# STUDIES IN CEREBRAL FAT EMBOLISM

## WITH REFERENCE TO THE PATHOLOGY OF DELIRIUM AND COMA *

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### INTRODUCTORY

In a previous study[1] of the tissues of fourteen persons who died following fractures complicated by fat embolism, an attempt was made to correlate the amount of fat present in the blood vessels of the various organs, demonstrable by histologic methods, with the severity of the symptoms noted clinically and the frequency with which the delirium occurring after fractures was ascribed to alcoholism was emphasized. In eight of the fourteen, delirium tremens had been diagnosed clinically, although histories of alcoholism had not been definitely established in each of the cases. The study was made on the bodies coming to necropsy from the Cook County and Presbyterian hospitals, Chicago. One of these, which will be called Case A, because of the pronounced clinical manifestations and marked anatomic changes was chosen as the standard.

Preparation of the tissues for purpose of accurate estimation of the fat content was as follows: The tissues were embedded in a 10 per cent. gelatin solution, hardened in formaldehyd vapor at 37 C. for seventy-two hours, or until they were sufficiently hard to permit cutting with the usual sliding microtome, stained with sudan III, and counterstained with hematoxylin, then mounted in glycerol. This method is discussed in the previous report. It has the advantage of keeping the fat globules in their vascular beds, preventing their loss or displacement in cutting, and the counterstain enables a simultaneous histologic study. Sections so embedded were cut to from 5 to 15 microns without loss of the fat globules. Of each piece of tissue, fifty sections were examined; and of these, five sections containing average amounts of fat emboli were set aside for comparison. When these were collected they were carefully examined, and the amount of fat in ten fields of each organ was compared to the amount in ten fields of the same organ of Case A, which was regarded as containing 100 per cent. Then the percentages of fat emboli in the sev-

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1. LeCount and Gauss: A Study of Fat Embolism Associated with Fractures, Tr. Chicago Path. Soc., 1915, ix, 251.

eral organs of each body were averaged and compared to Case A. The result was that the other thirteen bodies were found to contain 5 to 45 per cent. of fat emboli in the organs. The fat emboli were most numerous in the lungs. In addition to the presence of fat emboli, there were certain circulatory alterations, as edema and hemorrhages, besides fatty changes of some of the organs. Edema of the brain was observed in seven, fat droplets in the blood stream noted at the time of necropsy in six, petechial hemorrhages, also noted at the time of necropsy, in the skin or organs in nine. In the lungs of all the bodies there were large numbers of fat emboli, and in half there were microscopic hemorrhages. In the heart muscle of thirteen bodies there were fat emboli, microscopic hemorrhages in twelve and fatty degeneration in six. In the kidneys of all fourteen bodies there were fat emboli, fatty degeneration in thirteen and microscopic hemorrhages in ten. In but six of the livers were emboli found, while in twelve there was venous engorgement and fatty infiltration, the latter being marked in seven. Fat emboli were also found in the brain, suprarenal, gastric mucosa, testis and spleen, in several instances.

Comparing the clinical symptoms of the fourteen patients, one does not find such diversity; on the contrary, the clinical pictures of all have many points in common. All the patients after a variable period of consciousness passed into a restless stage; and in twelve this took the form of delirium, eleven becoming so violent that restraint was applied, and a similar number passing from their delirium into a comatose condition. In all fourteen there was marked dyspnea, and the respiratory rate increased, the maximum rates averaging fifty-three per minute for the fourteen. This average was made from the rates recorded on the history sheets a few hours previous to death. Two of the patients developed Cheyne-Stokes respiration, four suffered from air hunger, and two developed a marked cough. The pulse in all became weak and shallow, the maximum averaging 153 for the fourteen. Urine and feces were passed involuntarily in twelve, and in the other two the records are incomplete. Thirteen of the patients came into the hospital with a normal or slightly subnormal temperature, and in all it rose steadily to the time of death, the maximum temperatures averaging 105.2 for the fourteen. The bones fractured were the femur in four patients, the humerus in three, the tibia and fibula in five, the calcaneous in one and the pelvis in one. The ages of the patients varied from 35 to 90, averaging 53. The time that they lived after injury varied from two to seventeen days, averaging six days. A more complete discussion of this study is given in the previous report, already referred to.

The failure to correlate the amounts of demonstrable fat emboli in the organs with the clinical symptoms was rather to have been

expected, for the amount of fat in the organs varies from time to time. Following a fracture in which fat is liberated from the bone marrow, absorption takes place through the regional veins and lymphatics which are torn by traumatism. The emboli are carried to the venae cavae, thence to the right heart, which pumps them to the lungs, where they become lodged in the capillaries. After a variable period some of the emboli are forced through the capillaries, are returned to the left heart, and are then sent into the general circulation to reach the various tissues, where they again become lodged in the capillaries. Here also they are forced through after a variable period, but are replaced by new emboli which had been temporarily arrested in the pulmonary circulation. The fat is finally excreted, at least in part, by the kidneys.

Observers along other lines of study have frequently noted a failure of correlation between morphologic lesions and functional disturbances. Barker,[2] who has carefully reviewed the literature on the relations of alteration of the central nervous system following various forms of injury, concludes that the correspondence lies in the finer structural alterations not discoverable by present methods of examination, admitting, however, that histologic alterations have functional equivalents.

In view of the marked cerebral symptoms so often occurring in fat embolism associated with fractures, notably delirium followed by coma, which is so frequently ascribed to alcoholism, a detailed study of the central nervous system was undertaken, with the hope of finding alterations which would establish a pathologic basis for these cerebral symptoms occurring after fractures. This study was suggested by Dr. LeCount, who kindly supplied me the brain of Case A.

## LITERATURE

The history of the occurrence of fat emboli in the central nervous system and the resulting symptoms forms the largest and most interesting chapter of the subject of fat embolism. Scriba[3] cites Cohn as the first to describe fat emboli in the brain. Cohn in 1860 found them in the capillaries of the cortex, but thought that they were the result of degeneration of the arterial walls. Muller[4] also in 1860 described fat emboli in the choroid coat of the eye, and he is generally cited by writers as the first to describe fat emboli in human tissue. Bergmann[5] in 1873 called attention to cerebral fat embolism and suggested its clinical importance. Czerny[6] in 1875 named it as a possible cause of

2. Barker: The Nervous System, New York, D. Appleton & Co., 1901, Chap. 25.
3. Scriba: Deutsch. Ztschr. f. Chir., 1880, xii, 118.
4. Muller: Wurzb. med. Ztschr., 1860, i, 45.

death. Fenger and Salisbury[7] in 1879 were probably the first in this country to describe fat emboli, as well as multiple ecchymoses in the brain. At this time there were numerous case reports in which cerebral fat emboli or symptoms were mentioned, without contributing new facts. Scriba[8] in 1880 gives a good description of the brain changes. He found hyperemia, multiple small punctate hemorrhages, anemic areas, fat emboli in the capillaries; and in some of the animals in which he produced experimental oil embolism the brain was edematous and the ventricles dilated. He regarded the changes in the brain and cord as the most important lesions of fat embolism, declaring that death could occur only from changes in the nervous system. Later writers do not agree with this dictum. His account of the clinical symptoms is also complete. He mentions collapse, stupor, disturbances in the pupillary reaction, loss of consciousness, convulsions, coma, etc., and attributes them to changes in the brain. Payr,[8] 1899, recognized cerebral fat embolism as a distinct clinical form, and divided them into cerebral and pulmonary types. Hamig[9] in 1900 made a careful study of the clinical aspects of cerebral fat embolism. He reports five cases in which the patients developed the typical symptoms, and in all of whose brains fat emboli were found in the capillaries. He expressed the belief that the clinical symptoms are due to the secondary changes, as hemorrhage and degeneration, rather than the presence of the fat emboli in the vessels. He contends that following many fractures no distressing symptoms of fat embolism occur, although fat may be found in the urine as evidence of the occurrence of fat embolism; and since the brain receives a more direct and larger amount of blood than the kidneys, it must also receive a considerable amount of circulating fat.

As to the time of the appearance of the secondary changes, especially the hemorrhages, there are different opinions. Ribbert[10] says that they appear after the third day following the injury. Grondahl[11] found them after fifty hours; Warthin[12] after twelve hours. Ribbert thinks that one third of the deaths associated with fat embolism is due to changes in the brain; Grondahl puts the figure at one half. The latter divides the cerebral symptoms into three stages: the initial stage, before the onset of the symptoms; the second or restless stage, in which the patient frequently develops delirium, and the last or coma-

5. Bergmann: Berl. klin. Wchnschr., 1873, xxxiii, 385.
6. Czerny: Berl. klin. Wchnschr., 1875, xliv, 593.
7. Fenger and Salisbury: Chicago Med. Jour. and Exam., 1879, xxxix, 587.
8. Payr: Ztschr. f. orthop. Chir., 1899, vii, 338.
9. Hamig: Beitr. z. klin. Chir., 1900, xxvii, 333.
10. Ribbert: Cor.-Bl. f. schweiz. Aerzte, 1894, xxiv, 457.
11. Grondahl: Deutsch. Ztschr. f. Chir., 1911, cxi, 56.
12. Warthin: Internat. Clin., 1913, iv, Series 23.

tose stage. Amberg[13] lays great stress on the recognition of the initial stage as an early diagnostic point of fat embolism. As pointed out by Benestadt,[14] the changes in the brain are not necessarily fatal. He reports the cases of three patients who developed symptoms of fat embolism following fractures of bones. All three passed through the first two stages and subsequently recovered. Godlee and Williams[15] contribute a valuable article on cerebral fat embolism in which the association of the cerebral symptoms and brain changes seem to be quite evident. In a railroad accident there were nineteen persons who sustained fracture of one or more bones. Of these, four died, one almost immediately, and the other three after different periods following the accident. In one of the last three a postmortem was not allowed, but in view of the almost identical symptoms, they think that he also possessed the same anatomic changes. One patient suffered from a simple fracture of the femur. He was brought to the hospital within one hour and had not lost consciousness, but that evening he became comatose and could not be roused. His pulse was 130, temperature 103, and respiration was of the Cheyne-Stokes type. He remained in coma and died four days later. Another patient suffered from a crushing injury of both femurs. He also was fully conscious when brought to the hospital, but within a few hours he became restless, his pulse was 160, temperature 102, and rapid respiration of the Cheyne-Stokes type. The following morning he became comatose and died on the second day. The brains of these two patients contained many punctate hemorrhages, and on microscopic examination the capillaries were found filled with fat emboli, and there were numerous small hemorrhages.

In our series all the patients developed marked cerebral symptoms. Five were brought to the hospital in the restless stage, and one was wildly delirious. In the case of these five a period of several hours had elapsed after the injury. The others suffered from no distressing symptoms on admission, but became restless in twelve to twenty-four hours. Most of them lay for hours at a time muttering incoherently, tossing about their beds and trying to get up. They became stuporous in twelve to thirty-six hours, and gradually comatose in twenty-four to seventy-two hours, from which they could be aroused at first by supraorbital pressure, but later failed to respond. One patient partly recovered from his symptoms, but had a relapse, and two remained delirious for about ten days. In two patients the pupils were constricted on admittance, but dilated before death; one developed ptosis of one lid subsequent to his admittance and one strabismus.

13. Amberg: Wien. klin. Rundschau, 1914, xxviii, 95.
14. Benestadt: Deutsch. Ztschr. f. Chir., 1911, cxii, 194.
15. Godlee and Williams: Lancet, London, 1911, i, 1062.

EXPERIMENTAL DEMONSTRATION OF THE INFLUENCE OF FAT ON THE CIRCULATION

In order to obtain some idea of the processes that take place in the capillaries following the entrance of fat emboli, the following experiments were devised to study the viscosity of the blood in fat embolism, also the capillary resistance associated with the altered conditions of the blood. It is realized that these capillary experiments cannot be held a strict counterpart of the phenomena that take place in the blood vessels, in view of the ability of the blood capillaries to alter their physiologic state in response to altered physical states of the blood; nevertheless, for a given instant, the conditions may be regarded as being analogous. The experiments were repeated a sufficient number of times to insure uniformity of results.

To determine the alterations in the viscosity of the blood, a simple apparatus was set up for measuring the rate of flow of fluids through a long capillary tube of a small bore, under constant pressure. The apparatus consists of a capillary tube 30 cm. long having a bore of less than 1 mm. connected with a 5 c.c. glass bulb used as a reservoir for the fluids to be tested, which in turn is connected with a buret containing a column of water having a pressure of 70 mm. mercury. A T tube placed between the bulb and the buret is used to empty and refill the bulb (Fig. 15). One cc. of the fluid was allowed to flow through the capillary, the amount being determined on the buret. A series of fluids was then examined, for the rate of time that it required 1 c.c. to flow through the capillary; in each instance the experiment was started with the column of water in the buret having a pressure equal to 70 mm. mercury. Emulsions were then made, using 9 c.c. of each of the respective fluids and 1 c.c. olive oil, and the rate of flow determined. To insure the proper escape of the emulsions through the capillary, the bulb was placed slightly lower than the capillary; and to eliminate the source of error due to alterations of the emulsions by mixture in the T tube, only the first cubic centimeter was measured, the remainder being discarded. The following results were obtained:

TABLE 1.—TIME REQUIRED FOR ONE CUBIC CENTIMETER OF FLUID TO PASS THROUGH THE CAPILLARY UNDER CONSTANT PRESSURE OF 70 MM. HG, AND CONSTANT TEMPERATURE OF 24.5 C.

| | Alone, Seconds | Plus Olive Oil, Seconds |
|---|---|---|
| Salt solution | 33 | 100 |
| Ascitic fluid | 45 | 130 |
| Human blood serum | 57 | 180 |
| Human blood slightly diluted with citrate solution. | 160 | 480 |

As seen from the table, the viscosity of the blood is increased approximately four times in these experiments, which gives ground for the belief that a similar increase may occur in fat embolism. In study-

ing the resistance occurring in capillary tubes the same apparatus was used, the resistance being measured in terms of millimeters of water as determined by the height of the column in the buret required to force the fluid through the capillary. The system was filled with water until the water level in the buret was the same as in the capillary. In this condition no fluid escaped from the open end of the capillary. The column of water was then raised until the fluid just escaped from the capillary. The column of water above the capillary being read in millimeters was taken as the pressure necessary to overcome the capillary resistence. The same series of fluids was tested. The figures in the first column of the following table give the pressure required to cause the several fluids to pass through a capillary 205 mm. long and one-fourth mm. in diameter. In the second column is given the pressure required after the addition of olive oil, mixed as in the previous experiment. It is seen that it required approximately ten times the pressure after the addition of the oil. Various sized capillaries ranging from 10 microns to 1 mm. in diameter were used, and the same principle was observed in all. The figures, however, denote only approximate relationships, for one of the variable factors was the size of the oil droplets, and this factor we were able to control only approximately. The principle, however, of increased capillary resistance of fluids following the addition of oil nevertheless holds true.

TABLE 2.—PRESSURE IN MILLIMETERS OF WATER REQUIRED TO OVERCOME THE CAPILLARY RESISTANCE OF A TUBE 205 MM. LONG AND ONE-FOURTH MM. IN DIAMETER; TEMPERATURE 23 C.

| | Alone, mm. | Plus Olive Oil, mm. |
|---|---|---|
| Salt solution | 4 | 41 |
| Ascitic fluid | 5 | 46 |
| Human blood serum | 5 | 49 |
| Human blood slightly diluted with citrate solution | 11 | 95 |

These tables at least give an idea of the processes taking place in the capillaries, and help explain the obstruction to the circulation which results in the observed phenomena of focal edema, focal hemorrhages and focal necrosis following the entrance of fat into the blood vessels.

## REPORT OF CASE *

The clinical history and pathologic alterations of the subject of this study are as follows: Patient A, a railroad fireman, 35 years old, was struck on the head by a projection of a low viaduct while removing the signal flags from the top of the tender, Oct. 4, 1909. He was picked up unconscious by the engineer, who said that the patient's leg was doubled under him. He was

* As noted in the previous report (LeCount and Gauss, loc. cit.) Dr. Evarts A. Graham reported some of the details of this case of fat embolism to the Illinois State Medical Society March 23, 1910, but so far as known did not have them published.

brought to the Presbyterian Hospital, several hours later, and by this time had recovered consciousness. There was found on examination a superficial scalp wound over the left anterior parietal region, although no skull fracture could be determined, a fracture of the tibia at the junction of the middle and lower thirds, and a fracture of the fibula above that of the tibia. A diagnosis of the fracture of the tibia and that of the fibula of the left leg was made, to which was added later, complication by fat embolism.

The patient lived four days. On admittance he was fully conscious and answered all questions, though somewhat slowly. His pupils were equal and exhibited no abnormal signs. The muscular power was equal in both hands, there was good movement of the toes, the general cutaneous sensations were equal on both sides, the tongue was extended in the median line when the patient was asked to do so, and he did not complain of headache or dizziness. He remained quiet all day, but toward evening complained of pain. He took nourishment when fed, and appeared dull mentally. He slept nearly all of the night. On October 5 he awoke at 8 a. m., and complained of pain in the back. He became restless and morphin was administered, but the restlessness continued during the morning and afternoon. In the late afternoon he became drowsy, then stuporous and failed to respond to questions. He was temporarily aroused by supra-orbital pressure. He ate little. On October 6 he was in coma; the pupils had contracted to pinpoint size, the eyes were turned upward, and there was a slight strabismus with deviation to the left. Later in the day the pupils enlarged, and the patient sank deeper into coma, from which he could not be aroused to consciousness, by supra-orbital pressure. He continued in this state to the time of his death, October 7, at 3 p. m. The respiration on admittance was normal in rate and rhythm. On the morning of October 5 it became irregular; by the afternoon it developed into the Cheyne-Stokes type, in which form it continued. On October 7 the patient developed singultus, the breathing became labored, and there was dulness and bronchial breathing over the right lower lobe posteriorly and many coarse râles were heard. The respiratory rate, which had been steadily increasing, reached 64 per minute before his death.

The pulse was normal on admittance, with a rate of 74. It increased steadily, reaching 164 per minute before his death. On October 6 the patient became cyanotic, this condition becoming more marked the next day. Blood drawn from the patient contained fat droplets. The patient perspired profusely during the last few days. Urine and feces were passed involuntarily. Petechial hemorrhages were first noticed at 8 a. m. on October 5, in the scapular regions. They developed rapidly, breaking out in crops. On the morning of October 6 they were all over the trunk, and by noon the neck was also covered with them. The temperature on admittance was 97.8. It rose steadily during the four days, reaching 106.2 before his death.

The postmortem examination was performed the following morning by Dr. E. R. LeCount. Anatomic diagnosis: "Comminuted fracture of the tibia; fracture of the fibula and skull; petechial hemorrhages of the skin, conjunctiva, serous and mucous membranes; parenchymatous hemorrhages of the lungs; hemorrhages in the anterior mediastinum; infarction of both testicles, with fatty changes; icterus; cloudy swelling of the kidneys; recent operative wound of the head; therapeutic puncture wounds of the trunk (sodium chlorid infusion); latent tuberculosis of the lungs; fibrous pleuritis and peritonitis; fibrous mural endocarditis; edema of brain."

From the necropsy record the following items are taken: "Over the trunk, especially the upper part, were innumerable minute petechial hemorrhages, which were in some places clustered, but over the upper part of the chest they were 1 cm. apart. In the pericardium were numerous petechial hemorrhages, which varied in size, some being 1 cm. long and irregular. The lining of the right heart chamber contained numerous small hemorrhages. Both of

the testicles were studded with minute hemorrhages. In the roof of the left orbit there was a fracture, obliquely directed, 2.5 cm. long, with the forward end out. There were small hemorrhages in the gastric mucosa."

In microscopic preparations fat emboli were found in the brain, lungs, myocardium, kidneys, suprarenals, liver and testis. All sections of the lung contained emboli in large amounts. They were well distributed in the capillaries throughout the lung. In shape the emboli were round, oval or elongated; in size from 10 to 50 microns. Under high power there were observed many capillaries running across the microscopic field filled and distended with strings of emboli. The arteries and capillaries were engorged. There were scattered areas of lung tissue in which the alveolar spaces were filled with a hemorrhagic exudate. All sections of the kidney contained emboli, found chiefly in the capillaries of the glomeruli. Nearly all the glomeruli contained some emboli, and about one third were completely blocked by them. In shape the emboli were irregular and tortuous, lying in and distending the glomerular capillaries. Many of the vasa afferentia contained elongated emboli at the entrance to the glomerulus, some 50 to 80 microns in length. The capillaries and arteries were engorged, and there were small intertubular extravasations of blood.

The liver contained emboli in small amounts, found in the capillaries between the hepatic cords. In some of the sections there were capillaries measuring about 100 by 30 microns, which were filled with strings of emboli from 20 to 30 microns in diameter. Near the central veins of many of the lobules the hepatic cells had undergone fatty degeneration. Many of the capillaries just beneath the hepatic capsule contained emboli. There was venous and capillary congestion. All sections of the heart contained emboli, chiefly in the capillaries between the muscle cells. They were round, oval, elongated or spindle-shaped and from 10 to 40 microns in diameter. The muscle cells adjacent and near the emboli had undergone fatty degeneration. These areas of fatty degenerated tissue, containing emboli, were separated from each other by normal tissue in which there were few or no emboli. There was also considerable infiltration of the myocardium by fatty areolar tissue. The arteries and capillaries were distended with blood.

Most sections of the suprarenal contained emboli in the capillary sinuses between the cells of the zona fasciculata, also in the zona glomerulosa. The emboli were elongated and from 20 to 40 microns. In the zona fasciculata there were distended straight capillaries running across the high power microscopic field filled with emboli of various sizes and shapes. The parenchyma cells contained more than the usual amount of fat, especially in the zona fasciculata. A few sections of the testis contained emboli in the capillaries about the seminiferous tubules, from 10 to 20 microns, and usually elongated. The interstitial tissue contained numerous fine fat droplets, suggesting fatty degeneration. The seminiferous tubules were normal.

*Study of Brain.*—The brain was placed in 10 per cent. dilution of liquor formaldehydi for preservation, and in this condition it was received for study. The brain was normal in size, weight and configuration. The gyri were of normal width and the sulci of normal depth. The pial vessels were moderately engorged. The arteries at the base of the brain were collapsed and there were small regions of thickening in the basilar, posterior cerebral, and middle cerebral arteries. On surfaces made by sectioning the brain transversely there were several small hemorrhages in the anterior half of the corpus callosum, especially in the genu. These hemorrhages measure from 0.5 to 2 mm. in diameter. They were well defined, sharply limited and generally were round or slightly irregular. Similar punctate hemorrhages were found in the white substance throughout the entire cerebrum, especially in the frontal and parietal lobes. The lateral ventricles were moderately dilated.

A preliminary examination of sections taken from the frontal, parietal and occipital lobes was made, and there were found in all the sections fat emboli,

hemorrhages, and foci of degeneration. A more detailed study of this brain was undertaken to (*a*) identify these alterations with relation to the intrinsic circulation of the encephalon, (*b*) to study the finer histologic alteration in the areas of focal degeneration by means of differential stains, and (*c*) to localize the lesions with reference to the various functional centers and pathways of the brain.

It became evident that an accurate identification of the various sulci and gyri of the brain was essential. This was done with the aid of numerous standard textbooks on the morphology of the brain, which were freely consulted. The brain was then accurately plotted. Four views were made; a lateral view of the left hemisphere (Fig. 1), a view of both hemispheres from above (Fig. 2), a view of a transverse section just anterior to the mammillary bodies (Fig. 3), and a mesial view of the left hemisphere (Fig. 4). These plots were made as follows: A plane resting on a prominent point of the cortex was imagined, all points of the sulci projected to it by parallel lines, measured with a ruler and drawn; that is, it is as if a piece of glass were laid on the brain, which being held firmly in the desired position, its configuration was copied with a wax pencil, the range of vision being kept constant.

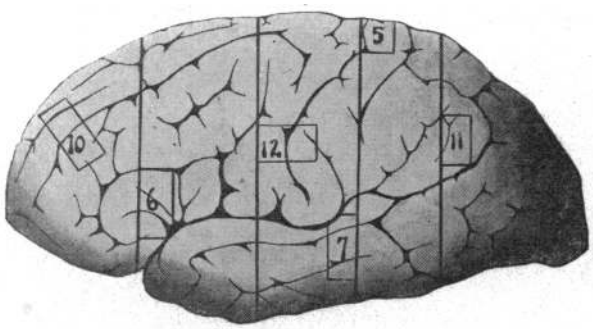


Fig. 1.—Plot of brain, giving lateral view of convex surface of the left cerebral hemisphere, and showing configuration and the location of the sections removed for study; reduced.

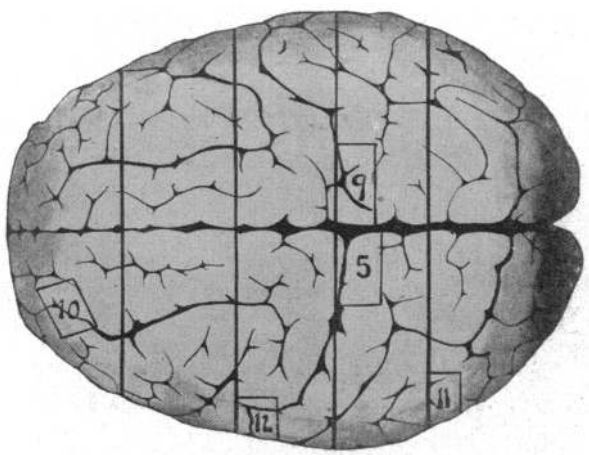


Fig. 2.—Plot of brain, representing convex surface from above, and showing configuration and the location of sections removed for study; reduced.

It would of course have been desirable to examine all of the functional areas of the brain; however, such a study was beyond the scope of our present effort, and consequently only representative areas were examined, these being chosen from the more important known centers. They were taken from the following regions as indicated in Figures 1, 2, 3 and 4:

1. Spinal cord at the upper border of the decussation of the pyramidal tract.
2. Vermis cerebelli.
3. Right cerebellar cortex and dentate nucleus.
4. Left cerebellar cortex and dentate nucleus.
5. Left cerebral cortex, central sulcus, leg area, sensory and motor sides.

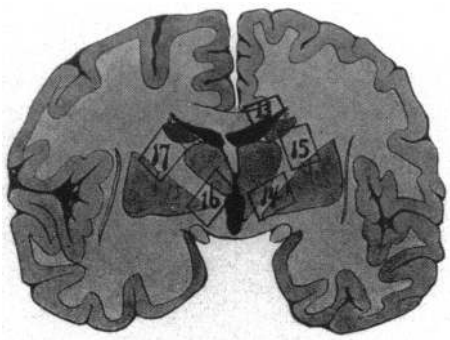


Fig. 3.—Plot of brain, representing transverse section just anterior to the mammillary bodies, and showing the location of the sections removed for study in relation to the internal capsule and the internal nuclei; reduced.

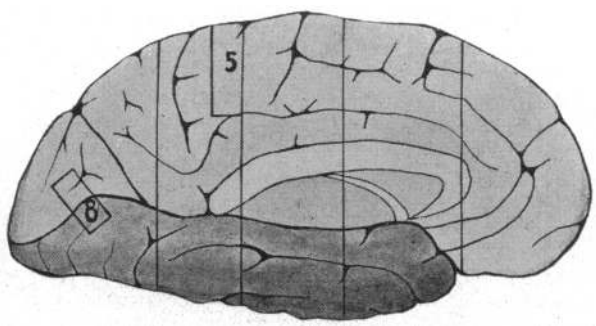


Fig. 4.—Plot of brain, representing mesial surface of left cerebral hemisphere, and showing configuration and location of sections removed for study; reduced.

6. Left cerebral cortex, triangular part of inferior frontal gyrus, motor speech area (Broca's convolution).
7. Left cerebral cortex, superior and middle temporal gyri, auditory area.
8. Left cerebral cortex, calcarine fissure, including portions of the cuneus and lingual gyri, vision area.
9. Right cerebral cortex, leg area, central sulcus, including sensory and motor sides.
10. Left cerebral cortex, superior and middle frontal gyri, association area.
11. Left cerebral cortex, gyrus angularis, inferior parietal lobule, association area.

12. Left cerebral cortex, central sulcus, arm area, including sensory and motor sides.

13. Body of corpus callosum near the middle of its anteroposterior extent, right side.

14. Right ventral limb, internal capsule, including portions of the globus pallidus and thalamus. This and the following three sections were taken from a transverse section of the brain just anterior to the mammillary bodies.

15. Right dorsal limb, internal capsule, including portions of the putamen and caudate nucleus.

16. Left ventral limb, internal capsule, including portions of the globus pallidus and thalamus.

17. Left dorsal limb, internal capsule, including portions of the putamen and caudate nucleus.

Large blocks of tissue several centimeters in length were removed from these areas, and these in turn were cut into smaller blocks and rehardened, frozen and cut, or embedded in paraffin or gelatin, according to the need. In order to bring out as many of the neurologic elements as possible, as well as the pathologic lesions, a variety of stains were used, including sudan III, osmic acid, hematoxylin and eosin, Mann's methylene-blue eosin, toluidin-blue Nissl stain, phosphotungstic acid hematoxylin, Marchi, Golgi, Weigert's myelin sheath stain, Weigert's neuroglia stain, the Ranson-Cajal neurofibril stain, Bielschowsky neurofibril stain, Heidenhain iron hematoxylin stain, Apathy after-gilding chlorid stain. These stains were adapted to the material examined. In view of certain postmortem alterations which occurred in the central nervous system, sections of another brain obtained about the same time and preserved in a similar manner were run in a parallel series as a control, to eliminate artifacts of preparation and postmortem changes.

The alterations will be discussed under the several headings of edema, hemorrhages, fat emboli, focal necrosis, changes in the nerve cells, round cell infiltration, changes in the spinal tracts.

Edema: This condition was observed in the fresh brain at the time of the postmortem. At the present examination after formaldehyd fixation, the ventricles are moderately dilated. It is of course impossible to make any observation of the intermeningeal fluid content. Microscopically, many of the ganglionic cells of the dentate nucleus and of the pyramidal layer of the cerebral cortex are slightly swollen; in the Purkinje layer of the cerebellum there also occur groups of cells that appear swollen. In the cerebral cortex there are present small diffuse areas that suggest focal edema. These areas are associated with fat emboli, and are found principally in the portion included by the lamina granularis interna and the lamina multiformis, and in the molecular layer of the cerebellum. These focal areas are irregular in shape and cover an area whose greatest diameter varies from 500 to 900 microns. Observed in sections stained with Mann's methyl-blue eosin,[16] there are seen scattered through these areas empty capillaries, markedly distended, round or oval in outline, which represent the site of fat emboli. About these vessels are irregular shaped small clear spaces that are extravascular. The extravascular spaces are much more numerous than the larger, definite intravascular spaces, and they comprise the bulk of the focus. The neurophil in these foci appears slightly compressed.

Hemorrhage: Grossly punctate hemorrhages are easily seen in the anterior genu of the corpus callosum and in the white substance beneath the cortex of the cerebrum (Figs. 5 and 6). Microscopically, small hemorrhages are found in all the blocks removed for study. Of each block of tissue removed for study, from

16. Encyklopädie der Mikroskopischen Technik, Berlin, 1903, i, 262.

fifty to two hundred sections were examined, and in about half of these hemorrhages are present. The distribution is uniform in all the blocks when compared to each other. In the spinal cord they occur principally in the gray matter. In one run of sections, the posterior horn, the gelatinous substance of Rolando is a common site (Fig. 7). In the cerebellum a count of one hundred hemorrhages was made. There are forty-four in the granular layer, thirty-two about the Purkinje cells, twenty-one in the molecular layer, two in the dentate nucleus, and one in the medullary substance. In a count of one hundred in the cerebral cortex, the three blocks removed from the central sulcus being used, the distribution is as follows: one in the lamina zonalis, four in the lamina granularis externa, fourteen in the lamina pyramidalis, three in the lamina granularis interna, seventeen in the lamina ganglionaris, twenty-four in the lamina multiformis and thirty-seven in the medullary substance. In the corpus callosum, internal capsule and portions of the adjacent caudate, thalamus and lentiform nuclei, the hemorrhages are present in large numbers (Fig. 8). The hemorrhages cover an area whose largest diameter varies from 100 to 700 microns, generally 300 to 500. They are sharply defined, round or oval in outline, commonly placed about a capillary, the lumen of which is distended, appears empty in the paraffin sections, but is frequently seen to contain a single fat embolus in the gelatin-embedded and fat-stained sections. The hemorrhages are compact, but occasionally appear as circular bands (Fig. 9).

Fat Emboli: These are present in every section stained with sudan III or osmic acid, after gelatin embedding or frozen section. In the spinal cord they are present in both the white and gray substance, more frequently in the latter. In the cerebellum the order of frequency is as follows: molecular layer, Purkinje layer, dentate nucleus, granular layer, and medullary substance. In the cerebrum they are present in largest numbers in the middle layers of the cortex included in and between the lamina pyramidalis and lamina ganglionaris. The peripheral layers and medulla contain lesser amounts. The number of fat emboli per low power microscopic field varies from ten to fifty, they are long, cylindrical, club shaped, or occur in strings of small, round globules, and some of the longer emboli measure 100 microns in length. Many occlude the vessel in which they lie, and branch with it at a point of bifurcation (Fig. 10). In some of the microscopic fields measuring 250 microns under high power, there are capillaries running across the field that are filled with emboli.

Focal Necrosis: In addition to the areas described under "focal edema," characterized by a diffuse area containing many small clear spaces surrounding the sites of multiple fat emboli, there are present smaller, sharply defined areas which will be described under the term "focal necrosis." The appearance of these areas varies somewhat with the stain employed. They are, however, observed with most of the stains used. Within their border there seems to be a loss of some of the neurologic elements, so that they appear as light staining areas surrounded by the normal darker staining tissue. These areas are round, oval or spindle shaped, and frequently placed about a single capillary occluded by fat emboli. In the methyl blue eosin preparations there appears to be a loss of the eosin staining elements. The loss is most marked toward the periphery of the focus where it terminates abruptly at the border; towards the center of the lesion the loss is less marked. In some of these there is an increase of the neuroglia cells in the centers. In other foci the loss of tissue is uniform, the center and periphery staining alike. A few foci with clear centers are surrounded by hemorrhagic bands, suggesting the hemorrhagic infarct. In the phosphotungstic acid hematoxylin preparation there is a loss of the blue staining elements, with an apparent decrease of the neuropil or *Punktsubstanz*, the fine granular background of the tissue. In Weigert myelin sheath stained preparations definite information is obtained of these foci. Here is seen a loss of the

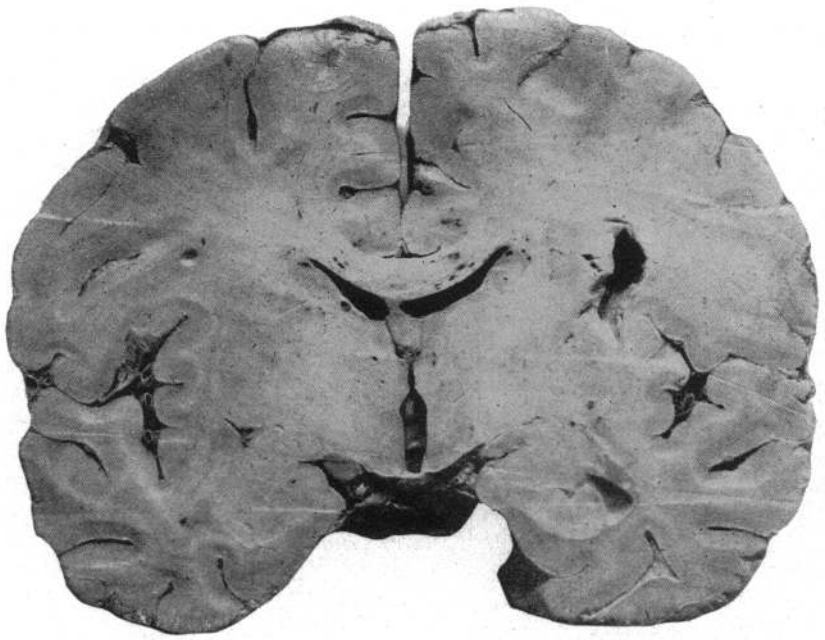

Fig. 5.—Photograph of transverse section of brain just anterior to the mammillary bodies. In the corpus callosum there are punctate hemorrhages.

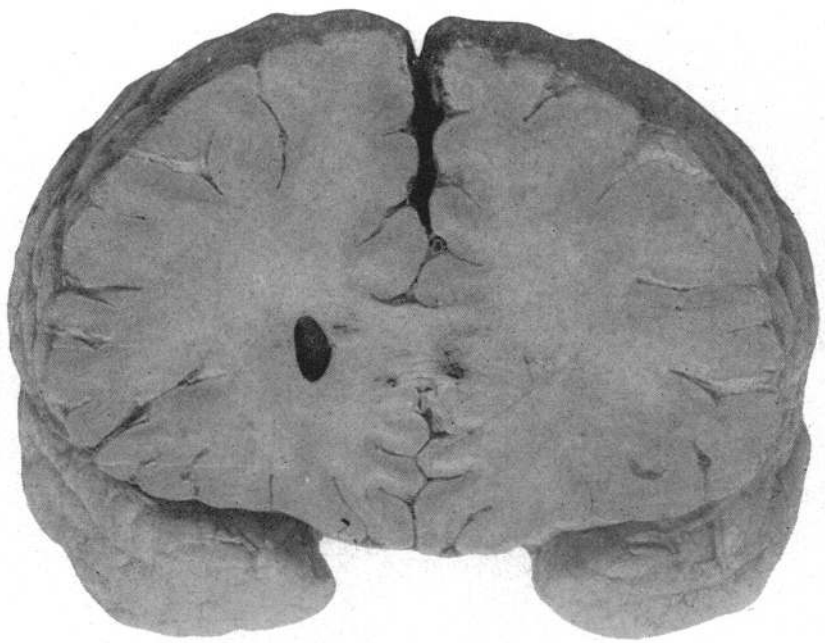

Fig. 6.—Photograph of transverse section of brain just anterior to the poles of the temporal lobes. In the corpus callosum and frontal lobes there are punctate hemorrhages.

Fig. 7.—Photomicrograph, × 110, showing hemorrhage and round cell infiltration into the gelatinous substance of Rolando, dorsal gray horn of spinal cord at level of decussatio pyramidum; methyl blue eosin stain.

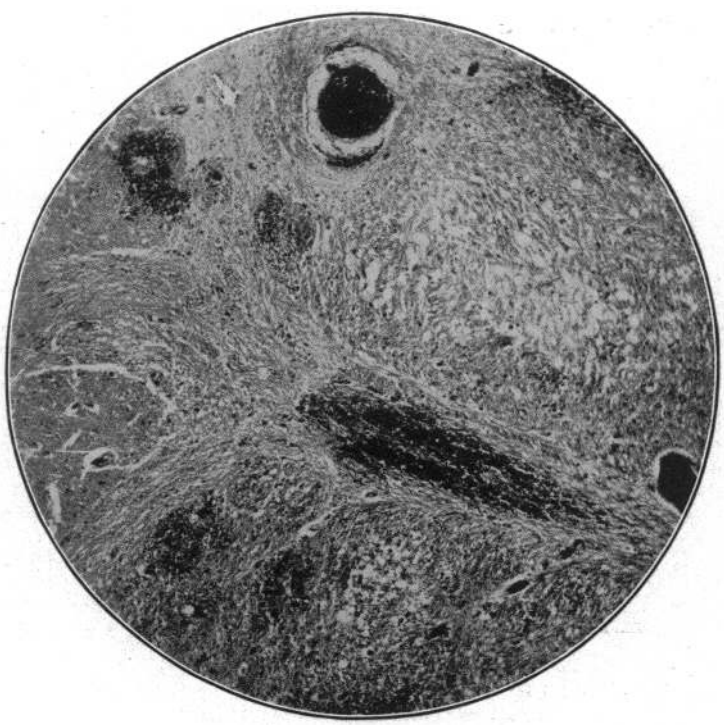

Fig. 8.—Photomicrograph, × 60, showing hemorrhage and round cell infiltration into the ventral limb of the left internal capsule; at left of the photomicrograph is an adjacent portion of the thalamic nucleus, taken from a transverse section of the brain just anterior to the mammillary bodies; methyl blue eosin stain. Block 16.

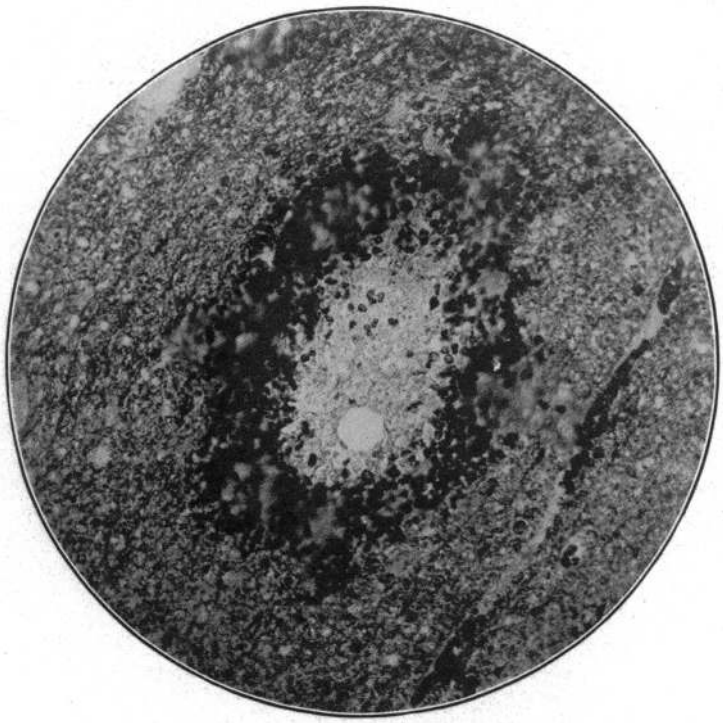

Fig. 9.—Photomicrograph, × 230, showing circular hemorrhage in the leg area of the precentral gyrus, right hemisphere; Weigert myelin sheath stain. Within the hemorrhage the myelin sheaths are entirely destroyed.

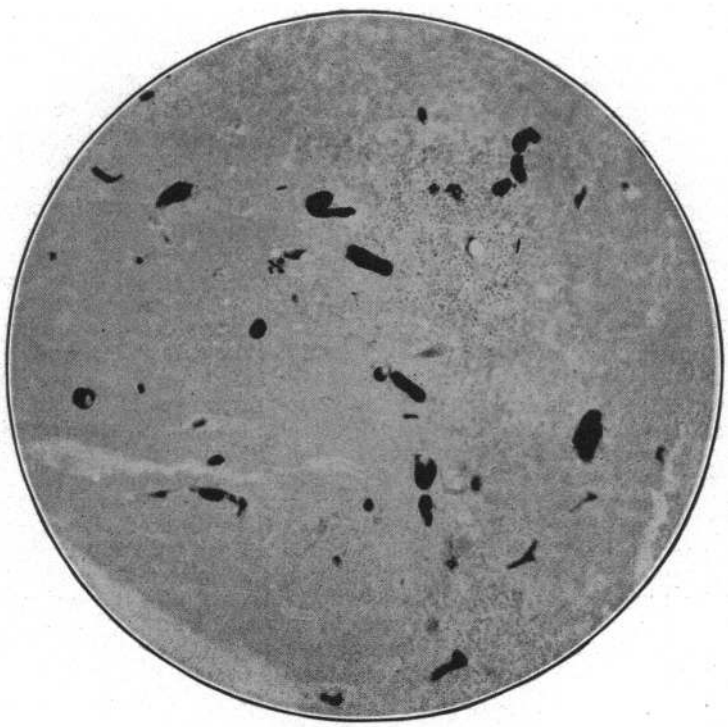

Fig. 10.—Photomicrograph, × 110, showing fat emboli in cerebellar cortex; osmic acid stain.

myelin sheath (Fig. 11). In some of the foci, there is a total loss of the myelin sheath, but in general a few sheaths are present, these being thinner and more granular than the sheaths of the surrounding tissue, although occasional strands of sheaths traverse the focus and appear to be unaltered. In a few foci seen in the leg area of the left central sulcus a peculiar type of lesion is present. It is a circular hemorrhage, within which there is a total loss of myelinated fibers (Fig. 9). In the silver-pyridin preparation for neurofibrils further information is obtained of these foci. Here is seen a loss of neurofibrils. In the lesions found in the medullary substance of both cerebrum and cerebellum this means a localized destruction of the axones. In some of these foci nearly all of the neurofibrils are lost, in others varying amounts up to about one fourth remain[17] (Fig. 12).

Within the focus the remaining neurofibrils are more irregular and broken up than in the surrounding tissue, although here also a few unaltered strands are present. These foci are present in every block of tissue removed for study and in the majority of the sections. As many as six to the low power field are observed. All parts of the brain are equally affected, there being no noticeable difference in the sections from the various areas of the cerebrum or cerebellum. Within each section they seem to predominate in the regions of the myelinated axons. In one hundred counted in the cerebellum there are forty-three foci in the dentate nucleus, thirty-eight in the medullary substance, fourteen in the granular layer, and five about the Purkinje cells. In the cerebrum, one hundred foci being counted, all are in the medullary substance or in the cortex immediately adjacent to it.

Nerve Cell Changes: The loss of myelin sheaths and axons demonstrable in the preparations just discussed permits an interpretation of the changes in the nerve cells with a greater degree of certainty. The dentate nucleus is a very common site of the focal necrosis. Many of the ganglionic cells in the region of these foci, including those cells within the focus, immediately adjacent to it or a short distance from it, appear to have undergone profound changes. The Weigert preparation, in which destaining had been arrested before the cell bodies were fully decolorized, was chosen for this study because in it are seen the cell changes in relation to the focal necrosis of the myelin sheaths. A normal cell in this preparation is polygonal in shape and has a definite outline, although no definite cell membrane is visible; there are several dendritic processes attached to it for a short distance. The cytoplasm is finely granular and stains deeply, the nucleus is centrally placed, generally round in shape, occupies about two fifths of the diameter of the cell, contains a dark intensely staining nucleolus centrally or slightly eccentrically placed, which is surrounded by a clear zone containing some light staining chromatin. In the early changes observed in these cells there is a shifting of the nucleus so that it occupies an extremely eccentric position, coincident with the cell assuming a round or oval appearance in place of the more polygonal form; the cytoplasm may still stain deeply. In other cells the nucleus has remained central, but the nucleolus occupies an extremely eccen-

17. Our material had been in formaldehyd for several years. Several neurofibril stains were tried with unsatisfactory results. A definite, clear-cut picture of the axons and dendrites that would permit of quantitative as well as of qualitative study was not obtained, either through faulty technic or acid reduction of the neurofibrils by the commercial formaldehyd used as the preservative. After numerous trials, it was found that if small pieces of tissue 1 cm. square and not over 2 mm. thick were placed in a 1 per cent. ammonia solution for twenty-four hours with repeated changes, then placed in a 1 per cent. ammoniacal 95 per cent. alcohol for seventy-two hours, with repeated changes, then fixed according to the method given by Ranson (Jour. Comp. Neur., 1912, xxii, 487) starting with 1 per cent. ammoniacal absolute alcohol and increasing the period of silver impregnation to from four to five days, a very satisfactory neurofibril preparation resulted from the formaldehyd fixed material.

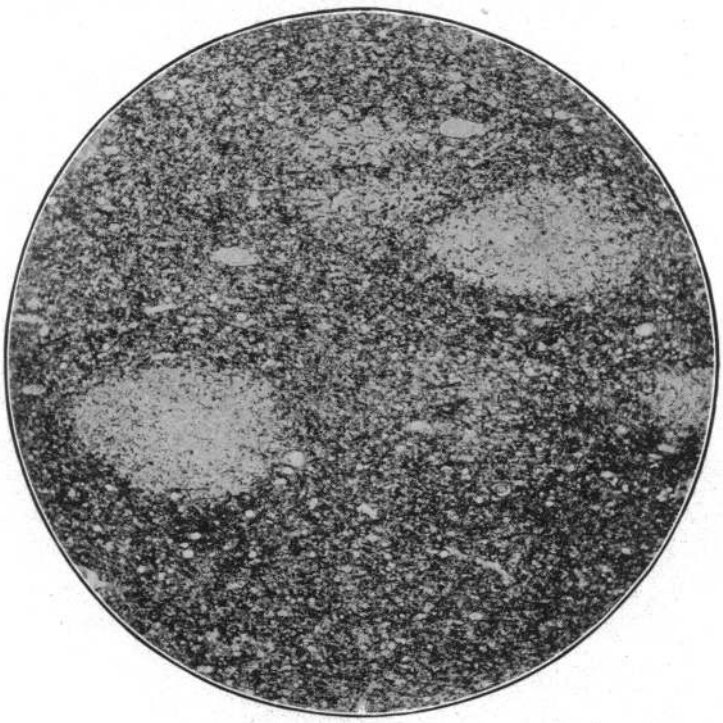

Fig. 11.—Photomicrograph, × 60, showing multiple foci of necrosis in the arm area of the precentral gyrus, left hemisphere; Weigert myelin sheath stain. In the light staining areas there is a loss of most of the myelin sheaths.

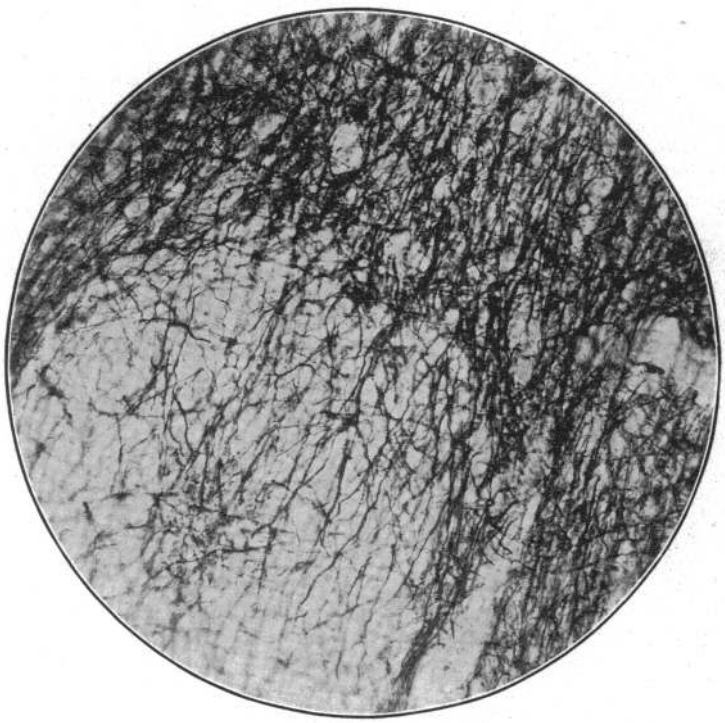

Fig. 12.—Photomicrograph, × 325, showing focal necrosis in the motor speech area from the triangular part of the inferior frontal gyrus of the left hemisphere. Silver pyridin preparation for neurofibrils. Within the focus four fifths of the axons have been destroyed.

tric position. The cells that have undergone further changes look swollen with the entire pattern slightly blurred. The cytoplasm stains lightly, the nuclear membrane is irregular, broader and less distinct; the nucleus appears swollen and may occupy one third to one half of the diameter of the cell; the nucleolus is also swollen and less distinct; and there is an increase in the stainable nuclear chromatin. In still later changes the nucleus has entirely disappeared and all that remains of the cell is a round or club shaped mass of granular, irregular staining protoplasm, containing a lighter staining round area placed near its center or eccentrically (Fig. 13). These changes are observed in many of the cells of the dentate nucleus and to a lesser extent in the pyramidal cells of the cerebrum. Whether they are consequent on the changes in the axons and myelin sheaths cannot be determined on the basis of this single study; although

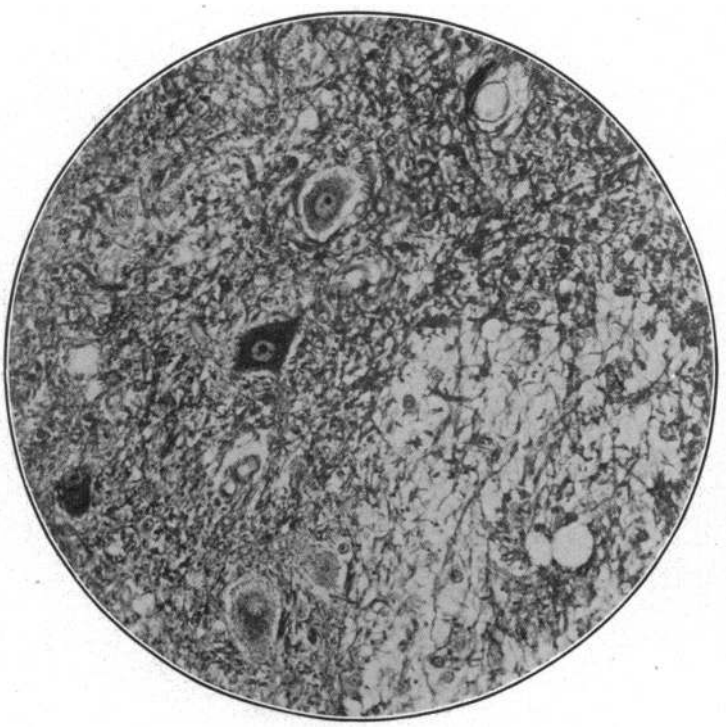

Fig. 13.—Photomicrograph, × 275, showing changes in the dentate nucleus; Weigert stain. In the lower right quadrant there is an area of focal necrosis in which most of the myelin sheaths are lost. Two ganglionic cells immediately adjacent to it have undergone karyolysis and partial cytolysis. A cell in the left lower quadrant has an eccentric nucleus; the dark staining cell in the center of the field is normal, and the cell above it stains lightly.

in all probability some relation exists between them. Warrington[18] has carefully studied the structural alterations of nerve cells following injury to their processes. On cutting the posterior spinal nerve roots in cats and monkeys he observed profound changes in the ganglionic cells of the posterior root; and on cutting the anterior spinal roots he observed marked changes in the corresponding cells of the anterior horn of the spinal cord. *The results enabled him to accept*

18. Warrington: Jour. Physiol., 1898, xxiii, 112.

*as a general law that in a cell loss of continuity of its processes is followed by definite structural changes.* He reviews the work of Marinesco, Lomy, Ballet, Munzer and Wiener to show that nerve cells undergo profound changes in consequence of disturbances of the vascular system; and he cites Nissl to the effect that nerve cell alterations may appear within twenty-four hours after injury to the processes.

Round Cell Infiltration: This lesion occurs less uniformly than any of the previously described lesions, and is generally associated with hemorrhages occuring near or adjacent. The infiltrated area differs from the hemorrhages in that while the hemorrhages are found sharply limited and round, the infiltrated areas tend to be diffuse and bear no special relation to the blood vessels.

Fig. 14.—Photomicrograph, × 110, showing degenerated nerve fiber sheaths, Marchi preparation, in the fasciculus anterolateralis of the spinal cord at the level of the decussatio pyramidum.

Changes in the Spinal Tracts: To determine what, if any, were the effects of the various lesions of the cerebellum and cerebrum on the pathways of the spinal cord, a block of cord was prepared by a slight modification of the Marchi method for degenerated myelinated fibers. This section was taken at the level of the decussatio pyramidum, and contains in the dorsal funiculus the fasciculus gracilis and the fasciculus cuneatus and their nuclei, of which a few fibers from the nucleus of the fasciculus cuneatus pass anteriorly to form the lower border of the medial lemniscus. In the funiculus lateralis there are the fasciculus lateralis proprius, the fasciculus cerebellospinalis of the Basle anatomical nomenclature, properly called the tractus spinocerebellaris dorsalis by Herrick[19] and others, and the fasciculus anterolateralis, which includes the tractus

19. Herrick: An Introduction to Neurology, 1915, Chap. 8.

spinocerebellaris ventralis, the spinal lemniscus of Herrick or the tractus spinothalamicus of Cunningham,[20] the tractus rubrospinalis. In the funiculus ventralis there is the narrow bundle of the fasciculus proprius ventralis on either side and the rather large pyramids of the fasciculus cerebrospinalis, which cross the midline and deflect the anterior sulcus. The spinal V tract is lateral to the substantia gelatinosa Rolandi, and there are portions of the dorsal and ventral spinal roots attached.

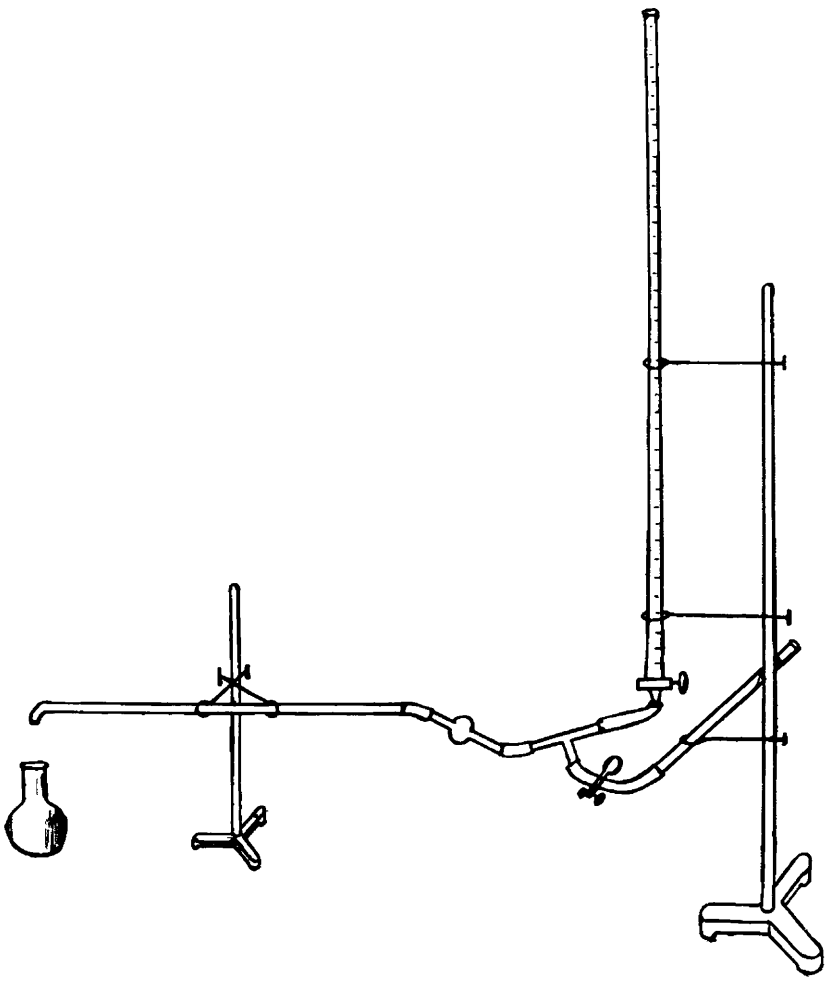

Fig. 15.—Apparatus, diagrammatic, used in studying viscosity and capillary resistance.

In the funiculus ventralis, there are numerous degenerated fibers scattered among the normal fibers. The degenerated fibers form about 1 to 2 per cent. of the total number. They are uniformly distributed throughout the funiculus. In the funiculus lateralis, both in the ascending and the descending tracts, and in the spinal V tract there are degenerated fibers (Fig. 14); the number in

20. Cunningham: Text Book of Anatomy, New York, 1909, p. 468.

this funiculus is not so large as in the funiculus ventralis and the largest numbers occur in the fasciculus spinocerebellaris. In the funiculus dorsalis the degenerated fibers are present in about the same proportion as in the funiculus ventralis, and in the adjacent portions of the spinal roots a moderate number of degenerated fibers are present. The presence of degenerated fibers in the descending pathways was expected after demonstration of frequent nerve destruction at the higher levels, and their presence in the ascending pathways was anticipated. In view of the wide and uniform distribution of the lesions in those parts of the central nervous system examined it seemed not unlikely that they should also occur in other parts. The demonstration of degenerated fibers in the spinal roots and ascending pathways is strongly suggestive of lesions in the lower part of the cord and the more peripheral nerves, that were not available for study.

## CORRELATION OF CLINICAL AND ANATOMICAL FINDINGS

In attempting to correlate these lesions with the clinical symptoms, it first becomes necessary to establish the alterations in the physiologic pathways of the central nervous system. In view of the various descriptions given to these tracts by authors, we shall for uniformity follow the nomenclature and descriptions given in chapters 8 and 9 of Herrick's Introduction to Neurology. It is not essential to correlate every observed lesion with these tracts. It is sufficient simply to establish an alteration of each of the constituent neurons, namely, the peripheral sensory neuron of the first order, the central neuron of the second order, etc.

In the exteroceptive conduction paths there are at the level of the neurons of the first order degenerated fibers in the dorsal spinal root; of neurons of the second order degenerated fibers in the spinal lemniscus; of neurons of the third order hemorrhage and destruction of nerve fibers in the internal capsule and cerebral cortex. In the lateral proprioceptive path there are of neurons of the first order degenerated fibers in the dorsal spinal root; of neurons of the second order degenerated fibers of the fasciculus anterolateralis superficialis and in the fasciculus spinocerebellaris, as well as destruction of nerve axons in the dentate nucleus. In the ventral proprioceptive conduction path there are at the levels of the neurons of the first order degenerated fibers in the fasciculus gracilis and cuneatus; of neurons of the second order hemorrhage and destruction of nerve fibers in the thalamic nucleus; of neurons of the third order hemorrhages and destruction of nerve fibers in the internal capsule and cortex. In the descending cerebrospinal pathways for voluntary muscular control there are at the level of neurons of the first order hemorrhage and destruction of nerve fibers in the motor areas of the precentral gyrus, also degenerated fibers in the fasciculus cerebrospinalis of the spinal cord; of neurons of the second order degenerated fibers in the ventral spinal roots. In the descending cerebellar pathway there are at the level of neurons of the first order destruction of nerve fibers in the dentate nucleus.

There is then in fat embolism of the central nervous system a condition that produces profound injuries to the anatomical pathways and centers which represent all types of functional connections.

To attempt to correlate the symptomatology with the observed lesions on the basis of the study of a single case is unsafe, irrespective of the completeness of the study. We can, however, point out certain relationships in which the observed lesions might have been contributory, if not the cause, of the clinical manifestations.

Delirium: Hirsch[21] defines delirium as a psychopathic condition observed in the course of numerous diseases, characterized by incoherence in the chain of conceptions and by the appearance of symptoms of psychosensory and psychomotor irritation, in which the incoherence of conceptions is evident in the disconnected and confused speech and in the aimless movements of the patient. Gowers[27] defines delirium as a condition characterized by a loss of concord of the mental processes with the actual sensory impressions of the present or the memory of those of the past; in which the mental processes cease to correspond to reality, and these may be accompanied by false sensory images without sensory impressions, or perverted sensory impressions. We shall take the liberty of assuming that the observed focal lesions of the brain initiated stimuli to the regional tissues prior to causing their destruction. Fat embolism is an acute condition, in the clinical sense of the word, but nevertheless develops gradually over a period of from twelve to seventy-two hours or longer. *Delirium invariably comes in the early part of the clinical course,* shortly after the accident, and is followed by the comatose stage three to twenty-four hours later. There is then, in most instances, a short delirious stage followed by a longer comatose stage. The delirious stage is probably initiated by the stimuli from the fat emboli, which in the smallest capillaries are separated from the nervous tissue by only a thin wall, and the distention of which by the emboli might easily cause a mechanical irritation of the nervous tissue; or possibly it is the first effect of the asphyxia that follows occlusion of the capillaries. Further, it is not unlikely that the focal hemorrhages, focal edema, and focal necrosis also produce a mechanical irritation before causing destruction of the tissue. This is compatible with the commonly accepted phenomenon that many substances which cause a final inhibition of cell activity produce an initial stimulation. Cushing[23] has demonstrated that stimulation of the postcentral gyrus in the conscious patient resulted in cutaneous sensations which were subjectively localized as if coming from the skin, and that stimulation of the precentral gyrus[24] resulted in typical motor responses.

21. Hirsch: Ref. Handb. Med. Sciences, 1901, iii, 398.
22. Gowers: Diseases of the Nervous System, 1896, ii, 104.
23. Cushing: Brain, 1909, xxxii, 44.
24. Cushing: Jour. Am. Med. Assn., 1908, L, 847.

In the three blocks of tissue examined from the somatic muscular and cutaneous sensory areas of the postcentral gyrus, taken from the regions adjacent to the motor areas of the left and right legs and the motor arm area of the left cerebral hemisphere, multiple focal lesions are found; and in the auditory area of the superior and middle temporal gyri and in the sensory visual area of the calcarine fissure the lesions are observed. It is also quite likely that they are present in every other sensory area of the brain. *These lesions caused initial stimuli of the regional tissue and probably resulted in psychosensory irritation.* In the three blocks of tissue from the somatic motor areas of the precentral gyrus multiple lesions are observed. *These probably caused initial psychomotor irritation.* In the area of motor speech coordination in the triangular part of the inferior frontal gyrus multiple lesions are observed. The lesions in this area alone might account for incoherence of speech. Further, in the frontal and parietal association areas multiple lesions are also observed, which may have caused a loss of the stereognostic sense and incoherence in the chain of conceptions; and finally, similar lesions are observed in the great coordinating center, the cerebellum. That delirium may be caused by multiple focal lesions has been noted many times. Gowers states that among the organic lesions producing delirium is multiple degeneration. Hirsch states that delirium may arise in organic diseases of the brain as a sequel to minute hemorrhages, and Smith[25] describes punctiform hemorrhages in the morbid anatomy of delirium.

Coma: This does not permit of as careful an analysis as does delirium. Most writers regard it as a symptom occurring in a large variety of diseases, and as such there has been a reluctance to describe definite pathologic changes to it. Gowers[22] defines coma as a prolonged loss of consciousness, in which the patient cannot be aroused and in which the reflexes of the limbs are decreased or lessened, accompanied by a general loss of muscular tone and by disturbance in the respiratory rate and rhythm. Mercier[26] describes coma as being associated with those cases in which there is a state of evident defect of consciousness, together with a tendency to death by asphyxia; it is accompanied by a paralysis, more or less complete, of the voluntary muscles and an incomplete paralysis of the visceral musculature; independent movements of the eyes may occur, and death may result from a failure of respiration. He regards coma as a late stage in the operation of the law of dissolution, in which the highest nervous processes, being the latest and least organized, are the first to disappear; and the lowest nervous processes, being the longest and most completely organized, are the last to disappear; this law being a reversal of the law of evolution. This analogy is very interesting from the phylogenetic point of

25. Smith, Allbutt and Rolleston: System of Medicine, 1910, viii, 899.
26. Mercier: Brain, 1886-7, ix, 467.

view and from the fact that it removes the phenomenon of coma from the phase of an accidental occurrence in disease and places it definitely in the working order of a great fundamental law; but it nevertheless does not aid in its analysis along anatomic-pathologic lines. We believe that irrespective of the cause of coma the functional alterations of the nervous system have anatomic-pathologic equivalents. Edema, hemorrhages, necrosis, among others, have been mentioned; these are present in fat embolism. We regard the wholesale injuries to the entire system of conduction pathways and the functional areas of the brain of greater significance. The violent delirium of the patient forbodes impending necrosis of the regional nervous tissue of the brain in fatally terminating cases of fat embolism; and this necrosis has been amply demonstrated throughout the central nervous system.

In attempting to prove a direct relationship between the brain changes and the clinical symptoms, it is evident that if similar lesions can be demonstrated in other diseases associated with delirium and coma, the relationship in fat embolism tends by analogy to become established. Accordingly a study was made of the literature of those diseases in which occlusion of the brain capillaries is likely to occur. This is true of all parasitic diseases in which free parasites circulate in the blood, and in certain diseases associated with embolus formation. The study has been partially successful; and while the results have not been as gratifying as was to be hoped, this is not to be taken as failure to establish the connections between the brain changes and the clinical manifestations in all these diseases, but rather to the limitations of our study.

In malaria of the so-called pernicious type an almost identical relation exists between the cerebral symptoms and brain changes. Clinically, delirium followed by coma has often been described. In Ewing's[27] study of nine cases of fatal malaria five of the patients developed delirium followed by gradually deepening coma, two went into coma without delirium, but the cause of death in these two was not shown to have been due to malaria. In one the probable cause of death was endocarditis, and in the other the diagnosis of malaria was only questionably established. The length of time that the patients lived after the appearance of these symptoms varied from a few hours to several weeks. Ewing concludes that the cerebral symptoms were due to the obstruction of the brain capillaries and the subsequent circulatory disturbances. The brains of persons dying of material coma have been described as edematous, hyperemic, discolored by pigment, and containing numerous punctate hemorrhages (Spiller[28]). Microscopically, there is a massing of infected red blood cells and malarial

27. Ewing: Jour. Exp. Med., 1901-5, vi, 119.
28. Spiller: Am. Jour. Med. Sc., 1900, cxx, 629.

parasites in the capillaries, with occlusion of the vessels; occasionally there is thrombosis followed by secondary changes in the adjacent tissue. Emge[29] describes multiple small, well-defined, circular areas of necrosis about the capillaries which are filled with masses of red cells and parasites, in the brain of an old man found comatose in the street, and later shown to be suffering from pernicious malaria. In Ewing's series parasites were found in the capillaries of the brains of three patients.

In trichinosis a similar correspondence exists. Thompson[30] made a clinical study of fifty-two cases, in which there were two deaths, one patient dying from complications of lobar pneumonia and erysipelas; but in the other patient death was due to the trichina infection. This patient died in delirium with a respiratory rate of 60, pulse 132, high fever and an eosinophilia of 14 per cent. Herrick and Janeway[31] report an outbreak in an Italian family in which the mother, after a week of mild symptoms, became delirious, with a temperature of 104, pulse 130 and a rapid respiratory rate. In trichinosis the parasites circulate freely in the blood according to Herrick and Janeway, also Packard,[32] and as such may become emboli. Frothingham[33] tells of having found them in the brain tissue. The capillaries were occluded and some were broken through by the parasites, which then made their way into the brain substance, where they incited round cell infiltration and caused local destruction of tissue and punctate hemorrhages.

Armstrong and Mullally[34] report two fatal cases of filariasis that strongly suggest the presence of parasites in the brain, but unfortunately the brains were not examined. Both patients were young girls, who soon after admittance to the hospital developed a high fever, 103 and 104, the pulse became weak and rapid, 136 and 134 respectively; the respiratory rates were 24 and 60; both became delirious, then comatose, and died without regaining consciousness. Filarial parasites in the blood have been frequently demonstrated. Connal[35] found them in the blood of 25 per cent. of seven hundred Langos natives. Our efforts to find a specific instance in the literature where they have been demonstrated in the brain have not been successful thus far; but in view of their frequent and repeated demonstration in the blood it seems probable that a thorough search might meet with success.

Cerebral embolism from valvular endocarditis is frequently reported in the literature. A single instance by Peabody[36] will be

29. Emge: Tr. Chicago Path. Soc., 1914, ix, 133.
30. Thompson: Am. Jour. Med. Sc., 1910, cxl, 157.
31. Herrick and Janeway: THE ARCHIVES INT. MED., 1909, iii, 263.
32. Packard: Jour. Am. Med. Assn., 1910, lix, 1297.
33. Frothingham: Jour. Med. Research, 1906, xv, 483.
34. Armstrong and Mullally: Surg., Gynec. and Obst., 1914, xix, 699.
35. Connal: Jour. Trop. Med., 1912, xv, 5.
36. Peabody: Med. Rec., New York, 1883, xxiv, 633.

cited, because it is typical for our purpose. The patient, a young man, suffered from palpitation of the heart, dyspnea, edema of the feet, shortness of breath, fluid in the pleural cavities; the apex beat was diffuse and there was a loud systolic murmur. On Oct. 20, 1883, he became restless and had incontinence. During the two following days the restlessness increased, and on October 22 he was quite delirious, so that he had to be restrained; morphin was administered, but it failed to quiet him. On October 24 the delirium subsided, he became quiet and was removed from the straight-jacket. He soon sank into a stupor, which gradually deepened, and he died on October 25 without regaining consciousness. On postmortem examination the basilar artery was seen to be plugged with emboli. The entire lumen of the vessel was obliterated. There was edema of the brain and the ventricles were dilated. In the mitral valve both cusps were markedly thickened and quite rough. On the roughened edges could be seen many little vegetations of fibrin and fibrous connective tissue. Peabody thinks that this was the origin of the numerous emboli in the cerebral vessels, and that the cerebral symptoms were coincident with the lodgment of the emboli in the brain.

TABLE 3.—A COMPARATIVE STUDY OF CEREBRAL EMBOLISM

| Disease | Delirium | Coma | Observer | Emboli and changes in the brain | Observer |
|---|---|---|---|---|---|
| Fat embolism... | + | + | Scriba | + | Scriba |
| Endocarditis ... | + | + | Peabody | + | Peabody |
| Malaria ..... | + | + | Ewing | + | Emge |
| Filariasis ..... | + | + | Armstrong and Mullally | — | |
| Trichinosis .... | + | — | Thompson | + | Frothingham |

The pathology of delirium and coma has not been definitely established. From the data in the literature, there is evidence indicating that they may be caused by a variety of anatomical lesions in addition to those mentioned. Hoch[37] has studied the brain of a man dying of delirium tremens, and finds alterations in the pyramidal cells of the cortex cerebri, no mention being made of alterations of fiber tracts or evidence of focal necrosis.

## CONCLUSION

In view of the profound disturbance in the central nervous system produced by the secondary changes of fat embolism, it is reasonably safe to conclude that these multiple lesions are intimately associated with the clinical manifestations of delirium and coma.

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37. Hoch: Am. Jour. Insan., 1897, liv, 589.