THE NEUROPATHOLOGICAL ASPECTS OF THROMBOCYTIC ACROANGIOTHROMBOSIS

A CLINICO-ANATOMICAL STUDY OF GENERALIZED PLATELET THROMBOSIS

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(RECEIVED FOR PUBLICATION, DECEMBER 27, 1947)

During the past two years we have been able to study the neuropathological changes in four patients in whom the principal symptomatology was fever, purpura, thrombocytopenia, and anaemia. In each instance the onset of symptoms was acute, the course of the illness rapidly progressive, and the termination fatal in a few days to weeks. The outstanding morphological finding was an increased cellularity and thrombosis of arterioles and capillaries in many organs, including the brain, by what are presumed to be agglutinated masses of platelets. In this respect it differs from the better known thrombocytopenic purpura of Werlhof and, as far as we know, from other diseases.

In our cases and in all of those which have hitherto been reported (see Table), neurological symptoms such as muscular weakness, hemiplegia, convulsions, drowsiness, confusion, stupor, or coma became manifest at some time, usually in the later stages of the illness. For this reason, and also because the neuropathological changes in a series of cases have not been described in detail, it was deemed advisable to bring this unusual syndrome to the attention of neurologists and neuropathologists.

This disease entity, if it be such, was first described in 1925 by Moschowitz. He had examined the organs of an adolescent girl who had succumbed to an acute febrile illness with joint pains, anaemia, petechial haemorrhages in the skin, left hemiplegia, coma, and death within two weeks. In many of the capillaries and arterioles of the heart, liver, kidneys, and spleen there were thrombi of the

"hyalin" type. Unfortunately a platelet count was not done. The brain was not examined.

In 1936 Baehr and others summarized the findings in four similar cases, each characterized by fever, progressive anaemia, mild icterus, and purpura. There were leucocytosis, reticulocytosis, and marked thrombocytopenia. Neurological symptoms consisting of convulsions, hemiplegia, delirium, or coma were present in three of the four cases. Necropsy revealed diffuse arteriolar and capillary thrombosis. The thrombotic material was believed to be composed of platelets.

Since the paper by Baehr and others nine other cases (Gitlow and Goldmark, 1939; Altschule, 1942; Bernheim, 1943; Trobaugh and others, 1946; Engel and others, 1947; Fitzgerald and others, 1947) have been reported, bringing the total to fourteen. All have shown platelet thrombi in the arterioles and capillaries, anaemia and thrombocytopenia. All have ended fatally within a few days to weeks. Four of the fourteen cases have been adult males and the rest adult females. The brain was examined in eight of these cases. Grossly the only changes were a few petechial haemorrhages, and these were not demonstrable in all the cases. Bernheim was the first to report the brain lesions in detail. In addition to platelet thrombi she noted small foci of ischaemic necrosis. Engel and others have described vascular and parenchymal lesions in a further case which differed from others in that the illness lasted three months, occurring in two phases separated by an interval of three weeks. However,

some of the symptomatology in the first stages may have been due to a verrucous endocarditis with brain embolism.

The present communication summarizes the neuropathological findings in four cases which have been examined at the Mallory Institute of Pathology and the Neuropathology Laboratory of Boston City Hospital. One of our cases was reported by Trobaugh and others in 1946, and three others were described along with a general review of the subject in the paper of Fitzgerald and others in 1947.

Summary of Cases

Case 1. (Case II of Fitzgerald and others, 1947).—The patient was a 24-year-old negress who was brought to the hospital because of deepening coma of twelve hours' duration. She had had many illnesses during the previous three years. In 1942 she had had gonorrhoea and toxemia of pregnancy, and was delivered of a full-term stillborn infant. In 1945 she had an incomplete miscarriage. In the fall of 1945 she developed a skin rash after being given sulphonamide prophylactically during the extraction of abscessed teeth. In 1946 she was hospitalized for chest and joint pains and urticaria which were diagnosed as rheumatic fever. The urticaria continued intermittently and was being treated with benadryl when she first complained of faintness, suffocation, nausea, hæmatemesis, epistaxis, and menorrhagia about one week before admission. In the following days she became very weak and stuporous, and then, a few hours before entry, comatose.

Physical examination upon final admission showed a poorly nourished woman whose blood pressure was 98 mm. Hg systolic and 76 diastolic, pulse 90, respiration 30, and temperature 97° F. There was a macular rash over the skin of the chest, abdomen, back, and thighs. The pupils were equal in size but reacted sluggishly to light. The knee jerks were absent and the other tendon reflexes were one plus and equal. There were no other abnormal neurological signs.

The red cell count was 2.74 million per c.mm. of blood, hæmoglobin 7 g. and white blood cells 14,900 with 50 per cent. neutrophilic leucocytes, 46 per cent. lymphocytes, and 4 per cent. monocytes. The icteric index was 25. The blood sugar, non-protein nitrogen, and chloride values were normal. The CO₂ combining power was 35 vol. per cent. The cerebrospinal fluid was normal.

The patient remained in coma and died six hours after entry to the hospital, about a week or less after the onset of acute symptoms.

ANATOMICAL DIAGNOSIS.—There were arteriolar, capillary, and venular thrombi with minimal endothelial proliferation in the œsophagus, lungs, heart, liver, pancreas, spleen, kidneys, ovaries, uterus, vagina, lymph nodes, bone marrow, and brain; focal necroses of the myocardium, pancreas, and brain; multi-nucleated giant cells in the lung capillaries; extramedullary myelopoiesis of the spleen; hyperplasia of the vertebral marrow; petechiæ and ecchymoses of the heart and

kidney; healed pleuritis of the left apex; and splenomegaly.

NEUROPATHOLOGICAL FINDINGS.—The brain was of normal size and configuration. There were no gross lesions in the cerebrum or brain stem.

Microscopic examination disclosed both vascular and parenchymatous changes in the cerebrum and brain stem as well as other changes of lesser significance.

The leptomeninges were thickened by an increased amount of relatively acellular collagenous connective tissue which in some places, particularly near the bottom of the sulci, contained small numbers of lymphocytes. The meningeal arteries and veins were normal.

There was an increased number of glia-cells in the marginal layer of the cerebral cortex, most marked in the sulci. They consisted of small clusters of astrocyte nuclei, some with visible perikaryon (amœboid cells), and scattered, elongated, microglial cells with irregular bipolar processes.

In all the parts of the cerebral cortex which were examined, that is, the hippocampus, premotor, sensorimotor, temporal, parietal, and occipital lobes, and in the caudate nucleus, putamen, thalamus, and substantia innominata, there was an increased cellularity of the arterioles, capillaries, and possibly small veins and thrombi of amorphous material partially or completely filling the lumen of many of these vessels. The adventitial cells of the aforementioned vessels were pale and swollen, and small granules of pigment, appearing yellowish in thionine-stained sections (probably "lipofuscin") could be seen in their cytoplasm. The endothelial cells of these vessels were increased in number and in size. Not infrequently the proliferating endothelial cells crowded concentrically into the lumen of extended diagonally or transversely across it. The thrombotic material which filled many of the vessels was finely granular and sometimes mixed with a few red corpuscles and white blood cells. In thionine stains the thrombotic mass was greyish and contained some minute chromatin particles and in hæmatoxylin and eosin stains it had a pink colour. One or two mast cells lay outside the adventitia of some vessels (Fig. 5 B).

In the tissue adjacent to many of the affected vessels in a small zone approximately 100-microns in size the nerve cells were pale with loss of Nissl substance and nuclear chromatin. In some of these minute foci several pleomorphic microglial cells* were found. In sections stained for myelin by Loyez technique there was no demonstrable change in the myelinated fibres. A few petechial hæmorrhages of well-preserved red corpuscles were also present in the cerebral cortex.

No significant changes could be demonstrated in the cerebellum or in sympathetic ganglia. The medulla, pons, and midbrain were not available for microscopic examination.

The arteries and veins, though occasionally surrounded by a few lymphocytes, macrophages with "lipofuscin" pigment and mast cells, showed no endothelial reaction or thrombi.

* We are referring, by this term, to microglial cells which are enlarged and have visible cytoplasm and processes and elongated or irregular nuclei.

NEURO-ANATOMICAL FINDINGS.—Multiple small vessels with endothelial reaction and thrombi; a few petechial hæmorrhages; multiple small foci of perivascular necrosis, some with microglia reaction; hyperplasia of glia-cells in the first cortical layer; fibrotic thickening of leptomeninges.

COMMENT.—The neuropathological changes which could be related to the acute disease process were the cellular proliferation in the walls of the arterioles and capillaries, the thrombi, the multiple small foci of nerve-cell alteration, and the scattered petechial hæmorrhages. The age of the glia-cell reaction in the marginal layer of cerebral cortex was difficult to judge. Unquestionably some of these glial changes and certainly the fibrotic thickening of the meninges were much older than the disease process under consideration.

The vascular and parenchymal lesions in the brain were of the same type as those in many of the other organs but differed from those in the heart by being less hæmorrhagic. Some of the cerebral changes may have been several days, possibly a week old, which was soon after the time of the onset of the hæmorrhagic diathesis; but most of them seemed to be more recent, corresponding more nearly to the development of stupor and coma.

Case 2 (Reported by Trobaugh and others, 1946).—The patient was a 24-year-old white man who had been well until two weeks before admission when he developed a cold with fever, prostration, and cough. His condition improved slightly in the next ten days, and on the eleventh day he felt generally ill and noticed hæmaturia. Severe vomiting of several hours' duration preceded entry to the hospital.

At the time of arrival to the hospital his temperature was 101° F., blood pressure was 120 mm. Hg systolic and 70 diastolic, and the pulse was rapid. He was restless and stuporous. His skin was pale and slightly jaundiced, with petechiæ over the abdomen, lower legs, and in the mouth and conjunctivæ. There were no other abnormal physical findings.

The hæmoglobin was 36 per cent., red cell count 2.18 million per c.mm. of blood, white blood cells 9,200. The differential count of white blood cells was 37 per cent. segmented neutrophilic leucocytes and 17 per cent. band forms, 23 per cent. lymphocytes, 17 per cent. monocytes, 4 per cent. eosinophils, 2 per cent. basophils, and 1 per cent. blast forms. Reticulocytes made up 10 per cent. of the red blood cells. The osmotic fragility test gave normal results and there were no cold agglutinins. Platelets were markedly reduced in stained smears of the blood. The icteric index was 20.

The patient became more deeply confused and restless and died on the third day in the hospital, the seventeenth day of the illness or six days after the onset of the hæmorrhagic diathesis.

ANATOMICAL DIAGNOSIS.—There were widespread arteriolar and capillary thromboses in the heart (myocardium), liver, pancreas, kidneys, adrenal cortex (mostly glomerular zone), ileum, and duodenum (mucosa), lymph nodes, bone marrow, and brain; small foci of necrosis, both anæmic and hæmorrhagic, in the myocardium, adrenal cortex (fasciculate zone) and

pancreas; petechial hæmorrhages in the heart (epicardium, myocardium, and endocardium), lungs, and intestinal mucosa; multinucleated giant cells in the lung capillaries; hæmolytic icterus as evidenced by moderate hæmosiderosis of the liver and spleen and by hyperactive bone marrow; and bronchopneumonia.

NEUROPATHOLOGICAL FINDINGS.—No gross abnormalities of the brain were detected.

In microscopic sections of the cerebral cortex the leptomeninges appeared thickened owing to an increased amount of connective tissue. A few lymphocytes and an occasional neutrophilic leucocyte were seen in the pia. One small flat subarachnoid hæmorrhage of well-preserved red corpuscles was present. Some of the subarachnoid arteries were filled with blood cells, and in many of them minute granules of red colour in aniline-blue-stained sections were found on the endothelial surface and between the red corpuscles within the vessel lumen. In one medium-sized artery the endothelial cells were larger and more numerous than usual. No thrombi could be found.

In the marginal layer of the cerebral cortex, especially near the bottom of the sulci, there were clusters of astrocyte nuclei and single hypertrophied astrocytes with visible cytoplasm and pleomorphic microglial cells.

Throughout the cerebral cortex arterioles and capillaries of pronounced cellularity were noted. The endothelial cells were increased in number and had a pale, indented nucleus and a basophilic or even metachromatic cytoplasm in thionine-stained sections. These cells were arranged circularly or they protruded into the lumen, in some places appearing almost to occlude it. Smaller, more elongated cells with darker nuclei were found outside the endothelial cells. An occasional mitotic figure could be seen in an endothelial cell. There were a few lymphocytes and an occasional unidentified mononuclear cell or neutrophilic leucocyte in the wall of the vessel or its perivascular space. The external diameter of these vessels was larger than normal. The lumen of many vessels was partly or completely filled with a granular amorphous material similar to that in Case 1.

There were only slight parenchymal changes consisting of a small zone around the most severely affected vessels where the nerve cells were pale, that is, loss of Nissl substance and pale nuclei, or, less often, had disappeared. In some of these foci microglial cells had increased in number and were pleomorphic. A few small hæmorrhages were found in the cerebral cortex.

These vascular and parenchymatous changes were present in all parts of the cerebral cortex, being most conspicuous in layers II, III, and IV. Similar vascular lesions were seen in the medulla, and in fact the tissue damage was much more pronounced here than in the cortex. These medullary lesions took the form of small foci of necrosis and hæmorrhage in which there were clumps of swollen astrocytes and pleomorphic microglial cells. Such lesions were situated in the lateral part of the magno-cellular reticular formation and nucleus of Burdach (Fig. 5A). In addition to the focal lesions, all the nuclei appeared to contain a few scattered swollen astrocytes and microglial cells.

NEURO-ANATOMICAL FINDINGS.—There were multiple small vessels with endothelial proliferation and thrombi; a few petechial hæmorrhages in the cerebral cortex and subarachnoid space; endothelial reaction in one medium-sized leptomeningeal artery; infiltration of leptomeninges by a few lymphocytes and an occasional neutrophilic leucocyte; multiple small foci of necrosis in the cerebral cortex and in the nuclei of the medulla—some, particularly in the medulla, with glia-cell reaction; and diffuse glia-cell proliferation in the medulla and first cortical layer.

COMMENT.—In this case it was concluded that the alteration of the walls of the arterioles and capillaries, the thrombi, the perivascular tissue changes, and the petechial hæmorrhages were the underlying pathology of the disease under consideration. The significance of meningeal fibrosis and glia-cell reaction in the marginal layer of cerebral cortex and in some parts of the medulla could not be determined.

The vascular lesions in the brain were exactly like those in other organs. Many of the parenchymatous changes were of such a character as to be adjudged about a week old. Presumably the vessels in all the different organs had been involved at about the time of, or slightly before, the hæmorrhagic tendency became manifest. The vascular changes in the brain were apparently slightly older and somewhat more advanced in this case than in Case 1.

Case 3 (Case I of Fitzgerald and others, 1947).—The patient was a 34-year-old white male who had been well until three weeks before admission, when he first experienced slight nausea and severe epigastric pain. He continued to work for the next three weeks until weakness, fatigue, anorexia, and constipation necessitated entry into the hospital for examination. In the past the patient had had an obscure abdominal disorder for which he took bismuth and aluminium hydroxide. There was no history of exposure to other drugs or toxic agents or of allergy.

The patient was restless and apprehensive. His temperature, pulse, respiration, and blood pressure were within normal limits. The skin was pale and dry. There were numerous recent retinal hæmorrhages. The remainder of the examination was not remarkable.

The red cell count was 2.14 million per c.mm. of blood, and the hæmoglobin was 42 per cent.; the white cell count was 13,700, with 60 per cent. neutrophilic leucocytes, 10 per cent. band forms, 1 per cent. juvenile forms, 1 per cent. myelocytes, 27 per cent. lymphocytes, and 1 per cent. monocytes. The platelet count was 88,000; the clotting time was 3 minutes, and the bleeding time 11.5 minutes. The prothrombin time was considerably prolonged in comparison to a normal control. The osmotic fragility of the red corpuscles was normal. The icteric index was 13.

His temperature varied from 99 to 102° F. but was normal after the sixth hospital day. The patient was very restless and often confused. He complained of dizziness. On the twelfth hospital day he became comatose and died a few hours later, twelve days after the exacerbation of the disease and five weeks from the onset of his illness.

ANATOMICAL DIAGNOSIS.—There was diffuse arteriolar, capillary, and venular thrombosis with endothelial proliferation in the heart, lungs, liver, spleen, adrenals, gastrointestinal tract, kidneys, prostate, testicles, lymph nodes, bone marrow, brain, and spinal cord; petechial hæmorrhages and ecchymoses in the skin, pericardium, myocardium, lungs, peritoneum, small intestines, and brain; multiple foci of necrosis in the myocardium and brain; multinucleated giant cells in the capillaries of the lung; cardiomegaly, hepatomegaly, and splenomegaly; hyperplasia of the bone marrow; tracheo-bronchitis and bronchopneumonia; atelectasis; and interstitial cell hyperplasia of the testicles.

NEUROPATHOLOGICAL FINDINGS.—The only gross abnormality in the brain was the presence of petechial hæmorrhages. They were fifteen to twenty in number and could be seen on the cut surface of the cerebral cortex, lenticular nucleus, thalamus, superior colliculi, pontine nuclei, and cerebellar cortex.

In microscopic sections the leptomeninges were normal except for a few scattered lymphocytes and an occasional neutrophilic leucocyte. The large arteries showed slight reduplication of the internal elastic lamina and irregular basophilic staining of parts of the media. In the walls of some middle-sized arteries there were irregular "calcareous" bodies situated chiefly in the media and sometimes in the intima and adventitia.

In some parts of the grey matter there was cellular proliferation and partial or complete thrombosis of most of the arterioles and capillaries (Fig. 1 A and B). The endothelial cells were increased in number, had pale and enlarged nuclei which protruded into the lumen and encircled or invaded thrombi of granular character (Fig. 2 C). The cytoplasm of some of these cells was quite basophilic and contained small dark granules. No definite mitotic figures were found. In a few vessels the cellular reaction was not accompanied by thrombosis. In some of the vessels, stained for reticulum, silver-impregnated fibrils often ending in bulbs were found between the intimal and adventitial cells of the vessel wall (Fig. 2 A and B). In van Gieson-stained sections a slight trace of reddish colour but no fully developed fuchsinophilia of the intercellular fibrils could be seen. In the choroid plexus were some vessels with a pronounced cellular reaction nearly completely obliterating the lumen (Fig. 5 C).

Parenchymatous lesions were found in the cortex of the frontal, parietal, temporal lobes and the thalamus, midbrain, pons, and medulla but they varied greatly in different regions. In the cerebral cortex the vessels with reactive changes were surrounded by a zone in which nerve cells were poorly stained. The nerve-cell alteration was more pronounced in the sensori-motor cortex, where in some foci these cells had completely disappeared or were shrunken, homogeneous, and pale, with a darkly stained nucleus. Many swollen astrocyte nuclei and pleomorphic microglial cells were found in some of these foci. There were also several collections of extravasated red corpuscles. In the marginal layer of the cortex, small clusters of naked astrocyte nuclei and scattered "ameboid" astrocytes were found.

The most severe lesions were in the superior colliculi

FIG. 1.—A. Cortical vessels with granular thrombi and cellular reaction of the wall. Case 3. Giemsa stain. Magnification $\times$ approx. 400.

B. Cortical vessel with thrombus and increased number of endothelial cells, growing inwards at the indentation of the thrombus. Mobilization of pleomorphic microglia in tissues. Case 3. Giemsa stain. Magnification $\times$ approx. 600.

FIG. 2.—A. Small artery of medulla with thick wall with an increased number of cells, argentophil fibrils, and some lymphocytes. The lumen is filled with red blood corpuscles. Case 3. Silver reticulum stain. Magnification x 1,800.

B. Small artery of medulla with cellular reaction of intima and argentophil; adventitial fibrils. The lumen is partly occluded by granular mass, the black irregular material in the lower half. Case 3. Silver reticulum stain. Magnification x 1,800.

C. Small artery of hypoglossal nucleus with proliferated intimal cells filling the lumen. Normal nerve cell and oligodendrocytes to the right. Case 3. Silver reticulum stain. Magnification x 1,800.

D. Small vein in the substantia innominata. Greyish coloured granular masses filling the lumen except for a segment in the upper right where there are a few white and red blood corpuscles. Above is a perivascular collection of lymphocytes. There is almost no cellular reaction in the wall of the vessel. Case 4. Thionine stain. Magnification x 1,800.

FIG. 3.—A. Cortical vessel showing cellular reaction of the wall from the point of bifurcation and downwards. The nerve cells mostly to the right of the vessel are very pale but without characteristic pathological alterations. Case 4. Thionine stain. Magnification $\times 200$.
 B. Radiating vessel from the superior colliculus. Note that the vascular reaction extends for a short distance above the point of bifurcation and downwards along both branches. At the tip of the left branch the lumen is filled with a granular thrombus. Case 3. Haematoxylin and eosin stain. Magnification $\times 200$.
 C. Note increased number of elongated microglia to left of a small thrombosed vessel with cellular reaction of the wall. From the gyrus hippocampi. Case 4. Thionine stain. Magnification $\times 200$.
 D. Thrombosed vessels in the centre with hæmorrhages at the periphery above and below, the latter one a "ring" hæmorrhage with central necrosis. From the superior colliculus. Case 3. Haematoxylin and eosin stain. Magnification $\times 100$.

FIG. 4.—A. Thrombosed vessels with cellular wall surrounded by a narrow zone with altered myelin sheaths. From the mesencephalon. Case 4. Loyez stain. Magnification $\times 100$.
 B. High-power view of the group of vessels to the left in A, showing myelinated fibres around a few of the vessels. Loyez stain. Magnification $\times 340$.
 C. High-power view of the vessel to the right in A, with a broad zone of non-impregnable myelin sheaths. Loyez stain. Magnification $\times 340$.
 D. Rounded focus of ischaemic necrosis with partial destruction of myelinated fibres between several damaged vessels. From mesencephalon. Case 4. Loyez stain. Magnification $\times 100$.

FIG. 5.—A. Minute pericapillary (?) necrosis with surrounding hypertrophied astrocytes and microglia from the cuneate nucleus. Case 2. Thionine stain. Magnification $\times 200$.

B. Mast cell adhering to the surface of a small vessel, the intimal cells of which are seen in the midline of the figure. To the right is the lumen of the vessel and to the left the brain tissue. Case 1. Thionine stain. Magnification $\times 1,800$.

C. Choroid plexus. Arrows point to vessels showing cellular proliferation and obliteration of their lumens. Case 3. Thionine stain. Magnification $\times 800$.

and tegmentum of the midbrain. The vessels passing from the surface of the colliculi towards the aqueduct were conspicuous on account of their cellularity and the thrombi. One of them, an arteriole which was cut in longitudinal section, contained a thrombus in one portion on either side of which were normally coloured red corpuscles (Fig. 3 B). Swollen astrocytes and pleomorphic microglial cells were present in the tissue adjacent to the thrombus. There were several fresh perivascular and "ring" hæmorrhages (Fig. 3 D), and in some few places microglial cells were filled with hæmosiderin. There was quite extensive nerve-cell destruction in these areas.

In the pons and medulla practically all the nuclei showed vascular changes, focal nerve cell loss, and clumps of astrocytes and pleomorphic microglial cells. Similar changes were found in the upper part of the cervical spinal cord and at the level of the decussation of the pyramidal tracts.

NEURO-ANATOMICAL FINDINGS.—There were multiple small vessels with endothelial proliferation; cellular endothelial reaction and thrombi; multiple small perivascular foci of altered nerve cells; multiple small, recent and older hæmorrhages, especially in the colliculi; and diffuse glia-cell reaction in the first cortical layer.

COMMENT.—The vascular and parenchymatous lesions were of the same type as in Cases 1 and 2 but were considerably older as judged by the increase in reticular connective tissue and in one lesion many microglial phagocytes containing hæmosiderin. The latter represents a reaction to hæmorrhage that was probably ten to twelve days old and correlates well with the clinical exacerbation which occurred at that time.

Case 4 (Case III of Fitzgerald and others, 1947).—The patient was a 28-year-old white man who had had rheumatic fever at the age of 12 years and had been rejected by the army in 1941 because of cardiac murmurs. Since 1943 he had been subject to frequent attacks of precordial pain, palpitation, and occasionally fainting spells. In February, 1947, five weeks before admission to the hospital, he began to have mild pains in both knees; there was no redness or swelling of these joints. Four weeks later he had fever and chills, cough, and back pain. A dull, generalized headache began shortly afterwards. Sulphadiazene was given two days before entry to the hospital. On the following day he vomited clotted blood, had a severe epistaxis, and voided urine of red colour. A rash appeared over the face and neck.

Once before the patient had taken sulphadiazene without untoward reaction. He had not been exposed to other toxic drugs, such as benzene, inorganic solvents, or fava beans.

EXAMINATION.—The temperature was 99° F., the pulse 88, the respiration 20, and the blood pressure 114 mm. Hg systolic and 76 diastolic. The patient was lethargic, but when aroused responded appropriately to questions. There were petechial hæmorrhages in the skin over the face, and in the oral mucous membranes and conjunctivæ. The cervical, axillary, and inguinal lymph nodes were slightly enlarged. The heart was of normal size and the rhythm was regular but there were apical systolic

and diastolic murmurs and an aortic systolic murmur. The liver and spleen were not palpable. No abnormal neurological signs were present.

LABORATORY DATA.—The urine was normal. The hæmoglobin was 7 g., the red cell count 2.3 million per 100 c.mm. of blood, the white cell count 11,650 with 86 per cent. neutrophils, 11 per cent. lymphocytes, and 3 per cent. monocytes. The hæmatocrit was 17. The bleeding and clotting times were normal. The platelets numbered less than 50,000. The blood culture was negative. The electrocardiogram was normal.

COURSE IN HOSPITAL.—The patient remained drowsy until the fourth hospital day, when he was seized with several generalized convulsions during which the head and eyes turned to the left. He was confused for several hours after the seizures, and during this time his temperature rose to 103° F. Penicillin was given in a dosage of 100,000 units every three hours. On the eighth hospital day he went into status epilepticus which could be controlled only by large doses of paraldehyde, given intramuscularly. Following this the patient remained comatose. No other abnormal neurological findings were noted. His cerebrospinal fluid was under a pressure of 110 mm., was clear and colourless, and contained no cells and a protein of only 26 mg. He was transfused with whole blood several times and his red cell count rose to 3.5 million. However, the coma persisted and he died on the twelfth day in hospital, or thirteen days after the first symptoms of hæmorrhagic diathesis.

ANATOMICAL DIAGNOSIS.—There were multiple thrombi in the arterioles, capillaries, and venules in the heart, kidney, bone marrow, and brain; petechial hæmorrhages in the heart and brain; multiple foci of necrosis in the heart and brain; multinucleated giant cells in the capillaries of the lung; hyperplasia of the bone marrow; and diffuse myocardial fibrosis of moderate degree.

NEUROPATHOLOGICAL FINDINGS.—Three or four petechial hæmorrhages were visible on the surface of the cerebral and cerebellar hemispheres, and about 20 more in the form of discrete round hæmorrhages, 1 to 2 mm. in diameter, were seen in the cortex, basal ganglia, and substantia nigra when the formalin-fixed brain was sectioned.

There were moderate numbers of astrocytes with visible cytoplasm and elongated microglial cells in the marginal layers of the cerebral cortex. Arterioles, capillaries, and possibly small veins were exceedingly cellular and were in some places filled with red corpuscles and white blood cells and in others occluded by homogeneous or slightly granular masses.

The cells in the vessel walls had an elongated, thin cytoplasmic body and were arranged concentrically around the lumen. The most centrally placed cells had large multiformed nuclei and more abundant cytoplasm. Both the endothelial and adventitial cells appeared to have undergone hyperplasia. Sometimes the thrombus had retracted from the vessel wall, and the detached surface was covered by a thin basophilic process of an endothelial cell. In places where an arteriole was

fortuitously cut in longitudinal section the mural cellularity and thrombosis could be traced past a bifurcation of the vessel into capillaries for a short distance (Fig. 3 A). Basophilic granules were seen in the cytoplasm of some cells of the vessel wall. An occasional mitotic figure was found. A few lymphocytes, mononuclear cells, and neutrophilic leucocytes had infiltrated the wall or the perivascular space of the affected vessels.

Some of the nerve cells and glia-cell nuclei immediately adjacent to the affected vessels were pale or in some places the neurones had disappeared. There were a few swollen astrocyte nuclei in some of these foci, and in one of them many pleomorphic microglial cells as well (Fig. 3 C). In rare instances damaged blood vessels were surrounded by "ring" hæmorrhages. The nerve cells were preserved in Sommer's sector of Ammon's horn.

A Loyez-stained section from the mesencephalon demonstrated the loss of a few myelinated fibres next to the most severely damaged vessels (Fig. 4 A, B, and C).

The vascular lesions were quite pronounced in the putamen and less so in the globus pallidus, thalamus, caudate nucleus, paraventricular hypothalamic nucleus, and substantia innominata (Fig. 2 D), in the substantia nigra, the abducens, inferior olivary, and magnocellular part of the lateral reticular nuclei, and the superior cerebellar peduncle and dentate nucleus. In the brain stem there was a slight diffuse increase in astrocytes and microglial cells and also several minute foci of swollen astrocytes and pleomorphic microglial cells. In the walls of many of the arteries in the pallidum there was a deposition of basophilic material; some of these vessels also showed cellular hyperplasia and thrombosis. In one focus in the dorsal part of the superior cerebellar peduncle all the vessels were damaged in a quite large area (Fig. 4 A, B, C), and the intervening nerve and glia cells were shrunken and pyknotic, while the myelinated fibres were damaged (Fig. 4 D).

In the choroid plexus of the lateral ventricles there were a few arterioles or small arteries which showed a slight but definite cellular hyperplasia. At the base of the brain a few meningeal arteries showed a slight proliferation of endothelial cells but no other changes. The subependymal glia had multiplied focally near the fourth ventricle, the aqueduct of Sylvius, and the lateral ventricle.

NEURO-ANATOMICAL FINDINGS—There were multiple small vessels with endothelial proliferation and platelet thrombi; multiple small perivascular foci of partial or complete necrosis in the cerebral cortex and brain stem; several old foci of ischaemic necrosis in the cerebral cortex; diffuse glia-cell hyperplasia in first cortical layer, subependymal zone, and brain-stem nuclei; and a few petechial hæmorrhages.

COMMENT.—All the damaged vessels in the brain did not show the same degree of reaction; some of them exhibited only a markedly increased cellularity, and others were partly or completely occluded by thrombi without any cellular reaction. In comparison to the myocardial lesions there was in the brain a more pronounced cellular reaction and considerably fewer

hæmorrhages. Some of the lesions in the brain were mild and acute, whereas others, in which a definite glial reaction was demonstrable, must have been of one or two weeks' duration. Presumably these older lesions coincided approximately with the progression of symptoms thirteen days before the patient's death.

Discussion

Symptomatology.—Although subject to considerable variation, the clinical picture of this disease, as formulated from all of the published cases, tended to follow a recognizable pattern. Usually it presented three main features: the signs of hæmorrhagic disease, severe anæmia, and neurological symptoms.

Both sexes were affected, female more often than male. The disease was somewhat more common in adolescents and young adults and occurred in both white and coloured races.

Some of the patients had enjoyed excellent health before the onset, whereas others had suffered from rheumatic fever, urticaria, or a recent upper respiratory infection. Several of them had rather vague prodromal symptoms, such as nausea and vomiting, weakness, malaise, and abdominal pain. When first seen the patients were, as a rule, quite pale and complaining of weakness, lassitude, vague pains in their joints, abdomen, or in other parts, or fever and chills. Usually small hæmorrhages in the form of purpura, epistaxis, hæmatemesis, hæmaturia, or menorrhagia had already occurred. Quite soon the bleeding became more profuse, and fever, if not already present, appeared. Neurological symptoms most often developed at this stage of the disease but were occasionally present from the onset. For the most part they were cerebral in nature and consisted of confusion, coma, motor paralysis, and convulsions.

The onset of symptoms was usually acute and the course progressive with a fatal termination in from one to eight weeks.

The blood presented the appearance of moderately severe anæmia with red corpuscles ranging from 1.0 to 2.74 million per 100 c.mm. of blood. The hæmoglobin was low, usually giving a colour index of about 1.0. The white cell count was normal or elevated, with a neutrophilic leucocytosis. In stained films there was anisocytosis, polychromatophilia, and reticulocytosis. Occasionally a few nucleated red cells and myelocytes were present. Platelets were reduced in number, usually below 50,000. The Rumpel-Leede sign was present. Bleeding time was often prolonged; over 30 minutes in some cases; and, although clotting was usually not delayed, the coagulum retracted poorly. Erythrocyte fragility was normal. The icteric index ranged from 8 to 25 and the quantitative Van den

TABLE
SUMMARY OF CLINICAL FINDINGS IN THE 13 REPORTED CASES WITH THROMBOCYTIC ACROANGIOTHROMBOSIS

Case	Sex and colour	Age	General clinical findings	Neurological findings	Total duration of illness
1. Moschowitz, 1925	F,W	16	Weakness and joint pains and pallor, petechiæ, (?) jaundice	Left hemiparesis Kernig sign	14 days
2. Baehr, Klemperer, Schiffrin, 1936	F,W	9.5	Listlessness, hæmaturia, pallor and skin purpura, retinal hæmorrhages, splenomegaly	None	7 weeks
3. Baehr, Klemperer, Schiffrin, 1936	F,W	18	Weakness and pallor, icterus and petechial skin hæmorrhages	Headache, convulsions	2 months
4. Baehr, Klemperer, Schiffrin, 1936	F,W	22	Urticaria, purpura, retinal hæmorrhages, nausea and vomiting	Delirium and stupor	9 days
5. Baehr, Klemperer, Schiffrin, 1936	F,W	48	Upper respiratory infection, purpura, icterus, retinal hæmorrhages	Right hemiparesis, coma	2 weeks
6. Gitlow and Goldmark, 1939	F,W	18	Upper respiratory infection, purpura, enlargement of spleen and liver	Right hemiparesis, coma	18 days
7. Altshule, 1942	F,W	50	Malaise, pallor, hepatomegaly, and splenomegaly	Confusion, left facial weakness, delirium	13 days
8. Bernheim, 1943	F,W	33	Weakness, dermatitis, pallor, purpura	Left facial weakness, hemianæsthesia, convulsions	2 weeks
9. Trobaugh, Markowitz, Davison, and Crowley, 1946	M,W	24	Upper respiratory infection, icterus, and purpura	Restlessness, stupor, coma	15 days
10. Carter, 1947	M,C	66	None	Confusion, aphasia, unequal tendon reflexes, right Babinski, coma	12 days
11. Engel, Schemker, and Humphrey, 1947	F,C	15	Sore throat, fever, malaise, purpura, hæmaturia, menorrhagia, vomiting, ECG changes; improved. 5 weeks later: recurrence of systemic and hæmorrhagic symptoms	Blurred vision, headache, delirium Coma, deviation of head and eyes to right, left hemiparesis, right facial weakness, flaccid paraplegia	50 days 7 days
12. Fitzgerald, Auerbach, and Frame, 1947	M,W	24	Nausea, vomiting, abdominal pain, pallor, purpura	Restlessness, confusion, and coma	5 weeks
13. Fitzgerald, Auerbach, and Frame 1947	F,C	27	Urticaria, faintness, epistaxis, hæmatemesis, menorrhagia, pallor, hepatomegaly	Stupor, coma	1 week
14. Fitzgerald, Auerbach, and Frame, 1947	M,W	28	Rheumatic fever, precordial pain, syncope, joint pains, chills and fever, epistaxis, hæmatemesis, hæmaturia, pallor and purpura	Status epilepticus, confusion, coma	2 weeks

Bergh analyses from 0.5 to 2.5 mg. The cerebrospinal fluid was normal in the three cases in which it was examined.

As shown in the Table, twelve of the thirteen cases had neurological symptoms at some stage of the disease. Some alteration in the state of consciousness was most frequent. This was variously designated in the records as irrationality, restlessness, confusion, delirium, stupor, or coma. It usually began with confusion and progressed terminally to coma. The latter was a sign therefore of grave prognostic import; once coma set in, death always followed within a few days.

Motor paralysis was observed in seven of the fourteen cases. The paralysis was not complete in any of them. In five of the seven there was a hemiparesis with involvement of face, arm, and leg, and diminished tendon and abdominal reflexes and a Babinski sign on the side of the weakness. In three cases a facial weakness was present, but from the meagre descriptions in the records one could not decide whether it was due to involvement of the facial nucleus or nerve or to a supranuclear lesion.

Seizures occurred in three cases. They were generalized in each instance, and in one case went on to status epilepticus which undoubtedly contributed to death. Focal or unilateral convulsions were not observed, which is rather surprising in view of the focal character of certain other neurological findings.

Less frequent findings were a left hemianæsthesia and deviation of the head and eyes to right as in Bernheim's case (1943); the latter finding was also present in the case of Engel and others (1947). In the case reported by Carter (1947) there was agrammatism, acoustic and verbal agnosia, and ideokinetic apraxia, but inasmuch as the patient was both confused and aphasic the validity of some of these interpretations of the mental state might be questioned.

Evidence of spinal cord or possibly peripheral nerve damage was observed in only three cases. The second of Fitzgerald's cases had nuchal rigidity and absent knee jerks, the case of Engel and others had a flaccid paraplegia, and in Carter's case there were at times hypoactive knee jerks, absent ankle jerks, diminished pain and touch sensation in the legs, and diminished temperature sensation in all four extremities but no motor weakness. As stated above, Carter's patient was confused and aphasic and some of the signs were probably not dependable.

Central Nervous System Lesions.—In the present material the outstanding neuropathological changes were (a) cellular hyperplasia, endothelial and

probably adventitial, of arterioles, capillaries, and venules; (b) thrombi of agglutinated platelets in arterioles, capillaries, and venules of cerebral cortex, basal ganglia, and brain-stem nuclei; (c) foci of nerve cell damage and in places glial proliferation; (d) petechial hæmorrhages.

The character of the vascular change has already been described in the case summaries. An excessive cellularity of the arterioles, capillaries, and venules and an increase in their total diameter were the most noticeable findings in hæmatoxylin-eosin and thionine stains (Fig. 1 A). It was not always possible to be sure of the exact identity of these cells. Those nearest the lumen had rather pale, indented nuclei and moderate amounts of basophilic cytoplasm and were abnormally oriented to the vessel, some encircling and narrowing the lumen and others traversing the lumen and dividing it. In Cases 2 and 4 a few mitotic figures were found. The outer cells in the vessel wall were more elongated, had more heavily chromatinized nuclei and, in Case 1, granules of lipofuscin in their cytoplasm. Occasionally a few lymphocytes, a neutrophilic leucocyte, or an unidentified mononuclear cell were interspersed between these cells. In silver stains for reticular connective tissue there was in some vessels a slight increase in argentophilic fibrils either separating the proliferating cells or extending outward from the adventitia. In van Gieson stains some of these fibres were faintly fuchsinophilic. All stages of vascular changes could be demonstrated in each individual case (Fig. 2 A, B, and C).

The arterioles, capillaries, and venules were occluded by thrombi which on differential staining appeared to be masses of agglutinated platelets. In the phosphotungstic acid hæmatoxylin stain the thrombi were a pale brown and no fibrogia were present. Weigert's stain for fibrin coloured the thrombi a dull grey, and in this and the phosphotungstic acid hæmatoxylin stain only an occasional bluish strand of fibrin was present. With Mallory's aniline blue stain the thrombi were a lavender colour and no fibrillar elements could be seen. In reticulum stains no argentophilic fibrils were seen within the thrombi. In Giemsa stain (Wolbach's modification) the thrombi were pale grey to blue. The earlier lesions stained a dark blue, older ones a greyish-blue, and no red colour was apparent in either. In the normal vessels between red corpuscles and leucocytes fine granules of about the size of normal platelets also stained a bluish colour. The van Gieson stain gave a pink colour to the thrombi, whereas the red blood corpuscles were yellow. No bacteria or inclusion bodies could be seen. Hæmoglobin stains showed the thrombi to be a red or brownish-red in contrast

to the olive green or green of the red blood corpuscles. From these studies it was concluded that the thrombi were composed of agglutinated platelets and not of erythrocytes, leucocytes, fibrin, hæmosiderin, or hæmoglobin. The failure of the platelets to appear as reddish bodies with bluish granules in the Giemsa stain does not disprove this possibility. Platelets often disintegrate so rapidly in post-mortem material that they cannot be identified by specific stains.

The blood vessels which were involved in this pathological process were the arterioles, capillaries, and possibly venules of the grey matter. In sections where the vessels could be followed for a distance in longitudinal section both the cellular reaction and the thromboses were restricted to a portion of the vessel extending for a short distance into the branching capillaries. In the cases of longer duration there was a tendency for larger veins to become thrombosed.

Cases 1 and 2 presented the "earliest" reaction and Cases 3 and 4 the "oldest" changes (see page 41). In the latter cases, however, it was possible to find vascular lesions of all different ages, indicating that the process had continued over the entire period of the illness. In Cases 2 and 4 one or two small arteries in the leptomeninges had been involved.

Damage to parenchyma, although present in every case, was slight. Alteration of some of the nerve cells in small foci around the thrombosed vessels was the usual finding. Even in the oldest lesions the change in the neurones was not commensurate with longstanding vascular occlusion (Fig. 3 A). The nerve cells had seldom undergone complete disintegration: they were usually faintly stained, with a pale bluish cytoplasm and nucleus. In some foci there were a few enlarged astrocytes and elongated or pleomorphic microglial cells. By Loyez myelin stains and Gros-Bielschowsky axis cylinder stain it has not been possible to demonstrate any massive destruction of myelinated fibres or axis cylinders next to the altered blood vessels, but there was some demyelination (Fig. 4 A, B, C). In the brain stem there were a few larger foci with necrosis of nervous tissue and a more marked glial reaction (Fig. 4 D, and Fig. 5 A).

Petechial hæmorrhages were found in all our four cases. They were easily visible to the naked eye in Case 4, and mistaken for congested blood vessels in Cases 2 and 3. In Cases 2 and 4 they were more numerous in the midbrain than elsewhere. They ranged in size from a fraction of a mm. to 2.0 mm., and at most numbered 25 or 30 in all*.

* An exception was the case of Allen, in which a large brain hæmorrhage was the cause of death.

Unlike some other types of brain purpura they were for the most part confined to the cortical grey matter, basal ganglia, and brain stem. Only a few were seen in white matter. In microscopic sections the hæmorrhages were discrete and of two types, perivascular, and ring-shaped around a necrotic centre. Usually they were in close relationship to damaged vessels. Sometimes an altered vessel or cluster of histiocytes were situated in the centre of a ring hæmorrhage. In older lesions there was a well-marked proliferation of pleomorphic microglial cells amongst which pale red corpuscles and swollen astrocytes were visible. Microglial phagocytes containing hæmosiderin pigment were noted in Case 3. Wherever the reaction of glial cells was intense, evidences of hæmorrhage could usually be found.

In the case in which the neurological symptoms were of briefest duration there were mast cells in the adventitia of the walls of damaged vessels (Fig. 5 B). This finding was of interest when viewed in the light of the recent discovery of Jorpes and others (1937), Holmgren (1940), and Sylven (1945), that the mast cell contains and secretes heparin. Conceivably they constituted in our case a reaction of the organism to thrombosis of small vessels. In the other three cases some of the outer cells of the vessel wall had a "basophilic," metachromatic, or slightly hyperchromatic cytoplasm in thionine stained sections but no true mast cells were present. The exact nature and purpose of these cells could not be ascertained.

The distribution of the vascular and the parenchymal lesions were fairly uniform in each of the four cases. For the most part they occurred in grey matter and not the white. In the cerebral cortex the second to fourth layers were affected more than the others. Changes of the same type were found in the grey matter of the caudate and lenticular nuclei, the thalamus, hypothalamus, and subthalamus and nuclear structures of the midbrain, pons, and medulla and to a lesser degree the grey matter of the cerebellum. Definite vascular abnormalities were found in the vessels of the choroid plexus in two cases (Fig. 5 c) and questionably in subarachnoid, vessels of two cases.

It was difficult to determine the age of the vascular changes because, as this is a new type of pathologic reaction, one dare not use as a standard of comparison the general pathological concepts of tissue reaction to injury. From a study of our material and previously published cases we have been impressed by the fact that all lesions were in about the same stages of development and were of relatively uniform character. Even in those cases in which the disease had been present for the longest

period of time, the vascular changes in the brain, as well as other organs, did not appear to be much more advanced than in the cases of shortest duration. However, within rather narrow limits slight individual differences between cases could be detected. As judged by the degree of glial reaction to parenchymal damage and the proliferation of cells in the vessel wall our Cases 1 and 2 presented a somewhat earlier reaction than Cases 3 and 4. In all of these cases the brain lesions seemed to correlate best with symptoms of the terminal phases of the disease, that is, with the acute onset of the hæmorrhagic diathesis or the exacerbation of the illness.

The significance of the fibrotic thickening of the meninges, and the gliosis in the marginal layer of cerebral cortex, in the inferior olivary nuclei, and sometimes in other nuclear structures is doubtful. These changes are not specific and were of such character as to have preceded the acute illness under consideration.

Ætiology and Pathogenesis.—The cause of this disease is as yet unknown. Moschowitz was of the opinion that the thrombi were of the hyaline type and made up of compact masses of erythrocytes. Baehr and his associates formulated the hypothesis that the disease was the result of sensitization of the vascular endothelium with secondary platelet thrombosis, and of thrombopenia due to the withdrawal of platelets from the circulation. They pointed out the resemblance between the vascular lesions in this disease and those which occurred in the veins in the Schwartzman phenomenon. The fact that two of our cases (1 and 4) had had allergic manifestations, as did the case of Engel and others, gives some support to this hypothesis. Appertaining to the matter of sensitivity it is of interest that three of the thirteen reported cases have had urticaria.

The absence of inflammatory exudate, bacteria, or inclusion bodies rules out most infectious agents. The possibility of a bacterial or other toxin acting on the endothelium cannot be as readily dismissed. On the experimental side Kielanowski and Selzer (1937) have demonstrated platelet thrombosis in the vessels of rabbits after the intradermal injection of *B. coli* culture filtrate. This reaction was, however, accompanied by infiltration of neutrophilic leucocytes in the vessel wall, which occurred only in slight degree in our Cases 2, 3, and 4. Also it has been shown by Dameshek and Miller (1946) that the injection of colloidal particles into animals will produce agglutination of platelets and severe thrombopenia.

We agree with Baehr and his associates and with subsequent writers on this subject, that the thrombi

are probably composed of platelets. This conclusion is arrived at partly by the exclusion by special stains of other blood elements in the thrombi and not by the positive staining of platelets, which is very difficult in post-mortem material.

The relation of the thrombi to the vascular proliferation could not be settled with finality. In every case there were many cellular vessels which were not thrombosed and also thrombosed vessels without cellular hyperplasia. From available evidence we find it impossible to decide whether thrombosis or endothelial proliferation is the primary event.

Relation of Neurological Symptoms to Brain Lesions.—Our four cases did not have the kind of neurological symptoms that lend themselves to exact clinico-anatomical correlation. The confusion, stupor, coma, and convulsions were indicative of a widespread disorder of the cerebral cortex and basal ganglia and could be related to the widespread vascular damage in these parts of the brain. In those cases showing perivascular necrosis and hæmorrhage in the nuclei of the brain stem there had been no symptoms pointing to damage of these structures. In all probability the lesions were in these cases too small and widely scattered to cause focal neurological symptoms. Perhaps in those cases previously reported in which aphasia, hemiparesis, facial weakness, etc., had occurred there was unusually severe affection of the blood vessels in one region so as to produce a much larger focus of ischæmic necrosis similar to that in the tegmentum of the midbrain in our Case 4. In neither our case nor that of Bernheim in which generalized convulsions occurred was it possible to find the "pseudolaminar degeneration" of cortex which has been observed in some cases of epilepsy.

Differentiation as a Disease Entity.—From the clinical point of view thrombocytic acroangi thrombosis must be distinguished from idiopathic thrombocytopenic purpura, other acute diseases in which there is a hæmorrhagic tendency, and diffuse vascular disease, particularly disseminated lupus erythematosus, subacute bacterial endocarditis, and acute hæmorrhagic encephalitis.

We have studied the pathological material from six cases of idiopathic thrombocytopenic purpura, some of which had been presented by Nickerson and Sunderland (1937) and were unable to find any vascular hyperplasia or thrombosis of the type which occurs in thrombocytic acroangi thrombosis. The marked anæmia so often seen in the platelet thrombosis cases is not usually found in Werlhof's syndrome. Also, there are important clinical differences inasmuch as frequency of symptoms of cerebral

disorder in Werlhof's syndrome is much lower, estimated at about 15 per cent., and when present are almost always related to hæmorrhage into the brain and spinal cord or the meninges (Weisfuse; see footnote page 40).

The pathological findings in "allergic" purpura and in disseminated vascular disease, that is, post-exanthematous encephalomyelitis, disseminated lupus erythematosus, and periarteritis nodosa, differ from those of the disease under consideration in regard to the brain. In our cases of lupus erythematosus the most striking brain lesions were embolic and were secondary to Libman-Sachs type of verrucous endocarditis. In many respects they resembled the focal necroses in Engels and others' case. Furthermore the subarachnoid arteries were occluded, whereas in thrombocytic acroangiothrombosis the small vessels in the grey matter were exclusively involved. In our cases of lupus erythematosus fibrinoid necrosis of connective tissue and vascular thrombosis or hyperplasia of endothelial cells were not present in the brain. The close relationship of platelet thrombosis and lupus erythematosus and rheumatic fever cannot be denied, but until more is known of the ætiology of these diseases they must be separated.

On morphological grounds alone the occurrence of petechial hæmorrhages in the brain requires that one consider such diseases as pericapillary encephalorrhagia (acute hæmorrhagic encephalitis or hæmorrhagic leucoencephalitis), post-exanthematous encephalomyelitis, fat embolism, and other varieties of brain purpura. So little is known about acute hæmorrhagic encephalitis that it is difficult to construct a clear concept of its clinical and pathological features. Some cases have apparently been the result of the administration of arsenic or some other compound, whereas others have occurred in the course of a virus pneumonia, influenza, or without known antecedents. The outstanding clinical symptoms have been stupor, coma, and convulsions. The cerebrospinal fluid has been normal. At autopsy myriads of petechial hæmorrhages were widely disseminated through the cerebral white matter and to a lesser extent in the white matter of the brain stem. Unlike thrombocytic acroangiothrombosis there have been no hæmorrhages in the skin or other organs, anæmia, or thrombopenia, and the vascular lesions of the brain are dissimilar. Other types of brain purpura and post-exanthematous encephalomyelitis can be readily distinguished by histopathological examination.

It should be pointed out that one of the unique and distinctive pathological features of thrombocytic acroangiothrombosis is the occurrence of

prominent vascular lesions with only slight parenchymal lesions. The discrepancy between the marked vascular reaction and the slight parenchymal change was quite remarkable. By comparison the degree of tissue damage was much less than in cerebral fat embolism where vessels of similar size may be occluded. The most likely explanations of this discrepancy are that platelet thrombosis occurred slowly, so that adequate collateral circulation could be established; and that the occlusion was in many vessels incomplete. Undoubtedly many of the thrombi formed shortly before death so that there was insufficient time for tissue necrosis to become manifest.

Since the real cause and pathogenesis of platelet thrombosis are unknown, one of us (P.F.) has suggested the descriptive term thrombocytic acroangiothrombosis. "This term designates the location of the lesion (acro-terminal, angio-vessel), states the nature of the process (thrombosis-plugging of a blood vessel by clot), and identifies the chief constituents of the thrombus (thrombocytes or platelets)" (Fitzgerald and others, 1947).

Summary

The neurological and neuropathological findings in four cases of thrombocytic acroangiothrombosis are presented. This is a rare disease of unknown ætiology which begins acutely, runs a rapidly progressive course, and usually causes death in a few days or weeks. The leading clinical features were fever, purpura, anæmia, thrombopenia, and symptoms of cerebral disorder such as muscular weakness, hemiplegia, convulsions, confusion, stupor, and coma. The cerebrospinal fluid was normal. The most important pathological changes were a striking increase in cellularity of the walls of arterioles and capillaries and thrombi of platelets. These vascular abnormalities were quite pronounced in the brain of each of the four cases, and were sometimes associated with multiple small foci of parenchymal necrosis and petechial hæmorrhages.

The neurological data of fourteen reported cases are summarized.

Clinically the disease must be distinguished from idiopathic thrombopenic purpura, disseminated lupus erythematosus, subacute bacterial endocarditis, and rickettsial diseases. This usually is possible by taking into consideration the total clinical picture and the laboratory data. The diagnosis of the disease can probably be established by bone-marrow biopsy in which platelet thrombi and vascular hyperplasia can often be seen. The brain lesions are believed to represent a unique picture unlike any other neuropathological type of reaction to disease.

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