction becomes acid. This is due to the lactic acid of fermentation (optically inactive ethylidene lactic acid) and not to sarcolactic acid. The cerebrospinal fluid is also alkaline during life, but readily becomes acid after death. The effect of long continued activity of the nervous system and muscles upon the reaction of the fluid, such as occurs in convulsive seizures, we shall return to later. Turner,⁴ using Uffelmann's reaction, showed the acidity of the cerebrospinal fluid to be due to lactic acid, and that it appeared

to increase with the length of the interval which had elapsed between the time of death and the time of testing. Panzer,⁶ in the cerebrospinal fluid from two hydrocephalic fœtuses, found a feebly alkaline reaction. We are thus able to see what an intimate connection exists between the reaction of the brain tissue on the one hand and the cerebrospinal fluid on the other, if indeed the latter be not the direct result of the former. The specific gravity is usually low, varying from 1007 to 1010. Panzer, in his analyses of fluid from two hydrocephalic fœtuses, found it to be respectively 1008.62 and 1009.17. Of the nitrogenous glucocides but little is known, especially in regard to the relation of these bodies with the reducing substance in the cerebrospinal fluid. This reducing body, which is present in small quantities, has been especially investigated by Halliburton. After removal of the proteid by the usual methods, there is found in the fluid a substance which reduces copper salts but not bismuth, does not ferment or rotate polarized light and yields no osazon with phenylhydrazin. This substance is probably pyrocatechin. Both Panzer⁶ and Cavazzini⁷ found glucose in cases of hydrocephalus. Nauratzski⁸ showed that, in the cerebrospinal fluid of calves, there was a substance which reduced copper in alkaline solution and had all the characteristics of dextrose, but that this reducing power gradually disappeared after death and finally became nil.

Schaefer⁹ records the case of a patient suffering from hereditary dementia who in later years developed diabetes. The urine continued 8 per cent of sugar and the patient died in diabetic coma. After death 77 cc. of cerebrospinal fluid were removed, which was light yellow, with a specific gravity of 1010, and contained one per mille of albumin. After removal of the albumin, Nylander's test was positive and by titrating with Fehling's solution, he found .32 to .35 per cent sugar. That this reducing body was undoubtedly sugar, although no record is given of the fermentation and phenylhydrazin tests, is shown by the fact that it reduced bismuth, a property not possessed by pyrocatechin. In normal cerebrospinal fluid the total proteid (globulin, nucleoproteid, protalbumose) is very low. According to Quincke, it is from .2 to .5 per mille; according to Ricker, .5 to 1 per mille; according to Gumprecht, only .25 per mille. As a

rule, however, it does not exceed one part per thousand. The amount is increased in hydrocephalus, general paralysis, in stagnation from brain tumors and in hydrocephalus. Both Schaefer and Halliburton found a constant increase of proteid in general paralysis, the former giving an average of 1.23 per mille, the latter 2.39 per mille. Babcock, in 12 cases of general paralysis, also found an increase; and Nauratzski, in six cases of the same disease, found the albumin weight varying from .468 to .696 per mille. Panzer, in his two cases of hydrocephalus, gives the albumin figures as .599 and 0.99 respectively, and Abadie also found an increase in acute meningitis. Abnormally albumose and peptone have been found in meningocele.

The toxicity of the cerebrospinal fluid has been shown by Halliburton to be increased in general paralysis, the effect being due, as will be afterwards shown, to cholin and other products of nerve katabolism. Bellisari has also shown that the cerebrospinal fluid of individuals suffering from general paralysis is more toxic than normal, and that this toxicity is at its maximum after epileptiform seizures. Pellagrini¹⁰ determined the toxicity of the fluid in epileptics. The fluid was obtained during life by lumbar puncture and the amounts varied between 10 and 15 cc. He investigated six cases of epilepsy and arrived at the following conclusions. He found that the cerebrospinal fluid of epileptics is markedly toxic, and that, on being injected into guinea-pigs, there always resulted grave and intense convulsive phenomena, so much so, that in some cases a status epilepticus was produced. The fluid extracted immediately after a convulsion was more toxic and convulsive than that obtained at periods far removed from the paroxysm, and anti-epileptic drugs exercised no influence upon the toxic power. Cultures were sterile. That this toxicity is due to the potassium salts can be readily eliminated, because the quantity which exists in the fluid is so small and would be entirely out of proportion to the intensity of the symptoms. If the cerebrospinal fluid plays the part of the lymph of the central nervous system, and if one of the decomposition products of lecithin, glycerophosphoric acid, be eliminated in the urine, and the other, stearic acid, combine with the glycerol radicles to form neutral fat which replaces the myelin sheath, the third decomposition product, cholin, must be the one on which

the toxicity of the cerebrospinal fluid depends. That this is a fact and not a mere hypothesis, will certainly stand rigid inquiry and critical analysis. Cholin is a substance which is widely distributed in the animal and vegetable kingdom, but is best known as an hydrolysis product of lecithin. It differs from neurin in being less toxic, in producing no precipitate with tannic acid, and in its physiological action. It produces a fall in arterial pressure, while neurin creates a fall, followed by a marked rise and a subsequent fall to a normal level, while with small doses the preliminary fall may be absent. Neurin is intensely toxic to the nerve trunks and produces a marked effect on the respiration, first greatly increasing it, then lessening it, and finally causing it to cease altogether. Cholin has no action either on the nerve trunks or on respiration. It is absent in normal cerebrospinal fluid, but is present in the fluid of those patients who have died from some brain disease in which there is great disintegration of the cerebral substance and it must be looked upon, as has previously been stated, as a decomposition product of lecithin. It is found in general paralysis, combined sclerosis, disseminated sclerosis, alcoholic neuritis and beriberi. In those conditions in which it is present in the cerebrospinal fluid, the blood may also contain it, although it is absent from the urine, this doubtless being due to the fact that it is decomposed before being eliminated by the kidneys. Halliburton,¹² in a series of eighteen cats, in which both sciatic nerves were divided, found that cholin appeared in the blood, the amounts being parallel with the extent of the nerve degeneration as measured by the Marchi reaction.

In every one of the cases of general paralysis, Halliburton¹² found in the cerebrospinal fluid, removed both during life and after death, a large excess of nucleo-proteid, and a substance which was identified, both chemically and physiologically, as cholin. In cases in which the blood was examined, cholin was also found. This he explained on the basis of the myelin decay in general paralysis, with a consequent diminution in the brain weight, and he found the evidences of this myelin degeneration in the black degenerated fibres and in the black particles in the leucocytes and endothelial cells in the perivascular lymph spaces, as revealed by the Marchi reaction. That the epileptiform seiz-

ures of general paralysis are not the result but the cause of the appearance of cholin in the cerebrospinal fluid and in the blood, finds its explanation in the non-convulsive action of cholin when injected into animals. The toxæmic theory of general paralysis, which would regard the condition as the result of auto-intoxication by cholin and other products of nerve degeneration, is yet to be proven. In a recent contribution on the toxic action of the decomposition products of lecithin, Wood¹¹ gives a summary of the action of cholin and presents the results of a series of experiments upon neurin, which he finds is similar in physiological action to cholin with certain differences. He has done but little more than repeat the work of Halliburton.

In the field of phosphoric acid metabolism but little is known. The amount of glycerophosphoric acid eliminated in normal urine is about 15 milligrammes per liter, but so far no thoroughly systematic investigation has been made of its increase or diminution under pathological conditions. This is due in a measure in part to the extremely complicated method for the accurate quantitative determination of glycerophosphoric acid, and in part to the fact that a substance eliminated normally in so small an amount would either be so slightly increased or so slowly eliminated that painful accuracy would be necessary. Folin and Shaffer,¹² in a case of manic-depressive insanity, exhibiting a state of manic-exaltation alternating with a lucid interval from day to day, have shown that on the active days the phosphoric acid was in excess of that of the normal periods. This they explain on the basis that on every second day the system is unable to assimilate a part of the ingested phosphates, and more phosphoric acid is therefore eliminated on this (the manic) day. On the contrary, in the quiet condition, a less amount is eliminated because on this day the body is repairing the loss of the previous one. Laborde¹³ fed tuberculous guinea-pigs with lecithin and found a decrease in the excretion of phosphorus.

Noll¹⁴ divided the sciatic nerve of a dog on one side and fifteen days after the operation the animal was killed. The phosphorus in the degenerated nerve was 67.4 per cent of that on the healthy side, but the alcoholic extract of the nerve was 77 per cent of that on the healthy side. Mott and Barrett¹⁵ made complete analyses of two cords from cases of hemiplegia and report the

following findings on the degenerated side of the cord: (1) A breaking up of the phosphorized fat occurs. (2) The amount of lecithin present is diminished. (3) The amount of fat is present in excess. (4) The amount of extractives soluble in ether is increased. (5) The proteid residue diminishes in amount with the increase of the extractives in ether. (6) The phosphorus in the residue diminishes at a still greater rate than the residue itself. (7) The per cent of phosphorus in the one-half of the cord is, as a rule, diminished. (8) The ether extract has an appearance of butter instead of being crystalline. Barrett,¹¹ also in the brains from five cases of general paralysis, found the phosphorus to be decreased, and the water increased, the degree being parallel with the amount of fibre degeneration. In two cases of mania with moderate fibre degeneration, the water and phosphorus were about normal. The largest amounts of water and the smallest percentage of phosphorus were found in a case of alcoholic dementia. In the cords of seven cases of general paralysis the amounts of water were also increased and the phosphorus was diminished, the largest increase of one and decrease of the other being parallel with the amount of sclerosis and degeneration of the pyramidal tracts. Halliburton¹² divided both sciatic nerves in a series of eighteen cats, and the animals were subsequently killed at periods varying from 1 to 106 days. The nerves were practically normal so long as they remained irritable, that is, up to about three days after the operation. They then showed a progressive increase in the percentage of water and a progressive decrease in the amount of phosphorus until degeneration was complete. When regeneration occurred, they returned to practically their normal condition. The amount of degeneration was measured by the extent of the Marchi reaction. Gutnikov¹³ made elaborate chemical analyses of fifteen foetal brains, of the brains of seven persons who, without previous illness, had died suddenly, and of the brains in thirty-one pathological conditions, comprising both mental and physical diseases. He estimated water, phosphorus, nitrogen and sulphur in both the dry and moist gray and white substances. From his numerous analyses I select only those that have a direct bearing upon this paper. In four cases of acute alcohol poisoning, the amounts of water and phosphorus were about

normal. In a case of general paralysis in a man of 42 who had died of heart paralysis following fatty degeneration, the water was increased in both the white and gray substances, the phosphorus of the gray substance was decreased to about one-half of its amount and in the white to about one-third. In a case of senile dementia in a man aged 73, who had died of senile marasmus, the water was increased in both the white and gray substance, and the phosphorus in the gray substance was decreased to about one-third and in the white to a little less than one-half its former amount. In another case of senile dementia who had died from exhaustion the phosphorus had diminished more than half. In a case of stuporous melancholia who had died from exhaustion the phosphorus was increased in the gray but diminished in the white matter. With regard to the above results on the quantitative estimation of phosphorus, three principles seem to have been clearly and uniformly established by independent observers. When degeneration occurs in the central nervous system, chemical analysis of the affected portions shows a diminution of lecithin and the phosphorus and an increase of water, the amounts being parallel with the extent of nerve degeneration.

This then is the present status of the chemistry of nerve degeneration as revealed by metabolic disturbances and the findings in the cerebrospinal fluid and the nerve tissue itself. It is very unsatisfactory and fragmentary, because metabolism has offered little; microchemical reactions have been limited to mere observation of morphological changes, and chromo- and cytodiagnosis of the cerebrospinal fluid, especially in the hands of the French investigators have, with a few exceptions, overshadowed everything else. But certain facts seem fundamental and well established, yet even these are somewhat invalidated, because bare chemical analyses were given, without any effort to harmonize them with the clinical picture and the anatomical findings. It is with these data in mind, as shown by the review of the literature given above and an earnest desire to simplify and elaborate them, with the not vain hope of establishing new facts, that the following investigations were undertaken. I have been extremely fortunate in being able to utilize the material of a large hospital like ours. My cases in all number thirty-four and comprise a large

range of psychoses. Instead of a mere mention of the diagnosis, I have given short abstracts of the cases in order that the reader may judge of the varying clinical picture under which the chemical products of nerve degeneration may appear in the cerebrospinal fluid. In addition, I have given the anatomical findings in the central nervous system in order to show what relation exists between the pathological anatomy and the results of the chemical analyses. With a few exceptions the fluid was obtained by lumbar puncture after death, the time varying from ten minutes to twenty hours. In the longer periods, the body was kept in cold storage so as to exclude all post-mortem changes. The reaction was taken with litmus and the specific gravity by means of an accurate urinometer. To detect the presence of lactic acid, both Uffelmann's and Kelling's tests were used. The reducing body was tested for by means of Fehling's solution and also by the formation of an osazon with phenylhydrazin and sodium acetate after removal of the proteid with acetic acid and heat. The amount of proteid was roughly determined by the appearance of the fluid after the addition of 95 per cent alcohol. The method for the isolation and the detection of cholin was as follows:

The proteids were first precipitated by the addition of an excess of 95 per cent alcohol and the filtered solution was evaporated to dryness over a water bath at 40° C. This was extracted with absolute alcohol, again filtered and evaporated to dryness, and the operation repeated, care being taken in all cases to keep the temperature low. By this means all traces of proteid and the potassium salts were removed. The final residue after extraction with absolute alcohol was of a light color and of a syrupy consistency, and was divided into two portions, one being dissolved in distilled water, the other in 15 per cent alcohol. The watery solution was tested for proteid by the ordinary tests (biuret, Millon's, xanthoproteic, Adamkiewicz'), and for cholin by the usual alkaloidal reagents. In all cases the proteid was found to have been entirely removed by the treatment with alcohol. The alkaloidal reagents used were tannic, phosphotungstic and phosphomolybdic acids, and occasionally iodine in potassium iodide and platinum and gold chloride. To the second solution in 15 per cent alcohol there

were added a few drops of a 4 per cent solution of platinum chloride, and this was allowed to evaporate in a watch-glass over calcium chloride. Cholin was not designated as present unless all of the following characteristics were found:

Tannic acid, no precipitate (thus distinguishing it from neurin).

Phosphotungstic acid, white precipitate.

Phosphomolybdic acid, yellow precipitate.

Gold chloride, yellow precipitate.

Platinum chloride, yellow precipitate.

Iodine in potassium iodide, brown precipitate.

The most important feature was the double platinum salt which was obtained on slow evaporation from the solution in 15 per cent alcohol. In all cases in which cholin was present, large, yellow octahedra were formed, in both single and twin crystals, and easily soluble in water, thus differing from the double salt of neurin. It was furthermore differentiated from any traces of the potassium salts, that might have failed of extraction with the absolute alcohol, by the large size and easy solubility in water of the cholin salt, and by the fact that the watery solution gave the alkaloidal reactions in all cases in which the double platinum compound was obtained. In a few cases the gold salt was isolated, which crystallized in golden yellow prisms or needles. For the isolation of cholin from the brain, the brain substance was macerated in a mortar and extracted for a long time with absolute alcohol, and after filtration and evaporation of the alcoholic extract to dryness, the same method was used as detailed above.

CASE 1.—Female, aged 42. Alcoholic hallucinosis of three years' duration. During the last two years in the hospital she lost 84 lbs. in weight, and for two weeks before death there were fever, diarrhea, delirious stupor, rigidity, and marked general twitchings. The autopsy showed the cause of death to be pulmonary tuberculosis. Brain weight, 1360 grammes, no gross lesions or granulations in the 4th ventricle. The axonal reaction was found in the Betz cells of the para-central lobule. Marchi reaction of the corresponding fibres.

Cerebrospinal Fluid.—Amount, 10 cc.; color, opalescent; time after death, 45 minutes; proteid pp., small; cholin, absent.

CASE 2.—Female, aged 41. Dementia præcox, of fourteen years' duration. Acute anterior poliomyelitis during childhood. For three days preceding death, there were marked rigidity and twitchings, fearful agitation,

fever, albuminuria, and acetonuria. The autopsy showed broncho-pneumonia to be the cause of death. Brain weight, 1210 grammes, no gross lesions, residuals of anterior poliomyelitis in the cord. The axonal reaction was present in the Betz cells of the para-central lobule. The urine was examined for toxic products by the Stas-Otto method, but the results, both chemically and physiologically, were entirely negative.

Cerebrospinal Fluid.—Amount, 50 cc.; time after death, 30 minutes; color, clear; proteid pp., small; cholin, present.

Cholin was also demonstrated in 100 cc. of blood removed from the pulmonary vein at the time of the autopsy.

CASE 3.—Female, aged 46. Melancholia of two years' duration. There was some loss in weight for the last six months and for a week before death, slight fever, diarrhea, a little rigidity and a few twitchings were noted. The cause of death was broncho-pneumonia. Brain weight, 1160 grammes, no oedema or granulations in the 4th ventricle. Axonal reaction in the Betz cells of the para-central lobule.

Cerebrospinal Fluid.—Time after death, nine hours; amount, 35 cc.; color, clear; proteid pp., heavy; cholin, present.

CASE 4.—Male, aged 42. General paralysis, expansive tabetic form with circular periods of stupor and excitement. Duration, five years. Cause of death, pulmonary oedema and lobar pneumonia. Brain weight, 1385 grammes; pia, oedematous and hazy; grayness of the posterior columns and roots of the cord.

Cerebrospinal Fluid.—Time after death, 15 hours; amount, 105 cc.; color, clear; reaction, neutral; spec. grav., 1010; proteid pp., heavy; reducing body, absent; cholin, present.

CASE 5.—Male, aged 71. Senile dementia of two years' duration. Death from exhaustion. No autopsy.

Cerebrospinal Fluid.—Time after death, 1 hour; amount, 18 cc.; color, cloudy; proteid pp., very small; cholin, absent.

CASE 6.—Female, aged 63. Manic-depressive insanity of 15 years' duration. The cause of death was cerebral hemorrhage and broncho-pneumonia. Brain weight, 1110 grammes; hemorrhage around the Sylvian fissures, occipital poles, cerebellum and tips of temporal lobes.

Cerebrospinal Fluid.—Time after death, 2½ hours; amount, 15 cc.; color, clear; proteid pp., small; cholin, absent.

CASE 7.—Female, aged 71. Huntington's chorea of many years' duration. The cause of death was hypostatic pneumonia. Brain weight, 960 grammes; pia oedematous; no granulations in the 4th ventricle. Cerebellum of normal size.

Cerebrospinal Fluid.—Time after death, 6 hours; amount, 15 cc.; color, slightly cloudy; proteid pp., small; cholin, absent.

CASE 8.—Male, aged 35. Alcoholic delirium. Death from pneumonia. Brain weight, 1330 grammes; slight haziness of the pia; convolutions a little atrophic.

Cerebrospinal Fluid.—Time after death, 6 hours; amount, 25 cc.; color, slightly blood-tinged (contamination). Proteid pp., small, cholin, absent.

CASE 9.—Female, aged 38. Epilepsy of 16 years' duration. Death in status epilepticus. Brain weight, 1355 grammes; pia thin, little oedema.

Cerebrospinal Fluid.—Time after death, 3 hours; amount, 30 cc.; color, slightly blood-tinged (contamination); proteid pp., small; cholin, absent.

CASE 10.—Male, aged 35. General paralysis of 11 months' duration. Death from hypostatic pneumonia, and for two days preceding death there were continuous epileptiform convulsions. No autopsy.

Cerebrospinal Fluid.—Time after death, 5 hours; amount, 10 cc.; color, clear; proteid pp., small; cholin, present.

CASE 11.—Female, aged 27. Dementia præcox of three years' duration. Cause of death, tuberculous broncho-pneumonia. Brain weight, 1240 grammes; no granulations in the 4th ventricle; tubercles in the pia at the junction of the medulla with the pons.

Cerebrospinal Fluid.—Time after death, 12 hours; amount, 25 cc.; color, slightly blood-tinged (contamination); proteid pp., small; cholin, absent.

CASE 12.—Male, aged 67. Senile melancholia of two years' duration with the typical attitude of Parkinson's disease. The cause of death was broncho-pneumonia. Brain weight, 1835 grammes; dura adherent; no oedema.

Cerebrospinal Fluid.—Time after death, 12 hours; amount, 10 cc.; color, clear; proteid pp., small; cholin, absent.

CASE 13.—Male, aged 64. Senile dementia. For four days preceding death there were semi-stupor, refusal of food, slight rigidity and twitchings. Death from exhaustion. Brain weight, 1210 grammes; considerable oedema; no granulations in the 4th ventricle. No axonal reaction of the Betz cells of the para-central lobule.

Cerebrospinal Fluid.—Time after death, 5 hours; amount, 10 cc.; color, clear; proteid pp., very small; cholin, absent.

CASE 14.—Male, aged 47. General paralysis of 8 years' duration. The cause of death was asphyxia from aspiration of vomitus. No autopsy.

Cerebrospinal Fluid.—Time after death, 12 hours; amount, 65 cc.; color, clear straw; proteid pp., large; reaction slightly acid; lactic acid, present; spec. grav., 1009; reducing body, present; cholin, present.

Microscopically.—A large number of small mononuclear cells and a few polynuclear and red blood cells. No cholesterin. No osazon was found with phenylhydrazin and the sodium acetate.

CASE 15.—Male, aged 36. General paralysis of two years' duration. Death from hypostatic pneumonia. No autopsy.

Cerebrospinal Fluid.—Time after death, 45 minutes; amount, 20 cc.; color, clear straw; reaction, slightly acid; trace of lactic acid; proteid pp., large; cholin, present.

CASE 16.—Male, 47 years of age. General paralysis of 5 years' duration. Death from hypostatic pneumonia. Brain weight, 1185 grammes; pia œdematous and milky; granulations in the 4th ventricle.

Cerebrospinal Fluid.—Time after death, 11 hours; amount, 20 cc.; color, cloudy; proteid pp., large; cholin, present.

CASE 17.—Male, aged 50. Alcoholic hallucinosis of four months' duration. For three weeks before death there were rapid emaciation, diarrhea, delirious stupor, rigidity and twitchings. The autopsy showed death to be due to broncho-pneumonia. Brain weight, 1610 grammes; slight haziness of the pia. No granulations in the 4th ventricle. The axonal reaction was found in the Betz cells of the para-central lobule.

Cerebrospinal Fluid.—Time after death, 10 hours; amount, 20 cc.; color, clear; proteid pp., small; cholin, present.

CASE 18.—Male, aged 56. General paralysis of four years' duration. The cause of death was hypostatic pneumonia. No autopsy.

Cerebrospinal Fluid.—Time after death, 7 hours; amount, 40 cc.; color, cloudy yellow; reaction, slightly acid; lactic acid, present; proteid pp., large; cholin, present.

CASE 19.—Female, aged 40. General paralysis of six years' duration. Death from pulmonary tuberculosis. Brain weight, 950 grammes; thickened and hazy pia; subdural hemorrhage in both the brain and cord. The brain substance was soft and flabby, the convolutions atrophic, the temporal lobes adherent and there were granulations in the 4th ventricle.

Cerebrospinal Fluid.—Time after death, 45 minutes, amount, 50 cc.; color, very bloody; proteid pp., very large (due to the serum albumin and globulin); cholin, present.

CASE 20.—Male, aged 40. General paralysis of two years' duration. Death from hypostatic pneumonia. Brain weight, 1195 grammes; thickened dura; atrophic convolutions; granulations in the 4th ventricle.

Cerebrospinal Fluid.—Time after death, two hours; amount, 17 cc.; color, slightly cloudy; reaction, neutral; proteid pp., large; cholin, present.

CASE 21.—Male, aged 41. General paralysis of three years' duration. The cause of death was septicæmia from decubitus. Brain weight, 1105 grammes. Pia very œdematous and opaque; convolutions markedly atrophic; no granulations in the 4th ventricle.

Cerebrospinal Fluid.—Time after death, 30 minutes; amount, 66 cc.; color, clear; reaction, slightly acid; lactic acid, trace; spec. grav., 1008; proteid pp., very large; reducing body, present; cholin, present.

CASE 22.—Female, aged 45. Melancholia of 1½ years' duration. The patient was stuporous and resistive and for a couple of days before death there were marked rigidity and some twitchings. The cause of death was pulmonary tuberculosis. Brain weight, 1195 grammes; vessels thickened; no granulations in the 4th ventricle. The axonal reaction was found in the Betz cells of the para-central lobule.

Cerebrospinal Fluid.—Time after death, 1 hour; amount, 25 cc.; color, clear; proteid pp., very small; cholin, absent.

CASE 23.—Male, aged 39. General paralysis of two years' duration. Death was due to continual epileptiform convulsions. No autopsy.

Cerebrospinal Fluid.—Time after death, 10 minutes; amount, 65 cc.; color, clear and slightly yellow; reaction, slightly acid; lactic acid, present; spec. grav., 1006; proteid pp., very large; reducing body, present; cholin, present.

CASE 24.—Male, aged 29. Delirium tremens of five days' duration. For several hours before death the temperature was 107.3° F. Death from lobar pneumonia. Brain weight, 1370 grammes. Pia hazy, injected and markedly œdematous.

Cerebrospinal Fluid.—Time after death, 30 minutes; amount, 100 cc.; color, clear and slightly yellow; reaction, slightly acid; lactic acid, present; spec. grav., 1010; proteid pp., small; reducing body, present (marked reduction of Fehling's solution); cholin, present.

With phenylhydrazin and sodium acetate an osazon was formed resembling phenylglucosazon (fine yellow needles arranged in sheaves). Cholin was also demonstrated in 10 grammes of brain tissue taken from the first right frontal convolution.

CASE 25.—Male, aged 42. General paralysis of five years' duration. Death from exhaustion. Brain weight, 1220 grammes; considerable œdema; thickened and adherent dura; no granulations in the 4th ventricle.

Cerebrospinal Fluid.—Time after death, 8 hours; amount, 125 cc.; color, clear, slightly yellow; spec. grav., 1010; reaction, slightly acid; lactic acid, present; proteid pp., heavy; cholin, present.

Cholin was also found in 5 grammes of brain tissue taken from the first left frontal convolution.

CASE 26.—Male, aged 37. Delirium tremens of three days' duration. Death from lobar pneumonia. No autopsy.

Cerebrospinal Fluid.—Time after death, 4½ hours; amount, 20 cc.; color, clear, slightly yellow; proteid pp., very small; cholin, present.

CASE 27.—Female, aged 71. Organic dementia (aphasia) of seven years' duration. The cause of death was broncho-pneumonia. Brain weight, 990 grammes; adherent dura; considerable œdema; pia hazy and opaque over the right central area. There was marked atrophy of the posterior central regions in both hemispheres; the cisterna was hazy, and the first left frontal convolution was softened. There were no granulations in the 4th ventricle. Pigmentary degeneration of the Betz cells of the para-central lobule.

Cerebrospinal Fluid.—Time after death, 2½ hours; amount, 115 cc.; color, slightly bloody (contamination); proteid pp., heavy; cholin, present.

CASE 28.—Male, aged 31. Alcoholic depressive hallucinosis of 22 months' duration with a loss of 83 lbs. during this period. There was some slight diarrhea before death which resulted from exhaustion. Brain weight, 1595 grammes; dura thickened; substance rather soft in the posterior portions of both hemispheres. There were no granulations in the 4th ventricle. The Betz cells of the para-central lobule were deeply stained, both the protoplasm and the nucleus, and to a considerable distance into the processes.

Cerebrospinal Fluid.—Time after death, 1½ hours; amount, 40 cc.; color, cloudy; proteid pp., moderate; cholin, present.

CASE 29.—Male, aged 55. General paralysis of one year's duration. The cause of death was hypostatic pneumonia. Brain weight, 1300 grammes; pia hazy and markedly injected; granulations in the 4th ventricle.

Cerebrospinal Fluid.—Time after death, 15 minutes; amount, 35 cc.; color, clear; proteid pp., moderate; cholin, present.

Cholin was also found in 5 grammes of brain tissue taken from right frontal lobe.

CASE 30.—Female, aged 37. Toxic delirium of 11 days' duration. The cause of death was exhaustion from uncontrollable emesis, the vomitus being of a coffee-ground color. Brain weight, 1540 grammes; adherent dura; cloudy pia; sclerosis of the basal vessels. The 4th ventricle was free from granulations. Carcinoma of the pylorus and first part of the duodenum.

Cerebrospinal Fluid.—Time after death, 12 hours; amount, 45 cc.; color, bloody (contamination); proteid pp., large; cholin, absent.

No cholin could be demonstrated in 5 grammes of brain tissue taken from the first right frontal convolution.

CASE 31.—Male, aged 32. General paralysis of 19 months' duration. Death from hypostatic pneumonia. Brain weight, 1195 grammes; pia œdematous and hazy; granulations in the 4th ventricle.

Cerebrospinal Fluid.—Time after death, 20 hours; amount, 145 cc.; color, bloody (contamination); proteid pp., heavy; cholin, present.

Cholin was also found in 10 grammes of brain tissue taken from the first left frontal convolution.

CASE 32.—Male, aged 36. General paralysis of 3½ years' duration. Death from lobar pneumonia. Brain weight, 1170 grammes; dura thickened; pia hazy and œdematous. The frontal lobes were soft, the convolutions narrow and the right post-central and pre-central convolutions were markedly atrophic. Granulations in the 4th ventricle.

Cerebrospinal Fluid.—Time after death, 18 hours; amount, 150 cc.; color, bloody (contamination); proteid pp., heavy; cholin, present.

Cholin was also found in 5 grammes of brain tissue from the first right frontal convolution.

CASE 33.—Male, aged 52. Organic dementia (aphasia) of 23 months' duration. Death was sudden from acute dilatation of the heart. Brain

weight, 1250 grammes; dura strongly adherent; pia hazy and thickened along the longitudinal fissure. There was atrophy of the first left frontal convolution with a depressed cicatrix in its inferior portion.

Cerebrospinal Fluid.—Time after death, 9 hours; amount, 70 cc.; color, bloody (contamination); proteid pp., heavy; cholin, present.

Cholin was also found in 5 grammes of brain tissue taken from the first right frontal convolution.

CASE 34.—Female, aged 40. Dementia præcox of 2½ years' duration. The chief features of the psychosis were a depressive persecutory hallucinosis, fear, sudden outbursts of violence without apparent provocation, a period of mutism with refusal of food and stereotyped attitudes and finally absurd expansive ideas. Within seven months the weight decreased 13 lbs., and for the last four months there was increasing weakness and finally persistent diarrhea. Suddenly there developed general explosive twitchings and jerkings, fever and semi-stupor, the twitchings being rather more marked on the left side. There was rapid failure, and after the above phenomena had continued for two days, the patient died. The autopsy showed death to be due to broncho-pneumonia. Brain weight, 1035 grammes; moderate amount of œdema; pia injected; frontal convolutions somewhat atrophic; small linear depression in first left temporal convolution; no granulations in the 4th ventricle. There was a well-marked axonal reaction in a few of the Betz cells of the left para-central lobule; in the right para-central lobule many cells were involved.

Cerebrospinal Fluid.—Amount, 75 cc.; time after death, 45 minutes; color, bloody (contamination); proteid pp., heavy; cholin, present.

Cholin was also present in 10 grammes of brain tissue taken from the first right frontal convolution.

Having grouped the clinical picture with the chemical and anatomical findings, for the sake of convenience and clearness, I tabulate the chemical analyses above. The numbers correspond to the cases.

The fluid was obtained at times varying from ten minutes to twenty hours after death; in the longer periods the remains were kept at a low temperature in order to avoid post-mortem changes. The amounts obtained showed a wide range, from 10 cc. to 150 cc. The figures in the alcoholic cases (hallucinosis, delirium, depression, delirium tremens) varied from 10 cc. to 100 cc., the latter and largest amount being in a case of delirium tremens (Case 24). In this case, the pia was very hazy and markedly œdematous and the amount of fluid was only equalled in some of the general paralytics. In two cases of dementia præcox the amounts were 50 cc. and 25 cc., respectively, and

TABLE OF FINDINGS IN THE CEREBROSPINAL FLUID.—(THE NUMBERS CORRESPOND TO THE CASES.)

Case.	Psychosis.	Time after death.	Amt.	Color.	Reaction.	Lactic acid.	Spec. Grav.	Proteid.	Reducing body.	Cholin.	Remarks.
1	Alcoholic Hallucinations	45 min.	10 cc.	Opalescent.	Small amt.	Absent.
2	Dementia Præcox. 30 min.	50 cc.	50 cc.	Clear.	Small amt.	Present.	Cholin also found in the blood.
3	Melancholia	9 hrs.	35 cc.	Clear.	Large amt.	Present.
4	General Paralysis (expansive tabetic form)	15 hrs.	105 cc.	Clear.	Neutral.	1010	Heavy amt.	Absent.	Present.
5	Senile Dementia ..	1 hr.	18 cc.	Cloudy.	Very small amount.	Absent.
6	Manic-depressive Insanity	2½ hrs.	15 cc.	Clear.	Small amt.	Absent.
7	Huntington's Chorea	6 hrs.	15 cc.	Slightly cloudy.	Small amt.	Absent.
8	Alcoholic Delirium	6 hrs.	25 cc.	Slightly blood-tinged.	Small amt.	Absent.
9	Epilepsy	3 hrs.	30 cc.	Slightly blood-tinged.	Small amt.	Absent.
10	General Paralysis.	5 hrs.	10 cc.	Clear.	Small amt.	Present.
11	Dementia Præcox.	12 hrs.	25 cc.	Slightly blood-tinged.	Small amt.	Absent.

TABLE OF FINDINGS IN THE CEREBROSPINAL FLUID.—(THE NUMBERS CORRESPOND TO THE CASES.)—Continued.

Case.	Psychosis.	Time after death.	Amt.	Color.	Reaction.	Lactic acid.	Spec. Grav.	Proteld.	Reducing body.	Cholin.	Remarks.
12	Senile Melancholia.	12 hrs.	10 cc.	Slightly blood-tinged.	Small amt.	Absent.
13	Senile Dementia..	5 hrs.	10 cc.	Clear.	Very small amount.	Absent.
14	General Paralysis.	12 hrs.	65 cc.	Clear, straw color.	Slightly acid.	Present.	1009	Large amt.	Present.	Present.	No osazon found.
15	General Paralysis.	45 min.	20 cc.	Clear, straw color.	Slightly acid.	Trace.	Large amt.	Present.
16	General Paralysis.	11 hrs.	20 cc.	Cloudy.	Large amt.	Present.
17	Alcoholic Hallucinations.....	10 hrs.	20 cc.	Clear.	Small amt.	Present.	Only a very few crystals of the platinum salt obtained.
18	General Paralysis.	7 hrs.	40 cc.	Cloudy, yellow.	Slightly acid.	Present	Large amt.	Present.
19	General Paralysis.	45 min.	50 cc.	Very bloody.	Very large amount.	Present.	Color not due to contamination, fluid clotted like blood.
20	General Paralysis.	2 hrs.	17 cc.	Slightly cloudy.	Neutral.	Large amt.	Present.
21	General Paralysis.	80 min.	66 cc.	Clear.	Slightly acid.	Trace.	1008	Very large amount.	Present.	Present.
22	Melancholia.....	1 hr.	25 cc.	Clear.	Very small amount.	Absent.

TABLE OF FINDINGS IN THE CEREBROSPINAL FLUID.—(THE NUMBERS CORRESPOND TO THE CASES).—Continued.

Case.	Psychosis.	Time after death.	Amt.	Color.	Reaction.	Lactic acid.	Spec. grav.	Proteid.	Reducing body.	Cholin.	Remarks.
23	General Paralysis.	10 min.	65 cc.	Clear, sl. yellow.	Slightly acid.	Present	1006	Very large amount.	Present.	Present.
24	Delirium Tremens.	30 min.	100 cc.	Clear, sl. yellow.	Slightly acid.	Present	1010	Small amt.	Present (marked).	Present.	Osazon found resembling phenyl-glucosazon; cholin also found in right frontal lobe.
25	General Paralysis.	8 hrs.	125 cc.	Clear, yellow.	Slightly acid.	Present	1010	Large amt.	Present.	Cholin also found in left frontal lobe.
26	Delirium Tremens.	4½ hrs.	20 cc.	Clear, yellow.	Very small amount.	Present.
27	Organic Dementia (aphasia).....	2½ hrs.	115 cc.	Slightly bloody.	Large amt.	Present.
28	Alcoholic Depression.....	1½ hrs.	40 cc.	Cloudy.	Mod. amt.	Present.
29	General Paralysis.	15 min.	35 cc.	Clear.	Mod. amt.	Present.	Cholin was found in right frontal lobe.
30	Toxic Delirium...	15 hrs.	45 cc.	Bloody.	Heavy amt.	Absent.	No cholin found in right frontal lobe.
31	General Paralysis.	20 hrs.	145 cc.	Bloody.	Heavy amt.	Present.	Cholin found in left frontal lobe.
32	General Paralysis.	18 hrs.	150 cc.	Bloody.	Heavy amt.	Present.	Cholin found in right frontal lobe.
33	Organic Dementia (aphasia).....	9 hrs.	70 cc.	Bloody.	Heavy amt.	Present.	Cholin found in right frontal lobe.
34	Dementia Præcox.	45 min.	75 cc.	Bloody.	Heavy amt.	Present.	Cholin found in right frontal lobe.

three of melancholia including the senile form, 35 cc., 10 cc., and 25 cc. But, as will be later shown, in some of this group of alcoholic psychoses, melancholia and dementia præcox, the fluid was obtained only at a terminal stage, in which there appeared a peculiar symptom-complex, which gave rise in those previously purely "functional" disorders to marked "organic" cell changes. In some of these, at least, the chemical findings were different and served to establish a harmony with the pathological picture which will be further elaborated in more detail. The largest amounts of cerebrospinal fluid were obtained in the cases of general paralysis. Here, on account of the pial oedema which is so characteristic of this disease, there were obtained in fourteen cases, amounts varying from 10 cc. to 150 cc. In four of these, the amount was over 100 cc., in four others at or above 50 cc. In two cases of senile dementia the amounts were small, 10 cc. and 18 cc.; in a manic depressive case associated with residuals of a cerebral hemorrhage and in a case of Huntington's chorea, only 15 cc. could be obtained. In an epileptic who died in status epilepticus only 30 cc. was secured, less than half of the amount than was obtained in a case of general paralysis who died in continual epileptiform seizures (Case 23). Two cases of organic dementia associated with aphasia yielded 115 cc. and 70 cc., respectively. In the case of a delirium appearing in the course of a gastric cancer the amount was 45 cc. The color was either clear, opalescent or straw-colored, except in a general paralytic with subdural hemorrhage (Case 19) and in those few instances where contamination accidentally took place.

The reaction in two cases of general paralysis was neutral and in these the fluid was obtained 17 hours and two hours after death, respectively. In seven other cases the reaction was acid, this probably being due to the post-mortem changes which had already set in. Why it should be neutral in Case 4, when it was obtained 15 hours after death and acid in other cases in which death was not due to convulsions, and yet the fluid was obtained at much shorter periods, is inexplicable. The acidity was due in all cases to lactic acid. Case 23 is particularly valuable, for here the patient died in continuous epileptiform convulsions, and, although the fluid was obtained ten minutes after death and was still warm, yet lactic acid was present. This can

only be explained on the basis that the nerve tissue becomes acid in long continued activity, just as the working muscle produces sarcolactic acid, and that this acid (optically inactive lactic acid) passed into the cerebrospinal fluid.

The specific gravity varied from 1006 to 1009, the amount of proteid present not affecting it; nor can any difference be noted in any of the various psychoses. The amount of proteid precipitate was smallest in the alcoholic psychoses, whatever their terminal disorder, and largest in the general paralytics, only one of these showing a small amount. In senile dementia and melancholia it was also small, but large in one case of involution melancholia and small in another, but both of these were associated with cortical cell changes. Two cases of dementia præcox, one of Huntington's chorea, and one of epilepsy, showed a small amount, but it was large in two cases of organic dementia and also in one case of toxic delirium. In a manic-depressive case, associated with the residuals of a cerebral hemorrhage, it was also small.

The reducing body was tested for in five cases. It was found absent in one case of general paralysis, but present in three others, and also in a case of delirium tremens. The failure to detect it in Case 4, was probably due to the long period which had elapsed after death, because the reducing property of the cerebrospinal fluid gradually diminishes after death, until it finally ceases to react at all. In Case 24, an osazon compound was obtained whose morphology exactly resembled phenylglucosazon, although no effort was made to determine the melting point.

Cholin was tested for in all of the cases and found absent in eleven and present in twenty-three. In one where it was present in the cerebrospinal fluid it was also demonstrated in the blood; in six cases it was found both in the fluid and in several grammes of brain tissue taken either from the first right or left frontal convolution. In one case it was absent both from the fluid and also the brain. It was demonstrated in two terminal disorders of dementia præcox (Cases 2 and 34), melancholia (Case 3), and in an alcoholic depressive hallucinosis (Case 17) characterized clinically by emaciation, diarrhea, fever, delirium or stupor, rigidity or general twitchings and anatom-

ically by the axonal reaction of the Betz cells of the para-central lobule with the Marchi reaction of the corresponding fibres.²¹ In one of these (Case 2) it was also found in the blood by the same method as detailed for the cerebrospinal fluid, but here the findings are open to question for the reason that it might have been derived from the lecithin which is a constituent of the stroma of the red cells. In Case 34, belonging to this group, cholin was also demonstrated in the brain. In Cases 1 and 22, which also had the syndrome of these terminal disorders, it was absent, although in both the amount and intensity of the cell destruction was equal to that in the other cases. In another case of alcoholic depressive hallucinosis (Case 28) cholin was also present, and although this did not present the typical clinical picture, yet there were diarrhea and extreme emaciation, and the Betz cells of the para-central lobule revealed changes which resembled an acute alteration.

In fourteen cases of general paralysis, cholin was constantly present and in four of these it was coincidentally found in the first right or left frontal convolutions. In these four there was marked brain atrophy and in addition, in Case 32, there was some softening of the frontal lobes. The brain weights in these four cases averaged about 1220 grammes. All the cases of general paralysis were characterized macroscopically by cortical injection, oedematous and adherent pia, granulations in the 4th ventricle and a diminution in the brain weight, and microscopically by the characteristic cell alteration, gliosis and vascular infiltration. The presence of cholin in this disease can be explained by the intense and comparatively rapid cortical degeneration. In two cases of senile dementia (Cases 5 and 13) it was absent, which can be explained on the basis of the extremely slow atrophy that takes place in this disease. In another case of senile organic dementia (Case 27) cholin was present, but here associated with extreme atrophy (brain weight only 990 grammes), with softening of the first left frontal convolution, pigmentary degeneration of the Betz cells and aphasic speech disturbance. In another case of organic dementia (Case 33) with aphasia, cholin was also present in both the fluid and the brain. It was absent in a case of manic-depressive insanity, Huntington's chorea, alcoholic delirium, epilepsy, dementia

præcox with death from tuberculous broncho-pneumonia, senile melancholia and in a toxic delirium occurring in the course of a scirrhus cancer of the pylorus and first portion of the duodenum. In the latter case it was also absent from the brain. Cholin was present in two cases of delirium tremens (Cases 24 and 26). In one of these there was hyperpyrexia before death and the pia was markedly œdematous; in the other case there was no autopsy. Its presence here can be explained as the result of the intense acute alteration of the cells, due in both cases to the high fever.

In the cases associated with cholin, the amount of proteid was small in four, moderate in two and large in seventeen, an interesting coincidence by which one can harmonize the amount of tissue destruction with the appearance of the lecithin decomposition products in the cerebrospinal fluid. The amounts of fluid do not compare so favorably, yet if all of it had been obtained, we should undoubtedly see the relation between the pial œdema and the myelin degeneration. No effort was made to determine the quantitative relation between the amount of cholin and the extent of nerve degeneration, the tests being only qualitative, with the feeling that the mere demonstration of a substance so abnormal was of sufficient importance, without any final resort to quantitative accuracy. We have here a method that delicately determines the results of nerve degeneration and it is an almost positive proof that degeneration cell alteration or both exist in the central nervous system, when its katabolic product, cholin, appears in the cerebrospinal fluid. For the present we can say that the findings furnish a fairly safe guide for the differential diagnosis between organic and functional nervous and mental disorders, and this diagnostic aid can be utilized during life by the examination of the cerebrospinal fluid, obtained by lumbar puncture, for cholin. It appears that cholin is present at any period of myelin degeneration, as shown by the duration of the cases cited, whether during the swelling of the axon, the collection of the fat droplets along the course of the nerve, the liquefaction of the myelin or after its absorption. Various disorders do not change the chemical findings, whether in general paralysis with its extensive degeneration and atrophy, in the organic dementias with their focal

lesions, in delirium tremens with its acute cell alteration, and finally in those terminal disorders of the various depressive states already considered, with their central fibre degeneration and the secondary reaction upon the nerve cell, the result perhaps of autogenous poisons circulating in the blood and derived from the katabolic products which follow the extreme emaciation.

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