THE PATHOLOGICAL CHANGES IN PELLAGRA AND THE PRODUCTION OF THE DISEASE IN LOWER ANIMALS.

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(With Plates IV and V.)

Almost from the time when pellagra was first described, a connection between the disease and maize as an article of diet has been noted, and a wordy and voluminous literature has arisen in the countries afflicted concerning the nature of this suggested relationship between maize and pellagra. Most of what has hitherto been written about pellagra is based upon observations on clinical material and epidemics. Probably the most neglected side of the disease is its morbid anatomy and histology; and the effects of feeding animals on preparations of maize are but scantily described.

My description[1] of the pathology of this disease is based on notes of eight post-mortems and microscopical sections of specimens taken from these subjects, and also on observation on an identical condition produced in rats by feeding them on the products of decomposing corn-meal.

It is evidently necessary that the pathological changes in the human being should be well ascertained before an attempt is made to compare them with the changes induced in animals.

In all these cases which I am considering the clinical picture was complete, but though dementia was present in every one of them, in the majority there was little indication of degeneration of the peripheral nerves.

Firstly the condition of these patients during life may be briefly

[1] The experiments described in this paper were carried out in St Lucia, B.W.I. The preparation of the microscopical sections etc. was done in the Quick Laboratory, Cambridge, by the kind permission of Prof. Nuttall, F.R.S.

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summarised. All were mulattoes belonging to the lower classes, and though none were white skinned several were relatively light coloured. Five of them were women and three were men, and their ages ranged from twenty-six to seventy-two. From the time when they first came under observation until death their temperatures were usually normal, and a rise up to 100° Fah. occurred only for a short time in one or two cases.

A superficial eruption on the dorsal surfaces of both hands had been present in all cases, and in several there were eruptions on other exposed parts of the body such as the ankles, shins, forearms, face and the back of the neck. A progressive and extreme emaciation was exhibited by all of them. Several had tremors and loss of knee-jerks. The curious, morose and irritable dementia which is almost pathognomonic of this disease was present in all.

They complained of soreness of the mouth and this was due to irregular exfoliation of the epithelial layer of the mucous membrane of the tongue and buccal cavity, which in two cases extended to ulceration at the angles of the lips. Loss of appetite and persistent diarrhoea usually extended through the course of the disease. In the later stages of these cases shrinkage of the liver and spleen could be easily demonstrated.

Traces of albumen and blood corpuscles in the urine occurred in one or two cases.

Two cases had eczematous ulceration between the thighs.

Post-mortem examinations.

The changes found in the bodies after death were of a very definite and uniform nature.

External appearances. All the bodies were extremely emaciated, three of them, notably two women aged thirty-two and thirty-four and a man aged twenty-six, had reached a stage of emaciation not often seen even in the post-mortem room. (These patients had been well cared for in a government institution for at least six weeks.) In each case soreness of the mouth and lips, and an eruption on the exposed surfaces were noted. Two cases, a woman and a man, had exfoliation of the skin between the nates, and this extended down the inner surfaces of the thighs.

Internal examination. On cutting through the skin of the thorax and reflecting it, an almost complete absence of adipose tissue was found, and extreme wasting of the muscles was noted.

Pleurae. In four examinations the pleurae were normal. In three there were a few old adhesions between the visceral and parietal layers. One case showed a few petechial haemorrhages on the pleural surfaces.

Lungs. In two autopsies the condition was normal. In two others there was oedema of the bases. One case showed marked hypostatic congestion, and one patient had died of a terminal pneumonia. Tuberculous areas were present in two cases, but in neither had the condition advanced so far as to produce caseous foci. The microscopical examination showed no changes which could be associated with the disease.

Heart and pericardium. The latter in several cases was of a dull appearance and slightly thickened; the thickening was confirmed by microscopical examination.

In most cases the heart was atrophied as evidenced by the loss in weight (*v.* chart). In one patient the heart appeared enlarged and was dilated, the muscle having undergone fatty degeneration.

Sections demonstrated that there was an increase of fibrous tissue in these hearts and a varying degree of thickening of the walls of the arterioles. In all cases the muscle fibre exhibited brown atrophy.

The aorta and the large vessels. In the three cases in which the patients were under thirty-five years of age, no pathological changes were noticed in the large vessels, the intima being entirely free from any signs of disease. In the two patients aged forty-three and forty-four respectively, there were a few areas in the aorta just above the semilunar valves which showed early degenerative changes; but the carotids and axillary arteries were free from disease.

In the three older patients more or less extensive arterio-sclerotic and atheromatous changes had taken place in the larger vessels.

The peritoneal cavity. The fat in the omentum and mesenteries was reduced to a minimum; the omentum being as thin and friable as tissue paper.

The liver. This organ was much reduced in weight; the average in seven cases in which the scales were used was 37½ ozs.; a very low weight, considering that the average for an African is 52 ozs. and for a European a little more. One of these patients was a heavy mulatto who, previous to this illness, had scaled 160 lbs.; his liver weighed 35 ozs. In all the cases the section of the organ was of a dull mottled colour, but showed neither the nutmeg phenomenon of venous engorgement nor the iodine staining of amyloid disease. Very advanced fatty degeneration had taken place in two patients. In all cases, however, the tissue of the organ showed increased resistance to the knife. There were petechial

haemorrhages under the capsule in some cases, and certain dark spots in the substance which were probably due to small haemorrhages.

Microscopical examination showed fatty degeneration, but only in two cases did this reach an extreme condition (Fig. 4).

In the older and more chronic cases there was an increase in the fibrous tissue around the vessels, and this was accompanied by great thickening of the vascular walls. In places there were areas of venous engorgement. There were general atrophy and degeneration of the liver cells, and often a considerable amount of pigment was present, possibly derived from previous small haemorrhages, for these were occasionally seen among the liver cells.

The spleen. The shrinkage of this organ was phenomenal, especially when it is remembered that all these patients belonged to malarial localities and must have suffered from attacks of malaria. In seven cases in which the organ was weighed, the highest was 5½ ozs. and the lowest was 7 drachms; the average weight was just under 3 ozs.!

The section of the spleen was very dark in colour, and in most cases the fibrous structure appeared to be increased. The tissue was resistant and tough.

The whole condition and appearance of the organ was the very opposite to what occurs in febrile infectious diseases.

The microscopical examination showed that the fibrous tissue of the capsule and of the splenic pulp was increased, and that the arterioles were thickened.

In some cases numerous haemorrhages from the finer vessels produced a very extraordinary condition, since in every field of the microscope the number of free red blood corpuscles far exceeded the number of splenic cells. Moreover, numerous small masses of pigment bore witness to the fact that these haemorrhages had occurred frequently.

The kidneys. Very little change in the kidneys was noticeable, but the organs were decreased in weight. In fact, compared with the obviously advanced degeneration of the liver and spleen, the comparatively natural condition of these organs was striking. In the two oldest patients early granular changes were present.

The suprarenals. In several cases these were very friable but were not shrunken. They did not appear to have taken part in the general wasting of the organs of the body.

The stomach. In all cases the walls of the stomach were thinner than usual. In two cases the organ was considerably dilated. In one case the contents were darkened by altered blood which had come from

two or three minute superficial ulcerations. In several cases minute petechial haemorrhages were present in the mucous membrane.

Normally the muscular coats of the stomach occupy a little more than two-fifths of the thickness of the wall of the viscus, in pellagra they are reduced to about one-third. There were a few areas of capillary stenosis in the mucous and submucous coats and occasional places where diapedesis of red blood cells had taken place.

The small intestine. The wall of the bowel was atrophied and the valvulae conniventes were thin and shrunken, in some cases having almost disappeared. In places the bowel wall was very friable. There were petechial haemorrhages of areas throughout the small intestine, and these were more pronounced the nearer one approached the ileo-caecal valve; in some places where they were in the mucous membrane, the condition somewhat resembled a surface which had been sprinkled with cayenne pepper. These haemorrhages also occurred in the serous covering of the bowel and a few even between the muscular coats. The mucous membrane was, in places, very superficially eroded and had a roughened appearance. The small haemorrhages and the erosion were most marked on the valvulae conniventes.

The large intestine. The condition was similar to that seen in the small intestine, but more exaggerated. In one or two places the mucous membrane was deep purple in colour, owing to the enormous number of capillaries, and small haemorrhages from them.

A single deep ulcer in the rectum was present in two cases.

The microscopical changes in the intestinal tract were of the same nature throughout, but increased in intensity from above downwards.

The atrophy of the muscular coats was such that they occupied about half of the thickness of the bowel wall, whereas normally they occupy about five-sevenths of the thickness of the jejunum and ileum. The mucous membrane was also wasted, and accentuated the muscle atrophy. The villous processes of this coat were very greatly degenerated, and where the degeneration was most advanced, the cells were almost replaced by thin fibrous tissue. Capillary stenosis was present in the deeper layers but was not well marked. In places capillary haemorrhages had occurred. Occasional areas were seen in which erosion of the mucous membrane has led to round cell infiltration and other signs of inflammatory reaction (Fig. 7).

The changes in the submucous coat consisted in an increase in fibrous tissue, degeneration and thickening in the smaller vessels, and

areas where haemorrhages have taken place; the latter occasionally caused local thickening of this coat.

The serous coat was thickened, and a few haemorrhages were present between it and the muscular coat.

The bladder. In two cases the mucous membrane of the bladder was dotted with petechial haemorrhages.

The brain and nervous system. In some cases the dura mater was thickened, and the pia mater showed irregular areas due to thickening. The convolutions of the brain were atrophied, and were of firmer consistence than normal.

In the two oldest patients the arteries at the base of the brain were sclerotic and had calcareous deposits.

Although mental symptoms are always present and many cases exhibit signs of nerve degeneration, it is only in a limited number of cases that a microscopical examination shows much pathological change. In these patients there was an increase in the fibrous tissue in the meninges and the arterioles supplying them were thickened, also the endothelium of the capillary vessels showed degeneration with a tendency to proliferation. The cortical cells of the brain were shrunken and degenerate.

Mott, Batten, Tuezek and others have examined the nervous system in cases of pellagra, and their results show that the cellular degeneration and subsequent sclerotic changes which take place in the other organs are also present in the nervous system in a number of cases. For example an increase in the neuroglial elements of the brain and a sclerosis of the posterior and lateral columns of the spinal cord have been described.

Microscopical examination of the skin at the site of the eruption. There was atrophy of the stratum corneum, with great tendency to desquamation in the exposed parts of the body; by the separation of the stratum corneum from the stratum granulorum blebs may be formed.

In the outer layers of the stratum mucosum irregular cell proliferation and some degeneration occur.

The vessels of the dermis became sclerotic, and there is capillary degeneration and stenosis; occasionally minute haemorrhages occur.

Summary of post-mortem and microscopical findings.

The accompanying table gives a summary of the post-mortem findings in these cases; in the last column the average weights of the organs in these cases are compared with the average weights of the organs of normal individuals.

	Case 1	2	3	4	5	6	7	8	Average weights in these cases.	Haran weights for Africans (usually less than Europeans).
Patient's initials...	M. P.	C. C.	A. St C.	M. Al.	G. A.	A. C.	T. A.	J. M.		
Age	34	60	58	26	43	70	32	44		
Sex	Female (Acute)	Female (Chronic)	Female (Acute)	Male (Chronic)	Male (Chronic)	Female (Chronic)	Female (Acute)	Male (Acute)		
External condition										
Eruption ...	Hands, arms, legs and face	Hands & feet	Hands, face and feet	Hands, legs and feet	Hands, feet, legs, face and neck	Hands and feet	All exposed surfaces	Hands and feet		
Emaciation ...	Extreme	Extreme	Great	Extreme	Considerable	Extreme	Extreme	Some		
Mouth and tongue	Ulcerated	Ulcerated	Ulcerated	Not as much as usual	Not as much as usual	Ulcerated	Ulcerated	Ulcerated		
Angles of mouth...	Ulcerated	Nil	Nil	Ulcerated	Nil	Nil	Nil	Nil		
Eczematous condition between thighs	Nil	Nil	Present	Present	Nil	Nil	Nil	Nil		
Internal condition										
Lungs	Nil 7 & 8 ozs.	Old tuber. lesions 6½ & 7 ozs.	Oedema at bases 12 & 13½ ozs.	Hypostatic congestion 11½ & 12 ozs.	Oedema at bases 10½ & 11 ozs.	Nil 5½ & 6¼ ozs.	Near two tub. areas 6 & 7 ozs.	Terminal pneum. 16 & 9 ozs.	9⅓ ozs.	13½ ozs. each
Pleurae... ...	A few adhesions	Old adhesions	Nil	Petechial haem.	Old adhesions	Nil	Old adhesions	Same fluid		
Pericardium										
Heart	7 ozs.	5½ ozs.	Myocardial disease 13 ozs.	7½ ozs.	9 ozs.	6½ ozs.	6 ozs.	5¾ ozs.	7½ ozs.	9 ozs.
Aorta and large vessels ...	Natural	Sclerotic	Sclerotic	Natural	A few early changes	Very sclerotic	Natural	A few early changes		
Peritoneal cavity...	Extreme loss of fat in omentum and peritoneum generally.									
Liver	Shrunken and adv. fatty degen.	Shrunken and fibrous 31 ozs.	43 ozs.	35 ozs.	46 ozs.	31 ozs.	35 ozs.	41 ozs.	37½ ozs.	52 ozs.
Spleen	Shrunken & very dark	1½ ozs.	4½ ozs.	1¼ ozs.	5 ozs.	1 oz.	2 ozs.	5½ ozs.	3 ozs.	12 ozs.
Kidneys ...	3½ & 3 ozs.	3 & 3½ ozs.	3½ & 3½ ozs.	2¼ & 3¾ ozs.	4 & 4½ ozs.	2¾ & 3 ozs.	2½ & 4 ozs.	4 & 4 ozs.	3½ ozs.	4½ ozs.
Suprarenals ...	Friable	Nil	Nil	Friable	Nil	Nil	Nil	Nil		
Stomach ...	A few petech. haem.	Very thin walls	A few petechial	Very thin	Nil	Atrophic	Nil	Nil		
Small intestine ...	The picture of atrophy, petechial haemorrhages, and patches of surface erosion, was the same in all cases.									
Large intestine ...	Ditto, small intestine.									
Bladder ...	Nil	Nil	Petechial	Nil	Nil	Nil	Petechial	Nil		
Meninges ...	Some thickening and in older cases, atheromatous arteries.									
Brain	Firmer than natural, and apparently shrunken in all cases.									

The pathological changes which take place in pellagra are to a great extent due to degeneration of the capillaries and smaller vessels; this gives rise to stenosis and blood stasis which cause leakage or actual haemorrhages from the weakened vessels. This explains the atrophy of the tissues by impaired nutrition, and the eruption on the exposed skin surfaces where solar radiations and possibly other factors accentuate the damage which has taken place in the vascular supply with consequent exfoliation of the stratum corneum, bleb formation from exuding serum, and pigmentation from altered haemoglobin. The tissue cells, especially those of the liver, spleen and alimentary tract are also attacked.

Assuming that the cause of pellagra is a toxin developed by micro-organisms in preparations of maize or possibly other farinaceous material, the pathological changes may be divided into three stages:

(1) The initial stage in which the toxin causes degenerative changes in the endothelium of the smaller vessels, and in the endothelial and glandular cells of the alimentary system.

(2) The acute stage in which the toxin acts in a more widespread manner, causing great damage to the capillaries and arterioles, resulting in repeated haemorrhages; it also acts upon the cells of the organs. It is in this stage that the mental symptoms and the skin eruption first appear.

(3) If the patient survives the acute stage the chronic stage sets in with great fibrosis of the arterioles and capillaries, general sclerotic changes, and much atrophy and degeneration of the cells of the spleen, the liver and the alimentary tract. The toxin may not be present in this stage of the disease, which is a natural result of the damage which has taken place in the acute stage. The eruption may disappear, but reappears on exposure to the sun. The general sclerosis of this period of the disease extends to the spinal cord and nerves, and thus gives rise to the nervous symptoms.

Three hypotheses on the etiology of pellagra at the present time attract some attention:

(1) The maize hypothesis which affirms that the disease is due to deleterious substances present in or formed in corn-meal and its products by micro-organisms.

(2) The sand-fly protozoal hypothesis which postulates that the disease is due to a protozoal organism which is carried from the infected to the healthy by the agency of the sand-fly.

(3) The third hypothesis suggests that the cause of the disease is a bacterium.

The first of these has been ably supported by Lombroso and a host of observers.

The second has more recently been brought forward by Sambon and Chalmers, who (*British Medical Journal*, Oct. 26th, 1912) actually make the following statement: "We have shown that pellagra is an infectious insect-borne disease...." Their evidence in support of the theory is of a very frail nature.

The third hypothesis has been urged by Tizzini, who, at the Italian Pellagra Conference of 1912, stated that in fifty consecutive cases he had isolated a bacillus from the blood. As in other diseases which affect the intestinal tract, blood cultures frequently give positive results due to leakage from the gut.

During pyrexial periods I have been able to cultivate from the blood organisms of the family Typhaceae.

Many attempts have been made to produce pellagra in animals, usually with little success.

Some time ago Raubitshek injected and fed guinea-pigs with extracts of good and damaged maize, but his results were negative; he also worked on fagopyrismus in animals, a disease produced by feeding animals on buckwheat, but the condition is far from analogous to pellagra. In further experiments he believes he demonstrated the presence of photo-dynamic substances in maize, which are allied to those extracted from buckwheat and which produce symptoms of disease.

He appears to lay too much stress upon the skin eruption, and to consider it the principal phenomenon of pellagra; but a toxin which produces a characteristic condition in one animal may be poisonous to another without its most marked symptom appearing. Thus in ergot poisoning the typical gangrene is absent when experimenting with such animals as rats, yet they may die of the poison.

Lombroso experimented with spoiled corn and extracts of it and numerous bacteria obtained from corn. Injections of *Bacterium maidis* (of the potato bacillus group) into white mice produced paralysis, coma and death. Cultures of this organism on polenta, the Italian maize bread, when given to mice produced diarrhœa and other symptoms referable to the alimentary system.

Lombroso and other investigators have produced symptoms resembling pellagra in chickens fed on spoiled corn. It is a well-known fact in certain tropical regions that feeding fowls on mouldy corn frequently causes their death. (I once made a post-mortem on a fowl

which had died after being fed on damaged maize, and the liver, spleen and intestines exhibited many lesions analogous to those seen in the bodies of human beings who have died in the acute stage.)

Hauseman, Erba, Tirelli, Pelizzi, Gosio, Fenati and other Italians have produced disease in fowls and other animals injected with maize extract, or mouldy corn-meal.

Lavinder fed animals on normal corn-meal for several months without producing symptoms of disease.

Anderson and Goldberger have attempted with practically no result to produce pellagra in monkeys by the injection of the blood or spinal fluid of patients suffering from the disease.

Babes and Manicatide describe experiments which they believe demonstrate that the blood of pellagrins can neutralise the toxins found in spoiled maize.

To expect that the exact picture or all the signs and symptoms which occur in man will be obtained in these experiments is to expect what is improbable. If, however, it can be shown that a certain organism or a material produces an analogous condition leading to the death of the animal, and the post-mortem and microscopical examinations show similar changes, evidence of the cause of the disease in man is afforded.

The production in rats of a condition similar to pellagra.

In September last I obtained two three-quarter grown rats of the same litter; they were placed in the contiguous compartments of the same cage. Their food was prepared in the same vessel, and into one half were stirred various preparations of decomposing corn-meal; this was given each day to one rat, whilst to the other was given the wholesome moiety.

The cage was of wire and was placed in the sun for about two hours each day, so that each rat enjoyed the same amount of sunshine.

By the sixth day of the experiment the condition of the two animals was very different. The one which had taken corn-meal had lost weight, its coat was staring, it was weak in its gait and crouched trembling in the corner of the cage; the consistence of its stools was very soft. The other rat remained normal. The administration of corn-meal preparations was stopped for two days and then recontinued. On the tenth day the bare skin of the ears and legs started peeling and became darker than in the normal rat; this eruption did not reach a very advanced stage, for the rat died on the 14th day. The control animal remained healthy.

Post-mortem. The lungs were normal, but the heart was of an irregular colour.

The liver was in an advanced stage of degeneration, being pale and friable with small patches of blood-red colouration, which appeared to be due to recent haemorrhages. There was not much alteration in the size of the organ, when it was compared with that of the healthy rat which had been killed for comparison.

The spleen was dark coloured, being blackish red; it was smaller and firmer, yet more friable than in the healthy animal.

The kidneys were paler and softer than normal.

The mucosa of the stomach showed one or two petechial haemorrhages.

The intestines were very friable, and there were areas of congestion and numerous haemorrhagic spots throughout their length.

Five other rats were similarly fed, three more being kept as controls:

(No. 1.) A small rat died on the 8th day, and the post-mortem showed a similar condition to that described above.

(No. 2.) This rat, which showed some signs of disease, escaped on the 9th day.

(No. 3.) The third rat died on the 31st day of the experiment, and atrophy, minute haemorrhages, and degeneration of the abdominal viscera were observed at the post-mortem.

(Nos. 4 and 5.) These were killed on the 34th day. One of them was seriously ill, but the other, in comparison, exhibited very few symptoms in life, or pathological changes at the autopsy.

The three control animals had remained healthy.

Microscopic examination of these rats.

The lungs showed no changes. The heart muscle in two cases showed fatty degeneration. In other rats there were haemorrhages between the muscle fibres.

The smaller vessels of the liver showed degeneration, and there were numerous haemorrhages among the liver cells.

Fatty degeneration was present in the glandular cells of this organ.

There was an increase in fibrous tissue in the spleen; numerous haemorrhages had taken place from damage to the arterioles and capillaries. There was a degree of pigmentation present which exactly compared with that which is seen in sections from human subjects who have died of pellagra.

The intestine showed some haemorrhages, but did not exhibit the same degree of degeneration and atrophy which are seen in human cases.

Thus practically all the changes seen in the organs of human pellagrins were present in the organs of these rats; but the advanced arteriole thickening and extreme atrophy and cellular degeneration of chronic human cases were absent.

The corn-meal used was prepared in three ways:

(1) It was boiled with water and the resulting paste allowed to become sour in the laboratory.

(2) Samples were moistened and allowed to remain open in the laboratory.

(3) Cultures of organisms which are present in damaged maize were mixed with moistened corn-meal and incubated for thirty-six hours.

Portions of these preparations were mixed with the food which was given to the rats each day.

These preliminary experiments show that corn-meal acted upon by various micro-organisms develops toxins which may produce in animals a condition analogous to pellagra in man. Though several organisms and active principles can be isolated from soured maize, the exact nature or relation of these to the disease has not yet been worked out.

EXPLANATION OF PLATES IV AND V.

PLATE IV.

Fig. 1. Section of the spleen of a rat which had been fed upon preparations of maize meal. The lower part of the photograph shows masses of red blood cells derived from haemorrhages. Line *A* points to the centre of a light coloured haemorrhagic area.

Fig. 2. A portion of the same section enlarged to show the small haemorrhages among the splenic cells.

Fig. 3. A section of human spleen from a chronic case. Note the general fibrosis and obliteration of small vessels with thickening of the larger arteriole. *A* points to a mass of red blood cells (when highly magnified red blood cells are seen to be very numerous).

Fig. 4. Section of liver showing extreme fatty degeneration; the most advanced condition of this type of degeneration met with in the series of human cases.

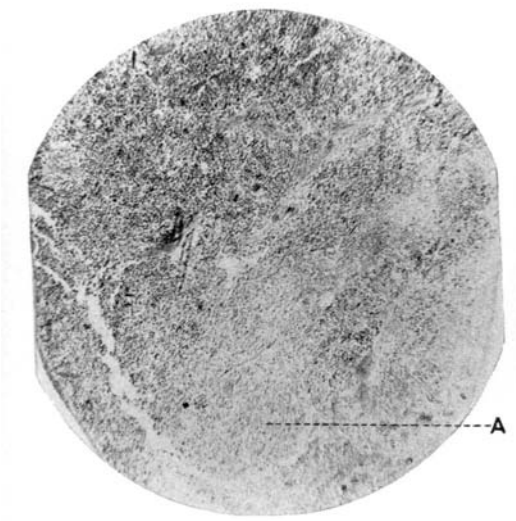

Fig. 1.

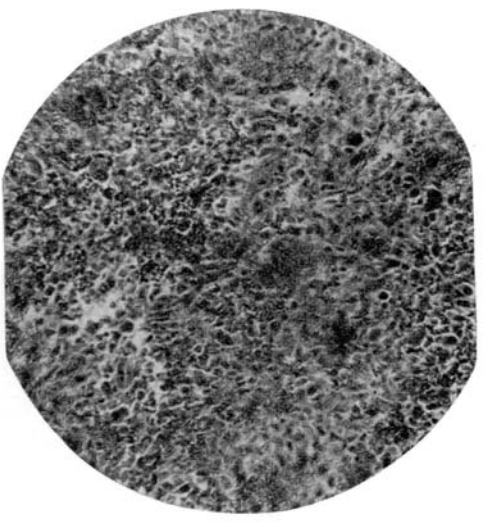

Fig. 2.

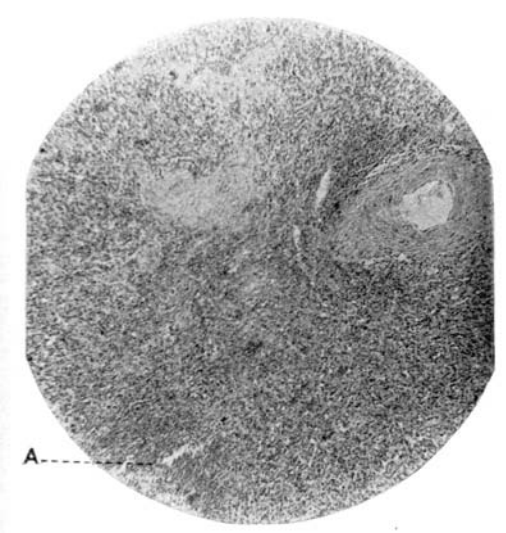

Fig. 3.

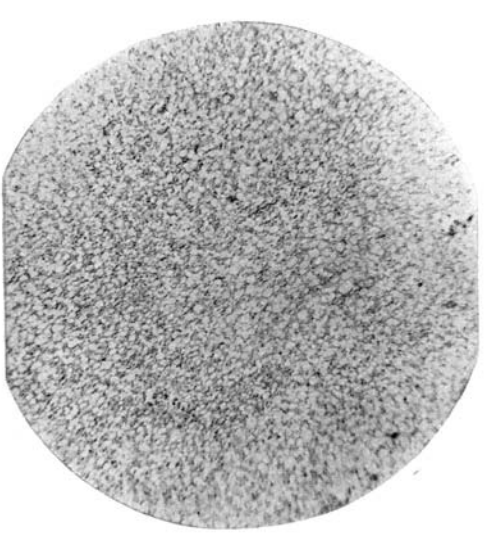

Fig. 4.

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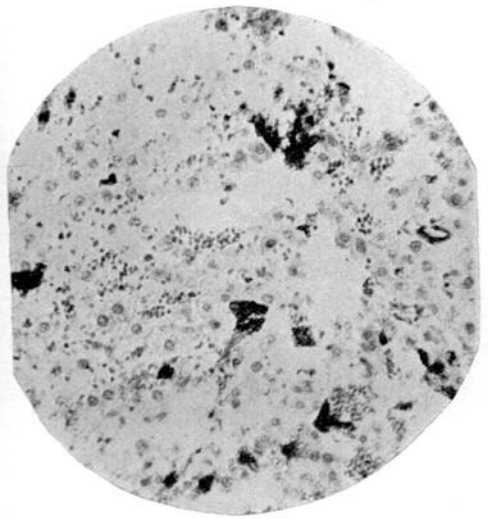

Fig. 5.

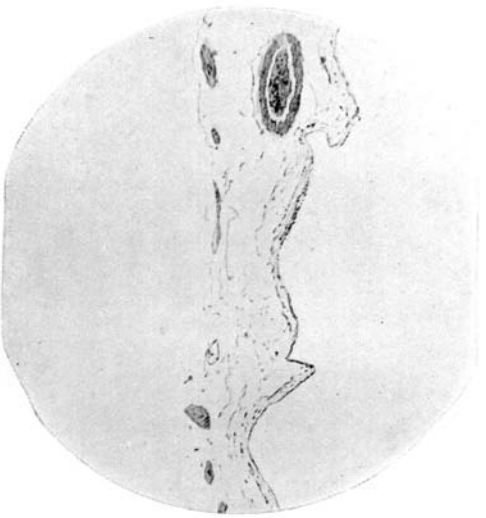

Fig. 6.

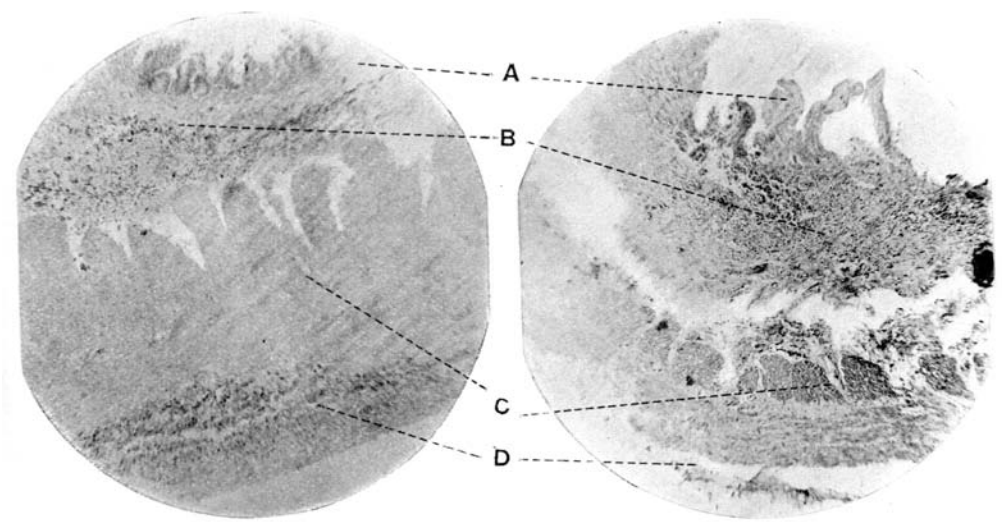

Fig. 7.

Fig. 8.

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PLATE V.

Fig. 5. A section of a rat's liver, in which the parenchymatous structure has been broken up by haemorrhages. Masses of pigment are present, and the liver cells show degeneration.

Fig. 6. A section of the pia mater from a human case; this shows thickening of the small vessels and capillaries. The vessels are stenosed.

Figs. 7, 8. Sections of intestines from two human cases.

A. Points to the atrophic and degenerate mucous membrane. Note the absence of nuclear staining in the villous processes of 7.

B. Points to the submucous coat. In 7 there is a thickened arteriole and to the left of this the coat is swollen by a haemorrhage which has left pigment and degenerate red blood cells. In 8 there is an area of round celled infiltration extending to erosion on the mucous surface.

C. The degenerate and atrophic muscular coats; note the vacuolation present in the fibres.

D. The thickened serous coat. In 7 it has been enormously thickened by a haemorrhage.

These two sections were taken from parts of the small intestine where the changes were most marked.

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