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STREPTOMYCIN IN TUBERCULOUS MENINGITIS IN CHILDHOOD:

THE PATHOLOGICAL FINDINGS IN SIX FATAL CASES.

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Feldman (1946), in his Harben lectures on the chemotherapy of tuberculosis, reported that in tuberculous guinea pigs, streptomycin therapy was accompanied by changes in the lesions which afforded morphological evidence of the chemotherapeutic effect. Baggenstoss, Feldman and Hinshaw (1947) gave detailed autopsy and histological findings of five fatal human cases (three of them children) of miliary tuberculosis treated by streptomycin, and more recently, in the series of cases published by Madigan, Swift, Brownlee and Wright (1947), Wright added reports of the microscopic findings in two fatal adult cases.

The changes described by these authors are regressive in character and are particularly well-seen in discrete and miliary follicles, presumably because isolated follicles are more readily permeated by the antibiotic. Epithelioid elements disappear, the follicles are replaced by hyaline collagenous tissue, some show encapsulation and fibrosis, and caseation is absent or reduced in amount. Wright noted two types of degenerative tubercles in his two cases : completely hyalinized follicles without tubercle bacilli (his type 1 reaction) in both cases, but in one there were also splenic histiocyte abscesses with acid-fast bacilli, a reaction which he classifies as type 2.

This paper records the pathological and, in particular, the microscopical findings in six children who died while under treatment with streptomycin for tuberculous meningitis in the Royal Hospital for Sick Children, Glasgow, during 1947. The clinical histories and gross pathological findings are summarised.

CASE 1. Female, M. A., aged 3 years 5 months, a known case of pulmonary tuberculosis with left upper lobe collapse, developed tuberculous meningitis while at a convalescent home and was admitted to hospital with a three-day history of drowsiness, vomiting and squint. On admission, the child was drowsy but co-operative. Her cerebro-spinal fluid was characteristic ; although acid-fast bacilli could not be demonstrated, initial cultures of the pellicle were positive and produced

tuberculous lesions in guinea pigs. Streptomycin treatment by intra-muscular and intrathecal routes was continued for 24 days, in all, 14.9 g. being exhibited. During treatment the child showed the toxic reactions of a morbilliform rash and albumin with casts in the urine, but had recovered clinically from these effects before death.

Post mortem. Brain : generalized opacity of the leptomeninges all over the brain and cord ; marked internal hydrocephalus. Basal tuberculous meningitis with well-formed tubercles, a moderate amount of exudate, and a small cortical tuberculoma in the right fissure of Sylvius. *Lungs* : in left apical lobe primary Ghon focus, 4 × 3 × 2 cm., caseous in centre, with caseous enlarged hilum glands stenosing and ulcerating the left upper lobe bronchus. Miliary tubercles scanty in lungs. *Liver* and *spleen* : more abundant miliary tubercles. *Kidneys* : diffuse cloudy swelling and fatty change.

Microscopic findings. Primary lung focus : this consisted of proliferative tubercle follicles with epithelioid cells and giant cells around a central caseous mass in which tubercle bacilli were demonstrated. The adjacent lung showed areas of collapse separated by air channels lined by cubical epithelium ; thus some resolution had taken place without fibrosis. Caseous tuberculosis involved the mucosa of the narrowed upper lobe bronchus, the regional tracheo-bronchial and broncho-pulmonary glands. *Meninges* : a fibrocyte layer, four or five cells thick, spread diffusely throughout the cerebral and cord meninges, which contained proliferative tubercle follicles with abundant lymphocytic and polymorph exudate ; tubercle bacilli were demonstrated. Many dilated blood vessels and capillaries were present ; endarteritis was seen in a few vessels only. *Liver* : tubercle follicles were scanty and of the hyalinized type, some with lymphocyte infiltration (Fig. 1) ; no follicles containing epithelioid cells or giant cells were seen. *Spleen* : there were no tubercle follicles in the sections examined, but there was hyaline vascular change which affected the intima of the penicillar arterioles in the form of circular rings. The renal glomerular capillaries, although wide, had thickened basement membranes and were of indistinct outline ; many nephrons showed intense cloudy swelling of their convoluted tubules.

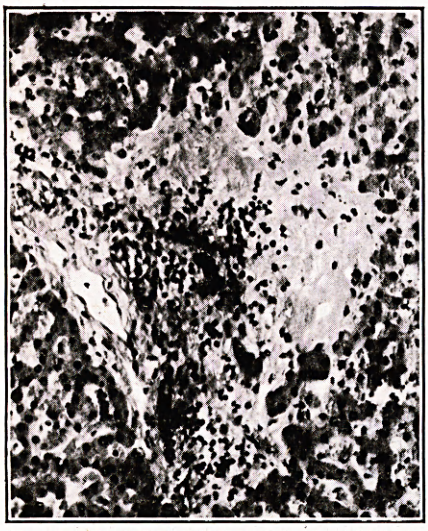


Fig. 1. Partially-hyalinized tubercle follicle in liver (Case 1). H. & E. ×160.

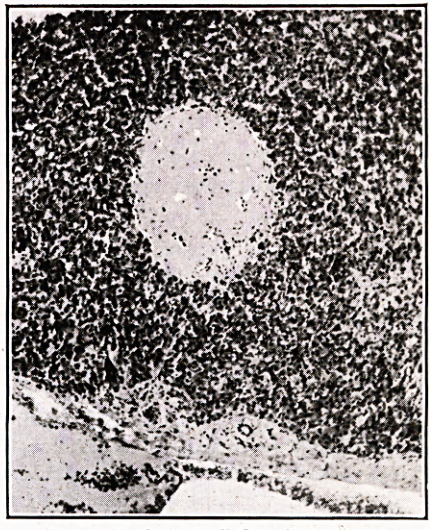
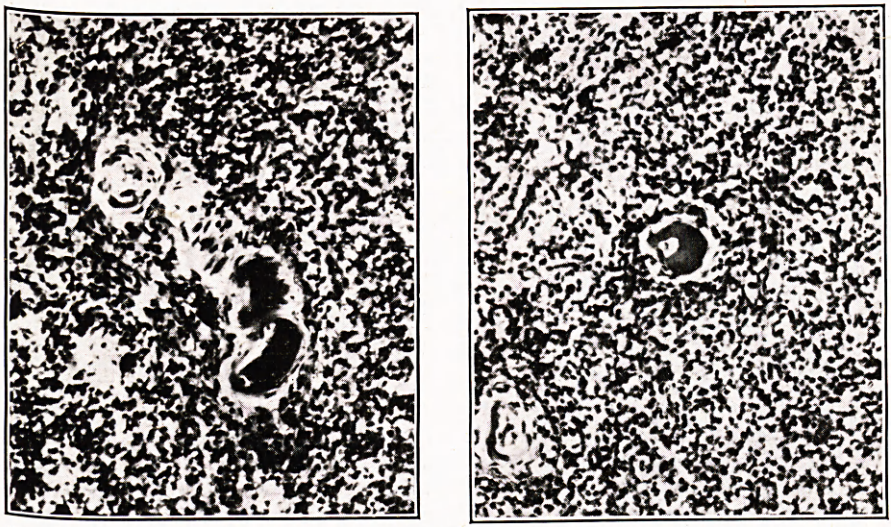


Fig. 2. Hyalinized follicle in liver (Case 2). H. & E. ×60.

CASE 2. Male, J. B., 4 years 11 months, previously well, admitted to hospital with a history of drowsiness, listlessness, irritability, anorexia, vomiting and constipation for 6 days. The child was semiconscious, with some neck rigidity. The cerebrospinal fluid findings were diagnostic ; tubercle bacilli were demonstrated in this fluid and grew on primary culture ; stomach washings inoculated in guinea pigs were also positive. Streptomycin was exhibited intramuscularly and into the theca, but initial general improvement was followed by gradual deterioration and he died after 71 days treatment, in all, 31 g. streptomycin being used.

Post mortem. Grossly emaciated child. *Brain* : moderate degree of internal hydrocephalus with matted exudate at brain stem and at optic chiasma ; recent tubercles in meninges of left temporal lobe. No tuberculomata in brain. *Spinal cord* : some fibrous thickening of the lumbar meninges : no discrete tubercles. *Lungs* : fibrosed primary focus in small wedge-shaped area of collapsed lung in the lower part of the right apical lobe : bronchiectatic spaces in hilar part of this tissue : single regional superior tracheo-bronchial gland calcified but not enlarged : no miliary tubercles in lungs or pleura. *Liver* and *spleen* both contained miliary tubercles but none in the *kidneys*. Small partly-healed tuberculous ulcer in the *ileum* about 3 feet above the ileo-caecal valve ; *mesenteric glands* slightly enlarged, apparently tuberculous but not caseous.

Microscopic examination. Lung : sections through the collapsed portion of the right apical lobe showed diffuse fibrosis with numerous completely hyalinized tubercle follicles in which reticulum had been laid down concentrically. The lung, although fibrotic, had re-expanded to some extent, and the connective tissue was fenestrated by alveoli and irregular air spaces lined with cubical epithelium. Near the hilum, connective tissue spaces lined by ciliated respiratory epithelium communicated with dilated bronchi which were free from cellular exudate. The hilum gland was partly fibrosed and in part calcified ; tubercle follicles or acid-fast bacilli were absent. The *liver* had numerous isolated completely hyalinized follicles (Fig. 2) ; some were infiltrated by lymphocytes but without reaction of the adjacent liver tissue. In the *spleen* there were hyalinized tubercle follicles but the most noteworthy feature was extensive hyaline change in the small arterioles (Figs. 3 and 4). This affected mainly



Figs. 3 and 4. Hyaline plaques in penicillar branches of splenic arteries (Case 2). Haemalum-Phloxine-tartrazine. ×160.

the penicillar vessels. The hyaline material was in plaques and rings in the intima and media of the vessels, producing stenosis and distortion. No similar change was found in the small vessels of the *liver* or *kidney*. *Mesenteric glands*: the glands, although containing some clumps of lymphocytes, had been converted almost completely into hyaline material which retained a follicular arrangement demonstrable readily by silver impregnation.

CASE 3. Female, J. K., 2 years 3 months, had 'meningitis' (variety unknown) at the age of 1 year and thereafter remained well until 14 days before admission, when she complained of headache and was fevered. This was followed by vomiting, constipation, drowsiness, irritability and loss of weight with ptosis of the left eyelid. On admission, a clinical diagnosis of tuberculous meningitis was made, the cerebrospinal fluid was typical and contained tubercle bacilli which grew on culture; positive results were obtained also from cerebrospinal fluid and stomach washings by guinea pig inoculation. Streptomycin therapy was intrathecal and systemic, but the child never responded well; at one stage ventricular punctures had to be undertaken for a spinal block; in all, 30.6 g. were used over a period of 74 days.

Post mortem. Brain. congested leptomeninges with recent acute tubercles on the inferior surfaces of both frontal lobes and in the fissures of Sylvius. Exudate of moderate density, particularly abundant in the regions of the optic chiasma, interpeduncular space and upper surface of pons. *Cord* leptomeninges thickened with exudate and some fine meningeal adhesions, both anteriorly and posteriorly; no obvious tubercles in the cord exudate. No tuberculomata in brain; tuberculous ependymitis of ventricular system. *Lungs*: extensively involved in broncho-pneumonia which is not tuberculous (confirmed microscopically). Partial calcification of right superior tracheo-bronchial gland, but no primary pulmonary focus and no miliary tubercles in lungs. Miliary tubercles scanty in liver; small group of caseous tubercles in the interpyramidal cortex of one kidney.

Microscopic examination. Meninges: numerous proliferative tubercle follicles were present on the basal meninges and on the meninges of the cord. The exudate was mainly lymphocytic; there was no caseation and no fibrosis; endarteritis was not marked. There was a well-marked tuberculous ependymitis in the fourth and lateral ventricles. *Lung*: sections showed a confluent pneumonia which was not tuberculous. *Liver*: the liver contained hyalinized tubercle follicles, some of them infiltrated with lymphocytes; where the liver tissue had encroached upon them, the hyaline follicles were often stellate, and many of them had central blood capillaries with accompanying fibroblasts. No recent tubercles were seen. The *kidney* showed cloudy swelling of the convoluted tubules but otherwise nothing of note.

CASE 4. Female, J. H., 4 years 4 months, a case of tuberculous meningitis with a history of listlessness and anorexia for 10 weeks and convulsions 3 weeks before admission. The cerebro-spinal fluid was diagnostic; acid-fast bacilli were seen in films from the pellicle. Intrathecal and intramuscular streptomycin was continued intermittently for 26 weeks. The child made a remarkable recovery clinically and was transferred to the country branch of the hospital, but 2 weeks later had a relapse of the meningitis and died in 11 days despite renewed streptomycin therapy.

Post mortem. Brain: well-established tuberculous meningitis affecting particularly the optic chiasma, the fissures of Sylvius and the cerebral peduncles; exudate soft, gelatinous, rich in tubercles and in no way different from that usually found in tuberculous meningitis of less than a fortnight's duration. No hydrocephalus. Small tuberculomata visible and palpable at various points on the surface of the brain, *e.g.*, on the medial wall of the intercerebral fissure, in the temporal region and in the

frontal lobes ; on cutting after hardening, tuberculomata varying from 0.5 to 2 cms. in diameter were scattered throughout the brain ; some were surrounded by congested brain tissue and many were at the base of sulci (Fig. 5). *Lungs* : miliary tubercles

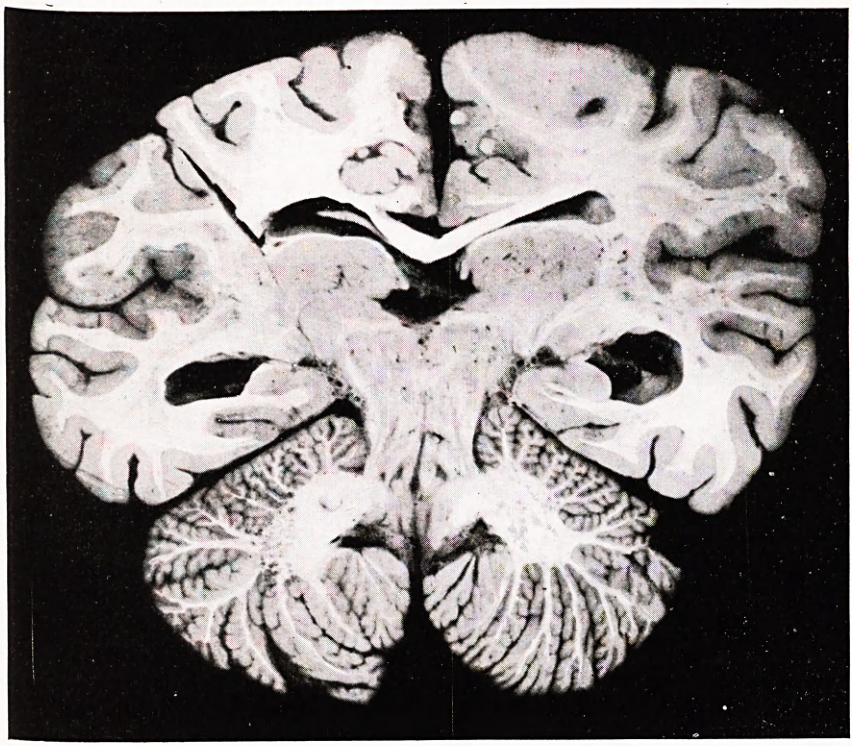


Fig. 5. Tuberculomata in Cerebral cortex (Case 4).

numerous on the pleural surfaces and throughout the lungs generally ; hilum glands of both basal lobes enlarged and caseous ; primary Ghon focus of caseous tuberculosis, about 1 cm. in diameter, in the left basal lobe about $1\frac{1}{2}$ cm. from the pleural surface. Miliary tubercles numerous in *spleen*, *kidneys* and *liver*.

Microscopic examination. Brain : the meninges contained numerous proliferative tubercles with diffuse mononuclear and polymorphonuclear exudate. Several cerebral tuberculomata were sectioned. Some were completely caseous with fibrotic walls and appeared inert ; others, and in particular those near the surface, had tuberculous sinuses communicating with the meninges, and many of them had small proliferative tubercle follicles in their connective tissue capsules. *Lung* : the primary focus showed a caseous central mass surrounded by connective tissue and condensed lung tissue. There had been no local extension of the lesion and no miliary tubercles were seen in the sections examined. The *liver* showed two types of tubercle follicles. Some were partially hyalinized with the hyaline fibres in reticular formation enclosing giant and epithelioid cells, and sometimes caseous material (Fig. 6) ; these follicles contained clumps of lymphocytes and slender acid-fast bacilli. The second type (Fig. 7) was the completely hyalinized follicle, some with and others without lymphocytes, none with demonstrable tubercle bacilli. The *spleen* showed hyalinized

follicles with a reticular distribution of the hyaline material ; epithelioid cells were absent but there were numerous lymphocytes in the hyaline meshes. Intimal hyaline degeneration affected some of the penicillar vessels and varied from small plaques to complete rings. Hyalinized areas were seen also in the centres of the lymph node germ follicles.

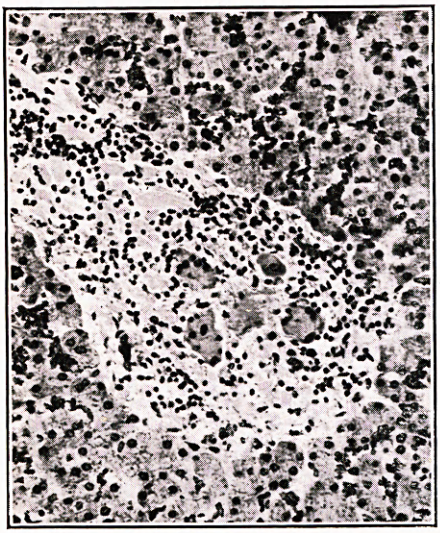


Fig. 6. Early involution of tubercle follicle in liver (Case 4). H. & E. ×160.

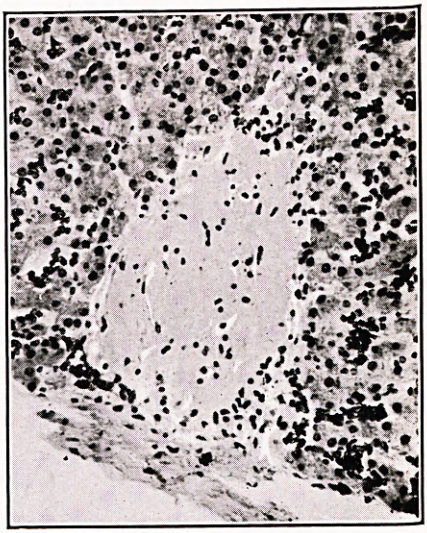


Fig. 7. Hyalinized follicle in liver (Case 4). H. & E. ×160.

CASE 5. Male, F. McC., 2 years 5 months, admitted with a history of a generalised convulsion lasting 2½ hours : he had a respiratory illness 3 months before and had not made a good recovery. Tuberculous meningitis was confirmed by a characteristic cerebro-spinal fluid with acid-fast bacilli. Intramuscular and intrathecal streptomycin was continued for 200 days (latterly intermittently), in all, 105 g. being exhibited. After initial improvement the child deteriorated slowly, became semiconscious and emaciated progressively for some weeks before death.

Post mortem. *Brain* : marked degree of hydrocephalus from thickening of the basal meninges ; fairly wide communication between the fourth ventricle and the basal cisterns. No recent tubercles on the meninges ; dense, hard exudate around the optic chiasma and cerebral peduncles. Sectioned after hardening, the brain had only one small tuberculoma, 4 mm. in diameter, at the base of a sulcus just posterior to the motor area on the left side. *Lungs* : primary Ghon focus (2 cm. in diameter and filled with semisolid caseous material) in the right basal lobe midway between its upper and lower surfaces in the mid-axillary line : overlying pleura puckered and thickened ; surrounding lung tissue somewhat haemorrhagic ; related broncho-pulmonary and tracheo-bronchial glands enlarged and caseous. Miliary tubercles scanty in lungs but numerous in the *liver* and *spleen*. Small tuberculous ulcers in the *ileum* : *mesenteric glands* slightly enlarged and caseous.

Microscopic examination. The *lung* showed a confluent non-tuberculous broncho-pneumonia ; there were no miliary tubercles in the blocks examined. The primary focus was a mass of homogeneous caseous tissue, roughly spherical, 7 cm. in diameter, surrounded by a narrow zone of hyaline vascular connective tissue, from which some organization of the focus had taken place. In the *spleen* there were no active tubercles

but many healed follicles. The penicillar arteries showed intimal hyaline degeneration. Numerous small hyalinized tubercle follicles, most of them containing lymphocytes and some with capillary blood vessels were present in the *liver*. *Brain* : there were proliferative tubercle follicles in the choroid plexus, in the meninges of the upper part of the vermis of the cerebellum, and in the basal aspect of the pons. This region showed some diffuse fibrosis of the meninges but healed tubercle follicles could not be identified with certainty. The tuberculoma which was noted at the base of a sulcus consisted of inert material surrounded by fibrous tissue, without giant cells and tubercle follicles.

CASE 6. Male, J. P., 1 year 4 months, admitted with tuberculous meningitis manifested first by a convulsion. The cerebrospinal fluid was diagnostic ; tubercle bacilli were found in the pellicle. Streptomycin was administered intramuscularly only, 23 g. being given in 45 days, but the patient did not improve and died on the 48th day. Spastic paresis of the right arm and leg persisted throughout the illness.

Post mortem. *Brain* : internal hydrocephalus of moderate degree. Well-established tuberculous meningitis with numerous fresh tubercles over the base of the brain and on the basal and lateral surfaces of the temporal lobes. Condensation and hardening of the exudate in the region of the chiasma. Basal nuclei and posterior part of the internal capsule on the left side softened with numerous small cystic spaces with clear fluid. No enlarged hilum glands ; right apical lobe consolidated from diffuse fibrosis with ectasia of the proximal bronchi. Other lobes of this and the left lung normally expanded and free from miliary tubercles.

Microscopic examination. *Brain* : there was proliferative tuberculosis of brain and cord meninges with endarteritis. The cerebral softening in the left basal ganglia showed lymphocytic and macrophage infiltration ; several of the adjacent blood vessels were completely thrombosed, and some, in addition, were infiltrated with polymorphs as in recent acute septic thrombosis. *Lung* : the right apical lobe was traversed by strands of connective tissue separating newly-formed alveoli and bronchial buds lined by cubical epithelium. Healed tubercles appeared as small circular collagenous areas, some containing lymphocytes and others surrounded by them ; these involuted tubercle follicles were discrete from the general fibrosis. Near the hilum, there were air spaces lined by respiratory epithelium which rested directly on connective tissue ; these communicated with bronchiectatic bronchi which were filled with pus cells. The *liver* had numerous small healed tubercles represented only by collagenous tissue, sometimes containing a bile duct or a blood capillary. In the *kidneys* there was cloudy swelling of the parenchymal cells ; no tubercles were present in the portions examined. There were recent tubercle follicles in the *spleen*, some of them caseous ; involuted follicles were seen. The venous sinuses had thickened walls and a lining of cubical cells, but there was hyaline change in the arterial system.

DISCUSSION.

In this paper, it is not proposed to discuss in detail the six fatal cases summarised above, but rather to group the noteworthy points under four headings.

The primary lung complex. This had healed in Case 2 only, where, in the residual lung lesion, fully-hyalinized tubercle follicles can be distinguished from the diffuse connective tissue of the contiguous lung by the concentric arrangement of their collagen fibres and of their reticulum ; some of the

hyalinized follicles are surrounded by lymphocytes. Tubercle bacilli are absent. In Case 6, similar involuted follicles are fairly numerous in the comparatively loosely arranged connective tissue strands which traverse the apical lobe, but in this case, in the partially expanded lung tissue which separates the connective tissue, there are also proliferative tubercles indicating that the infection had not been arrested. Both these cases show evidence of reformation of lung alveoli within the connective tissue ; new air spaces, many of them lined by cubical cells, have formed, and bronchial buds can be seen. Moreover, both cases show some degree of bronchiectasis in the hilar part of the fibrosed lobes ; not only are the bronchi themselves dilated but they communicate with fusiform air spaces in the connective tissue, and these spaces, although lacking the constituents of the normal bronchial wall, are also lined by ciliated respiratory epithelium. There is no evidence of bronchial stenosis in either lung and the bronchiectasis appears of the type met with in long-standing collapse ; in Case 2 the bronchi and air spaces are uninfected but in Case 6 some of them contain pus cells, a reminder that infected bronchiectasis is a possible sequel to healed tuberculosis.

Cases 1, 4 and 5 have caseous primary foci in which tubercle bacilli are readily demonstrable. In Case 1, numerous proliferative tubercle follicles surround the caseous centre, and obviously, this lesion had been progressive at the time of death. Vascular connective tissue encloses the lesions in Cases 4 and 5 but the degree of encapsulation is no greater than is seen from time to time in untreated cases.

No primary focus was found in Case 3, although the lung was examined minutely after fixation. There was an extensive non-tuberculous pneumonia which may have masked a small primary focus, but it is more probable that the focus had healed completely and been absorbed, an inference in accordance with the single small, partly calcified regional gland which remains.

Thus it would appear that with streptomycin the primary lung focus can be transformed into hyaline follicles provided the tubercle follicles are discrete, but where caseation or extensive pneumonic consolidation has taken place, healing is more likely to occur by centripetal fibrosis similar to the condition seen from time to time in chronic miliary tuberculosis. Where there is widespread fibrosis with collapse of lobules the possibility of residual bronchiectasis, sterile or infected, must be borne in mind.

Miliary tubercles. In all the cases, miliary tubercle follicles showed involution changes, always of a hyaline nature. Figs. 1, 2, 6 and 7 show characteristic examples in the liver. Some of the follicles are completely hyalinized and appear as oval whorled nodules, faintly pink with eosin, giving the staining reaction of collagen, and impregnating as reticulum

strands with ammoniacal silver. Lymphocytes are present around and in some of the follicles, but as a rule there is surprisingly little reaction on the part of the adjacent liver tissue. Nevertheless, some follicles have been encroached upon by the adjacent columns of liver cells and have assumed a stellate shape ; and when these collagenous follicles have in addition been penetrated by central blood capillaries or by a primitive bile duct. they afford morphological evidence of a functional rôle. The liver of Case 6 is particularly rich in organized, or partially organized follicles, and from their examination it may be concluded that hyalinized tubercle follicles in the liver ultimately may be canalized by blood or bile capillaries, or both, and thus incorporated in the hepatic economy.

Variations in the degree of involution in the follicles in a case implies that they represent different periods of bacillaemia. For example, in Case 4, the liver has numerous follicles partly hyalinized but still with epithelioid cells (Fig. 6), and in these lesions slender acid-fast bacilli can be seen ; in the same sections, however, there are completely hyalinized follicles without organisms (Fig. 7). These appearances can be correlated with the clinical history ; the patient responded at first to streptomycin and made an apparent recovery only to relapse 6 months later and die in 10 days despite renewed exhibition of the streptomycin. It may be inferred that fully hyalinized follicles relate to the early stages of the treatment ; the cellular follicles may be assumed to date from the terminal illness. In Wright's case (No. 11 of the series of Madigan *et al.*, 1947), hyalinized follicles and histiocyte abscesses occurred together, the latter alone having tubercle bacilli, but in his case the organisms isolated terminally were 30 times more resistant to streptomycin than those obtained at the beginning of treatment. Neither increased resistance nor histiocyte abscesses were noted in the six fatal cases which form the basis of this paper.

Involuted follicles occur also in the spleens, abdominal lymph nodes and kidneys of this series, but they are much more numerous and show a higher degree of involution in the liver. On the basis of local streptomycin concentration, regressive changes should be most marked in the kidneys since elimination of the drug is by this route, and according to Arnold (quoted by Baggenstoss *et al.*, 1947), the kidneys contain a high percentage of streptomycin. The liver, on the other hand, is stated to have a much lower streptomycin content, an observation difficult to reconcile with the comparatively marked involution of hepatic tubercles during streptomycin therapy. Microscopic examination of untreated cases, however, indicates that in the liver, tubercle follicles are more diverse in appearance than elsewhere in the body, and that there is a tendency to spontaneous regression of isolated hepatic tubercles. In the writer's experience, however, complete or even partial hyalinization of miliary tubercles has not been seen in untreated cases.

Nevertheless, hyaline change in tubercle follicles is not to be regarded by itself as a specific effect of streptomycin. Hyalinization is in fact not uncommon in healed tuberculous lesions, but it is usually preceded by fibrosis. In the examination of tissues from chronic miliary tuberculosis, hyaline change can be noted occasionally in follicles which show concentric fibrosis, and all transitions can be seen between partially fibrosed follicles which retain epithelioid cells and those which have become hyaline whorls. The remarkable feature of the streptomycin cases is the complete hyalinization of follicles which show no evidence of antecedent fibrosis ; and the occurrence of these follicles in crops of more or less uniform appearance is evidence of an agent not only capable of destroying the tubercle bacilli but also of exercising a direct necrotising effect on the specific tissue reaction which the organisms have induced.

Meningeal and central nervous system lesions. Proliferative tubercle follicles, many of them recent, were present in the leptomeninges of brain and cord in all six cases, and in none was there satisfactory evidence of reactive fibrosis. These findings, together with the abundance of tubercle bacilli in the meningeal lesions, the presence of caseation, and (in Case 4) of tuberculous ventriculitis, lead to the conclusion that in this series of fatal cases, the tuberculous meningitis had remained almost uninfluenced by the streptomycin. This is especially remarkable since the streptomycin was administered intrathecally as well as intramuscularly in five of the cases, and in the sixth, although exhibition was by the intramuscular route alone, cerebrospinal fluid streptomycin levels of from 2 to 8 micrograms per ml. were obtained up to 12 hours after the injection. Moreover, the strains of *M. tuberculosis* isolated before and during treatment, and at autopsy, were all sensitive to 0.5 to 1 microgram streptomycin per ml.

Baggenstoss *et al.* (1947) cite Arnold's evidence that streptomycin can not be recovered post mortem from the brain which in this respect is exceptional among body tissues. Thus it is easy to understand the persistance of tuberculomata in the brain throughout treatment, and that by their presence they contribute to the maintenance of the meningitis (Rich & McCordock, 1933). Further, in all the cases, many small proliferative and caseous lesions, rich in tubercle bacilli, can be seen in the depths of the cerebral sulci which have been closed superficially by the hydrocephalic flattening of the convolutions. There is no doubt that from all these sources tubercle bacilli must have been liberated through tuberculous sinuses into the leptomeninges, but that these streptomycin-sensitive organisms should have induced progressive lesions in meninges apparently bathed in streptomycin-containing fiuid is a fact difficult to reconcile with the involution of tubercle follicles elsewhere in the body. Baggenstoss and his colleagues (Baggenstoss *et al.*, 1947) were favourably impressed by the absence of meningitis in two of their cases, although tuberculomata were present in the brains of these patients ; but they

comment also on one case, a child, who was treated intrathecally as soon as signs of meningitis developed, and yet failed to show evidence of healing of the meningeal lesions. Obviously the bacteriostatic action of streptomycin in tuberculous meningitis is exposed to limiting factors, possibly anatomical or perhaps related more directly to the extent of the lesion before treatment begins.

Hyaline degeneration of splenic arteries. In Cases 1, 2, 3 and 4, the splenic arterioles and in particular their penicillar branches show this change in varying degrees, Case 2 being the most marked. The hyaline material is easily seen as eosinophilic plaques or rings (Figs. 3 & 4) in haemalum and eosin preparations, and it stains brilliantly with phloxine by Lendrum's phloxine tartrazine methods (Lendrum, 1939, 1947). It does not give the amyloid reactions, nor does it stain with Scharlach R ; the material is not refractile when viewed by crossed Nicol's prisms. For the most part the intima only is affected, and the internal elastic lamina remains intact, but in some vessels almost the whole thickness of the wall is involved. The earliest change in the intima seems to be the appearance next to the internal elastic lamina of amorphous eosinophile material which increases in amount until a ring or plaque is formed. In the media, nuclear fragmentation precedes the hyaline change and ultimately empty spaces replace the nuclear sites ; this may be due to a secondary pressure effect from an intimal plaque, but where the whole thickness of the vessel wall becomes hyaline apparently simultaneously, loss of nuclear staining precedes the hyaline change. Considerable narrowing of the lumen results but even when it is a crescentic slit, the endothelium is intact.

The literature of this subject is somewhat scanty. Hyaline degeneration of splenic arteries was described by von Recklinghausen (1883) in his general pathology of blood vessels, and Vallat (1892) had noted the occurrence in splenic tuberculosis but in ' normal ' (*i.e.*, non-tuberculous) areas and not limited to blood vessels. Stilling (1886), Herxheimer (1917), Matsuno (1923) and Nakonetschny (1923) all give descriptions of the condition, and their observations show that the degeneration may involve all calibres of splenic arteries—trabecular, precapillary, penicillar and follicular—and that the material occurs as a plaque or ring internal to the elastic lamina with resultant stenosis ; in some deposits there are droplets stainable by *Scharlach R.* The media is seldom affected primarily but rather by extension of the process ; it may atrophy secondarily. The condition appears to increase in frequency directly with age, and in subjects over 40 years it is a common accompaniment of generalized arteriosclerosis ; but even in advanced age, the splenic arterial degeneration can occur without generalized arteriosclerosis. In younger subjects (10 - 40 years) the lesion is much less common, and occurs usually without any other vascular degeneration ; chronic tuberculosis

is the cause of death in many of the published cases. Eppinger (1920) found hyaline change in a high proportion of spleens from cases of pernicious anaemia and haemolytic icterus, and regarded the change as characteristic of these conditions. Later writers dispute this claim: Matsuno (1923) and Nakonetschny (1923) consider that from the distribution of the lesion it is probably related to the particular functional activities of the splenic vessels and especially of their penicillar branches.

All authors are agreed that hyaline disease of the splenic arteries is exceptional in childhood and the routine examination of spleens from unselected post mortems in this hospital confirms the view. The condition has been reported, however, in acute deaths from diphtheria in a child of 1 year and scarlet fever in a child of 18 months and also in a 3 years old girl and a 5 years old boy who died 1½ days after severe burning (Henke & Lubarsch, 1927). These authors believe that in such cases the degeneration follows acute swelling of the intima of the vessels. In two spleens removed from children with acholuric jaundice, Cappell (1947) has observed similar hyaline arterial change to a marked degree. This degenerative change in these four cases of miliary tuberculosis is of some interest if only because it is an uncommon finding in children's spleens. It is not suggested that the degeneration is due to streptomycin; certainly it is not related to the amount of streptomycin exhibited, since Case 2, in which the change was most marked, had only half the amount of streptomycin of Case 4, in which the arterial lesions were only moderate in degree. But it is known that hyaline degeneration can affect the splenic vessels in chronic tuberculosis in young adults, and in the children reported here, streptomycin had transformed an acute miliary tuberculosis into a chronic type. Unfortunately, the acute course of miliary tuberculosis in childhood prohibits suitable control tissues from untreated cases, but it may be inferred that the hyaline change in the splenic arteries is the result of the unusually prolonged tuberculous process, and in this respect is analogous to amyloid degeneration from which, by staining reactions, it is otherwise quite distinct (Nakonetschny, 1923).

CONCLUSION.

The most remarkable feature of this group of cases is the persistence of progressive meningeal lesions due to streptomycin-sensitive organisms while in general the systemic foci of tuberculosis showed evidence of regression. It would appear that this paradoxical situation must be related to environment rather than to the micro-organism itself, that at a certain stage the local tissue reaction prevents the direct contact between the chemotherapeutic agent and the infecting organism. Accordingly, the pathology of fatal cases adds weight to the plea for earlier diagnosis so that treatment may begin before irreversible tissue changes occur.

SUMMARY.

Six fatal cases of streptomycin-treated tuberculous meningitis are described and discussed, especially with regard to the coexistence of proliferative meningeal and healed systemic miliary tubercles. Reference is made to hyaline degeneration of the splenic arterioles.

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