CLINICAL *and* PATHOLOGICAL STUDY

of a Case of General Tuberculosis, complicated by the presence of Ganglionic Neurogliomata in the Brain, and a Peculiar Vacuolar Degeneration of the Myocardium,

BY

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Contents.

Contents Continued.

Page.

List of Photo-micrographs and Drawings.

List of Photomicrographs and Drawings Continued

List of Photomicrographs and Drawings Continued.

Introduction

The following paper is a clinical and pathological study of the case of a child, admitted to the Royal Hospital for Sick Children, Glasgow, under the care of Dr. Geo. S. Middleton during my residence as house-physician in that institution. During life the case seemed merely an ordinary one of generalised tuberculosis, but at the necropsy some very unusual lesions were discovered — lesions which unfortunately had not been suspected during life, and the pathological examination of which forms the greater part of this work.

It was at the suggestion of Drs. Cowan and Ferguson that I undertook the study of the case, and to these gentlemen I am much indebted for valuable hints regarding pathological technique, and the interpretation of microscopic appearances.

To Prof. Muir of Glasgow University I have specially to express my thanks for kindly granting me permission to carry out the work in his laboratory, and for much valuable advice and encouragement during the research.

I must acknowledge my indebtedness to Prof. Sutherland of Dundee for information regarding his case of ganglionic neuroglioma, and for permission to quote the same.

In connection with the illustrations appended I have to thank Dr. J. H. Teacher for instruction in photo-micrography, and Dr. John Anderson, Pathologist, Victoria Infirmary, Glasgow, for permission to use his photo-micrographic camera. In the study of the different photo-

photo-micrographs a small hand lens will be found of great service for bringing out the details, as e.g., the transverse striations of the muscle cells.

Last but not least I must express my indebtedness to my late chief, D^r Geo. S. Middleton, for allowing me to make use of this case as a subject for study.

Accompanying this thesis is a box containing forty-one slides, with sections of the different organs showing the various points mentioned in the text.

Clinical History.

J.O., a male child, aet 14 months, was admitted to the Royal Hospital for Sick Children on 5th Oct. 1903 under the charge of Dr. Geo. S. Middleton.

According to the mother the patient was a plump healthy infant when born, and continued in good health until the onset of the present illness about three months previous to admission. At that time he developed a cough and commenced to wheeze a good deal. He was very short of breath, especially at nights, but he did not seem to be fevered. His appetite remained good, but occasionally he was sick and vomited, and the bowels were inclined to be constipated. The cough and shortness of breath increased in severity and he rapidly lost flesh. At night he was very restless and did not sleep well, but at no time was he noticed to perspire unduly.

Both parents are alive and well. Patient is the youngest and only surviving member of a family of three. One member died from acute gastro-enteritis, the other from "inflammation of the bowels", which from the mother's story could not be definitely considered of a tuberculous nature. It should be mentioned, perhaps, that patient, along with his parents, lived in a caravan. They were not itinerants, this form of dwelling only being used as a matter of economy. The father was a house-painter to trade.

On admission to hospital patient was described as being a well developed but pale and emaciated child. He was slightly rachitic as evidenced by the prominent

parietal bosses, by the slight rachitic rosary and the epiphyseal enlargement at the wrists and ankles. There was an enlarged and moveable lymphatic gland in the left submaxillary triangle. The temperature on admission was 99.° F..

Respiratory System:- Patient had a pretty severe cough. On swabbing the throat[1] some expectoration was obtained, and this on examination revealed the presence of a few tubercle bacilli and numerous diplococci. The breathing was rapid numbering 40 per minute. Examination of the chest revealed some impairment of the percussion note over the left front, in the left axilla and in the left lateral region. At the left apex in front slight tubular breathing was audible. Over the left apex, both back and front, and low down in the left lateral region, some moist clicking râles were detected, and slight wheezing was heard over both sides of the chest, both back and front.

Circulatory System:- The pulse which was small and regular numbered 130 per minute. There was no enlargement of the precordial dulness and the heart's sounds were pure.

Digestive System:- The tongue was coated and moist. Patient took his milk well.

Abdomen:- The abdomen was not distended nor was there any tenderness detected on palpation. There was no enlargement of either the liver or spleen.

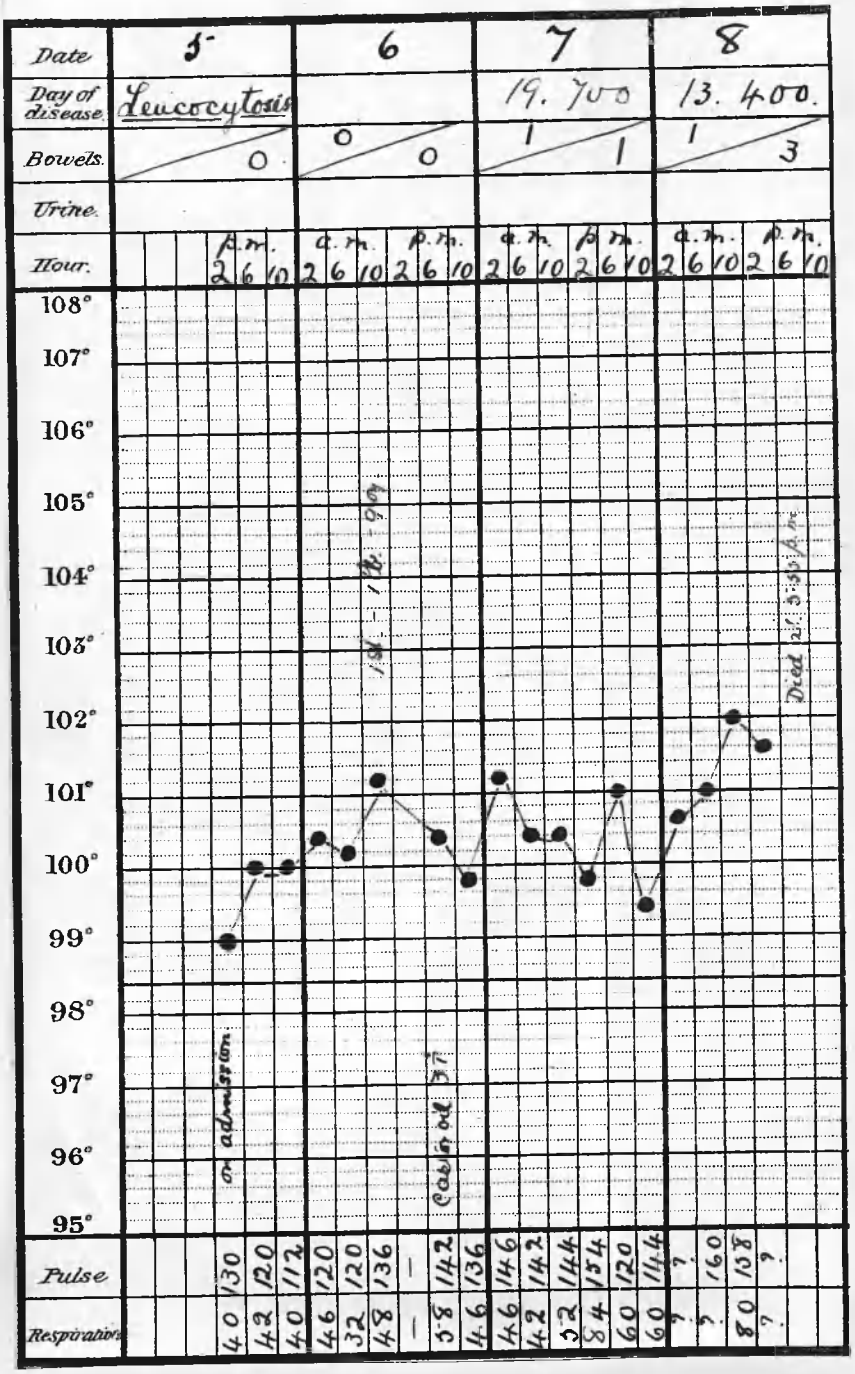
On the evening of the day after admission patient became suddenly collapsed, but with warmth and stimulants he improved somewhat. During the

[1] Findlay, L. "A New and Simple Method for Obtaining the Sputum in Children". Archives of Pediatrics. Feby. 1904. p. 126.

afternoon of the next day, i.e. 7th Oct., he seemed worse again and it was doubtful whether he could see or not. Both pupils were dilated and reacted slightly, and there was noticed for the first time an internal squint of the right eye. Nystagmoid movements of both eyes were observed at the same time, and there was also detected some rigidity of the muscles of the back of the neck. As the day advanced he became rapidly worse and by evening it was quite evident that patient was unconscious. The breathing became distinctly irregular. About 7-30 p.m. on the same day some twitching of the muscles of the right side of the face and of the right hand was noticed and this continued for about five minutes. Examination of the chest still revealed marked impairment of the percussion note over the left apex, both back and front, and in the left axilla: in all of these regions the respiratory murmur was deficient. All over the chest, both back and front, wheezing and coarse moist crackling rales were audible. The pulse became distinctly irregular and numbered 120 per minute. Lumbar puncture was performed during the afternoon, when about one ounce of a pale limpid cerebro-spinal fluid was withdrawn. On examination of the sediment, obtained by centrifugalising the fluid, numerous tubercle bacilli were detected. In the same films it was observed that the majority of the leucocytes were mononuclear in character, though many polymorphonuclears were present (see film I).

The blood was examined on two occasions. On the 7th Oct: the leucocytes numbered 19.700 p.c.m.m., and on the 8th Oct. 13.400 p.c.m.m. The majority of

1903 October.



of the leucocytes were of the polymorphonuclear variety.

The patient grew steadily and rapidly worse and by the night of 7th Oct. was quite comatose and required to be fed nasally. The face was now flushed and he perspired profusely. Occasionally twitching of the muscles of the right hand was noticed. The breathing was more irregular and latterly of the Cheyne-Stokes' type. The pulse also became more irregular and smaller, and ultimately imperceptible.

As will be seen from the accompanying chart, the temperature, which registered 99°F. on admission, rose slightly thereafter and on the two following days, 6th and 7th Oct., varied between 99°4F. and 101°2F., while on the day of death it varied between 100°6F. and 102°F. The temperature registered 101°6F. three hours before death.

Patient died at 5-30p.m. on 8th Oct., three days after admission to hospital.

Discussion:- In the above clinical history there are several points of sufficient interest to warrant a more detailed mention. There was no doubt on admission of the pulmonary lesion, and, while in all probability it was tuberculous in nature, it was only by an examination of the sputum that the diagnosis could be definitely made. My method* of obtaining the sputum in children here came

*"With a piece of gauze on the forefinger the pharynx, and especially the epiglottis, is irritated so as to induce coughing, and any expectoration that is coughed up is swept out of the mouth with the finger before it has time to be swallowed. The quantity thus obtained varies, but, as a rule, is quite sufficient for bacteriological examination. Several attempts may require to be made, but even in children as young as six months sufficient for diagnosis has been obtained."

came to my aid, and enabled me to make a definite diagnosis of tuberculosis on the day of admission. The sputum, as previously mentioned, contained tubercle bacilli and diplococci.

The history of sickness and vomiting with constipation is symptomatic of some cerebral mischief. This declared itself definitely two days after admission in unconsciousness, accompanied by strabismus and some rigidity of the muscles of the back of the neck. The pulse also had become slightly irregular. From the above combination of symptoms one would be justified in diagnosing tuberculous meningitis, especially in a case where a definitely tuberculous lesion had already been detected in the lungs. It is interesting to note, however, in this connection, the examination of the cerebro-spinal fluid, which so far as recent researches go, was typical of the fluid in tuberculous meningitis. The tubercle bacillus, which after all is the only pathognomonic sign of tuberculous meningitis, was discovered with great ease after centrifugalising the fluid. Regarding the leucocytic elements in the fluid it was found that the mononuclears were in the majority. The determination of the particular variety of leucocyte which is in the majority, has been regarded as an important aid in the differential diagnosis between tuberculous and nontuberculous meningitis.

D'Orlandi Pietro,[1] in a paper on cytodiagnosis, tabulates the results of examination of the cerebro-

1. "A Contribution to the Study of Cytodiagnosis in some Diseases in Children." Pediatria. July 1903 - page 8. Quoted in Archives of Pediatrics. Aug 1903. page 624.

cerebro-spinal fluid in eleven cases of tuberculous meningitis, and in ten of these cases it was found that the mononuclear leucocytes were in the majority. Osler[1], however, has not been able in his later researches to confirm this observation.

The blood was examined on two occasions, when a distinct leucocytosis (19.700 and 13,400 white blood corpuseles p. c. m. m.) was discovered. Osler[2] Cabot[3] and Da Costa[4] all say that a leucocytosis is the rule in tuberculous meningitis in contradistinction to uncomplicated tuberculosis of all other organs. Of course, in formulating an opinion from the examination of the blood, it must not be forgotten that in my case there was also a tuberculous cavity secondarily infected with diplococci. This circumstance in itself always produces a certain degree of leucocytosis (Cabot)[5]. Thus it is seen that from the clinical examination of the patient all the signs pointed to the existence of a tuberculous infection of the lungs and meninges, but the cardiac condition and the cerebral condition, discovered post-mortem, were not suspected during life.

Fuchs[6], while discussing the symptomatology of myocardial tuberculosis, lays stress on the occurrence

1. Osler. W, "The Principles and Practice of Medicine" 4th Editions. 1901. p. 107.

2. Osler W. Ibid. p. 279.

3. Cabot. M.D. Rich.C. "A Guide to the Clinical Examination of the Blood". 3rd Edition. 1898. p. 267.

4. Da Costa. Jr. M.D. J.C. "Clinical Haematology" 1902. p. 443.

5. Cabot M.D. Rich.C. Ibid. p. 225.

6. Fuchs. W.A. "De la Tuberculose du Myocarde". Thesis. Paris. 1898. p. 55.

occurrence of syncopal attacks. Can it be suggested that the cardiac tumours, discovered post-mortem, may have accounted for the syncopal attack from which the patient suffered on the evening after admission. However, so far as the mother's story goes, such attacks had not been a noteworthy feature of the child's illness.

Summary of Clinical History.

Male child aged 14 months.

Family History:- Father and mother alive and well. Patient is the only surviving child of a family of three. No history of tuberculosis.

Previous Health:- Good.

Present Illness:- Duration three months. Illness was characterised by cough - shortness of breath - wheezing in the chest - vomiting - constipation, and loss of flesh.

Condition on Admission (5th Oct. 1903):- Emaciated child, showing evidences of rickets. Tuberculous gland in neck. Tuberculosis of lungs evidenced by dulness to percussion over left upper lobe with clicking râles and tubular breathing. Tubercle bacilli were detected in the sputum.

Subsequent History:- Patient rapidly got worse. Two days after admission developed signs of tuberculous meningitis. Tubercle bacilli were discovered in the cerebro-spinal fluid. Patient died three days after admission.

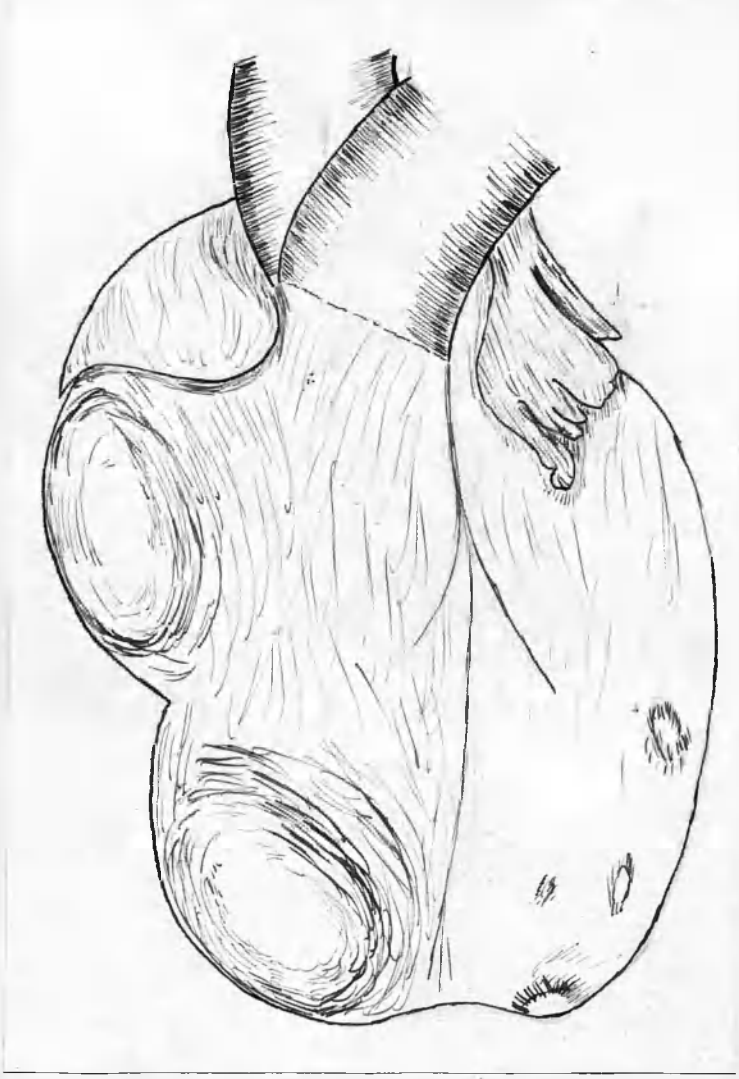


Fig. 1. The heart, showing the quadrangular form and the hour glass shaped contour of the right border, due to the two large masses in the wall of the right ventricle.

Post Mortem Report.*

The body is that of a much emaciated child. Rigor Mortis is passing off.

Thorax:- On opening the thorax a normal extent of the pericardium is exposed, and the pleurae are found to be non adherent. Heart:- The pericardium contains a normal amount of fluid and there is no pericarditis. The heart is slightly enlarged, especially on the right side, and it has a somewhat quadrangular form. In the wall of the right ventricle are two rounded swellings. One of these masses is situated at the apex while the other lies towards the auriculo-ventricular septum. They bulge into the pericardium giving the outline of the right side of the heart an hour-glass shaped contour (see fig. 1.). Several smaller and similar masses are scattered over the surface of the left ventricle. These are more numerous and larger towards the apex and give, along with the mass at the apex of the right ventricle, the apex of the heart a bifid appearance. The pericardium over all these masses is smooth, white and glistening. On incising the wall of the right ventricle the two aforementioned masses are encountered extending from pericardium to endocardium. Their fresh section is pale in colour and of a dull wavy appearance. The larger one at the apex bulges into the ventricle, and extends to and implicates the interventricular septum on the one hand, and the

* The examination was conducted about thirty hours after death.

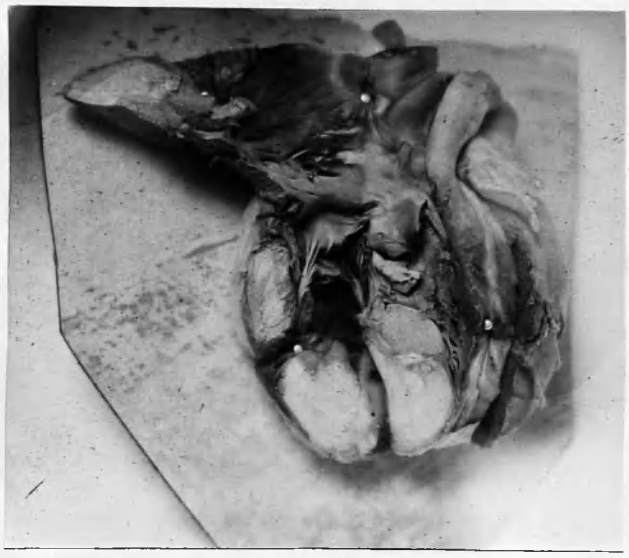


Fig. 2. Photograph of the heart. The right ventricle has been opened by means of raising a V. shaped flap of the anterior wall. The large masses in the wall of the right ventricle and also that on the interventricular septum are well seen.

the musculi papillares on the other. It measures in breadth 2 c.m. from pericardium to endocardium and 3 c.m. in length at its greatest part. The smaller one, separated from the former by a narrow piece of normal but pale cardiac muscle, has an ovoid shape, and measures 1 c.m. from pericardium to endocardium and 2 c.m. in length. There is another mass situated towards the base of the interventricular septum and bulging into the right ventricle: this seems to have been continuous with the mass at the apex, but the process of opening the cavity has broken the connection.

These points are well shown in the opposite picture (fig. 2), which is a photograph of the cavity of the right ventricle opened by means of a V shaped flap, one border of which passes from the apex along the edge of the interventricular septum and through the pulmonary artery, while the other extends from the apex along the right border of the heart to the auriculo-ventricular septum.

On incising the wall of the left ventricle it is found to be studded with numerous small masses of a dull white colour and hard consistency. They vary in size from that of a pin head to that of a split pea. On the internal surface of the left ventricle immediately below the anterior cusp of the aortic valve, and in close proximity to the anterior cusp of the mitral valve, is a small papillomatous growth about the size of a split pea, and with an irregular surface suggestive of ulceration. On section it is found to be of a dull yellowish colour, and to extend into the heart by a V shaped

shaped process. There is also a small mass having the size of a hemp seed situated at the base of the interventricular septum on the left ventricular aspect. A portion of one of the papillary muscles of the anterior cusp of the mitral valve is thickened, pale in colour and of a hard consistency and evidently composed of tissue of a nature similar to that of the other masses.

With the exception of the above mentioned papillomatous growth, none of these masses shows any appearance suggestive of ulceration on either the pericardial or endocardial aspects.

The aortic and pulmonary valves are quite competent, and there is no evidence of valvular endocarditis.

Lungs:—There are no pleural adhesions. Over the parietal pleurae are several small tubercles. These are most numerous on the diaphragmatic surface, and especially towards the right side. Both lungs are the seat of a general tuberculosis. The disease is most advanced in the left lung, in the upper lobe of which is a cavity about the size of a hen's egg, and with irregularly ulcerated walls. Throughout both lungs are caseous areas, varying in size from that of a pea to that of a bean, and at the base of the left lung there is a tuberculous broncho-pneumonia.

There are in the mediastinum some enlarged and caseous glands, which extend up towards the neck and down into the abdomen.

Abdomen:—There are no adhesions between any of the coils of intestine. The mesenteric glands are

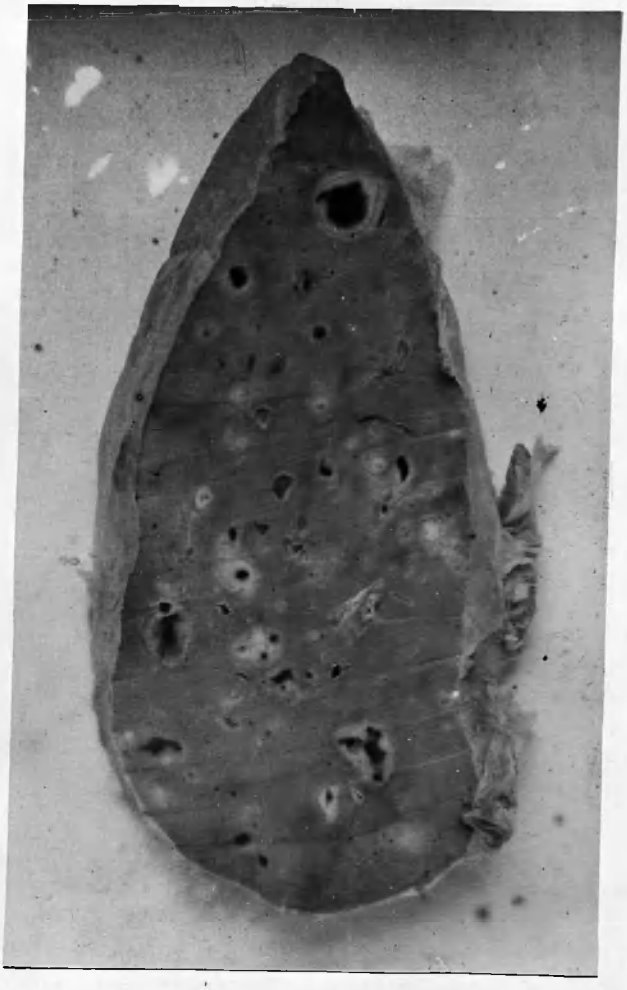


Fig. 3. Photograph of fresh section of the liver showing tuberculous foci and the cysts with bile-stained contents.

are enlarged and caseous, especially in the region of the portal vein where there are several matted together.

Liver:- The liver is adherent on its superior aspect to the diaphragm where there are numerous small tubercles. Throughout the liver, which is pale in colour, are numerous tuberculous foci, for the most part caseous. They vary in size from that of a pea to that of a bean. Here and there in its substance are cavities with a yellow caseous wall and bile stained contents. (see fig 3)

Spleen:- It is adherent by its peritoneal layers and infiltrated throughout with tuberculous caseous areas.

Kidneys:- They are not enlarged. The capsules are not unduly adherent. In the cortex of both immediately under the surface are several small unilocular cysts about the size of a large pin head and with clear contents. Here and there throughout the substance of both kidneys are a few pin-point tubercles. The suprarenals show nothing abnormal.

Pancreas:- This organ seems quite healthy and is devoid of any tuberculous infection.

Brain:- On removing the calvarium the membranes are found to be somewhat congested. On inspection of the cerebrum it is seen to present rather a curious appearance. Some of the convolutions are pale and swollen and stand out distinctly from the rest. On running the finger over the surface these swollen convolutions are found to be densely hard to the touch, in marked contrast to the intervening soft

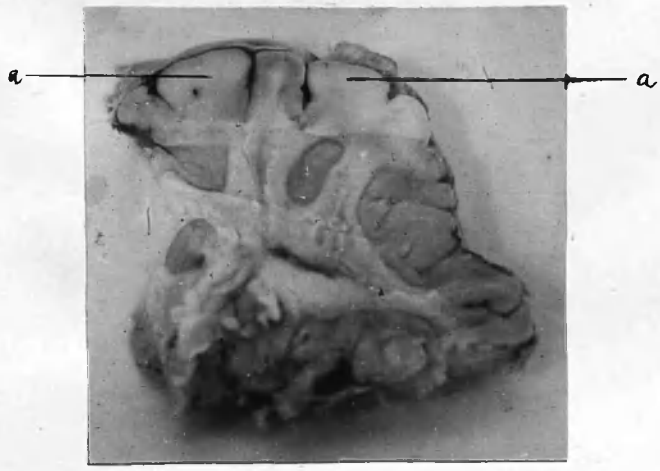


Fig. 4. Photograph of section through occipital lobe of brain.
a. Abnormal convolutions more or less devoid of grey matter.

Fig. 5. Photograph of section through occipital lobe of brain.
a. Abnormal convolutions more or less devoid of grey matter.

soft and apparently normal convolutions. These hard areas in the convolutions are irregularly disposed and vary in size, but they always retain the contour of the convolutions. Their surface is smooth and there is a slight dimple in the centre of the largest of them. In size they vary between ¼" square and 1" square. These areas, which are detected all over the cerebral hemispheres — the convexity, basal and mesial aspects —, are entirely limited to the cerebrum, and are not detected in the pons, medulla oblongata or cerebellum. They are practically symmetrically distributed. Thirty such masses were counted in the right hemisphere. On section through these altered convolutions the swelling and pallor are much more apparent (see figs. 4 and 5). On section they have a dull wavy appearance and are almost entirely devoid of grey matter. The condition is most marked on the surface of the gyri, but in several places it implicates the grey matter in one or both sulci as well, and as a rule it extends for some distance into the white matter.

The pia-arachnoid, though distinctly the seat of inflammation, is very easily removed from the surface of the abnormal convolutions.

The ventricles are not dilated nor are any sclerosed areas detected in their walls on the surface of the corpora striata or optic thalami. No ventricular granulations are observed.

In addition to the above changes there is a typical tuberculous meningitis. At the base of the brain there is a pale greenish yellow

yellow exudation obscuring the structures between the crura cerebri and the optic tracts. This exudation extends along the crura to the superior surface of the cerebellum and into both sylvian fissures, the opposing surfaces of which are adherent. Throughout the exudate numerous small sago-like bodies are observed along the course of the pia-arachnoid vessels. These are well seen while breaking down the adhesions in the sylvian fissures.

There is no distinctly caseous nor tuberculous focus detected in the substance of the brain even after minute examination.

Summary of Post Mortem Report.

Body of an emaciated child. Rigor Mortis passing off.

Thorax:- Heart - slightly enlarged. There are two large pale and hard tumours in the wall of right ventricle and numerous smaller ones in the wall of the left ventricle. Lungs - There are small tubercles over pleura - most numerous over the diaphragm - Seat of general tuberculosis with a cavity in left upper lobe, and a broncho-pneumonic condition in left lower lobe. Tuberculosis of the mediastinal glands.

Abdomen:- Tabes mesenterica. Liver adherent and seat of general tuberculosis. Spleen much infiltrated with tuberculosis also. Kidneys show a few miliary tubercles in cortex and several congenital cysts. Suprarenals and Pancreas both

both quite healthy.

Brain:- Seat of tuberculous meningitis mostly at base and in sylvian fissures. Over the cerebrum are numerous indurated pale swellings of portions of the convolutions. Pons, medulla, cerebellum and ventricles apparently healthy.

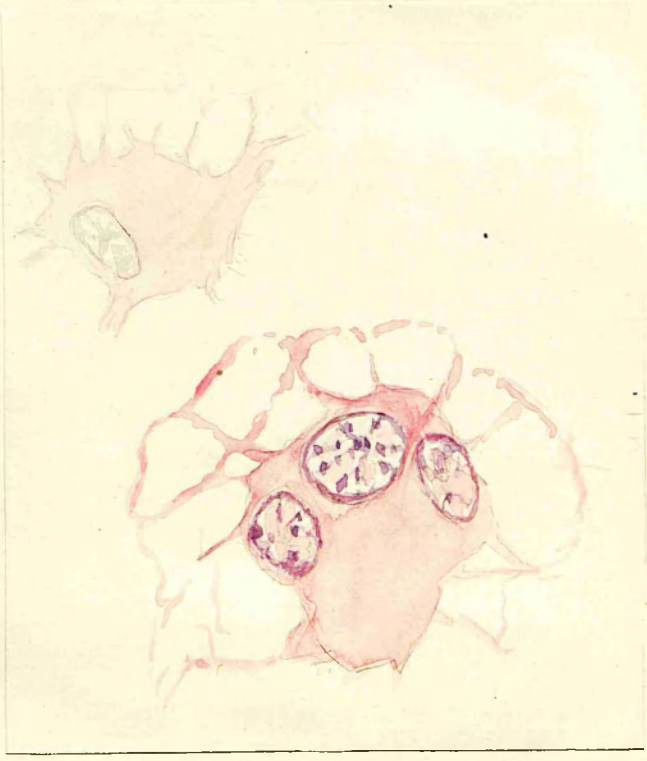


Fig. 6. Hypertrophied neuroglial cells stained with Ehrlich's triacid stain, showing three neutrophilic nuclei in one cell.

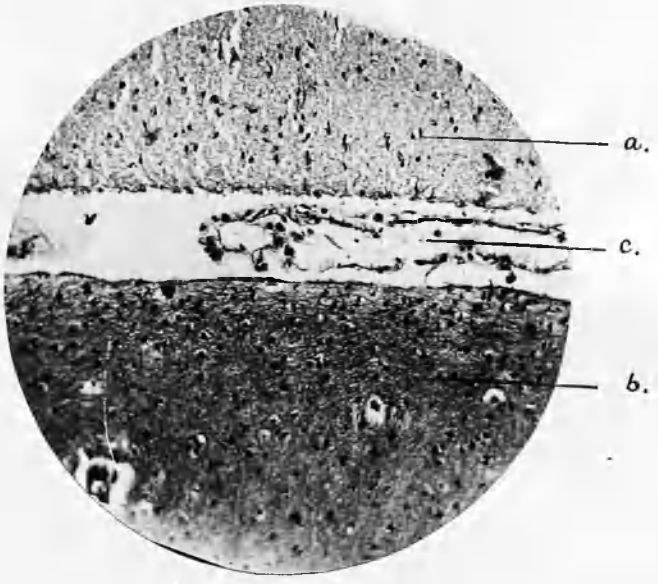


Fig. 7. Section of brain passing through a normal and an abnormal convolution with a sulcus between, showing hypertrophy of neuroglia in form of subpial felting in the sclerosed convolution. Robertson's methyl violet method. (X 140.)

a. Normal convolution.
b. Abnormal convolution.
c. Sulcus.

Fig. 8. Naked eye view of section of sclerosed convolution stained by Weigert's method for medullated sheaths.

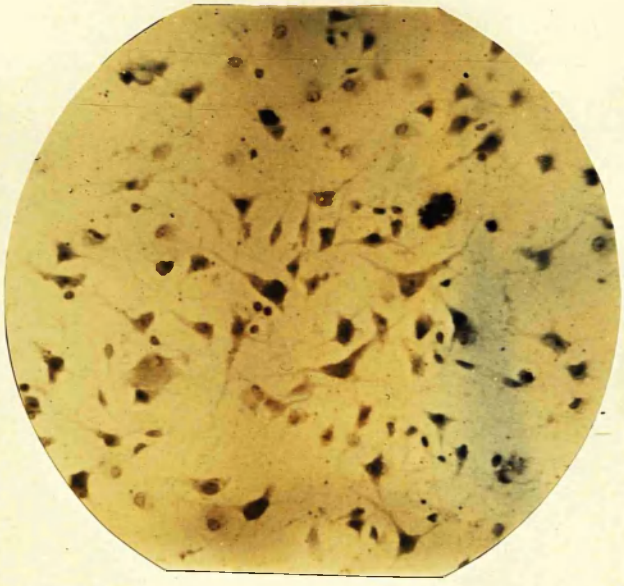


Fig. 9. Section of brain near margin of a sclerosed area in convolution showing the irregular disposition of the pyramidal nerve cells. Toluidin blue. (×400.)

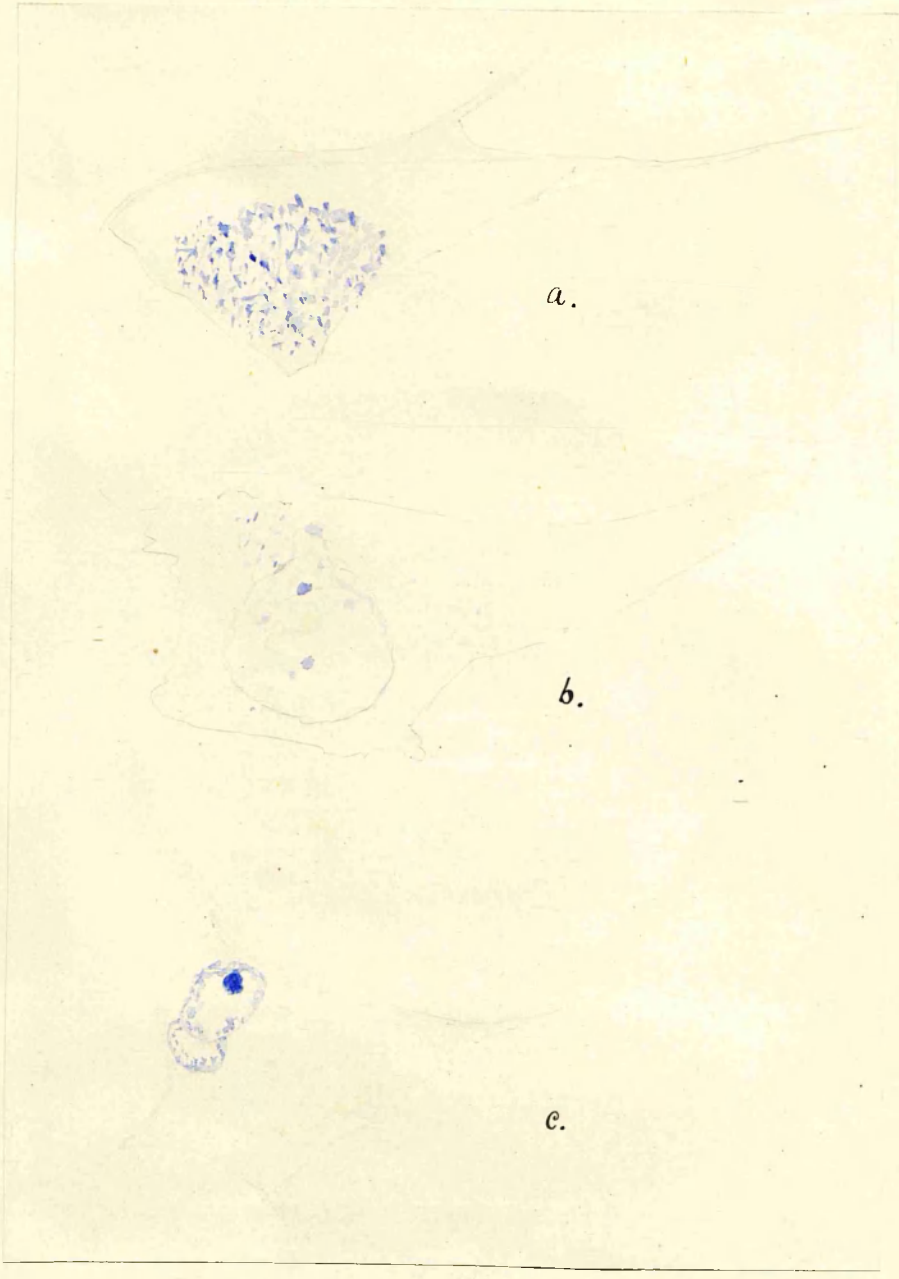


Fig. 10. Showing chromatolysis of pyramidal nerve cells in sclerosed convolutions. Toluidin blue.

a. Peripheral chromatolysis.

b. Marked chromatolysis "ghost cell" and commencing disintegration of the nucleus.

c. Marked chromatolysis with dislocation of the nucleus.

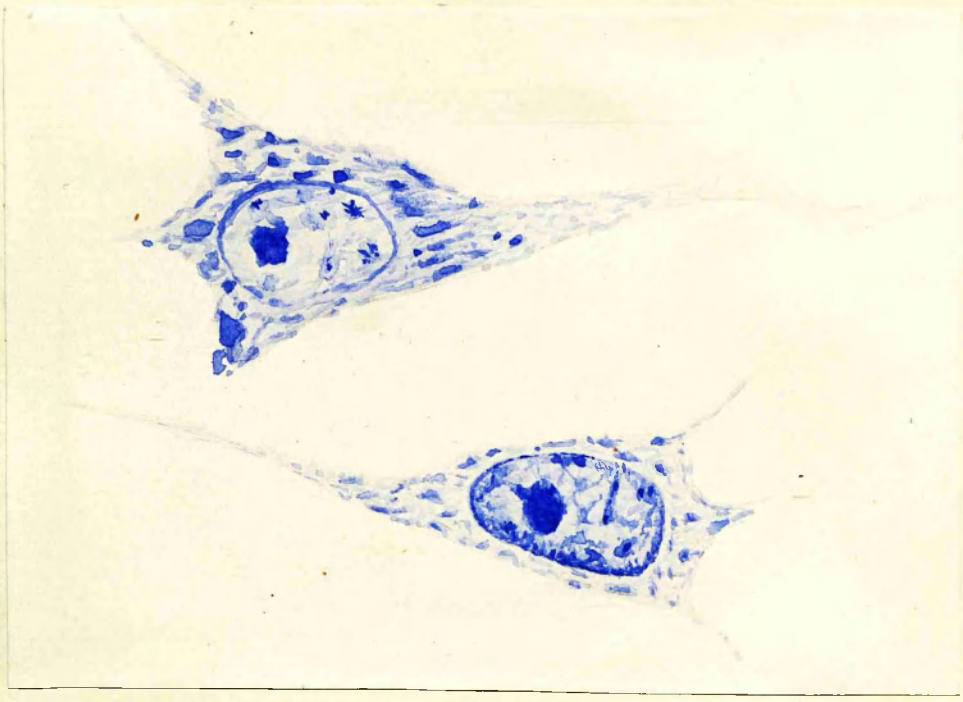


Fig. 11. Pyramidal nerve cells from normal convolutions, showing normal distribution and amount of chromatin in the same. To compare with preceding figure. Toluidin blue.

Histological Examination of the Brain.

On microscopic examination of the brain there is found, in the enlarged and indurated convolutions, a much denser felting of neuroglial fibres than normal, and a slight increase in the neuroglia cells, many of which are enlarged and contain two or more nuclei (see sect. 1, and fig. 6). The neuroglial fibres are coarser as well as more numerous than normal. This hypertrophy of the neuroglia is most marked, as a rule, towards the surface of the convolutions, where subpial felting is present, and gradually diminishes towards the white matter and as one follows the grey matter into the sulci, though here too it may be very distinct (see sect. 1, and fig 7). In these areas there is a great scarcity of nerve cells and axis cylinders (see sect 2, and fig 8), and at the same time it is observed that the layer of nerve cells extends more deeply into the cerebrum than normal. This deficiency of nervous elements is most apparent about the centre of the convolution, and as one passes towards the grey matter in the neighbouring sulci more nerve cells are encountered. Many of the nerve cells are very irregularly arranged with their apices pointing in all directions instead of, as normally, towards the surface (see sect. 3, and fig. 9). Many are atrophied and they show all degrees of chromatolytic degeneration — partial or complete loss of chromatic granules or Nissl's bodies, and dislocation or loss of the nucleus (see sect. 4, and fig. 10).

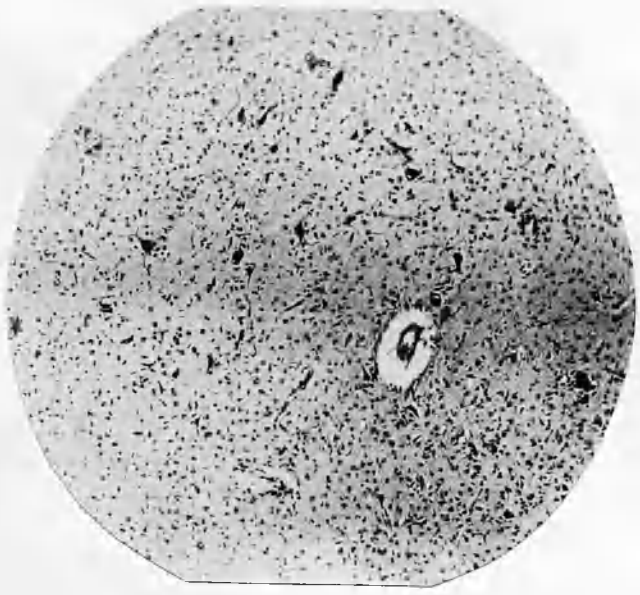
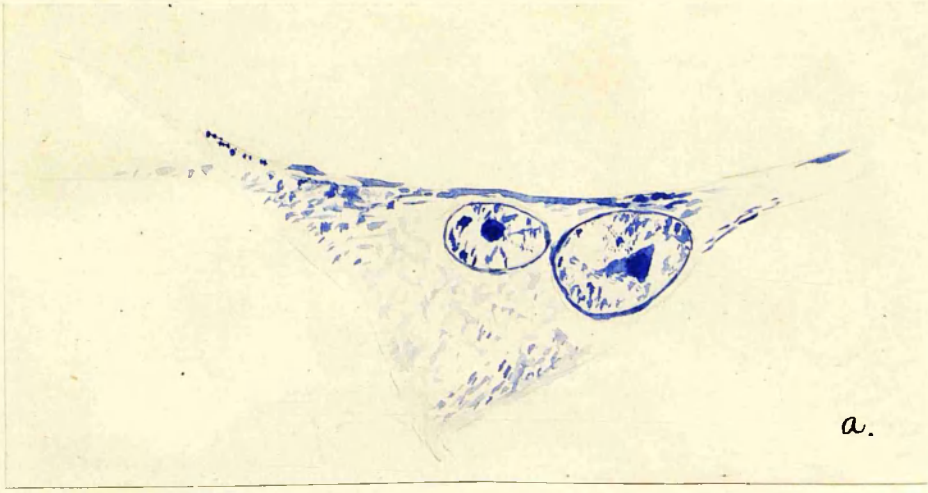


Fig. 12. General view of section of sclerosed patch showing numerous large ganglionic cells. Robertson's methyl violet method. (X 140.)



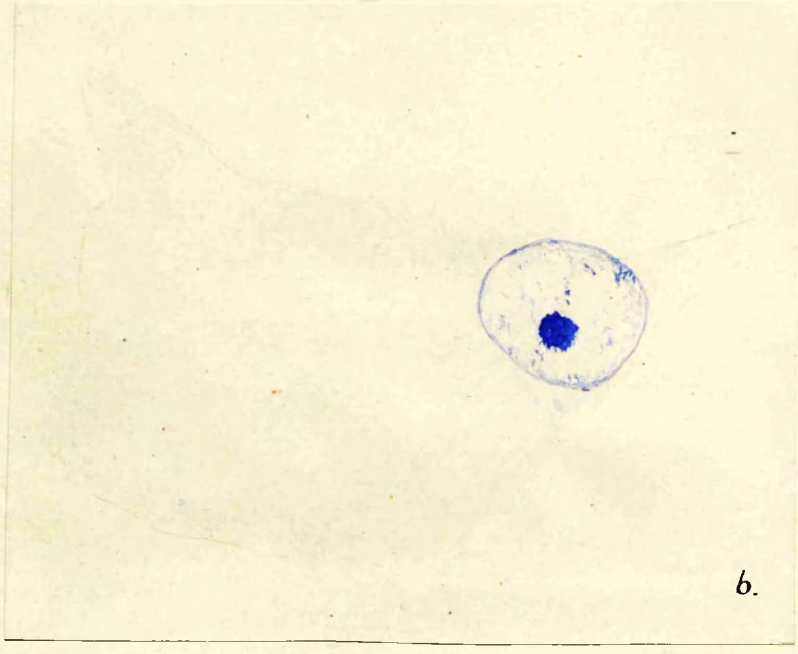


Fig. 13. Ganglionic cells showing chromatolysis.
a. Moderate chromatolysis in cell with two nuclei.
b. Extreme degree of chromatolysis with dislocation of the nucleus. (Toluidin blue.)

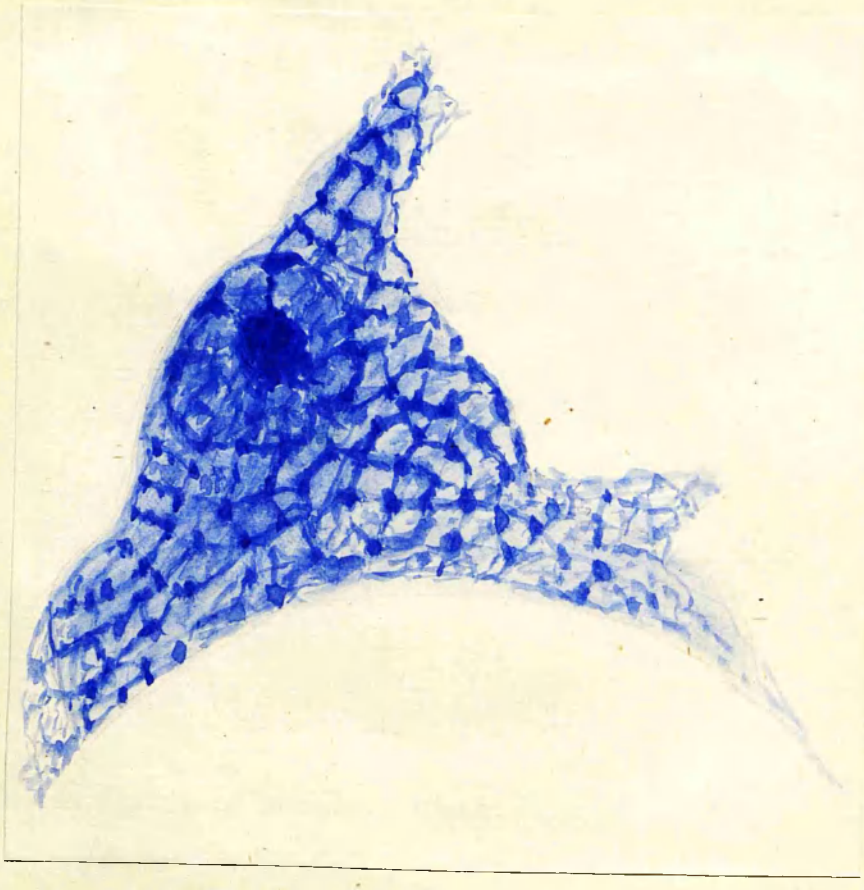


Fig. 14. Large ganglionic cell from sclerosed patch showing a normal amount of chromatin in the form of a reticulum. (Stained with toluidin blue.)

Fig. 15. Ganglionic cells from sclerosed convolution stained with Ehrlich's triacid stain. Note the diffuse homogeneous pink colour of the protoplasm and the oxyphilic character of nucleus and nucleolus. Two of the cells have three nuclei and the other not one.

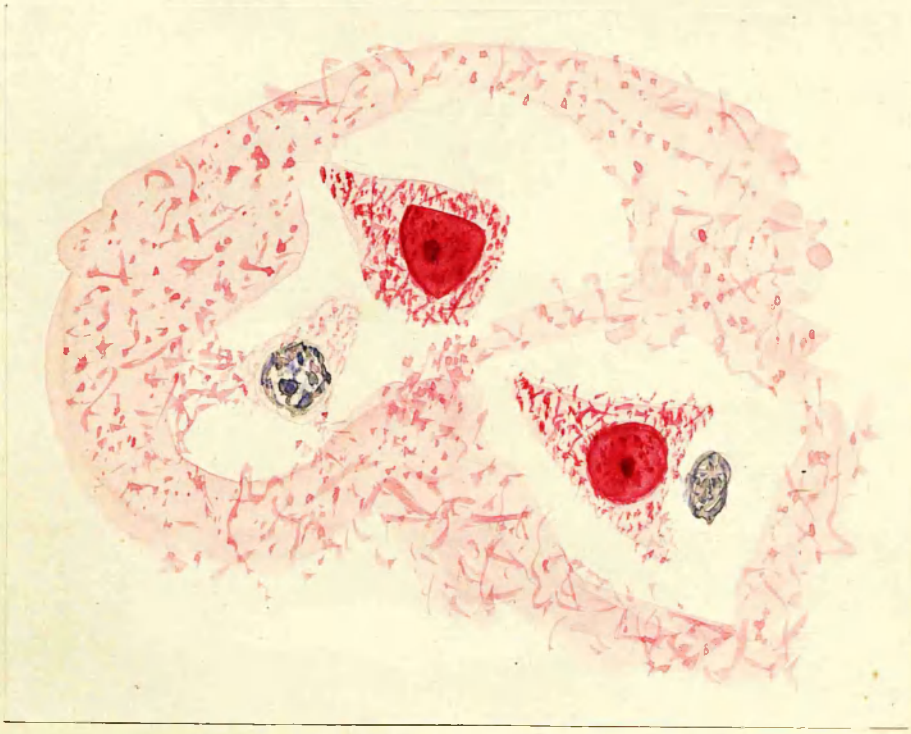


Fig. 16. Normal nerve cells from section of cerebral convolution, stained with Ehrlich's triacid stain, showing oxyphilic character of nucleus and nucleolus. Note the neutrophilic character of the neuroglial cells. To compare with preceding figure.

Throughout these areas of gliosis and degeneration of nerve cells there is observed, from the very surface of the convolutions to beyond the limits of the layer of nerve cells, numerous large pyramidal and ganglionic shaped cells (see fig. 12). Though scattered more or less throughout these areas they, as a rule, tend to be arranged in groups. These cells are two to four times the size of the largest pyramidal nerve cells found in the cortex, and many are similar in appearance to the multipolar cells found in the anterior cornua of the spinal cord. In each of these abnormal nerve cells a large nucleus with bright nucleolus is usually observed, though in several no nucleus is seen, and in not a few two or even three nuclei are detected. In sections stained with toluidin blue the majority of these cells show few and small chromatic granules usually arranged round the periphery leaving a pale homogeneous centre, though occasionally some are observed with a normal amount of chromatic granules, uniformly distributed and extending into the processes (see sect. 4, and figs. 13 and 14). The nuclei are frequently dislocated towards the periphery of the nerve cell and in a few instances are observed to be the seat of vacuolation. The nuclei and nucleoli, as in normal nerve cells, are markedly oxyphilic in character. In sections treated with Ehrlich's triacid stain the nuclei and nucleoli take up the acid fuchsin and stain a deep red colour, in marked contrast to the neutrophilic or greenish staining of the surrounding neuroglia nuclei (see sect. 5, and fig. 15).

As previously mentioned, this alteration of the cerebral cortex is most marked in the grey matter on the surface of the convolutions, but in not a few places it is observed implicating the grey matter in the sulci and extending deeply into the white matter, so that an entire convolution may be altered in its structure.

In the sclerosed convolutions and in neighbouring convolutions, which to the naked eye seem quite normal, and in which there is neither any subpial felting nor any disturbance of the normal arrangements of the layers of nerve cells, groups of these previously described ganglionic cells are encountered deep down in the white matter (see sects 6+9). There is always associated with these accumulations of ganglionic cells a certain degree of neuroglial hypertrophy, similar in character to that encountered in the sclerosed areas on the surface. These deeply situated areas, in which no normal pyramidal nerve cells are observed, but only the large ganglionic cells and a certain number of axis cylinders, are completely separated from the grey matter in the cortex by a band of normal white matter.

There is no sharp border to any of these abnormal areas, whether they be situated on the surface of the convolutions or in the depth of the white matter. The abnormal gradually merges into the normal; the neuroglial processes get thinner and the network becomes less dense. In the case of the areas on the surface, on following the grey matter into the sulci, where it is, as a rule, less affected, concomitant with the diminution in the gliosis, more nerve cells are observed. At

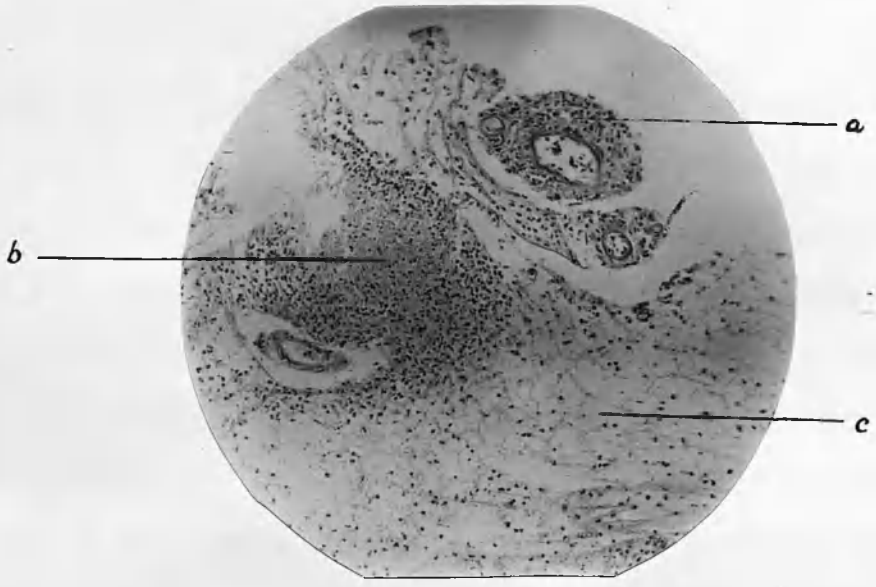


Fig. 17. Section of meninges at the base of the brain showing the periarterial tubercles.

a. Tubercle concentrically placed.
b. Tubercle eccentrically placed and undergoing caseation.
c. Pia-arachnoid.

first they are very scanty and atrophied, and show all stages of chromatolysis. A striking feature in the grey matter at the margins of these indurated patches is the irregular disposition of many of the nerve cells — a point previously referred to — and here and there a somewhat large but undoubted pyramidal nerve cell, with normal chromatic granules and containing two nuclei, is observed. At no part is there any evidence of round cell infiltration.

Throughout the sclerosed patches the blood vessels are, if anything, less numerous than in the normal cerebral tissue. In the white matter at the periphery of the nodules widely dilated blood vessels are occasionally observed, while here and there much dilated perivascular lymphatic spaces are seen.

Several sections of the sclerosed patches, stained with carbol-fuchsin and methylene blue, were examined for the tubercle bacillus but with negative results.

Sections of the base of the brain including the much thickened and infiltrated pia-arachnoid in the sylvian fissure were examined. These reveal a moderate round celled infiltration of the meninges, with accumulations of round and epithelioid cells in the adventitia of the arterioles (see sect. 10, and fig. 17). These cellular collections encircle the vessel completely in some places, while in others they are placed eccentrically. The cells are mainly of the epithelioid

epithelioid order, but are smaller than is usual in the case of these cells. Some of these perivascular granulomata show commencing caseation, and in sections stained with carbol-fuchsin and methylene blue numerous tubercle bacilli are observed lying between the cells (see sect. II).

There is no evidence anywhere of infiltration of the cerebral tissue by the tuberculous process.

Discussion :— From an examination of sections from different portions of the indurated areas in the brain, it is seen that in all there is a hypertrophy of the neuroglial tissue, as evidenced by the increased number and thickness of the fibrillar elements and the slight relative increase in the cellular elements, some of which are much enlarged and contain two or more nuclei. There is observed, concomitant with this sclerosis, a deficiency in number and degeneration of the nerve cells, and, further, one always encountered in these nodules numerous large pyramidal and ganglionic cells. That these large cells are nerve cells is shown by their shape, the presence of processes, by the fact that the cells and processes contain chromatic elements, and by the presence of a nucleus with nucleolus, both of which are markedly oxyphilic in character. According to Levi[1] — the pioneer in the histology of the nerve cell-

1. Levi, G., "Su alcune particolarita di struttura del nucleo delle cellule nervose", Riv. di patol. nerv. e ment., 1896, f. 4. (Quoted by Robertson "Critical Digest of normal and pathological Histology of Nerve Cell", Brain, pt. LXXXVI, 1899, p. 239.)

the nerve cell nucleus and nucleolus are chiefly oxyphilic in character, yet he describes in the nucleolus a few basophilic granules, which can be demonstrated in sections treated with Ehrlich Biondi stain in weak solution. My sections were treated with Ehrlich's triacid stain, which, though showing the strongly oxyphilic property of the nucleus and nucleolus, fails to reveal the few basophilic granules described by Levi as being present in the nucleolus. Had these large cells only been of the pyramidal type one might have considered them hypertrophied or proliferating nerve cells. But their shape in some instances, and their abnormal situation in other instances, prevent us from accepting such an explanation. Moreover, most of these large cells show degeneration in the form of chromatolytic changes, which is also against the idea that they are hypertrophied nerve cells, though Ford Robertson[1], while admitting that proliferation of nerve cells may take place, states that it does not, however, lead to any stable regeneration. Since the pyramidal nerve cells at the margins of these nodules are widely separated, irregularly placed, and in various degrees of degeneration, and the transition from the normal to the abnormal is gradual, one may conclude that this gliosis is gradually extending and infiltrating the surrounding healthy cerebral tissue.

This combination of gliosis and ganglionic cells makes up the picture of ganglionic neuroglioma, a very rare form of tumour. Most authors consider this

1. Robertson, W. Ford, "Pathology of Mental Diseases", Edinburgh, 1900, p. 239.

this tumour to be of congenital origin, and such a view is the only way in which we can satisfactorily account for the presence of ganglionic cells in regions, as, for example, the white matter of the cerebral cortex, where nerve cells do not normally exist.

The majority of authorities mention in these tumours the presence of nerve fibres or axis cylinders. This, to my mind, is of minor importance and subordinate to the presence of pyramidal or ganglionic nerve cells. One would expect to find axis cylinders to a greater or lesser extent in any tissue which contained nerve cells, but the presence of axis cylinders, independent of nerve cells, is a condition, which, according to the modern ideas of the neuron, does not and cannot exist.

Ziegler[1] describes the condition of "Ganglionic Neuroglioma" as "an apparent enlargement of some "portion of the brain not marked off by any definite "boundary from the surrounding tissue, or of a more "circumscribed nodose tumour. The pia mater overlying "the enlarged portion is not altered, and the configuration "of the gyri is in general left intact. On transverse "section the difference in tint, normally so striking, "between the cortex and the medullary white matter "is indistinct or entirely absent: the tissue looks uniformly "white or greyish-white. It is of firmer consistence "than the normal tissue, and sometimes is firm and "tough in texture.

"The matrix of the growth consists of

1. Ziegler, "Special Pathological Anatomy," English translation 8th Germ. Edit., London, 1896, Vol 1, Sect. VI., p. 436.

"of neuroglia similar in character to that of the "patches in disseminated sclerosis; it is sometimes "dense and firm, sometimes loose in texture. The "tissue contains ganglion-cells, not only in the "region of the original cortex, but also within the "white matter of the gyri and the centrum ovale; "these cells are loosely scattered or aggregated in groups. "Medullated nerve-fibres are visible only in some parts "of the tumour, but they never approach in size or number "the fibres that are normally contained in the white "matter of the brain."

It will be noticed how closely the cerebral lesions in my case resemble this description by Ziegler.

Stengel[1] states that these tumours as a rule are multiple, and are present as numerous "nodular condensations throughout the brain." This fact of the multiplicity of the growth is not mentioned by any other author, so far as I can find.

This condition is most likely to be mistaken for gliosis or a glioma, more especially perhaps when infiltrating an area where ganglionic cells normally exist, as, for example, the basal nuclei of the brain. Indeed, Thoma[2] states that there is no such tumour as a ganglionic neuroglioma, but that such appearances are produced by the infiltration of a cerebral ganglion by sclerosis or a glioma. This may be true in some cases, but assuredly it is not so in such as ours, where ganglionic cells are found

1. Stengel, A, M.D, "Text Book of Pathology", 1st Edition, London, 1899, p. 153.

2. Thoma, "Text Book of General Pathology", London, 1896, Vol 1, p. 552.

found in regions where they do not normally exist.

It must not be forgotten, however, that in the motor regions of the human cerebral cortex are nerve cells so large and so irregular that Bevan Lewis[1] has proposed to call them, "ganglion cells", and the layer which they form, "the ganglion cell layer of the cortex". This author considers them the cells which have to do with motion, and, as they are specially numerous and large in the regions which govern the movements of the lower limbs, that they are proportionate in size to the amount of muscular energy requiring to be expended. Betz[2] called them the "giant cells", and at one time they were supposed to be pathological. Though found all over the cortex they are most numerous and largest in the motor regions. They are situated immediately below the layer of large pyramidal cells and superficial to the fusiform layer of cells. "They are irregularly distributed or "in clumps; they vary in size and are irregularly "pyramidal in shape, and have a large oval "nucleus" (Bevan Lewis[3]). "Some of them resemble the motor "nerve cells of the spinal cord" (Gowers[4]). "These cells "are most typically ganglionic in shape in man, but "in the lower animals are definitely pyramidal in shape" (Bevan Lewis[5]).

1. Bevan Lewis, "Text Book of Mental Diseases", 1st Edit., 1889, p. 66.

2. Betz, "Anatomischer Nachweis zweier Gehirncentra", Centralblatt f.d. Med. Wissensch., Aug. 1884.
(Quoted by Bevan Lewis, Ibid., p. 95.)

3. Bevan Lewis, Ibid, p. 66.

4. Gowers, "Diseases of the Nervous System", London, 2nd Edit., 1893, Vol II, p. 10.

5. Bevan Lewis, Ibid, p.

However, all the figures and diagrams, which Bevan Lewis and Gowers give, show these cells as fairly definitely pyramidal in shape, and comparable to the other elements of the cortex. In my case, however, there is no gradation between the pyramidal nerve cells and the ganglionic cells, the latter being frankly ganglionic in shape. Again the ganglionic cells in my case are entirely limited to the areas of sclerosis, whether situated on the surface of the convolutions or deep down in the white matter, and whether the sclerosis be situated in the motor region of the cortex or not.

It is generally recognised that it is very difficult to differentiate between a gliosis and a glioma, as the two lesions may have exactly similar appearances, both macroscopically and microscopically. Gliomata may be very cellular and exceedingly vascular, and all gradations are met with between these two varieties. Gowers[1] states that the fibrous form of glioma has often been mistaken for sclerosis. Ziegler[2], while mentioning the difficulty of diagnosing between gliosis and glioma, at the same time remarks that it is equally difficult to differentiate between gliosis and ganglionic neuroglioma. To my mind this cannot be so, at least in the majority of cases, if it be true, as Ziegler states, that the tumour is most usually found on the surface of the brain. In my opinion the presence of ganglionic nerve cells in abnormal situations removes the pathological condition entirely from the sphere of sclerosis. Ganglion cells

1. Gowers, "Diseases of the Nervous System", 2nd Edit., London, 1893, Vol II. p. 496.

2. Ziegler, "Special Pathological Anatomy," English translation 8th Germ. Edit., London, 1896. Vol. I. Sect VI. p. 434.

cells, excepting of course these large irregular pyramidal cells described as such by Bevan Lewis, are not normally found in the grey matter of the cortex nor in the white matter of the cerebrum, so that their presence in these situations, as that of cartilage or bone cells, relegates ganglionic neuroglioma ta, equally with chondromata and osteomata, among the new formations; and, moreover, among those new formations called congenital inclusions. Nerve cells proliferate only in very rare instances, and then only to a slight extent; in fact until recently proliferation of nerve cells was greatly disputed, and it was only in 1896 that Levi[1] conclusively proved that nerve cells did proliferate, but only to a slight extent. Consequently, it is most likely that these areas arise at some period of foetal life by an inclusion of ganglion cells in the cortex of the brain. These cells, like other congenital inclusions, may be prone to proliferate, causing tumours with destruction of the surrounding nervous tissue and an increase in the supporting structure.

Though there should not, as a rule, be much difficulty in differentiating between ganglionic neuroglioma and ordinary glioma or gliosis, there is great risk of confounding ganglionic neuroglioma with what has been termed "tuberous or hypertrophic sclerosis of the cerebral convolutions." Tuberous sclerosis, like ganglionic neuroglioma, is also, at least according to Pellizzi[2], of congenital origin.

1. Levi, Giuseppe. "Ricerche sulla capacità proliferativa della cellula nervosa." Riv. di patol. nerv. e ment., 1896, f. 10. (Quoted by Robertson "Pathology of Mental Diseases". Edin. 1900. p. 238.)

2. Pellizzi. "Annali di freniatria", 1899, f. 4; 1900 f. 1, 2. (Quoted by Robertson, Ibid, p. 336.)

It must be noted in this connection, however, that, although these two conditions may be congenital, they owe their origin to opposite causes. The former – tuberous sclerosis – is a defective development, a want of material, and, so, comparable to congenital cardiac disease, which was found present in two out of five cases of this disease reported by Bourneville.[1] The other – ganglionic neuroglioma – is of the nature of a congenital inclusion, an excess of tissue, the abnormal presence of some special tissue in a region, and, consequently, is similar to such tumours as rhabdomyoma of the kidney and the compound parotid tumours. Ihibal[2], from whom most of my information regarding the clinical history and pathology of tuberous sclerosis has been obtained, in his thesis on the subject, gives the literature until the year 1888, and records in full six cases, five of which were observed and reported by Bourneville and the other by Brückner.[3] Pellizzi[4] in 1900, according to Ford Robertson, reviewed the literature on the subject up till that date, and at the same time reported three cases observed by himself.

According to Bourneville and Ihibal, the latter being indebted for most of his facts to the former, it seems that this disease has a very typical clinical history :– As a rule the first symptoms are noticed

1. Ihibal, "De la Sclérose Tubéreuse", Thesis, Sceaux, 1888, p. 10.

2. Ihibal, Ibid.

3. Brückner, Archiv. f. psych. und Nerven., 1882, B. XII, 3. (Quoted in full by Ihibal, Ibid. p. 51.

4. Pellizzi, Annali di frenistria, 1900, f. 1, 2. (Quoted by Robertson, "Path. of Ment. Diseases", 1900, p. 238.

noticed in early infancy. The infants are dull and apathetic from birth and show none of the gaiety natural to children. They are late in learning to walk and to talk, and, in cases where the onset has been delayed until the third or fourth years, the children gradually lose all the intelligence which they may have acquired and cease to speak and to walk. Usually, however, the first symptoms which attract the attention of the parents are convulsions. These may be either local or general and, in some instances, have appeared for the first time after some trifling accident. The most noteworthy feature about these convulsions is that they occur in series. Several convulsions occur in succession with longer or shorter intervals between each series. As time goes on the convulsions become more severe and at the same time more frequent, and later they undergo a change, becoming epileptiform in character but still retaining their serial tendency. Suddenly the child is seized with a tonic spasm of the trunk and limbs terminating in a loss of consciousness. It is not preceded by any aura or epileptic cry, nor is it followed by any clonic muscular contractions. There is never any pallor of the face, nor is there any stertorous breathing, no more does the patient ever bite the tongue. These attacks gradually become more severe, and the interval which elapses between each series becomes shorter, until ultimately the patient has a series of fits of this nature almost every day. Sometimes the convulsions remain local throughout the course of the illness. In the

the majority of cases no paralysis is observed, and, when there is any affection of motion, it is more of the nature of a paresis with a tendency to be paraplegic in distribution. Accompanying this disease there is usually a most profound degree of malnutrition causing great emaciation, and making the patient very liable to succumb to some intercurrent malady; of the six cases reported by Bourneville four died of broncho-pneumonia, one of pulmonary tuberculosis and one of encysted pleurisy.

It is seen therefore that this disease has a sufficiently characteristic symptomatology to enable a diagnosis to be made during life with some degree of certainty.

At the post-mortem examinations of all the six cases recorded by Bourneville, five of which, as previously mentioned, are incorporated in Thibal's thesis and the sixth being published some years later, the naked eye appearances of the brain are very similar to what was found in my own case.

Scattered all over the cerebrum, certain of the convolutions, in varying parts of their extent, are described as being enlarged, hard to the touch and of a white colour. The sclerosed areas, which preserve the contour of the convolutions, are irregularly disposed, and vary greatly in size and number. The sclerosis, as a rule, only implicates the grey matter on the surface of the convolutions, and does not extend into the grey matter in the sulci or into the

1. Bourneville, "Sclérose cérébrale hypertrophique ou tubéreuse," Le Progres Medical, 3rd Series, T. III, No. 9, Feby. 1896, p. 129.

the white matter. The pia-arachnoid, which may be the seat of a chronic inflammation and slightly adherent to the normal convolutions, is very easily separated from the abnormal convolutions, the surfaces of which are slightly granular. Occasionally little islets of sclerosis are detected on the surface of the corpora striata and optic thalami, but the pons, medulla oblongata and cerebellum are always free from any such change.

I have only had access to two reports of microscopic examinations of the brain in this condition. These were made by Brissaud[1], who found in both instances a complete absence of nerve cells and axis cylinders in the abnormal areas, the tissue being composed of a dense felting of neuroglial fibres, always most marked on the surface of the convolutions. The sclerosed areas did not appear to be any more cellular than other parts of the brain, and, while the majority of the cells were evidently, from the presence of long ramifying processes, neuroglial in nature, many had the appearance of round cells. In both cases the sclerosed area was markedly anaemic there being a great deficiency of blood vessels. An interesting point, but by the authors only considered a coincidence, was the presence of renal tumours in four of the cases incorporated in Thibal's thesis[2]: in one case microscopic examination

1. Thibal, "De la Sclérose Tubéreuse", Thesis, Bordeaux, 1898, p. 13.
also
Bourneville, "Sclérose cérébrale hypertrophique ou tubéreuse", La Progrès Medical, 3e Series, T. III, No. 9, July 1896. p. 134.

2. Thibal, Ibid, pp. 16, 36, 44, 49 and 60.

examination showed that the growth was of the nature of encephaloid cancer. Nevertheless, it must not be forgotten that gliomata have been described in the kidney[1], and Stengel[2] mentions that ganglionic neuroglioma has been found in the suprarenal; and if this latter fact be the case, it lends additional support to the view that ganglionic neuroglioma is a distinct new formation, and not a gliosis or glioma modifying the cortex or some other region of the brain. When one recollects that the suprarenals in part are developed[3] from the sympathetic ganglia, it is quite understandable how a tumour composed of nerve fibres, ganglion cells and neuroglia, in short a ganglionic neuroglioma, can arise in such a situation. Again, in the case of the kidneys, portions of the muscle plates of the abdomen are sometimes included developing into rhabdomyomata[4], and also portions of the neural arches forming enchondromata[4], and it is merely a step further, and anatomically quite possible, for a portion of the medullary canal to be included and develope into a glioma or neuroglioma.

In comparison with the above described condition of tuberous sclerosis my case shows several differences. During life there was entertained no suspicion of any cerebral mischief,

1. Thibal, "De la Sclérose Tubéreuse", Thesis, Sceaux, 1888, p. 17.

2. Stengel, A, "Text Book of Pathology", 1st Edition, London, 1899, p. 153.

3. "Quain's Elements of Anatomy", 9th Edition, 1882, Vol. II, p. 840.

4. Lazarus-Barlow, "Pathological Anatomy and Histology", London, 1903, pp 145 and 167.

mischief, excepting of course the tuberculous meningitis. The parents of the child – 14 months old at death – did not regard it as in any way wanting in intelligence, though probably their social position was not conducive to child study. When the child came under my charge it was, on account of the pulmonary and other lesions which killed it, too late to formulate any opinion on this score. As previously mentioned, tuberous or hypertrophic sclerosis sets in insidiously in early infancy with symptoms of defective intelligence, though it must be admitted in this connection that it is quite possible for a child to be undoubtedly mentally defective, even at the age of two or three years, and yet the parents will not have noticed anything markedly wrong. The naked eye appearances of the brain in my case are somewhat similar to those described by Thibal[1] in tuberous sclerosis, but, if anything, the lesions in the former are more extensive. In several places a whole convolution, not only the grey matter on the surface and in one or both sulci, but also the white matter is implicated. It is by microscopic examination, however, that the most important difference between the two lesions is discovered, namely, the presence of ganglionic cells, which as previously mentioned, to my mind entirely removes the condition from the sphere of sclerosis.

1. Thibal, "De la Sclérose Tubéreuse", Thesis, Sceaux, 1888, p. 12.

In the thesis by Thibal [1] there is included, along with the five cases of Bourneville, one diagnosed and reported as "tuberous sclerosis" by Brückner [2]. Although Thibal records it in full, he doubts if it really be of the same nature as those reported by Bourneville. To my mind it seems to be a case of ganglionic neuroglioma, and it may not be out of place here to give a short summary of Thibal's translation of Brückner's report:- The patient was a girl who died at the age of 22 years. Her family history was devoid of any neurotic taint, but her father and a brother died of tuberculosis. From birth it was noticed that she was mentally deficient. She was two years old before she commenced to speak, and four years old before she learned to walk. Gradually, but only very slightly, her mental condition improved, but she remained always below the average in intelligence. When nine years of age she had a severe epileptiform convulsion, and that without any apparent cause. From that time onward similar convulsive seizures recurred at intervals, and her mental condition gradually became more deficient. Occasionally the epileptiform attacks were replaced by choreiform movements of one limb and of the muscles of the face. Her gait, which heretofore had been normal, became

1. Thibal, "De la Sclérose Tubéreuse", Thesis, Geneva, 1888, p. 51.

2. Brückner, Archiv. f. psych. und Nerven., 1882, B. XII, 3. (Quoted by Thibal, Ibid. p. 8.)

became markedly altered. She walked in a jerky and spasmodic fashion, and as this peculiarity increased in severity Brückner compared her gait with that of a doll set in motion by clock-work. There was no paralysis of any of the limbs, nor was any anaesthesia ever detected. When about eighteen years of age she received a fright and, as a consequence, passed into a very excitable condition, and was removed to hospital. It was at this time that she came under the notice of Brückner, who describes her as a fairly well developed but extremely emaciated girl. She was a complete idiot. She required to be attended to like a child; she took no interest in her surroundings and only answered questions by an inane smile. During the first year of her residence in hospital she had no convulsive seizures, but at the end of that time epileptiform convulsions recurred. They were entirely different from those she suffered from at first in that they were choreiform in character, of short duration, and recurred at long intervals. When twenty-two years of age she was declared incurable and removed to an asylum, where shortly afterwards she developed pulmonary tuberculosis and died within a few months.

At the post-mortem examination there was found extensive tuberculous disease of the lungs and intestinal tract. The brain was enlarged and pale, and over the surface of both hemispheres were numerous large hard prominences

prominences, representing hypertrophied parts of the convolutions. These abnormal areas had a rounded shape, with a smooth surface, in the centre of the largest of which was usually a dimple, and they were sharply demarcated from the surrounding healthy convolutions. The pia-mater, which showed neither thickening nor loss of transparency, was easily separated from both the normal and abnormal convolutions. In the cerebellum there were two nodules of a similar nature of about the size of a hazel nut. Both lateral ventricles were dilated. On the ventricular aspect of the corpora striata and optic thalami were numerous small rounded nodules of a white colour, and varying in size from that of a pin-head to that of a small pea. Those situated towards the foramen of Monro were polypoid, with a soft consistency and granular surface. On section of the sclerosed areas in the cerebral convolutions it was observed that the transformation affected almost solely the grey matter of the cortex. These areas had a hard consistency and were opaque. The contrast between the grey and white matters was very indistinct, especially at the summits of the convolutions, where the condition was most marked. In the largest nodules it was observed that the layer of grey matter was thicker than normal, being 5–7 m.m. in thickness instead of 3 m.m., while at the umbilicated parts it only measured 2. m.m.

On microscopic examination of the sclerosed areas it was found that there was a

a great neuroglial hypertrophy, and that especially in the fibrillar elements. On the surface of the altered convolutions there was marked sub-pial felting. On passing into the white matter the hypertrophy of the neuroglia became less dense, and round cells and occasionally angular cells were observed. Here and there was seen a large irregular ganglionic cell, multipolar, with a large nucleus which was swollen and in some cases vesicular. Occasionally these large cells were grouped together. The pigmentation of these cells and their processes was little modified. The blood vessels in these areas were engorged with blood, and possessed in many instances widely dilated perivascular lymphatic spaces. Round the cortical vessels there were congregated round cells, which did not seem in relationship, by means of processes, with the vessels. On microscopic examination of the ependymal polypoid masses they were found to be composed of a fundamental fibrous stroma, with numerous spaces filled with large vitreous round cells. Towards the margin were some calcareous bodies similar to what are found in the normal pineal body, in fact, the general structure of these nodules simulated somewhat closely that of the above mentioned gland. These ependymal granulations Brückner considered inflammatory in origin, and quite distinct from the cortical change. The latter he considered of the nature of a hypertrophic sclerosis, and while comparing his case with this lesion

lesion discusses the question of vascular supply and gliosis, but in his argument omits to take into consideration the presence of the ganglionic cells. These are not present in sclerosis, and, as I have previously remarked, show the true nature of the lesion. It will have been observed that Brückner remarked in connection with the large ganglionic nerve cells, that their pigmentation was little altered. It is uncertain what this author meant by such a remark, but most likely he referred to the physiological pigment, and that it was not increased in amount. Of course one would not expect to find much pigment in the nerve cells of the brain in a patient aged twenty-two years. Whether or not he understood the significance of alteration of the pigment it is impossible to say, as it is only within recent years that any importance has been given to the subject. Although it has been known as a normal constituent of the adult nerve cell for many years, it was only in 1889, some years after Brückner reported his case, that Bevan Lewis[1] attracted special attention to it in this country, and since then the abnormal amount of the same in the nerve cell has been the subject of great controversy. The pigment appears first in the cells of the spinal ganglia about the sixth year, and gradually increases in amount

1. Bevan Lewis, "Text Book of Mental Diseases," 1st Edition, 1889, p. 475.

amount throughout life. The consensus of opinion seems to be that increase is significant of a degenerative process, and evidence of senile decay or loss of vitality or functional energy of the nerve cell. Though it increases with age and is most abundant in chronic degenerative lesions of the brain, W.K. Hunter[1] has described a case of gastric tetany in which this degeneration developed acutely. This author holds that it is merely another form of chromatolysis, and he succeeded in tracing the formation of the yellow globules from the chromophile bodies. Ford Robertson[2] is also inclined to think that it is of a degenerative nature and a derivative of the chromatic elements. At any rate, whether Brückner meant that there was no increase of the physiological pigment, or no diminution of the staining properties of the cell and its processes, the ganglionic cells seemed to be, so far as he could judge from the tests known at his time, fairly normal. He mentions, however, vacuolation of the nucleus, but it must be remembered that it is still "sub-judice" as to whether this is a true pathological phenomenon or merely a post-mortem change. In my case on the other hand there was marked chromatolysis of the ganglionic cells, and this difference might be accounted for by the non-vascularity of the nodules in my case in contradistinction to those

1. Hunter, W.K., "A Case of Gastric Tetany", Glasgow Hosp. Reports, 1899, p. 88.

2. Robertson, W.F., "Pathology of Mental Diseases", Edinburgh, 1900, p. 245.

those found in Brückner's case.

Bourneville and Brissaud, whose opinion[1] Thibal expresses in his thesis, think from the presence of round cells and the engorgement of the vessels, that Brückner's case might be an earlier and inflammatory period of the sclerotic change. It must not be forgotten, however, that probably many of the round cells Brückner describes were really gliomatous in nature, since it is only within recent years that it has been possible, by means of modified staining processes, to demonstrate the intimate connection between the neuroglial cells and their ramifications, and discriminate between round cells and glial cells. These authors do not allude to the ganglionic cells mentioned by Brückner in his report on the microscopic examination. Thibal[2], while discussing the symptomatology, doubts if Brückner's case be really an example of hypertrophic or tuberous sclerosis, as it differed from that condition not only in the clinical history, but also in the microscopic characters of the lesion. In sclerosis one sees a dense neuroglial network with a slight relative increase in the neuroglial cells, and an absolute diminution in the nerve cells; moreover the area is very deficient in blood vessels. I am inclined not only to entertain Thibal's doubts, but to go further and

1. Thibal, "De la Sclérose Tubéreuse", Thesis, Sceaux, 1888, p. 18.

2. Thibal, Ibid. p. 20.

and express the opinion that Brückner's case was one of ganglionic neuroglioma.

Professor Sutherland[1] in his last edition of Coats' "Manual of Pathology" figures a brain with fairly large pale masses in the convolutions, and describes the condition as that of "multiple glioma". Acting on the advice of Professor Muir I communicated with Professor Sutherland regarding his case. He very kindly gave me all the facts that were known concerning the history, and sent me for inspection some sections of the masses in the brain. The brain had been removed from a girl of three years of age and sent to his laboratory for diagnosis. Over the brain, as previously mentioned, were several hard pale masses not disturbing the contour of the convolutions. Microscopic examination showed that these masses were composed of a matrix of hypertrophied neuroglia, the fibrillar network being denser than normal; the nerve cells were diminished in number and were very irregularly disposed, while here and there throughout the sclerosed area, and also deep down in the white matter, were encountered large ganglionic cells. There was always associated with the presence of ganglionic cells in the white matter a certain degree of gliosis. The blood vessels in these sclerosed areas were fairly numerous, and in many instances engorged with blood.

It seems undoubted that these three cases — my own case — Brückner's case and that of

1. Coats, "Manual of Pathology", 5th Edition, 1903, Fig. 481, p. 745.

of Professor Sutherland — detailed in the preceding pages, had all similar cerebral lesions. They all more or less closely resembled the condition described as ganglionar neuroglioma. They all had their onset, or at least disclosed their presence, in early life. In my own case the condition was a post-mortem discovery when the child was aged fourteen months. The girl, who was the subject of Brückner's report, had cerebral symptoms from infancy, although she lived till she was twenty-two years old, and Professor Sutherland's case was, like mine, a post-mortem discovery at the age of three years. So far as the histories of these cases are concerned none of them showed unequivocal signs or symptoms of cerebral tumour during life. Two of the cases — my own and Brückner's — died of tuberculosis. At the post-mortem examination in all three cases the tumours were found to be multiple. In my case and Professor Sutherland's case these tumours were limited to the cerebral convolutions, while in Brückner's case similar growths were detected in the cerebellum as well. In all the cases the tumours were of a hard consistency, of a pale colour, and the pia-arachnoid was easily separated from their surfaces. On microscopic examination all three were found to have a matrix of hypertrophied neuroglial tissue, — comparatively avascular in my own case but vascular in Professor Sutherland's case and that reported by

by Brückner. The normal pyramidal nerve cells were deficient in all and there was the abnormal presence of large ganglionic nerve cells. There were no signs of inflammation in either my case or that of Professor Sutherland, and the presence of any in Brückner's case is very doubtful.

So far as I can ascertain there are very few cases of ganglionic neuroglioma reported. Ziegler, in his bibliography of the condition, mentions a case reported by Otto[1] in Virchow's Archives. On consulting this observer's paper, however, the case is found not to be one of ganglionic neuroglioma but of quite a different nature. The patient was an insane woman, aged sixty-four years, who died from infarctions of the lung and dropsy supervening on aortic disease. At the post-mortem examination several small protuberances were discovered over the convexity of the right frontal lobe and over the left anterior central convolution. The tumours were very small – about 2 mm. in diameter, – and were scattered about partly on the summits of the convolutions and partly in the depths of the sulci. They had a greyish colour similar to the neighbouring grey matter of the cortex. On the whole their appearance resembled that of the cortex. There was a

1. Otto, D. R., Virchow's Archives, Band CX, 1887, V. p. 81.

a central white zone of medullated nerve fibres in the interstices of which were nerve cells. These fibres were more numerous and lay more closely together than in the normal white matter, and distributed themselves radially towards the periphery of the nodule forming a fine network in the interstices of which were pyramidal nerve cells. The two innermost layers – that of the large pyramidal cells and the one next to it – were less cellular than normal. On the other hand the two outer layers showed a great development and spreading out of the layer of small pyramidal cells, and these, along with the finest nerve fibres, formed in reality the main portions of the tubercles. The nerve cells were more numerous and more irregularly placed than in the neighbouring cortex and were arranged radially. The cells were all distinctly pyramidal in shape. The neuroglia was not hypertrophied and the vessels showed nothing for comment.

Otto in his paper refers to four cases of a similar nature reported by Simon[1]:- all the cases were males, three of whom were between fifty and sixty years of age and the other was thirty years of age. The number of the small greyish tumours varied but they were always most numerous in the frontal regions. In size they ranged from that of a millet seed to that of a pea. They all had the appearance

1. Simon, "Ueber Neubildung von Gehirnsubstanz in Form v. Geschwülsten a. d. Oberfläche d. Windungen", V. A. B. LXVII, 1873, p. 310.

appearance of small convolutions and roughly had the microscopic structure of grey matter. In some there was a central white zone of medullated fibres continuous with the white matter and distributing itself radially throughout the tumour, while in the periphery were the nerve cells. In three of the cases the nerve cells were similar in nature to what were found in the cortex, while in the other case were some very large star-like ganglion cells. In two of the cases there was some neuroglial hypertrophy, and in the circumference of the nodules in one case the cerebral blood vessels were greatly thickened and the nerve cells much pigmented.

Simon regarded the central white zones of his tumours as white substance in miniature. Otto, however, points out that the presence of nerve cells shows this central part to be of cortical origin, and the arrangement of the nerve fibres in these same central zones is also, he claims, similar to what obtains in the cortex.

There is never any history of nervous trouble referable to these small protuberances, which look like miniature convolutions misplaced. Whatever their nature it is quite evident that they are different from what obtained in my case, and do not resemble in any point the ordinary description of ganglionic neuroglioma.

Summary of Macroscopic and Microscopic Examinations of the Brain.

The following are the salient features:-

Macroscopic.

1. The tumours are limited to the cerebral convolutions.

2. They retain the form of the convolutions being present as enlarged, hard, and pale portions of the same.

3. On section their fresh surface has a pale waxy appearance, being devoid of grey matter to a greater or lesser extent.

4. Their surface, from which the pia-arachnoid is easily separated, is slightly dimpled.

Microscopic.

5. These sclerosed areas are composed of a matrix of hypertrophied neuroglial tissue, most marked as subpial felting on the surface.

6. The vascular supply is below the normal.

7. The pyramidal nerve cells in these areas are deficient in number, are irregularly disposed and show marked chromatolysis.

8. Throughout the areas are numerous large ganglionic nerve cells, with one or more nuclei.

9. Smaller microscopic islands of

of gliosis with ganglionic cells are present in the white matter of both the normal and the abnormal convolutions.

10. There is no evidence of inflammation nor is tuberculosis of the cerebral tissue present.

11. In addition to the above multiple tumours a very typical tuberculous meningitis existed.

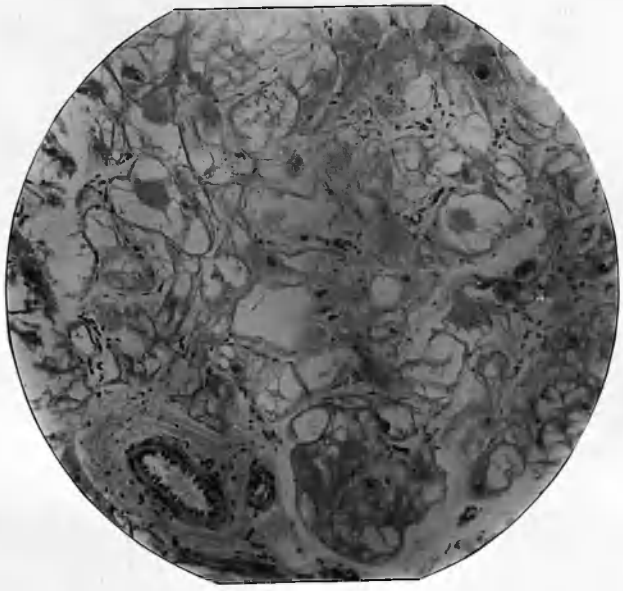


Fig. 18. Section of one of the nodules in the cardiac wall to give a general view of the vacuolated tissue. Haemalum eosin and orange. (x 140.)

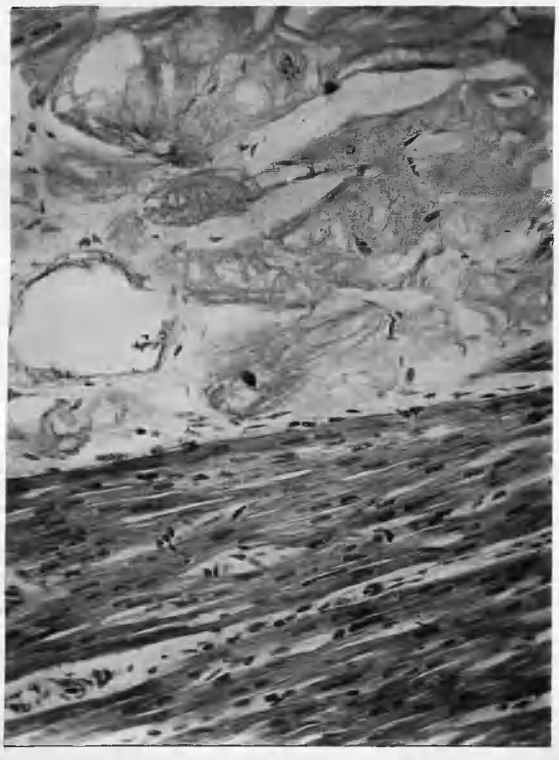


Fig. 19. Section at margin of one of the nodules in the cardiac wall to show sudden change from the normal to the abnormal. Heidenhain's iron and haematoxylin method. (x 280.)

Histological Examination of the Heart.

On microscopic examination all the nodules in the heart wall, previously described in the post-mortem report, are found to be of the same nature.

On examination of sections of the larger nodules, for instance, those in the wall of the right ventricle (see sect. 12), the tissue seems, at the first glance under a low power, to be composed of numerous large and irregularly shaped cavities. Some of these are empty, while others are crossed here and there by strands of tissue forming a kind of network, and other cavities again have in their centres a granular or homogeneous protoplasmic mass anchored to their walls by means of processes of varying thickness, giving the appearance of a huge spider all (see fig 18). In the centre of these protoplasmic masses there is usually situated a large more or less spherical nucleus with bright nucleolus. Occasionally more than one nucleus is seen in each mass. There is, at least in the larger nodules, (see sect. 13), a slight relative increase in the amount of fibrous tissue. This fibrosis is always most marked in the vicinity of blood vessels. As a rule the vacuolated tissue lies in immediate juxtaposition to the cardiac muscle (see fig. 19). though very occasionally around some of the larger nodules there is observed a dense fibrous tissue capsule, which, however, is rarely complete. In most of the nodules blood vessels are seen, and round them there is always a certain degree of fibrosis (see sect. 14). The rich

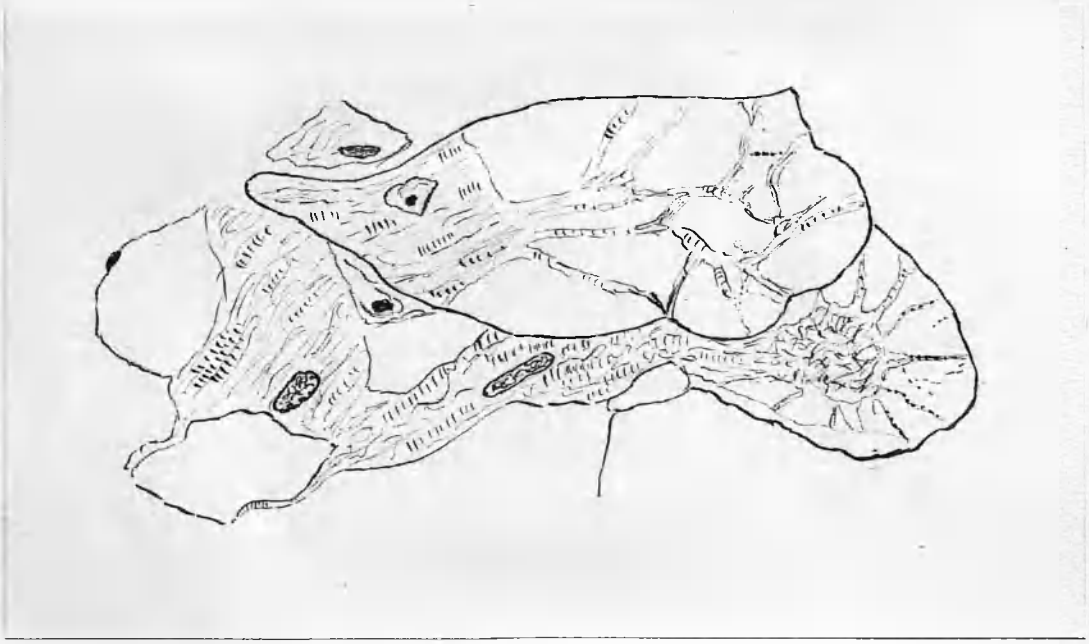


Fig. 20. Portion of degenerated tissue showing striation of the body and processes of the spider-cell shaped masses.

Fig. 21. Section of degenerated musele stained with Ehrlich's triacid stain showing oxyphilic character of the nucleoli in the large nuclei seen throughout the degenerated tissue.

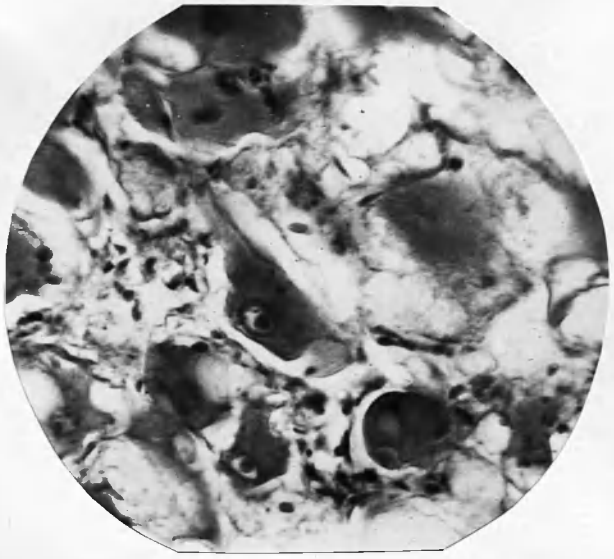


Fig. 22. Section of degenerated tissue in the cardiac wall showing vacuolation of the nucleus. Haematum eosin and orange. (X 480.)

Fig. 23. Section of one of the nodules in the cardiac wall showing the transition from the normal cardiac muscle to the degenerated tissue. Haematum eosin and orange. (x 140.)

Fig. 24. Section of same nodule as in preceding figure under a higher power. (x 480.)

rich capillary plexus present in the normal myocardial tissue is, however, absent in these degenerated areas, though small arterioles, which show, excepting periarterial fibrosis, no signs of degeneration, are still present. Here and there throughout these nodules strands of fibroblasts are seen, but nowhere is there any round-celled infiltration nor are any giant cells observed.

Under a higher power when the structure of these protoplasmic masses is studied more closely, it is observed that throughout, both in the central masses and in the processes, distinct transverse striation is visible here and there (see fig. 20). The nuclei are well seen in the centre of these masses, and many of them are observed to be vacuolated. This vacuolation frequently causes the nucleolus, which stains a brick red colour with Ehrlich's triacid stain, to be displaced towards the periphery (see sect. 12, and figs. 21 and 22).

Though in the majority of the nodules the transition from the cardiac muscle to the vacuolated area is most abrupt, yet in the small microscopic areas, and especially when the surrounding muscular fibres have been cut longitudinally, a more or less gradual transition from the normal muscle to the vacuolated tissue can be traced. This transition can be followed in sections treated with haemalum and Van Gieson's stain, or better, in those stained with haemalum, eosin and orange (see sect. 15, and figs. 23 and 24), but it can be best studied in

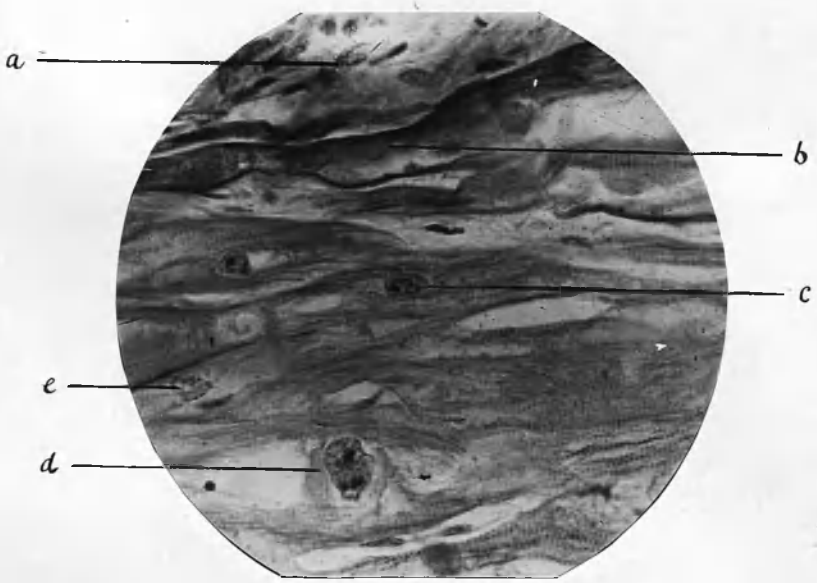


Fig. 25. Section at the margin of one of the nodules in the cardiac wall. Heidenhain's iron and haematoxylin method. (X 480.) In the upper part is some young fibrous tissue (a) round a blood vessel, which is situated at the margin of the nodule. Just below this is a muscular fibre (b) swollen up and granular in its centre while the periphery still shows striation. Striation is seen throughout the whole of the degenerated area. It is seen that the muscle cells are separated and split up by the vacuoles. The nuclei (c) towards the margin are more elongated and more similar to ordinary muscle nuclei than those (d) nearer the centre of the nodule. At the left margin of the field is a muscle nucleus (e) almost entirely devoid of chromatin, in fact practically a "ghost cell". The large nucleus apparently undergoing division in the lower part of the field was found under an oil immersion lens to be two nuclei overlapping.

Fig. 26. Portion of degenerated tissue showing vacuolation with marked separation of the muscular fibres and fibrils. Striation is seen practically throughout. Heidenhain's iron and haematoxylin method. (X 480.)

in sections stained with iron and haematoxylin after the manner of Heidenhain (see sect. 16).

The muscle surrounding such areas takes up the stain less deeply, and the transverse striation becomes more distinct than in the case of the normal fibres. The nuclei in these paler fibres also stain more faintly, and in some of them the chromatic elements tend to run together into one or more globules. The muscle fibres here and there at the margins of the nodules are seen to swell up, and in some of them the transverse striations instead of being straight and parallel describe the arc of a circle (see sect. 15). In other swollen fibres the centre has become granular, while the circumference still shows distinct striation (see sect. 16, and fig. 25). As one passes farther into the diseased area lozenge shaped cavities are seen to separate the fibres from one another, and to split up the individual fibres into fibrils (see fig. 26). This vacuolation causes the muscular fibres and fibrils to run in all directions, forming a kind of network. These vacuoles increase in size and number, and cause great splitting up of the fibres; in some places only a line of darkly staining "dots", arranged at regular intervals, is left. As well as this longitudinal splitting, transverse separation of the so-called muscle plates is observed in many places, and some of the areas, which appear granular under a high power, are, under an oil immersion lens, found to be composed of numerous short

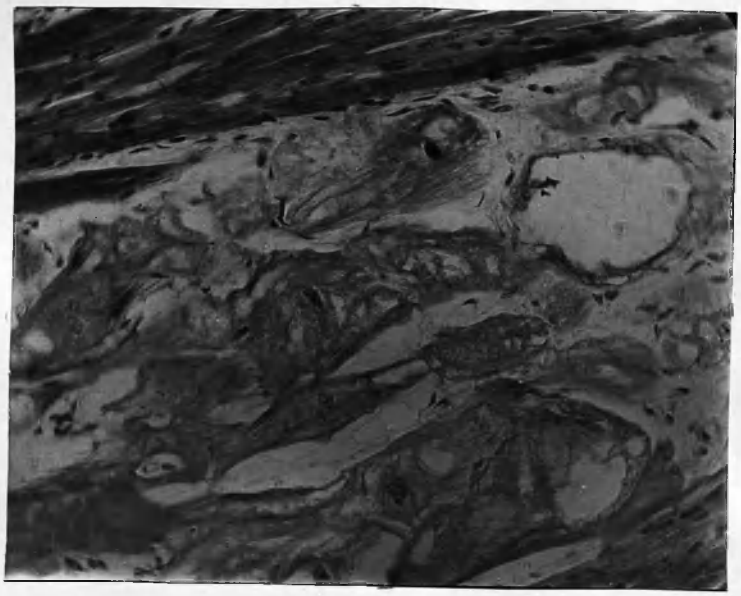


Fig. 24. Portion of degenerated tissue showing vacuolation of the muscle. Striation is seen practically throughout. Heidenhain's iron and haematoxylin method. (×280.)

Fig. 28. Section of one of the nodules in the cardiac wall showing the gradual increase in size of the nuclei towards the centre of the nodule. Heidenhain's iron and haematoxylin. (x280.)

Fig. 29. Section at margin of one of the nodules in the cardiac wall, stained with Ehrlich's triacid stain, showing muscle nucleus with oxyphilic nucleolus in a swollen muscle cell.

short bacillus-like portions of the muscle cell irregularly arranged (see sect. 16f). As a rule this latter form of breaking up of the muscle cell is observed in the vicinity of the large spherical nuclei. In longitudinal sections of the cardiac muscle, stained with iron and haematoxylin, it is difficult to find a shred of tissue in the degenerated areas that does not show striation in some degree (see fig. 27).

As previously mentioned the muscle nuclei for the most part disappear, and throughout the degenerated area (see sect. 16f and l) muscle nuclei, almost entirely devoid of chromatin, are seen, and in some places they are observed to be disintegrating, while those that remain hypertrophy. The first change observed is that the chromatic elements run together into one or more globules; they afterwards lose their elongated shape and become more or less spherical. In the nodules it will be observed that the nuclei nearest to the margin are more elongated and more similar in shape to normal muscle nuclei (see fig. 28). In sections stained with Ehrlich's triacid stain, (see sects. 17 and 18), a few undoubted muscle nuclei, with brick red coloured nucleoli, in slightly swollen muscle cells are seen towards the margin of the nodule (see fig. 29). Also in the sections stained with iron and haematoxylin nuclei with nucleoli are detected in muscle cells at the margin of the nodule (see sects. 16l and 19f). The nuclei, and also the nucleoli, increase in

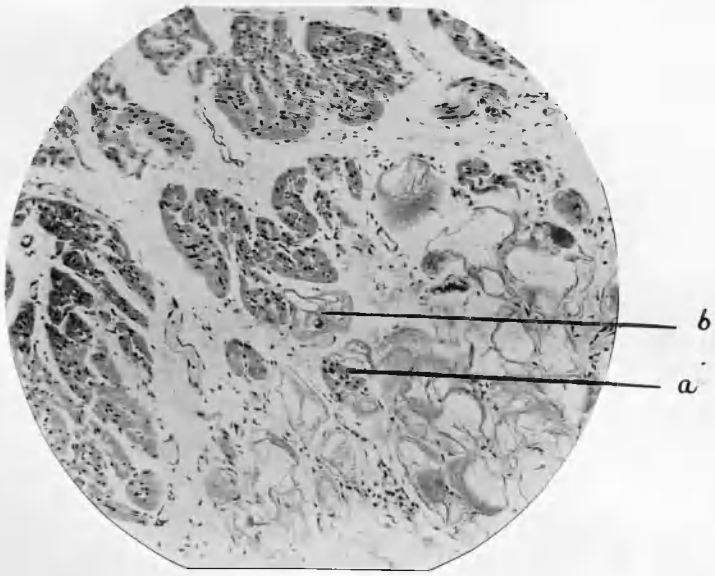


Fig. 30. Section of one of the nodules in the cardiac wall showing the vacuolar change overtaking fasciculi of muscle at the margin of the nodule. Haemalum eosin and orange. (X 140.)

a. Muscle bundle partly degenerated.
b. Muscle bundle wholly degenerated.

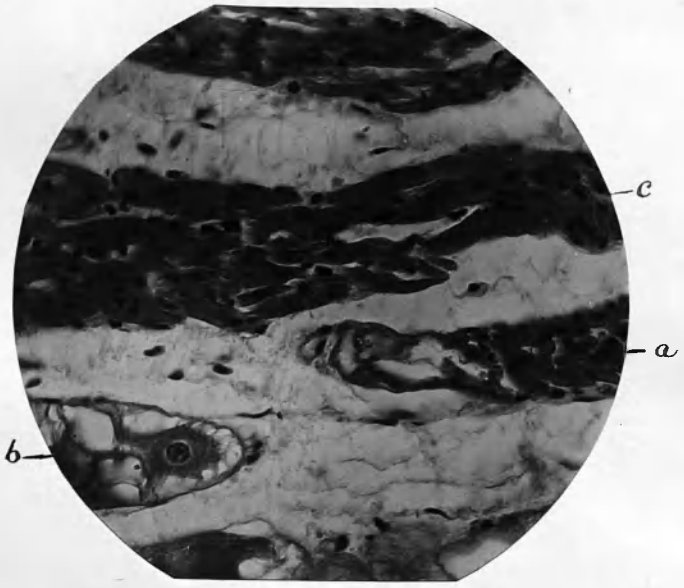


Fig. 31. Section of one of the nodules in the cardiac wall showing the vacuolar change overtaking fasciculi of muscle at the margin of the nodule. Haemalum eosin and orange. (×400.)

a. Fasciculus partly degenerated.
b. Fasciculus wholly degenerated.
c. Normal muscle bundle.

in size as the centre of the nodule is approached, and in many of them vacuolation has occurred. In some places two nuclei are noted lying side by side, with their opposing borders parallel, as though division had just taken place, but nowhere can it be affirmed that division of cells by karyokinesis is taking place (see fig. 25). Throughout all the sections fibroblasts are observed running between the masses of degenerated muscle, but there is never the slightest suggestion of transition from these fibroblasts to the large spherical nuclei.

This degeneration of the muscle seems to overtake groups of fibres, or rather fasciculi. This is seen to a certain extent in places where the cardiac muscle has been cut longitudinally, but much more distinctly when cut transversely. (see sect. 20, and figs. 30 and 31). The same changes — loss of nuclei, vacuolation with separation of the fibres, and hypertrophy of the remaining nuclei — are observed in the fasciculi cut transversely at the margins of the nodules. As one would expect, striation is not a marked feature in such (transverse) sections, but owing to the vacuolation causing the fibres and fibrils to course in different directions, definite striation is here and there visible.

Whether the degeneration assumes the form of a network of fibres, or that of a spider cell, depends on whether the vacuolation takes place throughout, or only at the periphery of, the

the muscle fasciculus.

There is no evidence of fibrinous exudation nor of ulceration over any of the nodules lying immediately under the endocardium or pericardium. In the case of the small papilliform nodule on the inner surface of the left ventricle just below the aortic valve, the endocardium, though thinned, can be traced, in sections stained for elastic tissue after the manner of Weigert, over the entire surface (see sect. 21).

Sections stained with osmic acid show that the degeneration is not of the nature of a fatty change; nevertheless, free globules of fat are detected throughout both healthy and degenerated muscle (see sect. 22). Sections were stained with gentian violet and acetic acid, and though in some places the fibrous tissue had a slightly reddish tint, the vacuolated and degenerated tissue showed no evidence of the amyloid reaction. Similarly, sections were treated with toluidin blue for the mucoid change but also with negative results (see sect. 23).

Throughout many of the sections groups of unicellular organisms are encountered. These are situated in the spaces, and mostly towards the free margins, and, though more numerous in the diseased than in the healthy areas are not confined to the former. They are oval or round in shape, have a distinct envelope, and granular contents. They vary in size from that of a minute organism to about three fourths of the size of a red

Fig. 32. Section of one of the nodules in the cardiac wall showing the transition from normal cardiac muscle to the degenerated tissue. Haemalum eosin and orange. (X 480.)

red blood corpuscle. They always stain more darkly than the rest of the tissue and are not decolourised by Gram's method (see sect. 24). The same organisms, though in smaller numbers, are encountered throughout the other tissues of the body, and especially in the meninges of the brain. They have been found in the fluid (glycerine and water), in which the tissues had been lying for some time previous to the microscopic examination. In the fluid, and very occasionally in the tissues too, it was quite evident that these organisms were proliferating by a process of gemmation.

Several sections (ten in all) were stained for tubercle bacilli, but in only two were any discovered, and in both instances they were situated in the vicinity of blood vessels in the normal myocardium. (see sects. 25 and 26).

Discussion:— Concerning the nature of this change in the cardiac wall it seems evident, from an examination of the various sections, that the altered and vacuolated tissue is due to a degenerative process of the normal cardiac muscle. Though, as a rule, the transition from the normal to the abnormal is very abrupt, and though in places the abnormal area is even surrounded by a band of fibrous tissue, yet in several instances a distinct and gradual transition can be traced. At certain places (see fig. 32) this gradual transition is very

very apparent. The muscle fibres nearest to the degenerated area are swollen, and yet show very distinct striation. The nuclei are less numerous than normal, and in places those that remain are hypertrophied. Still further into the degenerated mass the fibres can be seen separated and split up by vacuoles of various sizes and shapes, giving rise either to a network of fibres or a somewhat spider cell shaped mass of tissue. In several places two nuclei were seen lying side by side as if they had undergone division, but in no place were cells in process of fission by karyokinesis observed. The transition from the normal muscle nucleus, with neutrophilic chromatic elements, to the large spherical nucleus, with one or two distinctly oxyphilic nucleoli, could also be traced.

Concerning the cause of this change it is more difficult to speak, since nothing definite was found to account for it. From the absence of round cells it is evidently not of an inflammatory nature, and also the absence of giant cells and tubercle bacilli negative the idea of tuberculosis.

It must not be forgotten, however, that this peculiar lesion occurred in a case of general tuberculosis. Can it be possible that the tuberculous toxin has been the etiological factor here? The tuberculous toxin, while bringing about degeneration of tissue, causes a hypertrophy and proliferation

proliferation of the nuclei, as is seen in the epitheloid and giant cells. Anders,[1] in a paper on tuberculosis of the myocardium, mentions a case of diffuse fibrosis of the myocardium produced, according to Brehmer,[2] who reports the case, by the tuberculous toxin without the presence of the bacillus in the tissue. Anders[3] and Fuchs,[4] however, both doubt if such a claim can be based on the evidence of a single case; besides, the numbers of hearts subjected to the influence of the tuberculous toxin must be legion, while this degeneration is almost unique.

On searching the literature no reference to any degeneration of cardiac muscle, at all approaching what has been described above, can be found.

Fuchs,[5] in his thesis entitled "De la Tuberculose du Myocarde", describes a vacuolar atrophy of the muscle cells at the periphery of the miliary tubercle. He says that at first sight all the muscle cells seem to have disappeared, and to have become replaced by bright vacuoles. Under a high power it is easy, he remarks, to demonstrate that the spaces are

1. Anders, M.D., J.M. "Tuberculosis of the Myocardium" Jour. of Amer. Med. Assoc., Chicago, 1902, vol xxxix, p. 1081.

2. Brehmer: "Inaug. Dissert," Halle, 1883 Quoted by Anders, ibid.

3. Anders, M.D., J.M. Ibid.

4. Fuchs, D.A. "De la Tuberculose du Myocarde", Thesis, Paris, 1898, p. 34.

5. Fuchs, D.A. Ibid. p. 78.

Fig. 33. Section of ischaemic atrophy of the myocardium. Haemalum eosin and orange. (X 400.) Photomicrograph of a section kindly given to the author by Dr. J. M. Cowan.

are degenerated muscle cells enclosed in the tuberculous zone. The vacuolar state varies in degree from the presence of several irregular cavities around the central nucleus to a complete excavation of the cell, with a more or less prolonged preservation of the central nucleus and the periphery, which latter persists as a thin band of myosin, sufficiently characterised by the appropriate staining reactions. In the last degree of this change the cell entirely disappears, the thin band breaking up, but still recognisable as small shreds of tissue throughout the tuberculous mass. Fuchs, while describing this change, remarks on the fact that the endothelial cells of the capillary vessels persist in the same region, which is in process of vacuolation and degeneration.

Anders[1], in his paper on "Tuberculosis of the Myocardium", also mentions vacuolation of the muscle fibres in diffuse tuberculous infiltration of the cardiac muscle.

Cowan[2], in his thesis on "The Heart in acute Disease", describes a vacuolar change in the cardiac muscle, which he designates ischaemic atrophy (see fig. 33). According to this author, it is frequently seen in local atrophies due to degenerative changes in the coronary arteries. The muscle cells are smaller than normal, and the fibrils round the

1. Anders, M.D., J.M. "Tuberculosis of the Myocardium", Jour. of Amer. Med. Assoc., Chicago, 1902, vol xxxix, p.

2. Cowan, M.D., D.Sc., J.M., "The Heart in acute Disease", The Journal of Pathology and Bacteriology, Edin., August, 1903, p. 89.

the nuclei are granular and faintly staining. The peripheral bundles still persist and show marked striation. The central granular mass is very friable, and in sections is very liable to fall out, leaving a vacuole. The nucleus is also markedly altered. It may be enlarged to two or three times its normal size, and it varies in shape, being often rounded or pear shaped. The chromatic elements are scanty and sometimes aggregated into little clumps, which are most numerous at the circumference, or the nucleus may stain faintly and diffusely.

It is interesting to note, in connection with this vacuolar atrophy described by Cowan in cases of degenerated coronary arteries, that, though arterioles were frequently detected in the diseased areas in my case, the capillary plexus was very deficient. Excepting the periarterial fibrosis, which was merely a part of the general fibrosis of these nodules, no degeneration of the arterioles was observed. Irrespective of this fact is the point that these areas of degeneration did not show any definite relationship to the arterioles. Consequently, it is more likely that this disappearance of the capillaries is of the nature of a pressure atrophy, due to the swelling of the muscle cells, that is to say, secondary rather than primary to the degeneration.

Since reading the above references I have had the good luck to come across a case of acute miliary tuberculosis, with several small miliary tubercles in the wall of the left ventricle. On microscopic examination of this case, the vacuolar degeneration described by

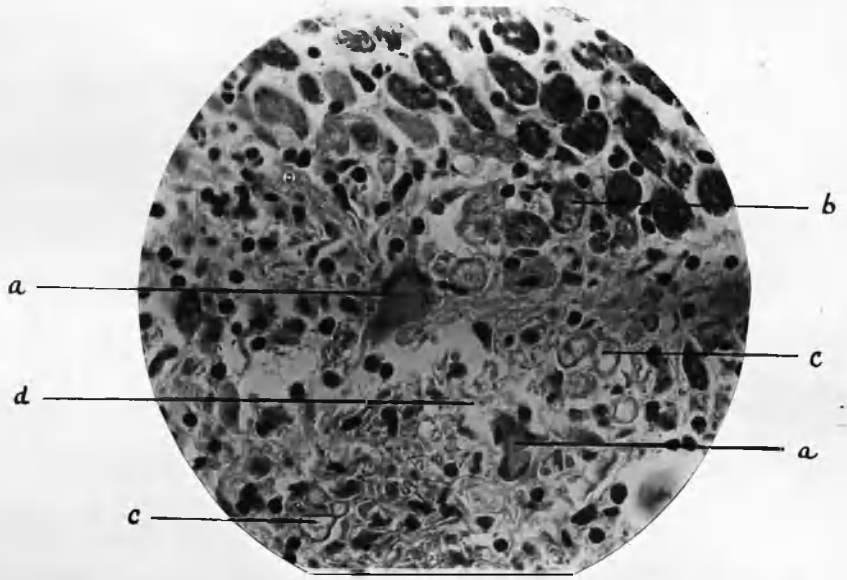


Fig. 34. Section of cardiac wall through a miliary tubercle showing the vacuolar degeneration of the muscle at the periphery of the tubercle. Heidenhain's iron and haematoxylin method. (X400.)

a. Giant cell.
b. Partly vacuolated muscle.
c. Completely vacuolated muscle.
d. Shreds of disintegrated muscle.

by Fuchs is seen in the periphery of the small tubercles (see sect. 27, and fig 34). When viewed in transverse section certain of the muscle cells at the periphery of the tubercle are seen to become vacuolated. The perinuclear fibres disappear, leaving the nucleus in a space surrounded by the remaining marginal fibres. The nucleus through time also disappears, and all that is left is a cavity with a thin wall, which stains in a similar fashion to normal muscle. Ultimately, this band disintegrates and is only recognisable as small shreds of tissue intermixed with the epithelioid and round cells of the tubercle. In longitudinal sections the muscular cells are observed to have lost their striation, to become vacuolated and to ultimately disintegrate into small shreds of tissue (see sect. 27). The lesion in this case was found to be undoubtedly tuberculous in nature, as in sections, stained with carbol-fuchsin and methylene blue, a few tubercle bacilli were observed in several of the giant cells (see sect. 28).

All these forms of vacuolar change of the cardiac muscle, it will be observed, are entirely different from what is seen in my case. In this latter case the fibres instead of atrophying swell up, the striation remains or even becomes more distinct instead of disappearing, and the nuclei hypertrophy instead of disintegrating.

The change in the muscle nuclei is also, so far as I am aware, unrecorded. The change which the nuclei in ischaemic atrophy undergo is quite different from what has taken place in my

my case, where the nuclei swell up, and the chromatic elements run together into one or two large bright nucleoli, most frequently centrally placed and markedly oxyphilic in character.

Summary of Histological Examination of the Heart.

The nodules in the cardiac wall are all of the same nature, and have the following outstanding features.

1. The tissue is much vacuolated.

2. It assumes either the form of a coarse and irregular reticulum of transversely striated fibres and fibrils, or of numerous spider cell shaped masses, which also show striation in their bodies and processes.

3. Scattered irregularly throughout are large spherical nuclei, with one or more distinctly oxyphilic nucleoli.

4. In these nodules there is a relative increase of the fibrous tissue, more especially around the blood vessels, and occasionally around the circumference of the nodules.

5. The rich capillary plexus, present in the normal myocardium, is absent in these degenerated areas.

6. There is no evidence of inflammation in or around these areas.

7. There is no evidence of a tuberculous infection in the form of either giant cells or tubercle bacilli.

8. A distinct transition can be traced

traced from the normal cardiac muscle and nuclei to this degenerated tissue and large spherical nuclei.

Histological Examination of the Liver and other Viscera.

Liver:— This organ is the seat of a chronic generalised tuberculosis, accompanied by marked fatty infiltration (see sects. 29 and 30). Scattered throughout are numerous tuberculous foci, composed of many individual tubercles, and surrounded more or less by fibrous tissue. In some places the fibrous tissue is very abundant, and extends for some distance into the hepatic tissue at the circumference of these areas. It has the disposition of an unicellular cirrhosis, and the fibrosis can be seen extending into the lobules, cutting off layers of hepatic cells, which atrophy and ultimately disintegrate. The course of events is as follows, viz., the nuclei stain more faintly and then become indistinguishable, while the cells shrivel up, their protoplasm becoming granular, and finally disappear altogether. Many of the tuberculous areas are caseous, and the cavities with bile-stained contents, mentioned in the post-mortem report, are found on more minute examination to be due to softening of large caseous areas. Their walls are composed of more recent tuberculous tissue with much round cell infiltration, which again is surrounded by a certain amount of fibrous tissue (see sect. 30).

Sections stained with carbol fuchsin and methylene blue reveal numerous tubercle bacilli in the caseated areas, and also in the as yet undegenerated tubercles (see sect. 32).

Throughout the fibrous tissue, which is

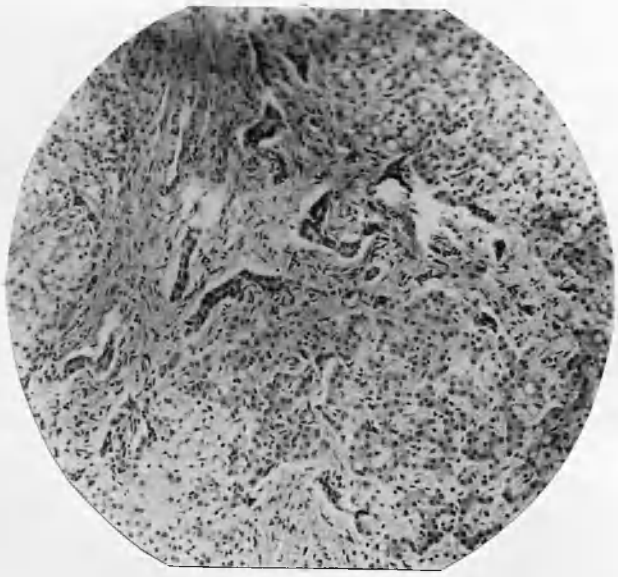


Fig. 35. Section of liver through a portal area the seat of cirrhosis. Note the apparent increase of the bile ducts, the fatty infiltration of the liver cells and the tubular disposition of the hepatic cells in the lower part of the field. Haemalum and Van Gieson. (×140.)

Fig. 36. Showing abrupt change from liver cells to those of bile duct.

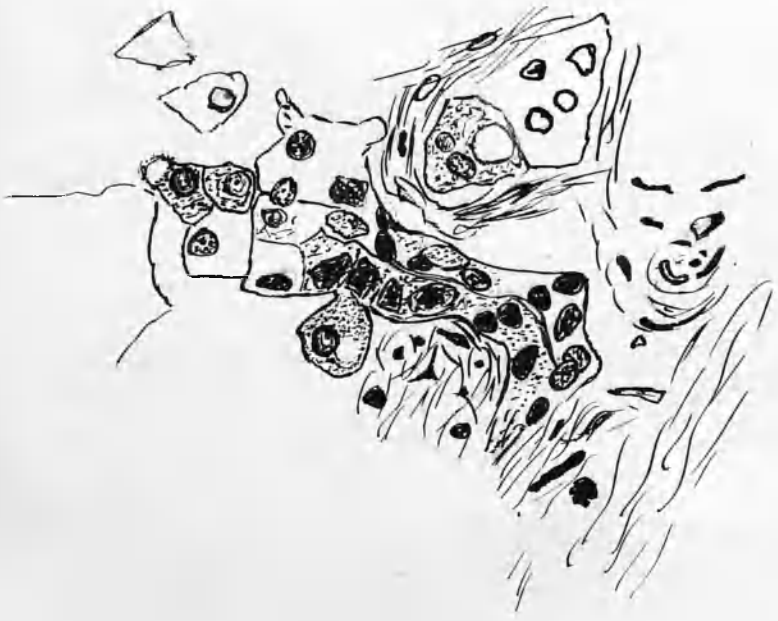


Fig. 37. Showing gradual change from hepatic cells to those of bile duct.

Fig. 38. Bile ducts among the newly formed fibrous tissue.

is most abundant in, but not entirely limited to, the vicinity of the tuberculous foci, are numerous duct-like structures (see fig. 35). These are seen in many instances to branch and as a rule to radiate from the centres of the portal areas. They are composed of one or more rows of cells having a somewhat cubical shape, with granular contents and darkly staining elliptical nuclei. The nuclei are very similar to ordinary liver cell nuclei. In many instances these cells are irregularly arranged and more numerous than one would expect in such small ducts, giving the impression of cells undergoing proliferation. Though occasionally a distinct lumen is detected, in the majority none such is observed, and occasionally towards one end there is only a single row of cells bounded on either side by fibroblasts (see sect. 30). There is never any basement membrane seen, nor is any muscular tissue observed in their walls. In no instance can they be observed in direct continuity with undoubted interlobar bile ducts, which are frequently enlarged and irregularly dilated. In many instances these duct-like structures are in direct continuity with hepatic cells. Sometimes the transition from the polyhedral hepatic cells to the cubical epithelium of the duct-like structure is very abrupt (see sect. 30 ƒ, and fig. 36), while in other places this change is more gradual, and occasionally a duct-like formation is observed in continuity with hepatic cells at either end.

From the examination of this organ there seems no doubt that it is the seat of a chronic tuberculous infection. Concomitant with this there is, as not infrequently occurs in tuberculosis of the liver, unicellular cirrhosis and fatty infiltration. The most interesting points, however, in the case are the presence of the increased number of duct-like structures and the question of their origin. As mentioned in the report of the microscopic examination they are in many instances in direct continuity with hepatic cells. The change from the form of the hepatic cell to that of the duct cell is too abrupt in some places to be anything but a normal condition, and thus it would seem that the view held by the late Prof. Coats[1], namely, that these apparently new formed ducts are merely normal structures coming into evidence through the disappearance of hepatic cells, is supported by this finding. However, here and there, the transition is more gradual, and the number of cells is more numerous than one would expect to find in such small intralobular ducts, consequently, there is also some support for the view propounded by Sims Woodhead.[2] He states that "these new "bile ducts are formed from the splitting up of "these liver cells - a process of division of the nucleus "and then of the cell, - followed by further subdivisions

1. Coats, Glasgow Medical Journal, October, 1892, pp. 289-295.

2. Sims Woodhead, "Practical Pathology", 1892, 3rd Edition, p. 202.

"subdivisions,— until in place of the three or four cells "surrounding the bile capillary, there are numerous "small flattened cells resembling those around the "smaller bile ducts; the process consists, in fact, of "a reversion of the liver cell to its embryonic or "epithelial type."

Spleen:— Examination of this organ reveals a chronic general tuberculosis. There is a mild degree of fibrosis, as evidenced by slight thickening of the capsule and increase of the interstial fibrous tissue. Throughout are numerous large caseous areas, which are specially numerous immediately under the cortex (see sect. 33). Tubercle bacilli, though scanty, are detected in the caseous areas, but especially in the giant cells (see sect. 34).

Kidneys:—These organs show a marked cloudy swelling, the epithelium of the tubules being granular and their nuclei staining defectively. A few of the vessels of the cortex are markedly congested. One or two small miliary tubercles are seen in the cortex, but no tubercle bacilli are observed. The small cysts immediately under the capsule are unilocular, and contain a certain amount of colloid material with an occasional desquamated epithelial cell. They are lined – not always in their entire circumference – by a single layer of cubical epithelium, which is supported by a thin wall of

of fibrous tissue of varying thickness. Outside this are the renal tubules, which are flattened out in many places, but nowhere breaking down as if to form the cyst (see sect. 35).

Lungs:- On microscopic examination these organs are found to be the seat of a chronic general tuberculosis. Throughout are many caseous areas, and much round cell infiltration, surrounded by a certain amount of fibrous tissue (see sect. 36). Round about the caseous areas there is a catarrhal pneumonic condition, and many of the bronchi are seen to be the seat of catarrh. Tubercle bacilli, though scanty, are occasionally observed, and most frequently in the giant cells (see sect. 37).

Summary of Microscopic Examination of the Liver and other Viscera.

1. The liver shows chronic tuberculosis: there is also fatty infiltration and unicellular cirrhosis, with an apparent increase of the bile ducts.

2. The spleen is the seat of a general chronic tuberculosis.

3. The kidneys are in a condition of cloudy swelling, and are the seat of miliary tubercles and congenital cysts.

4. The lungs are markedly tuberculous.