GENERALIZED XANTHOMA, WITH A CASE PRESENTING LESION OF THE CENTRAL NERVOUS SYSTEM.*

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GENERALIZED xanthoma is a cholesterol disturbance of the cells, coincident with a normal lipoid content of the blood serum.

The case described involves the skull, dura mater, brain, pleura and gall-bladder.

I propose to deal with the subject as follows :

A. Description of generalized xanthoma and allied conditions, with special reference to the central nervous system.

B. Clinical record, detailed morbid anatomy and discussion of a case which involves the central nervous system.

C. Differential diagnosis.

D. Conclusion.

E. Bibliography.

A. DESCRIPTION OF GENERALIZED XANTHOMA AND ALLIED CONDITIONS, WITH SPECIAL REFERENCE TO THE CENTRAL NERVOUS SYSTEM.

LIPOID DISEASES.—A disturbance of lipoid metabolism is protean in its manifestations, and the lesions are extremely variable both macroscopically and microscopically.

Generalized xanthoma is one of many lipoid disorders, which include gall-stones, atheroma, xanthomatous lesions of the skin, muscles and bones, xanthomatous lesions in the lungs, lipoid nephrosis, the intestinal lipodystrophy of Whipple, Gaucher's splenomegaly, xanthomatous lesions of lymph glands and von Gierke's disease.

Certain of these lipoid disorders affect the central nervous system ; such are amaurotic familial idiocy, Niemann-Pick's disease and the Schüller-Christian syndrome. In Gaucher's disease, too, the main symptoms may be cerebral (Pick, 1933).

HISTORY.—Rayer first described a xanthomatous lesion in 1836. Addison and Gull in 1851 recognized the characteristic large pale cells, and the systemic character of xanthomatous manifestations. Panzer in 1906 first discovered a lipoid content of the cells, and Pick and Pinkus, in 1908, identified cholesterol.

The first to be described of the three diseases which affect the central nervous system and are now known to be lipoidal diseases was amaurotic familial idiocy. Waren Tay in 1881 and Sachs in 1887 described this syndrome, now known as cerebromacular degeneration, and with which is associated Niemann-Pick's disease.

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Hand in 1893, Schüller in 1915 and Christian in 1919 described the syndrome known as the Schüller-Christian syndrome. Rowland, in 1928, renamed it xanthomatosis, and recognized it as a disturbance of lipoid metabolism. Seventy cases of the disease had been reported by 1940 (Jelsma, 1940).

AETIOLOGY.—*Age.*—Lipoid diseases occur at all ages. Lesions in the skin, for example, occur in young children (xanthoma multiplex) and in adults (xanthelasma palpebrarum). General visceral xanthomatosis is found at all ages. In the central nervous system amaurotic familial idiocy occurs in Hebrew children, and there is an adult type of Kufs and Schob. Niemann-Pick's disease is found in infants. Although Gaucher's disease occurs usually in children, it has been found at all ages, even up to 65 (Bloem, Groen, and Postma, 1936).

Schüller's original case was five years old, and most of the early cases described of the Schüller-Christian syndrome were in children, but cases have now been described in adults. Thannhauser (1940) mentions a case which was observed from the age of 35 to 51.

As a general rule it is said that the lesions in children are diffuse, and in adults nodular.

Trauma.—Trauma and friction are regarded as precipitating factors, where there is already a predisposition. Nodules in the skin, for example, may occur at the sites of hypodermic injections or of mosquito bites.

Sepsis and infection.—It is known that the blood cholesterol is altered in febrile diseases. Weber (1924) believes that, following an influenza-like infection, a symptomless hypercholesterolaemia may give rise to lipoid deposits.

Sepsis is obviously an aetiological factor when xanthoma forms in an old abscess. In these cases polymorphonuclear cells, lymphocytes and plasma cells may be seen in the lesions.

Abscess of the scalp, gingivitis, tonsillitis, otitis media and mastoiditis have been described in association with the Schüller-Christian syndrome. It is possible, however, that conditions so described may actually be not infection, but part of the xanthomatous process. Xanthomatous tissue may soften and a milky fluid containing cholesterol be found. A viscid brownish-red discharge from the middle ear in a case of the Schüller-Christian syndrome may not be a primary infection, but a degenerating xanthomatous lesion, which can be demonstrated by operation on the mastoid (Thannhauser, 1940).

Hyperlipaemia.—Xanthoma may be secondary to hyperlipaemia in diabetes mellitus, von Gierke's disease, chronic pancreatitis and lipoid nephrosis.

PATHOLOGY.—*Macroscopical appearances.*—The characteristic xanthomatous lesion is nodular or in plaques in whatever organ of the body it is found. The nodules may be solitary, but they are usually multiple.

In Niemann-Pick's disease the nodules are found in several viscera. In the Schüller-Christian syndrome they are found as yellow masses growing from the dura mater and periosteum of the cranium and pelvis with erosion of bone. The masses are also found at the base of the brain and in the lungs, liver, spleen and lymph nodes. Soft pearly-coloured, translucent masses have been described by Berman (1938) in xanthomatosis of the spine.

Xanthomatous lesions may be diffuse. Diffuse lesions may be coexistent

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with nodular lesions, which is well shown in Niemann-Pick's disease and the Schüller-Christian syndrome.

Amaurotic familial idiocy presents a diffuse lesion of the brain, which is found to be enlarged, hard and firm. The cerebellum in the late infantile type is very atrophied.

Microscopical appearances.—The sections in the early stages are usually vascular, but the microscopical picture is dominated by the presence of lipoid. It is usually cholesterol, and is stained orange by Sudan III and by Sharlach R. Sphyngomyelin is present in amaurotic familial idiocy and Niemann-Pick's disease and stains a dull brick red with Sudan III (Scheidegger, quoted by Thannhauser, 1940).

The lipoid may be seen free in the blood vessels, in the adventitia, in the perivascular spaces and in intercellular spaces. It is sometimes found in the parenchyma and always in the connective tissue, giving a foamy appearance to the cells. In so far as the lipoid does not stain with many dyes, the cells are termed pale and, as they transmit light well, they are bright.

There is a special type of " foam cell," regarded as a product of the reticulo-endothelial system. Rowland (1928) marshalled considerable evidence to show that lipoidosis is essentially a disease of the reticulo-endothelial system. This systemic conception has been very generally accepted, and has given impetus and direction to much subsequent research. Exceptions to the rule are, however, claimed. Pick (1933) states that in the varied lesions of Niemann-Pick's disease all the body tissue elements take part in the storage of lipoid and production of foam cells. The importance of the reticulo-endothelial system is accepted, but it is safer to say that the single common factor in all these diseases is the disturbance of lipoid metabolism.

" Foam cells " are described as being in sheets, columns, collections or fused to form a multi-lobular mass, often around the blood vessels. These cells vary in size and shape, but are usually large and distended by fine granules of lipoid. The nucleus is small, dark staining and eccentric. Foam cells may be absent, especially in old lesions. They have sometimes been found to be absent (Jelsma, 1940) in the central nervous system in the Schüller-Christian syndrome, but Davison (1936) has confirmed the findings of Chiari that typical foam cells may be found in demyelinated plaques in this disease.

The cells of the parenchyma may or may not be affected by the disturbed lipoid metabolism. A lipoid disturbance and degeneration of the ganglion cells is present throughout the brain in amaurotic familial idiocy, Niemann-Pick's disease and the Schüller-Christian syndrome. The changes are similar, except that differing areas of the brain are specially involved in each. The nucleus becomes displaced to the periphery of the cell and granules appear at the opposite pole. At first the axon may be increased in size and tortuous, but later the cell processes disappear as the cell swells in size and becomes globular. Normal protoplasm becomes confined to around the nucleus, and later there is disintegration of the tigroid bodies and chromatolysis. The nucleus retains its nucleolus. Finally the nucleus disappears and the cell dies and disappears.

There is always a connective-tissue hyperplasia, the histiocytes of Aschoff

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being filled with lipoid granules. Pollitzer and Wile (1912) have described the ultimate predominance of fibrous connective tissue over the true xanthomatous elements in xanthoma tuberosum multiplex. In the central nervous system the neuroglia is increased. Compound granular corpuscles (gitter cells) derived from the microglia are numerous, and act as phagocytes and scavenger cells. Their appearance very much resembles " foam cells " proper and the distended ganglion cells, but the nucleus of the compound granular corpuscle is smaller and darker (Hassin, 1940). Astrocytes are increased and contain lipoid, for they stain with the lipoid stains, but granules are not seen in them. The oligodendroglial cells proliferate and form perineuronal satellites, whose function is metabolic. The gliosis is very marked in the advanced and chronic cases.

Lipoid.—The lipoid present in the liver and spleen in a case of Niemann-Pick's disease has been estimated by MacFate (1928). He found 61·29 gm. per cent. total lipoids in the spleen, the normal figure given by Bloom and Kern being 22·851 gm. per cent.

Deposits of lipoid in the cells of the body may or may not be accompanied by excess of lipoid in the blood serum. In some cases the nodules follow hyperlipoidaemia and, in the case of xanthoma diabeticorum, have disappeared with treatment and improvement of the diabetes. In such cases the local conditions are clearly secondary to the increase of blood lipoids.

Excess of lipoid in the blood is not always followed by infiltration of the cells and lipoid deposits.

In most cases the blood cholesterol is not raised above normal and there appears to be a primary lipoidal degeneration of the cells.

Lipoids are unsaturated fatty substances. Phosphatides, cerebrosides and sterols are among the most frequently found in diseases of lipoid metabolism. Sphingomyelin is present in amaurotic familial idiocy and in Niemann-Pick's disease. Of the sterols, cholesterol is of outstanding importance and is the lipoid present in most lipoid diseases, including the Schüller-Christian syndrome and the case described in this paper.

Cholesterol is absorbed from the digestion of animal but not vegetable foods, and it is also synthesized in the liver.

Cholesterol as a free alcohol or as an ester of palmitic, stearic or oleic acids is believed to be present throughout the body. Vitamin D, the bile acids and the hormones of the suprarenal cortex are derived from sterols, to which the male and female sex hormones, androsterone and oestrin, are related chemically. Indeed, Cook, Dodds, Hewett and Lawson (1933–1934) consider the assumption justifiable that there is a biological relationship between the oestrogenic hormones and the sterols and bile acids.

Cholesterol is excreted in the bile and by the intestines.

Symptoms and Signs.—Nodules which are not in the skin are often unsuspected, for there is a remarkable absence of subjective symptoms. There are sometimes no symptoms in the mild diffuse lipoidal degenerations of the parenchyma, but as the degeneration proceeds the effects are devastating. Normal healthy babies are reduced by amaurotic familial idiocy to paralysis, blindness and progressive dementia and die before they are two years old.

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Niemann-Pick's disease also causes mental symptoms and death before the age of two.

The Schüller-Christian syndrome comprises defects of the bones, especially of the cranium, exophthalmos and diabetes insipidus. Atypical cases are described in the literature, and those which involve the central nervous system are included in this review of symptoms.

The defects in the skull are characterized by their multiplicity, great size and sharp outlines (Schüller, 1926). Reynolds (quoted by Rowlands, 1928) demonstrated the usual cranial lesions of such a case by X-ray examination, and 20 months later a second X-ray examination showed complete bony regeneration. A second case had resolved after an interval of three years.

Rowland's review of 14 cases of the Schüller-Christian syndrome showed that tumour of the brain was often vaguely suspected (Rowland, 1928), but there has been no report of definite signs of cerebral tumour (Thannhauser, 1940).

Hemiplegia has been found due to the Schüller-Christian syndrome in a girl, aged 10 (Thannhauser, 1940). She was still hemiplegic when examined again at the age of eighteen.

The nodules which arise from the dura mater and periosteum of the cranium are generally reported not to cause signs of cerebral pressure. Berman (1938) has, however, described a case, occurring in the spine but entirely extradural, which caused spastic paresis by pressure and not by invasion of the spinal cord by xanthomatous tissue. The patient was an unmarried coloured woman, aged 18.

In the case now to be described there were definite signs of cerebral tumour.

B. Clinical Record, Detailed Morbid Anatomy, and Discussion of a Case which Involves the Central Nervous System.

Clinical Record.—W. S— was born in 1883 and had a normal childhood and upbringing. He went to school until he was 13, was able to read and write, and was considered to be a "bright boy." He was left-handed, and had the full use of all his limbs. He became a file-grinder and earned £3 a week.

At the age of 30 he developed "epileptic fits." He started to wander away from home and get lost, and he admitted this. He commenced to laugh when questions were put to him, and he came to be considered childish and simple minded, and was certified (17.x.13) as an insane person.

On admission to hospital his teeth were in bad order, his lips were dry and his pulse was 75. The report on his nervous system reads: "Station and gait normal. Knee-jerks present and similar. No ankle clonus. Plantar reflexes (flexor), cremasteric and abdominal reflexes, all present. Pupils approximately equal; slight corectopia inwards. Outline of each uneven. They react to light (direct and consensual) and with near vision. Movements of unrest present. Speech—some difficulty in articulation of difficult phrases—slight slurring."

He was at first in fair general health, but 18 days after admission he was sent to bed as he had become dull, listless, in poor health and had had two fits. He continued in poor health for seven months. His condition then became fair, but he complained of malaise in association with his fits, and he was still dull, listless and variable. Nine months later he was able to assist in the ward.

During the first part of his stay in hospital it was noticed that there was an appreciable latent period before he replied to questions. He was amnesic and "in the morning he forgets where he has put his clothes the night before." He was repeatedly described as confused.

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In 1919, six years after admission, there was the first record made of a paralysis of the left leg and arm. Two years later he had a discharge from beneath the right eyebrow, which continued irregularly for four years. During this period his health was fair. He was described as having little facial expression. He had occasional fits, about once in three months. It was stated that he could not tell his name, and he had " gross deficiency of power of attention." It was noted that his condition resembled general paralysis of the insane.

His condition then remained stationary till his death another 12 years later. During this time he had infrequent fits, in which he did not lose consciousness or fall to the ground. The convulsions were confined to the hemiplegic side and caused the patient much distress, so that from the start to the finish of the attack he would repeat, " I wish I were ——— well dead." After a succession of fits he eventually died in coma, when he was noticed to have skew deviation of the eyes.

He died 24 years after admission to hospital.

Discussion of clinical record of patient.—The typical xanthomatous feature is the discharge lasting irregularly for some years from below the right eyebrow. Irritation has often been described as an etiological factor in xanthomatous conditions, and it is inviting to speculate whether inhalation of dust from the patient's occupation of file-grinder caused irritation to the frontal air sinus and localized the primary lesion in this site.

The teeth are described as being in bad order. This may be irrelevant, but it is remarkable how often disorders of the teeth and gums have been described in the Schüller-Christian syndrome.

The patient's condition on admission was suggestive of a lesion of the frontal lobe of the cerebrum.

Sachs (1930), in his paper on lesions of the frontal lobe, gives among other symptoms and signs disturbance of speech, convulsions, nystagmus and mental changes. In the case under discussion the slurring of speech and convulsions were present on admission. Sachs describes the nystagmus as being irregular twitchings, not so regular as in cerebellar nystagmus, and the notes on this case describe movements of unrest in the eyes. Among the mental changes he describes loss of memory for recent events, lack of concern about disease and its outcome, depression and emotional instability. In this case the patient was dull, listless and in poor health and was definitely amnesic, for " in the morning he forgets where he has put his clothes the night before," and he would laugh when questions were put to him.

Kolodny (1929), referring to tumour of the frontal lobe, described personality changes, mental confusion (marked in this case), fits, speech disturbance and pupillary changes. The pupils, he said, varied in size and shape, and in this case the pupils were only approximately equal and the outline of each was uneven.

The clinical record described an appreciable latent period before the patient replied to questions. Jefferson (1937) has recorded this sign in a young woman suffering from a frontal lobe tumour, who showed a hesitation and a brief pause before answering questions. Strauss and Keschner (1935) found that mental symptoms were present at some time in 90 per cent. of cases of tumour of the frontal lobe, and that mental symptoms were the earliest manifestation in 43 per cent.

" Variable " was a description given of the patient W. S—, and in this connection Macewen (1893) described a case of cerebral abscess in the left

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frontal lobe coming under observation ten weeks after injury. Of his case he said, " It was hard to convince those who saw him only during the blinks of sunshine that he was suffering from an abscess of the brain." Macewen recorded that three minutes after a fit had passed off the patient was able to speak intelligently. Macewen also described the reflexes as being normal on admission, as in this case.

It is reasonable, therefore, to presume that this patient had, on admission to hospital, a profound disturbance of a frontal lobe of the cerebrum, and it is believed that definite symptoms and signs of this have been demonstrated in a case of xanthomatosis.

Morbid Anatomy; Macroscopical Report.

General.—The body is well nourished. The right pupil is smaller than the left. The visceral pleura are studded with cream coloured, firm nodules, 5–7 mm. in diameter. There is oedema and congestion of the lungs, a dilated heart and congestion of the liver. The gall-bladder contains three stones, each 25 mm. in diameter.

Cranium and central nervous system—inspection.—There is an old scar and a sinus 12 mm. deep under the right eyebrow. The cranium is of solid bone and there is no separation of the tables. The bone is roughened for an area 25 mm. in diameter behind the right frontal air sinus and opposite the frontal lobe of the right cerebral hemisphere. In this roughened area of bone are several large perforations for blood vessels.

The dura mater immediately adjacent is grossly thickened, being 5 mm. thick, and adherent here to the pia arachnoid. The pia mater strips easily from the brain, except from the right frontal lobe, where it is thickened, dull, and shows evidence of having been vascularized, but at death is gelatinous and fibrotic.

There is atrophy of the whole of the right cerebral hemisphere, but this is especially apparent to inspection in Brodman's areas 1, 2, 3 and 4 in their lower portions, most of 6, all of 8, 9 and 10, most of 11 (but excluding that part of 11 which lies on the orbital plate of the frontal bone), all of 43, 44, 45, 46 and 47, and the anterior portion of 40. In these areas of the right frontal lobe the convolutions are shrunken and gelatinous. The convolutions of the right parietal and occipital lobes are somewhat flattened and appear to have " fallen in."

Opposite the air sinus of the frontal bone and lying in the superior right frontal sulcus is a depressed scar 8 mm. in diameter, extending deeply as far as the ventricle, and 22 mm. along the sulcus forwards and backwards.

Section of brain.—The brain was divided by a medial sagittal section, and the hemispheres were divided by three coronal sections into four parts, which were then examined before further section was made for histological examination.

The first coronal section passed through the head of the caudate nucleus and through the scar in the right superior frontal sulcus. The part of the right hemisphere anterior to this section shows that the anterior horn of the right frontal lobe is lined by a gelatinous and irregular ependyma. The frontal lobe is extremely atrophied. The white matter is sparse, structureless and gelatinous, except for a narrow subsulcine strip. There is almost no compensatory hydrocephalus of this anterior horn, for the frontal lobe is " fallen in " and shrunken.

The second part of the hemisphere extends from the head of the caudate nucleus to the middle of the optic thalamus. The foramina of Monro are patent and dilated. The ependyma of the right ventricle appears dull, tough and grossly thickened, except over the head of the caudate nucleus, where it is roughened and gelatinous. The head of the caudate nucleus on the right side is 4 mm. less in breadth than on the left side, is flattened, and has dropped below the normal level of the floor of the lateral ventricle. The anterior limb of the internal capsule is scarcely discernible. The external capsule is replaced by two cysts, which measure vertically 24 mm. and 12 mm., and are situated between the putamen and the orbital part of the inferior frontal gyrus. The rest of the white matter of the right hemisphere seen in this section is gelatinous except for the white matter of the tip of the temporal lobe, which is reduced in size.

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The third part contains the posterior half of the optic thalamus and most of the corpus striatum. The cortex of the right parietal lobe is pale and the sulci are shallow. The white matter of the right parietal lobe is seen to be almost completely replaced by cysts which do not communicate with the lateral ventricle. The minimum thickness of the brain between the surface of the cortex and the ventricle is, at the site of section, 6 mm., but posterior to this is an area where the diminished cortex of the parietal lobe is adjacent to the lateral ventricle and the resulting shell of tissue is translucent. The right optic thalamus is represented by an extremely thin strip of disorganized tissue, and the internal capsule is equally atrophied. The hypothalamus, corpus striatum and body of the caudate nucleus are comparable in dimensions with the left side. The right caudate nucleus has flattened out on the extended floor of the dilated ventricle.

The fourth part of the cerebral hemisphere includes the occipital lobes. The diminished, cystic and gelatinous white matter of the centrum semiovale is still apparent, and there is compensatory hydrocephalus. The right optic radiation can be traced as a band projecting into the right ventricle from below upwards, outwards and backwards. At the posterior portion of the band the narrowing ventricle (posterior horn) bifurcates around it. Moderate atrophy of the right hippocampus, fascia dentata and hippocampal gyrus is present. The minimum thickness of the right cortex and centrum semiovale on the surface of this coronal section is superiorly 9 mm., laterally 3 mm. and inferiorly 9 mm.

All sections of the brain stem are deformed, due to atrophy of the pyramidal fibres from the right motor cortex. The right crus is atrophied, and there is a flattening and atrophy of the right pyramid.

Cerebellum.—There is obvious atrophy of the left cerebellar hemisphere and of its folia. The irregular pattern of the dentate nucleus is absent on the left side. The centre of its nucleus appears partly gelatinous. The respective weights of the cerebral and cerebellar hemispheres demonstrate the contralateral cerebellar atrophy.

L. cerebral, 560 gm. R. cerebral, 355 gm.
L. cerebellar, 50 gm. R. cerebellar, 70 gm.

Cerebral arteries.—There is a little atheroma of the circle of Willis. The right anterior cerebral artery appears healthy at its origin but later is atrophied, and trace of it is lost in the gelatinous pia arachnoid over the convexity of the right frontal lobe.

Discussion of macroscopic report.—It is characteristic of xanthoma that the lesion of the visceral pleura is nodular. Small cavities and fibrosis of the lungs themselves have also been described (Rowland, 1929) in post-mortems of the Schüller-Christian syndrome.

The stones in the gall-bladder are interesting, for xanthoma is a disturbance of cholesterol metabolism and cholesterol is excreted normally in the bile.

One large granulomatous mass was probably the acute phase of the process, which is represented in its chronic state by the condition described post-mortem of the frontal air sinus, cranium, dura mater, pia arachnoid and scar in the frontal lobe. It should be remembered that this post-mortem is on a patient who died 24 years after the onset of the acute process, and fibrotic changes are characteristic of the chronic process.

The condition of the frontal air sinus was inactive at death, but the large perforations in its posterior wall speak of an earlier vascularity, which is typical of xanthomatous lesions in their acute phase.

There is no separation of the tables of the membranous bones of the cranium, the marrow being absent completely. It is known that resolution may occur after a few years of the multiple sharply outlined defects in the skull associated with the granulomatous masses which arise from the periosteum and dura in

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the Schüller-Christian syndrome. Pick (1933) refers to a type of lipoid disease in which there is dense osteosclerosis of the long bones.

The fibrotic process is seen in the dura and in the scar in the frontal lobe.

The exceptional atrophy of areas of the frontal cortex which are underlying the gelatinous pia arachnoid and thickened dura mater may be the result of pressure by a granulomatous mass in the acute phase, or the result of ischaemia from fibrotic changes in the pia arachnoid membrane.

Demyelinization has been exceptionally severe in this case, and by cutting off the thalamus from the cortex has contributed to the almost complete atrophy of the thalamus, with which is associated the crossed cerebellar atrophy.

Morbid Anatomy ; Microscopical Report.

Areas of sections and stains used.—The brain was hardened in 10 per cent. formalin saline, and sections were made from the following areas : Thickened dura mater opposite right frontal air sinus ; scar tissue of right frontal lobe ; motor area of right hemisphere ; left frontal lobe ; right and left parieto-occipital areas ; right and left angular gyri ; right and left hippocampi ; coronal section at level of infundibulum, anterior commissure and head of caudate nucleus from both sides ; coronal section at level of tuber cinereum, middle commissure and optic thalamus from both sides, coronal sections slanting upwards and backwards from corpora mammillaria through the central median nucleus ; right optic radiation ; midbrain to include right and left crura ; medulla at level of inferior olive and restiform bodies ; lower medulla ; and right and left cerebellar hemispheres to include dentate nucleus and part of cortex. Some of these were frozen sections, others were paraffin to obviate disintegration of necrotic tissue, and some sections which were irregular in shape were embedded in celloidin.

The stains used were Nissl's ; haemalum and eosin ; haemalum and van Gieson ; haemalum, van Gieson and Weigert's elastic ; Weigert Pal ; Holzer and Anderson's stains for neuroglia ; Gram ; Perl ; iron alum ; stain for amyloid ; and Scharlach R.

Microscopic report.—The fibrous structure of the thickened dura mater opposite the right frontal air sinus stains red with haemalum and van Gieson. The same stain on the scar in the right frontal lobe shows both red and yellow fibres in sheaves, some fibres having spindle-shaped nuclei. Scharlach R shows irregular lines of extra cellular granules of lipoid in the scar, which contains no foam cells and no pyramidal cells. No bacteria are present, but there are a few scattered polymorphonuclear cells and twice their number of small lymphocytes in the scar. These inflammatory cells are not found elsewhere in the brain.

The pyramidal cells of the remainder of the cortex of the right frontal lobe are in the last stages of lipoidal degeneration. The cells are oval or round, the nucleus, with the nucleolus present, is extremely eccentric, and the cytoplasm is replaced by granules of lipoid, which stain orange with Scharlach R in frozen sections, but in paraffin sections the lipoid is removed and clear spaces are seen in the cells. Extra cellular granules of cholesterol are also found, in frozen sections, stained by Scharlach R.

The cortex of the right frontal lobe stained by haematoxylin and eosin shows numerous neuroglial nuclei, 7–12μ in diameter. The larger nuclei, astrocytes, stain lightly and are stippled with granules of chromatin, and are without nuclei. The smaller oligodendroglial nuclei are darker. There are no compound granular corpuscles.

The cortex of the left frontal and parietal lobes, though normal macroscopically, shows lipoidal degeneration. The degeneration has not advanced as far as in the cortex of the right cerebral hemisphere, but the quantity of cholesterol present appears greater. Many pyramidal cells still retain some of their processes, but the nucleus is becoming eccentric and deposits of cholesterol are forming in the cytoplasm. The cells which have become globular contain a large crescent of lipoid at the opposite pole of the cell from the nucleus, but intervening cytoplasm around the nucleus is still present. Astrocytes are increased, but not so much as on the right side, and there is a marked perineuronal oligodendroglial satellitosis. The cortex of this hemisphere is more vascular than the right. The cortex of the occipital

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lobes was not examined. The cortex of the left hippocampal gyrus shows deposits of cholesterol in normally shaped pyramidal cells which have oligodendroglial satellites. A few pyramidal cells in these gyri are becoming globular. The cholesterol shows as a brown pigment in Nissl sections. In the right hippocampal gyrus chromatolysis is more advanced and cholesterol deposits are less. Several subpial corpora amylacea may be seen in sections of all parts of the cortex.

The subcortical white matter of the right cerebral hemisphere is far less degenerated than the centrum ovale, the fibres of which, where present at all, are few and broken, with bulbous ends. "Spider cell" astrocytes are stained orange by Scharlach R, and there is a marked increase of interfascicular oligodendroglia shown by Holzer's stain.

Weigert Pal sections of the left frontal and parietal lobes appear normal. Scharlach R stains the fibrous "spider cells" orange and they are increased in number.

There are no compound granular corpuscles in the white matter of either hemisphere.

The basal ganglia on the right side are extremely disorganized and degenerated. A few shadowy remnants of cells of the optic thalamus are all that is left of that body. A few ganglion cells are left in the caudate nucleus and corpus striatum and hypothalamus, but there is much cellular debris. Among the neurons of the hypothalamus are a few truncated, vacuolated cells in which the nuclei are not recognizable. Weigert Pal sections of this area stain very poorly. A few plump astrocytes are present in the head of the caudate nucleus, and there is a gliosis of the putamen and globus pallidus and in the hypothalamus. These sections are very vascular, especially at the anterior perforated substance.

All stages of cholesterol lipoidal degeneration are to be seen in the ganglion cells of the left basal ganglia, the process being most marked in the thalamus, and less in the corpus striatum and hypothalamus. Some cells still retain their processes, but the nucleus is displaced and granules of lipoid are present at the opposite pole of the cell from the nucleus. In other cells the lipoidal degeneration has progressed and the cells are globoid, swollen and devoid of processes. There are also irregular pale ghosts of cells without nuclei and surrounded and invaded by two to five oligodendroglial cells. The ependyma over the left basal ganglia is in places four or more cells deep, and has lost its columnar appearance. In some areas the ependyma is missing.

There is a bilateral subependymal gliosis with deposits of corpora amylacea. Corpora amylacea are also found scattered and in groups, often around blood vessels, throughout the basal ganglia. The corpora amylacea do not stain for amyloid or lipoid, but are blue in haematoxylin sections. Cholesterol globules may be seen in and around the blood vessels, especially of the corpus striatum, and granules of lipoid are present between its fibres.

The red nuclei of the midbrain show the same globoid swelling, cholesterol deposits and satellitosis. Gliosis is not marked except for a little in the tegmental decussation. The left crus is normal. The inner half of the right crus is almost devoid of nerve fibres, which are replaced by a thick neuroglial felting and there is a moderate gliosis of the outer half too. The white fibres of the outer half of the right crus appear smaller than the fibres of the left crus.

Occasional cells of the medullary cranial nuclei have lipoid deposits, but the cells have their processes and normal Nissl bodies are present around the nucleus. Chromatolysis of the cells of the olives is worse in the right olive and pigment is present between the cells. There is an absence of fibres in the right pyramid. Increased neuroglia is present in the right pyramid and in the right restiform body.

The cortex of the left cerebellar hemisphere is two-thirds the depth, and contains fewer fibres than are found in the folia of the opposite hemisphere. There is an almost complete absence of Purkinjë cells in both cerebellar hemispheres, occasional folia being less severely affected. There is slight narrowing of the depth of the granular layer, and the cells are reduced in number. The cells of the dentate nucleus, particularly the left, stain poorly, show chromatolysis, and are intermingled with globules of dark pigment. There is severe demyelination of the white fibres in this nucleus, very few fibres remaining. Neuroglia is increased in the cortex, medulla, and especially in the dentate nucleus. There is no ferrugination of the brain cells.

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Comment on microscopical report.—The special feature of the microscopical report is the presence of cholesterol granules, which stain brown with Nissl's stain and orange with Scharlach R. The cells tend to lose their processes and become globular. The nucleus becomes eccentric. Hassin (1933), in describing lipoidal degeneration of the central nervous system, says the importance is "not so much in the structure as in the microchemical properties of the ganglion cells."

The degree of lipoidal degeneration found throughout this brain is at first surprising. It is characteristic, however, of xanthomatous lesions in all parts of the body that deposits of lipoid in the cells do not appear necessarily to destroy the function of the cells.

The fibrous and neuroglial scarring of the dura mater and small portion of the right frontal lobe constitute a localized process, differing from the generalized degeneration of the brain.

Fibrosis is often found in chronic xanthomatous lesions to have followed an acute phase in which collections of "foam cells" and compound granular corpuscles are associated with increased vascularization. Similarly it is probable that the localized sclerotic lesion of this brain was the original acute lesion composed of foam cells and compound granular corpuscles, as is found in the nodules of the Schüller-Christian syndrome. Evidence of the original vascular character of the lesion is to be found in the large perforations in the posterior wall of the right frontal air sinus.

No bacteria were found in this localized area of the right frontal lobe, but some small lymphocytes and polymorphonuclear cells are present. Focal sepsis is often associated with xanthomatous lesions, either as a precipitating or as a complicating factor.

Generalized xanthomatous degeneration of the brain is found in amaurotic familial idiocy, Niemann-Pick's disease and in the Schüller-Christian syndrome.

The generalized degeneration present in this brain has not progressed so far as the localized lesion, although many ganglion cells are in advanced stages of cholesterol degeneration. The connective-tissue hyperplasia is present in the form of oligodendroglia and astrocytes, but the latter are protoplasmic and not fibrotic in type, as in the scar of the localized lesion.

The change from cellular to sclerotic structure is in different stages in the two cerebral hemispheres. There are more cholesterol deposits and less gliosis in the left hemisphere than in the more severely affected right hemisphere, in which there is less lipoid and more gliosis.

Numbers of oligodendroglial cells are present around the degenerating cells. These glial cells, though present in other chronic conditions, are metabolic, not scavenger in function, and their presence confirms the view that the case here described is essentially a metabolic disturbance in the cells.

Compound granular corpuscles are not present, and this absence of scavenger cells may point to an arrested process.

The demyelinization of the right cerebral hemisphere suggests that hyperlipoidaemia was not a primary factor in this case.

Two anatomical anomalies of the case are explained by the widely spread lipoidal degeneration of the central nervous system. These are the degenera-

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tion of the right centre median nucleus of the optic thalamus, and secondly the crossed cerebellar atrophy.

Le Gros Clark and Russell (1940) described a case of acquired atrophy of the optic thalamus, associated with diffuse porencephaly and sclerosis of the left cerebral hemisphere. The history was of the onset of hemiplegia in a girl, aged 13, who died five years later. The only undegenerated elements in the thalamic atrophy were the lateral geniculate body, the centre median nucleus and a narrow subependymal zone of cells. There were no undegenerated cells in the optic thalamus described in the case of W. S—. The few cells which were not dead showed lipoidal degeneration.

Crossed cerebellar atrophy is found in some congenital hemiplegics, and is generally only expected when the cerebral lesion occurs in a very young person (Hassin, 1935). Von Monakow (1885) observed atrophy of the cerebellar hemisphere after ablation of the contralateral cerebral hemisphere in newborn dogs and cats. Mott and Tredgold (1900) emphasized the importance of the basal ganglia, and pointed out that the changes in the cerebellum and fillet only occur in hemiplegia when the lesion is primarily basal. Claude and Loyez (1912) reported a case of crossed atrophy of the cerebellum from a traumatic lesion of the internal capsule. The unusual occurrence described in this paper of crossed cerebellar atrophy in the adult may be due to the effect of porencephaly and thalamic atrophy superimposed on a cerebellum already affected by lipoidal degeneration.

It is unfortunate that the lungs and pleura were discarded before their significance was appreciated. There might have been excess of lipoid found in other organs had they been kept, for xanthoma was not suspected in the left cerebral hemisphere until a microscopical examination was made.

c. Differential Diagnosis.

Congenital.—The atrophied convolutions of the right frontal lobe are distinguished from congenital microgyria by the normal pattern of the convolutions.

Crossed cerebellar atrophy is usually congenital, but in this case the history of the patient and the clinical examination on his admission to hospital are quite inconsistent with a congenital lesion. The relatives give the history that far from having his left side paralysed as a boy, he was actually left-handed and he was considered a bright boy. He learnt to read and write at school, and later earned his living as a file-grinder. He was 30 years of age when the thorough neurological examination already described found no paralysis, and finally there is the photograph of the patient when he was admitted to hospital. Both his hands are in the picture, and that there was no hemiplegia then is quite evident.

Industrial: Chronic manganese poisoning.—The nervous system is particularly affected in chronic manganese poisoning by inhalation of dust in manganese mines and in the manufacture of manganese preparations. Manganese damages all areas of the nervous system, particularly the pallidum (O. Bumke and E. Krapf, 1936). M. Canavan, St. Cobb and K. Drinker (1934) reported the post-mortem examination of the brain of a man who had developed

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chronic manganese poisoning. They found atrophy of the parietal lobe, enlargement of the lateral ventricles and shrinkage of the basal ganglia. H. Stadler (1935) described a disappearance of ganglion cells replaced by glial tissue in multiple areas of the brain. Similar cases have often been described since 1901, and especially in the last ten years. The perivascular changes described are similar to those of lead poisoning. These degenerative changes are similar to those found by post-mortem in W. S—, but are distinguished by the absence of intracellular cholesterol deposits in the brain and other organs. The symptoms of chronic manganese poisoning are essentially those of Parkinsonism—mask-like features, flexion of the trunk, pro- and retropulsion, monotonous speech, and tremors. Our case differed from this in resembling general paralysis of the insane. It is unlikely also that dust from file-grinding could cause chronic manganese poisoning, for the manganese content of the tool steel used by file manufacturers in 1912 was from 0·30 per cent. to not more than 0·40 per cent. (personal communication from Sheffield Chamber of Commerce).

Dietetic.—Diffuse pigmentary atrophy of the ganglion cells is found in pellagra. Pigment-laden macrophages are found in the perivascular spaces. Pellagra does injure the central nervous system, but there is no other evidence that pellagra was present in this patient, nor, if it had been present, would it explain the pathological findings in the cranium, dura, brain and pleura of this case.

Circulatory.—The microscopical findings of dissolution of a large part of the right cerebral hemisphere suggest a circulatory disturbance in the areas supplied by the right frontal and middle cerebral arteries. An intrauterine or infantile process has already been shown to be absent in this case, and it is established that the hemiplegia arose between the ages of 30 and 35. An embolism might have lodged in the cerebral arteries, but there is no evidence post-mortem of a primary lesion, such as ulcerative endocarditis. Haemorrhage appears unlikely, for the patient would not have survived a haemorrhage of that magnitude. There is no trace of a congenital aneurysm, and arteriosclerosis is not a factor in a young man, and there was very little arteriosclerosis of the circle of Willis, even at post-mortem 20 years later. The heart and kidneys are not suggestive of hyperpiesia; nor would haemorrhage account for the microscopical findings in the left cerebral hemisphere and brain stem.

Inflammatory.—Dural lesions following sinusitis are limited as in this case. Pickworth (1935) believes that a symptomless infection of an air sinus of long duration may cause thickening of the adjacent dura, but in this patient the process had advanced to hemiplegia before the frontal air sinus showed symptoms and discharged. It is doubtful whether that discharge was purely inflammatory, and of all the air sinuses subject to infection frontal sinusitis is uncommon.

If there was a primary inflammation of the frontal air sinus the probable spread of infection would have been infection of frontal air sinus, infective venous thrombosis, pachymeningitis, subdural infection, leptomeningitis (Turner and Reynolds, 1931). Retrograde extension of septic thrombosis along the arteries causing infarction or along the veins, usually the superior

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cerebral veins, may pave the way for an abscess, solitary or multiple, of the frontal lobe. A superior longitudinal sinus thrombosis, however, would have caused equal damage in both hemispheres. Courville (1937) states that abscess of the frontal lobe secondary to frontal sinusitis is rare. The connective-tissue scar in the superior frontal sulcus of the right cerebral hemisphere is not a characteristic end-result of a cerebral abscess, although the inflammatory cells present may indicate an infection either precipitating or secondary to another process. The porencephaly is of such dimensions that if due to an abscess it would be expected that the latter would, by spread of infection and rupture into decadent tissues, have burst into the anterior horn of the lateral ventricle, with consequent death from ependymitis and meningitis. Yet in this brain the cysts in the right hemisphere do not communicate with the ventricle, and the patient lived for 20 years after the onset of hemiplegia.

Diffuse encephalitis may follow otitis media, but is unusual secondary to frontal sinusitis. Diffuse suppurative encephalitis due to an assumed anaerobic organism is very rare.

Infection by a neurotropic virus causes damage to the central nervous system, including destruction of Purkinjë cells in the encephalomyelitis complicating chickenpox and in louping ill. Parker and Kernohan (1933) say that it is not impossible that parenchymatous cortical cerebellar atrophy is in some instances at least due to a virus disease.

Infection by a virus may occur at all ages, in children (encephalomyelitis complicating chickenpox) and in elderly people (encephalitis in St. Louis). Neurotropic infection should therefore be considered. Against the diagnosis in this case is the path of infection, which was not by the olfactory nerve or other nervous tissue, but, if there were a primary infectious process at all, by infective thrombosis.

The degenerative changes in this brain were probably not a toxic encephalitis due to a diffusion of toxins from a bacterial infection of the frontal air sinus. Pickworth (1932) discusses the effects of naso-pharyngeal sepsis on the calibre of small brain vessels, through the sympathetic system. A circulatory disturbance in the brain might thus have been linked with frontal sinusitis. This would be in accordance with the theory of apoplexy that severe vascular spasm produces necrosis of vessels and brain. When the spasm relaxes the weakened vessels break, and the blood leaks into tissues which are already dead or dying. A toxic process might thus result in haemorrhage, but the diagnosis of haemorrhage has been excluded above.

The diagnosis of a primary infectious process cannot explain all the findings in the central nervous system, in the cranium and pleura. An infection may, however, have precipitated or been secondary to a xanthomatous process.

Disseminated sclerosis.—This relatively common and usually chronic disease is found in persons of the age of this patient, and often causes spastic paralysis. There is histological evidence of an inflammatory origin, and in the demyelinated plaques fat-containing cells, which stain by Scharlach R, replace the normal brain structure. Disseminated sclerosis, however, shows very few changes in the ganglion cells, and the other viscera are not affected as in this case.

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Schilder's disease.—Schilder's disease causes a demyelinization of the axis cylinders of the centrum ovale, sparing the subcortical fibres. Compound granular corpuscles phagocytize the free fat, perineuronal oligodendroglial satellitosis is present, and overgrowth of neurolgia is found around the blood-vessels.

The frontal lobe is seldom involved, and the pons and cerebellum are unaffected in Schilder's disease. There are no generalized visceral changes.

Hereditary cerebellar ataxias.—Atrophy of the cerebellum is characteristic of this disease, and the Purkinjë cells are often severely affected. The cerebrum is not affected as in this case, in which there is no family history suggestive of hereditary cerebellar ataxia.

Senility.—Yellow granules are frequently deposited in the nerve cells of older persons. The age of this patient excludes the diagnosis of senility.

Hepato-lenticular degeneration.—Bilateral degenerative changes in the lenticular nuclei may also extend to the internal capsule, basal ganglia, motor cortex and pyramidal tracts. There is a symptomless cirrhosis of the liver. The combination of degeneration in the central nervous system and a symptomless visceral lesion is suggestive of xanthoma, but this interpretation has not been given to hepato-lenticular degeneration.

D. Conclusion.

The case here described is an atypical example of the Schüller-Christian syndrome, or, as Rowland calls it, xanthomatosis. In Thannhauser's classification it is an example of "generalized xanthoma of the normocholesteremic type," which is a subdivision of his "primary essential xanthomatosis of the normocholesteremic type."

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