Appendix to Thesis

on Infarcts of the Kidney

by Duncan Forbes.
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A Summary of Litten's Paper.

"UNTERSUCHUNGEN ÜBER DEN HAEMORRHAGISCHEN INFARCT UND ÜBER DIE EINWIRKUNG ARTERIELLAR ANAEMIE AUF DAS LEBENDE GEWEBE.

Berlin, 1879.

In his preface Litten points out the very great difference in the powers of resistance of various cells to arterial anaemia, for instance, while the secreting cells of the kidney necrose completely if deprived of blood supply for two hours, the periosteous cells withstand a two-days anaemia.

In Chapter I. he considers the conditions of circulation in the kidney - spleen - lung.

He ligatured the renal vein in the rabbit and found:—increase in weight (twice as heavy) also in size. The colour became dark violet to black and the kidney felt firm and hard to the touch. There appeared on section subcapsular haemorrhage and also smaller haemorrhages throughout the cortex and medulla. In the medulla these were very regularly arranged.

After/
After from 15 to 20 minutes ligature of vein there was blood extravasation. Every capillary became crowded with red blood-corpuscles, the outlines of which, although at first distinct, were gradually lost and there remained solid cylinders in the blood vessels. In the periglomerular space there was blood extravasation, compressing the glomeruli more or less. The lymph space around the glomerulus was also crowded with red blood corpuscles in three or four layers. The capsular veins gradually enlarged and formed venous channels which join the lumbar and suprarenal veins. The kidney never perfectly recovered and far more frequently atrophied. In the first quarter of an hour there was rapid increase in size; within two hours the maximum was reached. Secretion soon ceased and stopped before the kidney reached its maximum size. After two hours the affected kidney weighed 15 grammes.

Litten now goes on to compare the effects of ligature of both renal artery and vein and ligature of renal vein alone. He tied the renal vein of the left side, stripped off the fat capsule, and tied ureter; so that there was only a blood supply from the renal artery; on the right side he tied both artery and vein.
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<th>Left Kidney.</th>
<th>Right Kidney.</th>
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<tbody>
<tr>
<td></td>
<td>(vein tied)</td>
<td>(both artery &amp; vein tied.)</td>
</tr>
<tr>
<td>2 hours later: Weight</td>
<td>15.5 grammes</td>
<td>13.5 grammes</td>
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Original Weight -- 6 to 7 grammes.

In another experiment on the left side the renal artery and vein were both tied.

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<th>Left Kidney.</th>
<th>Right Kidney.</th>
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<tbody>
<tr>
<td></td>
<td>(untouched)</td>
<td></td>
</tr>
<tr>
<td>2 hours later: Weight</td>
<td>10.4 grammes</td>
<td>6 grammes</td>
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In two experiments in which the artery and vein were tied for a quarter of an hour and two hours before rabbit was killed, he found in the

\[
\frac{1}{2} \text{ hour experiment:} \quad 1.8 \text{ grammes gained in weight}
\]

\[
\frac{5}{2} \text{ " "} \quad 5 \text{ " " " " " "}
\]

Occasionally haemorrhages occurred under the capsule and all the vessels were dilated enormously.

The tubules were filled with blood and haemorrhages were seldom absent in Bowman's capsule.

In one rabbit the artery and vein were tied on both sides and the left splanchnic nerve was cut. The animal was killed one hour later.

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<th>Left Kidney.</th>
<th>Right Kidney.</th>
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<tbody>
<tr>
<td>Weight</td>
<td>9 grammes</td>
<td>7 grammes</td>
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So there is a more rapid gain in weight on the side on which the collateral vessels are artificially dilated.

So Litten shows that after ligature of renal vein the whole increase in weight is not due to blood derived from the renal artery, for if that blood supply is cut off, we still get nearly equal increase in weight in two hours. This increase in weight when the renal artery and vein are tied is not so rapid, as in the case of ligature of vein alone, in the first quarter of an hour.

Litten then refers to Ludwig's paper(1) which points out the principal arteries from which the renal collateral vessels come e.g., suparenal, phrenic and lumbar, but they are also derived from the ureter, for when both renal artery and vein are tied and the capsule is stripped there is still increase in weight; while if renal artery, vein and ureter are tied and fat capsule stripped the kidney remains the same size; while if ureter along with renal artery and vein are tied there still is increase in weight. Atrophy follows the ligature of renal artery and vein. The branches supplying the ureter are branches from the renal artery itself also branches from the spermatic artery. The vasa vasorum of the renal vessels supplying vessel coats which/
which become continuous with the true capsule must be included.

After the ligature of the renal artery alone hyperaemia begins in the medulla and is most intense at the base of the pyramids the medullary tubules are sometimes filled tightly with red blood corpuscles.

The renal arteries were considered end arteries and it was supposed that hyperaemia was due to a backward flow from the renal vein. After the ligature of the renal artery the kidney still receives a blood supply from collaterals and the blood from these is always sufficient to prevent any backward flow from the renal vein. Parts of the kidney are supplied with circulating non-stagnant blood for there are parts which still functionate after the renal artery is tied. When a watery solution of indigo sulphate of soda is injected into the jugular the epithelium of many convoluted tubules are coloured by it and have blue contents in lumen. The collaterals therefore by their supply to certain parts of the kidney perfectly preserve the integrity of those parts at least for a time.

(In no kidney in which there was complete ligature of the renal artery did I find any normal cells in the convoluted tubules at any time. As mentioned above there were areas supplied with blood just under the/
the capsule and more especially in region arches but in these regions although cells of the convoluted tubules appeared healthy still they had lost their uniform staining with eosin, and what eosin staining there was, was in fragments.)

The most conclusive experiment done by Litten, to show that venous backflow is not the cause of the hyperaemia which occurs after ligature of the renal artery are those in which he tied everything going to the kidney excepting the vein and also stripped the capsule, leaving the kidney connected to the body only by the open vein. In such cases when one would expect the condition to be most favourable for reflux we have at most only a slight hyperaemia.

Also if renal artery be tied and kidney be cut it bleeds, if thereafter the renal vein be tied bleeding continues, but if strip capsule and tie ureter bleeding stops at once.

Why do capillaries and small veins become dilated and their lumens crowded with red corpuscles while the renal vein remains patent? It is difficult to reconcile this with hydrostatic principles. If kidney vessels were rigid tubes equal amounts of blood would enter and leave the kidney.

The commonest site of hyperaemia is at the base of the pyramids. Ludwig has also noted this fact.
7.

If we had no collateral supply coming to kidney, then, after ligaturing the renal artery the blood in the distal arteries would be driven on by their elasticity and contractility through the capillaries into the veins. The flow would stop when the blood pressure in the capillaries was equal to that in the veins. On any increase of pressure in the venous system there would be a backflow into the capillaries. But there is a continuous flow of blood into the kidney from collaterals. Near the surface of the kidney the supply to capillaries is direct from collateral arterioles and we have the veins of the capsule offering a ready channel by which such blood can escape. The blood in the medulla, on the other hand, has a longer venous system to pass through before it reaches the renal vein. There is also much less pressure in the capillaries in the medulla, for they do not receive their supply from arterioles as the surface area does, but have only blood which has already passed through capillaries, reaching them. Litten concludes that to maintain the normal circulation in a part, the full arterial pressure of the supplying artery is necessary; if this is absent resistance is not overcome and blood accumulates in capillaries and veins, the walls of which have no powers of resistance and become passively dilated.
In Chapter II. Litten discusses the haemorrhagic infarct. Cohnheim's view was that when an end artery was ligatured there was, owing to arterial anaemia, a disintegration of the walls of capillaries and small veins. Then there came a backflow of blood into the part from the vein and on account of the abnormal permeability of the vessel wall diapedetic haemorrhages were produced. These along with the necrosis of tissues following arterial anaemia gave rise to the haemorrhagic infarct.

In kidney, as shewn in experiments in first chapter, after ligature of renal vein haemorrhage occurred which is easily explained, considering that blood was forced into small vessels from which it could not escape. After ligature of both artery and vein, bleedings occur for the same reason. But why should there be haemorrhage when only the artery is ligatured and the vein remains patent? Are haemorrhages due to venous backflow? Certainly not, as when the artery is tied and the kidney is left connected to the body by the renal vein alone such bleedings do not occur. We must seek the cause on the arterial side. A branch of a dog's renal artery was bound and there was found a haemorrhagic infarct in the part supplied by that branch. In another/
another case a branch of the renal artery was bound at the hilum but the sinewy capsule was stripped from the section supplied, and the ureter and neighbouring branches of the renal artery were ligatured and infarction did not occur. It is therefore apparent that haemorrhage is due to the collateral supply.

The hyperaemia following ligature of the renal artery Litten regards as a stasis hyperaemia, brought about by the taking away of blood pressure, which allows the blood to be heaped up in the capillaries and small veins. These become so much dilated as to be permeable by plasma and corpuscles. The stronger the circulation in the embolised area the more readily will the blood be able to gain the veins. This accounts for the frequent absence of haemorrhage in embolised parts. At the same time, everything which adds to resistance increases haemorrhage so that if the vein leading from the part be impervious we get infarction greatest. One ought not to consider haemorrhage infarct as due to blockage of the vein, which is Blessig's view\(^{10}\), as in a very great majority of cases the vein was found patent. When the vein is blocked infarction occurs in higher degree; this shows that venous backflow is of no account.

Cohnheim mentions one case in which after the renal artery was bound there was thrombosis of the vein and no infarct followed. Some argue that infarcts seldom happen in the extremities because of the presence/
ence of vein valves. In these there is such a rich anastomosis that there is sufficient pressure from collaterals to drive blood on through the capillaries.

(11) Litten has recorded one case, however, of haemorrhagic infarct from embolus in the axillary artery.

Cohnheim by direct observation of the tongue of the frog observed haemorrhage by diapedesis after ligature of the lingual artery. This, he held, was due to a molecular change caused by temporary ischaemia. He reasoned, similarly, in cases where he tied the renal artery and vein temporarily (1½ - 2 hours). The kidney was slack and pale grey until he untied the ligature, after which in a few hours it became crammed with blood and twice the size of the normal kidney. If the hyperaemia and bleeding be due to a molecular change produced by ischaemia, why does haemorrhage take place almost immediately after the artery is bound, and why do the haemorrhages not appear at all when the ligature is removed after 2, 3, or even 4 hours application (in the latter the capsule is stripped and the ureter bound to prevent collaterals giving rise to haemorrhages.)

After temporary ligature of the left renal artery for 1, 2 and 4 hours and injection of cold saturated/
saturated solution of indigo sulphate of soda into a vein blue urine came from the right ureter; then ligature was untied and the animal was allowed to live several hours. Litten never found indigo in an unusual place for instance in the periglomerular space, although the blood in the kidneys was coloured blue. Such a result is scarcely intelligible if the capillaries of the glomeruli were abnormally permeable. Litten has tied the splenic, renal and pulmonary arteries for 3 - 4 hours and after untying the ligature has had no bleeding. He also tied temporarily the mesenteric artery for two hours in the dog and got diapedetic haemorrhage, but had the same result from simple exposure mesentery for that time. The haemorrhage of first few hours was due to a mechanical cause. Even where an end-artery is blocked there are communicating capillary collaterals from which there is an inflow of blood into the end-artery's sphere, but there is not sufficient vis a tergo to drive the blood through the capillaries into the veins, and therefore the blood accumulates in the capillaries first leading to hyperaemia and then to haemorrhage by diapedesis. Of course there is a time when we get disintegration of vessel walls from ischaemia, but after 3 to 4 hours total anaemia in any organ of rabbit, there is no disintegration of the vessel walls; for, (1) if the abdominal aorta be tied at the level of the top of the left kidney
the blood supply is completely cut off from the lower half of the body. (If there is complete closure of the aorta, semi-erection of penis is produced.) After removal of ligature in four hours there is no haemorrhage in kidney, gut, bladder, nor spinal cord. The result is the same when the inferior cava is also tied at the same level. (2) If kidney is disencapsulated and ureter is tied at the same time as the artery and vein, and if artery and vein be re-opened after four hours, circulation proceeds with no trace of haemorrhage. After a longer application of ligature the changes described by Cohnheim appear: oedema, leucocyte emigration, diapedesis of red corpuscles and ultimate stoppage of blood flow and necrosis. After 6 - 8 hours ligature we get an inflammatory and haemorrhagic condition, although no lesion of vessel wall is seen on microscopic examination. The bleedings, however, are not of the same type, being much more irregular than in common infarct of lung and spleen.

If the vessel beyond the ligature becomes impermeable and no blood re-enters, vessels may become necrotic without any anatomical expression of this condition. Often in discoloured infarct of the kidney we find necrotic parts in vessels in which nuclei have crumbled or have disappeared.
Chapter III. The influence of arterial anaemia on living tissue.

(1) If one stops arterial supply, atrophy of the organ follows from a simple necrosis. If the organ is exposed to the air and septic matter there may be moist gangrene.

(2) If one limits the supply of blood to an organ, fatty degeneration is caused for

(a) in cases of long standing anaemia, also by repeated blood-letting in animals, fatty degeneration of the heart is produced;

(b) fatty degeneration of the kidneys follows where aorta is narrowed (Zielonko) (3) by starvation (Manassein) (2), and also by directly narrowing renal artery as was done by Platten (4).

There is a question as to whether mortification follows anaemia, or is caused secondarily by necrosis of vessels. Litten holds the former opinion which he proves by a large series of experiments in which the renal artery temporarily ligatured for 1½ or 2 or 4 hours and rabbit killed from 1 to 42 days after removal of ligature. (Wound made in back, left renal artery tied with leather ligature, after a time ligature removed and the artery gently stroked until pulse felt in it, then wound finally closed.)

After 2 hours ligature medulla is deep violet in colour and on microscopic examination regularly arranged/
arranged haemorrhages are seen and red corpuscles are found in the straight tubules.

Twenty-four hours after removal of two hours ligature, one finds no enlargement of the kidney; the capsule strips easily and the surface is sheenless. Microscopically epithelium in cortex and often in medulla is hyaline and often melted into large scales. The nuclei of the cells are either unstained or are seen only as nuclear crumbs. In some of the epithelium small grains soluble in acid are found. The cells may lie singly in the lumen of the tubule, or form scales, or hollow cylinders, the central lumen being filled by a fibrin network. On staining with methyline, Bismarckbraun, &c., periphery is more intensely stained than centre which is fibrinous. If stain first with purpurin and then with indigocarmine get peripheral zone red and a central blue.

Necrosis and cylinder formation are most marked in cortex, less frequent in medulla and in papillary region; in these latter have necrotic tubule cells only here and there. The epithelium of the straight tubules in the medulla is in perfect condition although there may be casts in their lumen. If bleeding has occurred blood casts are found especially in the medulla. There does not appear to be any change in the glomeruli, capillaries, or connective tissue. In these there is certainly no fatty/
fatty degeneration. In the periglomerular spaces there are occasionally small extravasations which compress the glomeruli, or the space may be filled by a fibrin net similar to that in the lumen of the tubules. In all experiments in both cortex and medulla there are strips of perfectly healthy tissue while there are some zones perfectly necrotic. The healthy parts are those which have been supplied by collateral vessels during the application of the ligature. The amounts of healthy tissue vary very much. The vessels are perfectly passable in all parts, as is proved by the injection of colouring matter after death. If cold saturated solution of indigo sulphate of soda be injected some time before death and the kidney be placed in spirit after syringing out with cold saturated solution of chlorate of potash, there are found intensely blue areas in the affected kidney, which are the healthy parts, but there is no secretion of blue urine on the affected side, as there is on the healthy side. In later specimens, after the two hours' ligature, the changes already described increase in intensity, but not in extent. This is followed by atrophy of the organ along with occasional proliferation and regeneration of the epithelium. After 48 hours all the epithelium has formed cylinders. In the next day all/
all trace of the outline of the cell is gone. The central fibrin net is recognisable for a long time. The vessels which are not more permeable than normal become impassable only near and where there is shrinkage of tissue. In 30 days after temporary ligature there are still healthy parts to be found. Indigo carmine is still secreted by healthy epithelium a week after operation. Secretion of glomeruli is re-absorbed because it cannot flow away, but cells of tubules are flattened out.

In 24 hours small grains singly or in groups, are found in the epithelium which have already lost their nuclei or in the midst of scales arising from epithelium. These grains are soluble in acid and are looked upon as chalk (Kalk). When they were acted on by:

(1) Solution of potassium they become even more evident.

(2) Acetic acid, there is gas evolution and partly disappear.

(3) Salzsaure for a long time they disappear entirely.

(4) Haematoxylin and weak alkaline solutions of purpurin, the cylinders in which they lie are coloured blue.

There is no doubt that we have to deal with calcium carbonate and phosphate which is present in the cylinder as an albuminate of calcium. The calcification of the cylinders is sometimes distinct on the second/
second day and becomes so intense on the tenth day that they blunt the razor in trying to cut. The chalky parts are the necrosed parts, the intact epithelium is free from calcification, the glomeruli and vessels are not affected, and cylinders, in the healthy straight tubules in the medulla where the cylinders are surrounded by healthy epithelium are not calcified. Later the kidney atrophies and the capillaries between calcified tubules die and we get a condition in 6 - 8 weeks similar to that which was described as occurring after permanent ligature of the vein, but in the latter, calcification, if it occurred, was slight, while calcification was always a marked feature of the former.

Regeneration is attempted from the healthy straight tubules. One finds very large cells with blister-shaped nuclei and at places little pillars are pushed out forming pear-shaped stalks. In healthy kidney compensatory hypertrophy is more marked earlier in vein ligature, because glomeruli shrivel very soon and no blood can pass through the capillaries. In neither case have I found hypertrophy of the heart.

In cases where one leaves ligatures on longer than four hours even those cells which are supplied by collaterals become necrotic.

After removal of the temporary ligature kidney secretes/
secretes very slowly and in such small amount that no chemical analysis was possible, but the urine always contained albumen. The off-flow of urine is soon stopped by the cylinder formation in the secreting tubules, but also by those formed in the collecting tubules, and so we have flattening out of cells lining the upper collecting tubules.

Hermann found albumen in the urine after a temporary stop of the blood stream through the renal artery of very short duration. In temporary ligation of the renal artery from \( \frac{1}{2} \) to 1 hours, albumen appears in the urine temporarily, but gradually disappears and the secreting epithelium at the same time recovers.

Litten believes that normally, along with the constituents of the urine secreted by the glomeruli, albumen is present; but that the cells of the secreting tubules take it from the urine during its passage along the lumen of the tubules. By temporary ligation of \( \frac{3}{4} \) to 1 hour we injure those cells and take away for a short time their power of exercising this function.

A permanent result of \( 1\frac{1}{2} \) to 2 hours temporary ligature is loss of power of the epithelium of the convoluted tubules to excrete indigo-sulphate of soda. This loss of power is not found after visible cell injury/
19.
injury from ligature of ureter or injection of neutral potassium chromate. In all three there is albumen present in the urine and in the last two visible changes in the secreting epithelium. After temporary ligature no change is seen in the epithelium immediately after untying the ligature, although its function is already lost. We may therefore have cells unchanged morphologically which have lost part of their functional power, which same power is retained by similar cells which are visibly changed by other injuring agencies. In cases of 24 hours permanent ligature of the renal artery, the cells are quite dead, but the epithelium and nuclei are apparently unchanged. The epithelium shows at most only slight fatty degeneration. Those cells have died suddenly. When an animal dies we have no visible changes in the cells one day afterwards, and similarly we have none here. In temporary ligature of from 1½ to 2 hours we have the secreting cells injured by anaemia, but the circulation recontinued. The same conditions exist when the secreting cells are injured by toxic material in the circulation. In both cases although the cells are injured they are still supplied with abundant nutriment. The changes produced by the above conditions were first referred to by Weigert (5). The cells are changed to a non-nucleated/
nucleated coagulated albuminous mass. Cohnheim proposed the term coagulation-necrosis. This condition is found in small-pox (Pocken), in croup, diphtheria, and certain forms of infarct, the waxy degeneration of muscle, also chrom-nephritis, and as Litten shews, by anaemia produced necrosis of the epithelium.

Weigert thinks that either the lymph dissolves the nuclei, or, and more likely, ferment is set free on the death of the cell which coagulates the lymph and obscures the nuclei. If small living sections of the trachea be placed in a rabbit's abdomen, there is no destruction of cells, nor solution of their nuclei. If before its introduction into abdomen a similar section of trachea be dipped in alcohol, a condition of coagulation necrosis is produced. Here dead cells are placed in a damp cavity at the body temperature, which contains fibrinogen. Small parts of dead kidney if introduced into the abdominal cavity only lose cell nuclei in parts which have become adherent to the serous membrane and have obtained from it a new blood supply. After permanent complete ligature of the renal artery, there are always some parts which undergo coagulation necrosis because, although they are nourished, they are nourished insufficiently.

Coagulation necrosis also occurs in death of the cell caused by heat, trauma, or toxic material, such as/
as concentrated carbol-glycerine.

When cells are killed by anaemia, fibrin nets are formed and the cells do not excrete indigo, while in chrome poisoning the reverse holds. In both there is loss of nuclei, loss of outline of secreting cells with connective tissue and allied cells still intact.

In coagulation necrosis produced by ischaemia the albumen forms with calcium salts a comparatively insoluble albuminate and forms double compounds with indigo-carmine and purpurin. In chrome and carbolic necrosis the tissues never calcify nor combine with colouring-stuffs. Fibrinous nets are tinged on application of analin stains and are completely soluble in A. They are due to fibrin exudation on a surface on which there is not living epithelium and are not derived from blood found in urine canals, for

(a) We find neither red nor white corpuscles entangled in the network;

(b) Where haemorrhages exist we have no trace of fibrin nets present;

(c) Fibrin nets are found as early as 12 hours and if derived from blood the corpuscles could not have disappeared in such a short time.

(d) Weigert touched the surface of the trachea with ammonia in the rabbit and produced a membrane composed superficially of a finely meshed fibrin network and deeper of epithelium in scaly non-nucleated masses.

Fibrin/
Fibrin network is found only after the epithelial changes are marked and probably comes from the loss of power of the epithelium to prevent a free flow of lymph from the capillaries to a free surface.

The necessary conditions for coagulation necrosis are: (1) death of epithelium; (2) continued nutritive supply.

Calcification:— The first granules of calcium appear 24 hours after the temporary 2 hours ligature. The calcium impregnates the degenerated epithelium and becomes greater in amount as time goes on. On the tenth day the cortex is dirty grey in colour and almost as hard as stone. If one stains sections of normal kidney in acid solution of indigo-carmine, the nuclei are stained beautifully, while if instead one uses a neutral or weakly alkaline solution, the nuclei are not coloured at all. Sections from a calcified kidney are coloured intensely blue, even in neutral and alkaline solutions. This staining is confined to the cylinders. In 24 hours this staining reaction is well marked. After this, calcification increases and part stained blue decreases in area until on the tenth day the cylinders are only stained at the margins, while in other parts have uncoloured chalk.
In coagulation necrosis produced in other ways there is neither the calcification nor the blue staining with indigo-carmine which is present when the condition is produced by anaemia.

The dead cell protoplasm has evidently a great affinity for chalk salts which it abstracts from the blood, but cannot keep in solution. The conclusion that the chalk is not in the cell and simply crystallises out in its death, is warranted by the large amount of calcium deposited.

Some writers suggest that the chalk salts are deposited on the tubular epithelium from the urine, but this is not the case, for,

(a) Rabbit was fed on pearl barley and urine was kept acid, but chalk precipitate appeared all the same.

(b) Calcification of the epithelium occurs in the medulla in cases in which the great blocking of tubules must have prevented any urine getting there, even if there was filtration through glomeruli.

If decalcify cylinders still stain deeply blue with weakly alkaline indigo carmine. Either cylinders possess a greater affinity for chalk than for stain, or stain cannot penetrate cylinders on account of the chalk. Probably the latter is the correct explanation.

Strelzoff found that cartilage of growing bone stains badly with haematoxylin but after calcification, if it is decalcified before staining, it stains intensely blue. He holds that this is due
to a change in the chemical composition, which makes cartilage unite readily with chalk salts, or with neutral or weakly alkaline haematoxylin stains.

Degree of petrification in kidney varies according to operation:

Is greatest when artery is temporarily tied for two hours:
Less if artery and vein tied:
Still less if vein alone tied:
Least of all if artery alone is tied.

In the last calcification occurs only in limited areas.

In half hour temporary ligature there is no calcification following at any time, because there is no death of epithelium.

In discoloured infarcts or fibrin wedges we have circumscribed areas of coagulation necrosis caused by local anaemia. Centrally the circulation is quite cut off, therefore calcification is not found, while it is seldom absent at the periphery where the blood supply still continues although not in sufficient amount to prevent necrosis of the epithelium of the tubules. This is the cause of the broad white seams surrounding infarcts. Calcification occurs in the epithelium of tubules and cylinders derived from these. It does not occur in blood and hyaline cylinders, nor is/
is it found in connective tissue, vessels or glomeruli.

One must be careful not to universalise those conditions, as there is great differences in the results according to method of destruction of cells, even although coagulation necrosis is produced.

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Chapter IV. The White Infarct:

Return of circulation, after a sufficient interval, during which a part is anaemic, leads to coagulation necrosis of renal epithelium and thereafter fibrinous exudation into the tubules devoid of living epithelium and calcification of the cylinders which arise from the dead epithelium. Shorter periods than 1½ hours anaemia do not make certain of killing the secreting epithelium.

If the renal artery is tied and is left so until the death of the animal, there is death of epithelium in 2 hours, and by 24 hours the glomeruli and vessels are also dead. There is no urine secreted after ligature. The arteries are quite impermeable after 12 hours and between 12 and 24 hours the organ continues to waste. The surface becomes sheenless and the substance sapless, just as if it had been boiled. On microscopic examination there is little change. The outlines of the cells and their nuclei are distinct/
distinct everywhere, except at the periphery where a small blood supply is still received. The cells are much the same as they are when the kidney dies from death of the animal. After permanent ligature there are certain parts of the kidney supplied from collaterals, but these do not give sufficient blood supply to permanently nourish the epithelial cells, which consequently die. In ligature of a branch of the renal artery in the dog, if the branch is a large one, the sphere, which that branch supplied, is only nourished by capillaries at its margin. In its central part there is entire loss of blood supply. This part is clay-coloured, dry, sapless, opaque, but in microscopic examination we find the cells perfectly intact.

If a small twig of the renal artery is ligatured the collateral capillary blood supply is sufficient to provide the small section with blood and lymph, although it does not give the epithelium of the tubules sufficient nourishment to keep it alive and we have the same results in that small section as we have in temporary ligature of rabbit's renal artery for 2 hours viz., a mass of epithelium which has undergone coagulation-necrosis with the blood vessels and connective tissue still intact. These necrotic masses are sharply defined and are found in the cortex/
most frequently; they may involve cortex, and medulla also; but are hardly ever found in medulla alone. They have a more or less distinct wedge-shape, the wedge having its base towards the capsule. Through the capsule they appear as intensely white spots. On section they are ash-coloured, pale, yellowish-white to grey, of dry consistence, with a small red seam, seen with naked eye, defining them sharply from the rest of the kidney. Under the microscope those white infarcts were found to be formed in great part of epithelium which had undergone typical coagulation necrosis.

Rokitansky suggested that those pale masses were discoloured infarcts and that they always had their origin in dark red haemorrhagic masses. Beckmann\(^7\) on the other hand, held that in the majority of cases the infarct is anaemic from the beginning. This view is supported by there being no remnant of blood present in the pale infarct, and the small amount of pigment found in the urine canals and surroundings. He holds that the anaemic part is quickly marked off from its surroundings by a red seam, also, that the haemorrhage, which has lead to the name infarct, is by no means so frequent as people believe, and serious bleedings are rarities, seeing that he found nothing of the kind in 20 cases.

Weigert/
Weigert also mentions the absence of the residues which one would expect if there had been bleeding.

In both experimental and endocardial emboli, we get cylinders in the tubules composed of non-nucleated cells without outline. Here and there we find fine-meshed fibrin nets. As in temporary ligature we found that, although the epithelium died first, still, if the ligature were permanent, the vessels died at a later date, so in this case the necrosis spreads to the connective tissue and vessels, and nuclei of these and of the glomeruli disappear. Repeatedly Litten has seen glomeruli and large vessels form homogeneous flakey masses, in which there were nuclear remnants only here and there.

In the white infarct we have dying tissue surrounded by living tissue which supplies the small dying part with a minimal circulation stream, which dissolves the nuclei and provides the tissue with material, from which fibrin is coagulated and calcium is precipitated. Very frequently these infarcts only shew calcification at the periphery, where circulation is still carried on by the collaterals. Calcification hardly ever occurs centrally since only a minimal amount of blood and lymph penetrate/
penetrate there.

Why are pale infarcts raised above the surface, and why are they of a firm, dry hard consistence? There is increase in size because, not only cell albumen is coagulated, but also, cells have absorbed fibrin from the blood. White infarcts in man appear to be the same as those above described.

The condition necessary for the appearance of the white infarct is an interruption of circulation, sufficient to cause necrosis of tissue, but not sufficient to deprive that tissue entirely of nourishment. If the artery tied is too large then the central parts of the infarct are entirely cut off from nutrition.

In some of Litten's experiments of temporary ligature for two hours, there were white infarcts found after one or two days, while the rest of the kidney was in the same condition as in the other cases of temporary ligature. In those white infarcts there was a total necrosis, not only of epithelium, as in the remainder of the kidney, but of all the tissues. The presence of an embolic plug was not proved in those cases. Virchow, who has seen those often, thinks that they are due to secondary coagulation. Litten believes that they are due to tearing of intima with temporary ligature and embolus upon its removal.
White infarcts have nearly always a fringe of red, which exactly surrounds infarct on all sides. This consists of pus cells, which penetrate the necrotic tissue, following the capillaries and often surrounding the glomeruli. Close to this zone there is a haemorrhagic zone without red corpuscles penetrating infarct proper.

The stimulus of the dead tissue in the neighbourhood of living tissue is the constantly present cause of the demarcating inflammatory periphery of the pale infarct. Bacteria are frequently present. If infarct is caused by septic emboli there is a more complete breaking up of the dead part and it may be set free altogether from its connections and a sequestrum may be formed in a cavity filled with pus.

Chapter V. Résumé and Application to Pathology

Cohnheim said that the arteries of the kidney, spleen, lung and brain, are end-arteries. Litten agrees that, in kidney, spleen and lung, the branches of the supplying arteries anastomose with each other by capillary anastomosis only; but points out that those organs have other arterial supplies, so that when their principal artery and vein are tied their weight, volume and blood content increase. These independent supplies are not sufficient of themselves to/
to nourish a section from which the usual blood supply has been permanently cut off.

There is no backflow through the vein into a part which is deprived of arterial supply, for if the main artery be ligatured in kidney, spleen or lung, there is no venous backflow. After ligature of the artery we have in all three organs swelling and haemorrhagic infarction, but these are entirely due to collaterals. Nothing occurred if the organ was entirely deprived of arterial supply and left attached to the body by the vein only. In the latter experiments there is nothing in any way approximating to what occurs when the collaterals are left open.

When the renal, splenic or pulmonary artery is ligatured, the blood contained in the vessel is driven on by the vessels contractile power until equilibrium is established between the pressure of blood in the artery and the pressure of blood at the point where the renal vein joins the inferior cava. Absolute rest would not occur if the organs had no other blood supply. The collaterals supply blood to the organ, but to maintain a normal circulation in an organ the full power of the supplying artery is required to overcome the resistance of the capillaries. Blood is supplied by the collaterals, but it cannot overcome the resistance which it meets/
meets and consequently it accumulates in the capillaries. The capillaries allow the components of the blood, both serum and red corpuscles, to come through the unwounded vessel wall. So we have haemorrhage and soaking of the tissues in lymph.

Cohnheim holds that there is material injury and disorganisation of the vessel walls due to anaemia, and that, as soon as blood flows back through the vein, there is haemorrhage. It was proved that backflow in the vein could not take place because of the positive pressure caused by the inflow of blood from the collaterals. It was also proved that injury of the vessel wall from ischaemia does not take place in the short time before a haemorrhagic infarct is formed. Cohnheim held that there was such serious injury to the vessels two hours after ligature that backflow from the vein caused haemorrhage. Litten finds that after four hours temporary ligature, with return of the full force of arterial supply, there is no haemorrhage if kidney has all along been separated from its collateral blood supply.

What happens in the case of the brain and retina which have real end-arteries? Here, as in the kidney, spleen and lung, when an artery is blocked the elasticity and contractile power of the artery drives the blood on through the capillaries to the vein and this/
this flow continues until there is equal pressure in the vessels of the organ, and at the point where the efferent vein joins the next vein trunk. A backward vein-flow may take place if there is vomiting or continued coughing. If there is no such abnormal increase of pressure in the veins, haemorrhage is always absent, after the blocking of the central artery of the retina or the artery of the sylvian fissure. In neither case is there ever found such haemorrhagic infarcts as we are accustomed to meet in other organs. Haemorrhagic infarction of the retina is produced by blocking of the vein. In ligation of the artery there is loss of function and necrosis, but no haemorrhage. There are similar results in the brain following ligation of an artery.

Where veins have valves as in the extremities a backflow is impossible. Litten has found haemorrhagic infarction in such positions.

In human pathology haemorrhagic infarct is commonest in the spleen and lung. In these the wide meshed porous tissue presents the least obstruction to the flowing away of red corpuscles from the capillaries and venules. Extensive haemorrhagic infarcts in the kidney are rare. Litten has no hesitation in referring the results of arterial blocking in man to the same causes as produce/
Fibrin wedges do not follow haemorrhagic infarct.

produce them in the rabbit. He therefore says that in man infarct is due to a mechanical stoppage of the circulation. In organs with no arterial anastomosis haemorrhagic infarct does not follow the complete stoppage of arterial supply in spite of the fact that the vein is patent and permeable. In other organs where there are collateral supplies after a haemorrhagic infarct has been formed, the bleedings are gradually absorbed and ultimately there is no residue left excepting either a scar which shows on the surface as a more or less deep contraction, or a cyst. The scar on section is yellow red approaching to orange in colour. On microscopic examination the remnants of blood colouring material are always to be found. These are quite different from the intensely white collections which are so often met with in the kidney and spleen, which up to this time have been called "entfarbte haemorrhagische Herde" or Fibrinkeln. These, as we have shown in Chapter IV., have nothing to do with former haemorrhage but indicate anaemic necrosis. If the renal artery is tied for two hours, immediately after untying the ligature (apart from occasional diffuse haemorrhage) no change in structure is found. If the animal is allowed to live for 20 hours or longer after untying the ligature there is found the most intense epithelial change in/
in both cortex and medulla. There is coagulation necrosis, loss of nuclei, and the epithelium forms homogeneous masses which run together and fill up the tubules forming hollow cylinders. After temporary arterial ligature of 2 hours all the epithelium dies, except in parts where there is a collateral supply. The interstitial tissue and glomeruli remain intact in all parts. This epithelium necrosis is therefore primary and not secondary to the degeneration of vessels. Vessels are much more resistant than was formerly believed. Vessels preserve their integrity after four hours temporary ligature.

The time at which the epithelium necroses depends upon its function and normal nourishment. The greater the activity of the organ the greater is its blood supply and the more sensitive is it to derangements of circulation. If the abdominal aorta is compressed immediately beneath the diaphragm for one hour there follows complete loss of power in the lower extremities and sphincters. This power is not regained after the removal of the ligature, because the spinal cord is permanently injured. One hour's ligature of the renal artery may give rise only to a transitory albuminuria. If abdominal aorta is compressed for only half an hour/
hour the animal recovers the power in its limbs and sphincters.

One and a half to two hours ligature of the renal artery produces permanent loss of function of the cells of the convoluted tubules, whilst a total interruption of the circulation of similar duration in the testicle is perfectly recovered from. After death of the epithelium the vessels remain intact and play a most important part in the necrosis formation.

It is possible to find out the various periods of time during which various cells and organs can resist and recover from the effects of temporary anaemia. The central nervous system resists for the shortest time, while the periosteum resists for a long period. W. Strawinski\(^{(9)}\) found that 2-3 days after the death of a rabbit the periosteum gave as rich a new formation of bone as a fresh periosteum. The rôle which the vessels play in epithelium necrosis is, that they supply, to the cells injured by anaemia, the material which causes the coagulation of albuminates of the cell contents and solution of their nuclei. If a cell after injury by anaemia is not supplied with a lymph stream coagulation necrosis and loss of nucleus do not appear but only that form of cell death which is present when the animal dies. The vessels also bring the material/
material for the formation of fibrin nets within the tubules, whose epithelium is dead. Well nourished epithelium retards coagulation. An apparent exception is found in the case of the hyaline cylinders which one often finds in the tubules with healthy epithelium. If those hyaline cylinders are excepted, the rule may be laid down that all cylinders, in which thready fibrinous structures can be found, are only present in urine canals whose epithelium has been killed. Weigert shews that in the trachea croup follows the death of the epithelium and the entrance at the same time of an inflammation producing agent into the mucous membrane stripped of its epithelium. An inflammatory agent is not necessary if regeneration of epithelium is prevented.

In the kidney after temporary ligature the cylinders are composed of two substances which chemically behave differently. The peripheral sphere consists of dead and altered epithelium, while the central part is composed of a thready mass. There are two other kinds of cylinders which are not of anaemic origin:

A. Blood cylinders which consist of red blood-corpuscles in a coagulated ground mass and which may occur independently of haemorrhagic infarct.
If haemorrhagic infarct takes place in man, red corpuscles and blood cylinders appear in the urine because of the haemorrhages. If these are absent blood is still found in the urine from red corpuscles passing into the tubules from the markedly dilated capillaries. In these latter the haematuria is limited and the interstices are free from haemorrhage. Bleedings from the kidney may begin as early as \( \frac{1}{2} \) an hour after the application of a ligature. If one places a cannula in the ureter then a bleeding from the ureter is found which is explained by a stopping of the circulation and a capillary stuffing.

**B.** The second kind of cylinder is homogenous and is present in the straight tubules, mostly however, in the large collecting tubules in the medulla, but sometimes also in the straight tubules in the cortex. If the papilla is cut at right angles to its tubules almost all the lumens are found filled with glassy plugs which can be stained with carmine, haematin and analin, and these always take a different colouring from the tissues around. The epithelium of tubules containing these casts are quite healthy. Litten believes that these plugs are formed in situ from a slimy secretion of the overnourished cells. These plugs are found in great numbers when the vein is tied.

Following/
Following temporary ligature of the renal artery is calcification which begins 24 hours after the operation and increases very rapidly during the next day. Calcification is only found in the necrotic epithelium and never in the blood or hyaline casts neither are the glomeruli, vessels nor connective tissue affected.

That modification of dead albumen which is formed in cells dying from anaemia attracts the calcium salts in the circulating blood and forms a comparatively insoluble albuminate of chalk. For the production of calcification it is necessary to have a brisk active circulation through the necrotic material. The calcium is derived from the blood and is not a simple precipitation of calcium salt normally present in the cell, for, in necrosis caused by toxic material, heat or trauma, we never have calcification in spite of there being a well-maintained circulation.

Calcification is not so extensive when necrosis of the epithelium is caused by binding both artery and vein or by permanent ligature of the renal vein. Chalk salts are not precipitated from the urine which passes through the cylinders, for calcification was found when by feeding the urine had been made acid. The conclusion is that in death from anaemia
the cell albumen is changed chemically, and combines readily with chalk salts and certain staining reagents. There is an analogy between the calcification of those dead cells and the calcification of cartilage in growing bone.

Virchow observed calcification of ganglion cells in the brain after trauma. The circulation in the part had been carried on after the death of the cells.

Litten's observations prove that cells in the kidney killed by trauma do not calcify, although the blood supply is continued.

Calcification is frequently found in the human kidney and has nothing in common with experimental calcification. In human kidney there is frequently calcification of the glomeruli. No necrosis precedes the glomerular calcification, for perfect integrity of the glomeruli and their nuclei as found after decalcification.

Calcification after temporary ligature of two hours increases in intensity but not in superficial area. The vessels and glomeruli remain absolutely intact. After two hours ligature of artery the epithelium has lost and never regains its function. After several weeks atrophic processes take place. In their highest degree this atrophy reminds me of
the "Schrumpfniere" of man. Grawitz and Israel found as Litten did compensatory hypertrophy of the intact kidney. They also found what Litten has not observed that, if compensatory hypertrophy of the healthy kidney did not take place, then hypertrophy of the heart followed. Litten points out that in man there may be complete destruction of one kidney as by hydronephrosis with no hypertrophy of the opposite kidney and still no hypertrophy of the heart. If ligature for six hours or more and then take away ligature vessels do not recover perfectly and if leave ligature much longer necrosis of vessels follows and they are found impassable after the ligature has been removed.

Permanent ligature of the renal artery leads to the destruction of the entire organ. There may or may not be histological changes depending on whether or not the tissue is bathed in blood or lymph at death. If all arterial supply is cut off there is death in toto with no secondary changes.

Litten now gives his views as to the origin and frequency of pale infarcts. In the great majority of cases by shutting a twig of the renal artery an anaemic, and not an haemorrhagic, infarct appears and the anaemic infarct is a primary condition and is not a secondary condition due to changes taking place/
place in extravasations. Litten explains that he
does not mean that typical haemorrhagic infarcts
cannot occur in kidneys as they do in the lung and
spleen. Undoubtedly the haemorrhagic infarct does
occur in man, but according to Litten's extended
observations, it is very rare, and in any case is
much rarer than such processes in the spleen and
lung.

Anaemic infarcts also occur in the spleen.
One group of infarcts occur in the spleen in some
infectious diseases which must be looked on as
white infarct, or primary necrosis caused by emboli,
but in which no bleeding occurs. These are most
frequently met with in recurrens and then in typhus
abdominalis, sometimes also in other illnesses, as
scarlet fever, in which Litten twice found white
infarcts in the spleen and kidneys without heart
affection. Even if it is not possible in every
case to find the embolus or demonstrate its origin,
still the form of infarct corresponds to the sphere
of distribution of an artery, and there is no doubt
that it owes its origin to an embolus. Emboli
may arise in the vessels themselves.

Similar areas are found in the liver. They
are due to anaemia necrosis and have no connection
with inflammation as white corpuscles are never
found/
found in their central parts. Equally little do they owe their origin to bacteria although they may be present but are more frequently absent.

In another disease (septic endocarditis) one finds quite similar masses which, however, are softened in the centre and always contain colonies of micrococci.

Occasionally white infarcts are surrounded by a haemorrhagic edge and one might conclude that the whole was at first haemorrhagic and had become pale in the centre afterwards. Microscopic examination however, shows no remains of blood in the pale part. Litten has found haemorrhagic edges in other kidney diseases, such as new growth (sarcoma). This raises the question whether the peripheral haemorrhage in the white infarct, as in the neoplasms named, is not to be classed as bleeding from stuffing (Stauung) as in the necrotic masses the vessels have become impermeable and the circulation is greatly interfered with. The capillaries surrounding all the above named masses are without exception widened and crammed full of red blood corpuscles. Between the peripheral haemorrhagic zone and the characteristic part of the infarct there is found frequently an inflammatory demarcation zone which surrounds the infarct as an encroaching edge. This consists of white/
white corpuscles thick and pressed together which fill the interstices at the periphery of the mass and are heaped up, especially around the glomeruli. These wander into the interior of the infarct and introduce absorption. They are found almost without exception in every infarct quite independently of the nature of the embolic plug. Apparently they originate from the inflammatory excitement which the sequestrum exerts on the neighbouring vessels. If this inflammation is influenced by an embolus loaded with bacteria and dissolved digestion products, the reaction is more marked and we have the infarct completely separated and lying in a cavity filled with thin evil-smelling pus. Absence of nuclei of the pus cells in the region of the demarcation zone is frequently met with and that quite independently of the sterility or septicity of the embolus plugging the artery.
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COHN'S CONCLUSIONS.

After a large number of experiments and much research work Cohn came to the following conclusions with regard to infarction of the kidney. They are to be found in Cohn's Work "Der Embolischen Gefäskrankheiten" Berlin 1860.

The results of ligature or embolism of the renal artery depend mainly: - on the duration of life after the operation, on individual sensitiveness, on the methods of operation and on the destruction or otherwise of collaterals in the hilum. The nerve is easily avoided, its direct destruction produces quite different results from those of artery ligature and it makes no difference to the results of artery ligature whether the nerve is included in the grasp of the ligature or not. Hyperaemia is the immediate anatomical lesion after ligature of the artery and this often is present after a few minutes in the cortex, and particularly in the medulla. Occasionally there is free bleeding into the connective tissue of the pelvis. This hyperaemia is the active
consequence of insufficient flow from collaterals and, in addition, lessened tonicity of the elements of the parenchyma and changes in the vessels. The morphological change consists more of a simple throwing off of epithelium, rather than a fatty degeneration. The capsules collapse (Kapseln collabiren) the collaterals rarely filling them. The connective tissue becomes more spongy, especially in the cortex. The urine canals break up. The connective tissue becomes doughey and oedematous, because of exudation from the capillaries, which are preserved. Later there is either a softening and total necrosis, or inflammation sets in, with in part a similar result; now and again a luxuriant growth of connective tissue is produced; in a few cases there is absorption and drying up and a calcified residue is left. Neither the medulla nor the serosa ever suffers in the regressive sense: one finds constantly in them a hyperplasia of the interstitial connective tissue. The cortex unites the conditions of relative integrity and total dissolution. A part of the cortex derives its nourishment from the renal artery alone and the collateral supply does not nourish it sufficiently. Gangrene never follows as a simple consequence of the operation but only appears when the contact of air and foul exudates act upon a previously softened or pus infiltrated kidney. The capsule,
in such cases, is commonly destroyed at the same time. The normal secretion of the kidney disappears completely especially that of the cortex, that of the medulla remains only in a certain sense; one sees it in the bloody urine and cylinder formations in the urine. If both vein and artery are tied at the same time the only additional effect is increased hyperaemia. According to Bernard, the usually red vein blood, after the ligature of the artery remains intensely black. The results of natural or artificial emboli of the renal artery are quite analogous to those produced by ligature. The kidney on the other side is hypertrophied; now and again it is infiltrated as in Bright's disease; still more seldom is it quite unchanged.

The result of the operation on the composition of the blood is unknown. It is also unknown why some animals die in a short time after the operation.

Heart hypertrophy never develops after degeneration of the kidney on one side. Cohn's experiments give no help in diagnosis, but give an indication in treatment. Collateral action in general has a tendency to overstep the limits of the wished for restitution, therefore it appears rational rather to hinder than to aid it.

Blocking of capillaries is far more frequent than that of the larger vessels. Capillary embol-
ism is not accompanied by significant change of texture nor by infarct except under the influence of specific irritating bodies. If infarct is formed it consists for the greater part of exudation products with a hyperaemic edge: seldom are there direct extravasations. Such infarcts are situated in both cortex and medulla. The smaller the emboli the more certainly will they locate themselves in the cortex.

The so called infarct of the kidney is so far distinct from that of other organs, especially it is seldom simply haemorrhagic in the cortex.

Fus injections give rise to abscesses in the usual way (piaformirender Arteritis) or by capillary abscesses of the size of pin-heads. In this the kidneys differ a little from other organs.

In the last place, changes take place less frequently in the medulla than in the cortex.
It is well known that infarcts of the kidney are:

1. not usually haemorrhagic in their whole extent;
2. more frequently pale in the early stage;
3. composed of a central necrosed anaemic part, hemmed in by a hyperaemic seam.

Shape of the kidney infarct:

Infarcts of the kidney, lung and spleen are described as wedge shaped masses. In the lung and spleen the wedge corresponds to the sphere supplied by an artery, that artery enters at the thin end of the wedge. In kidney, only those infarcts are wedge-shaped which affect both medulla and cortex. The artery does not begin at the apex, but supplies a wedge from the region of the arches in the centre of which it lies. If infarct be limited to cortex it is a quadrilateral area. If one intertubular artery alone is affected at its point of origin the long axis of the rectangle lies parallel to the medullary ray. If several adjacent interlobular arteries are affected at the same level in the cortex there may be a rectangular infarct formed with its
long axis at right angles to the medullary ray. If one of the arched vessels is affected near its origin there are several interlobular arteries affected and a quadrilateral infarct results, with two sides parallel and the sides parallel to the medullary rays converge slightly as they pass from the subcapsular area inwards.

Method of operation: (Ribbert does not mention what animal he used) The kidney was exposed, and a branch of the renal artery was cut and a cannula was introduced into its proximal end. Before operation agar (\( \frac{1}{10} - \frac{1}{20} \) cc.) had been sucked into the cannula in a fluid state. The agar, which was now solid, was easily expressed and entered the renal artery. Either an arch artery or an interlobular artery was plugged. In the kidney there was produced a large infarct corresponding to the ligatured branch and small infarcts from agar plugging the arteries.

In part of infarct which got no nourishment, at 16 hours:— Coagulated granular masses in (1) lumina of tubules which are wider than normal; (2) between epithelium and membrana propria if the former is separated from latter; (3) in Bowman’s capsules. Nuclei of epithelium smaller and darker like lymphocyte nuclei. The outlines of the cells are
indistinct. Nuclei of the intercalary segment (Schaltstucken) and of the loops shew crumbling as when karryorhexis becomes marked.

Infarct is raised above the rest of the surface.

At 24 hours: Epithelium of straight tubules, looped tubules and intercalary segment are loosened from their walls and lie in groups or singly. The cells of the convoluted tubules are much as before.

At 48 hours: Tubuli contorti have almost entirely lost their nuclei. The outlines of the cells of the loops (Schleifen) and intercalary tubules are badly outlined. The glomeruli still possess small dark nuclei.

At 3 days: All the nuclei of the infarct have not yet disappeared and some of the very few which are left are in fragments.

At 6 days: No nuclei except those of leucocytes.

Those remarks do not apply to the smallest infarcts. Those which correspond to the sphere of an interlobular artery or less, do not as a rule die in toto. Some connective tissue cells and single urine canals remain. The above changes appear to take place more rapidly in the human infarct. There was absence of nuclei in infarcts whose age was estimated at less than 24 hours.
The margin of the infarct:

There are three marginal zones. The most striking of these is the **hyperaemic zone**. Internal to the hyperaemic zone there is a **yellow seam** which appears quite early (16 hours) and consists of a cellular infiltration into tissue similar to the central dead part of the infarct.

The **hyperaemic zone** becomes less marked as time goes on, but is still recognisable on the 14th day. In this zone many of the cells of the urine canals show a loss of nuclei and those which remain are small and dark. The protoplasm of the cells is similar to that of the cells in the dead part.

Outside the hyperaemic zone there is a **bright white edge**. Here also the tubules are necrosed. The necrosis affects the **convoluted** (gewunden) tubules first and the straight tubules last of all. Connective tissue cells and glomeruli in the outer zone retain their nuclei.

After 24 hours there is compression of the tubular cells in the **infiltration zone**. In the **hyperaemic zone**, by far the majority of tubules have lost their nuclei. The lumens are wider and the cells are smaller. The connective tissue cells also have lost their nuclei and the few visible nuclei are
those of leucocytes. In the outmost zone condition is similar to the condition at 16 hours, but is more advanced.

Comparison of boundary zones with the central dead part.

The most obvious distinction is that whereas the nuclei are still present in the central parts they are absent (after 16-24 hours) in the peripheral parts.

During the first few days infarct is composed of:

(1) Infarct proper in centre;
(2) Zone of cellular infiltration;
(3) Hyperaemic zone;
(4) Zone of partial necrosis.

After a few days (2) and (3) are gradually lost. The peripheral zones take a few hours to develop after blockage of artery lumen.

Litten found that most renal infarcts are not haemorrhagic at any stage. On that account however they should not be considered anaemic. If a twig of the renal artery be tied and the capsule be raised from the sphere cut off from its normal blood supply, considerable bleeding occurs. Up to 10
hours after tying, the infarct is richer in blood than the normal. Blood is shed freely on cutting into it. Hyperaemia gradually subsides and after 24 hours cut surface has, in cortex, a dirty red colour, while the medulla, which is markedly hyperaemic from the beginning, is still entirely, or in great part dark red and remains so for some time.

The part of the infarct with the greatest blood content is the hyperaemic zone. Why should there be present, after 10 hours, a pale zone nearer to the normal tissue? Why is it, that, just where healthy tissue begins, there is found a zone with a small blood content? The slight pressure of the capillary lateral supply allows blood to accumulate in the capillaries of the infarct proper. In the outmost zone there is higher blood pressure and an easier off-flow. It is only relatively that it is poor in blood. Its pale colour is due, in part, to the occurrence of partial necrosis.

Surface of infarct is after 10 hours less red than that of the other kidney, and after 24 hours is clay yellow in colour.

Infarcts which embrace both cortex and medulla.

Between cortical and medullary parts of infarct there is an irregular zone running at right angles to the medullary rays or instead of a continuous band there may be unconnected islands of tissue.
These parts get their blood supply from the vessels in the ureter wall and pelvis. The blood supply from these collaterals gives only a small supply of nourishment, therefore there is a partial necrosis. These parts, just as the healthy tissue is, are separated from the central part of the infarct by the usual zones.

Kidneys in which the chief stem of the renal artery is shut.

The whole organ becomes necrotic except (1) a subcapsular layer, 1 mm. thick and (2) at junction of cortex and medulla unequal irregular island-shaped parts which are transparent grey and slightly red. In those parts there is only partial necrosis and in addition increase of connective tissue. Twice Ribbert has found the renal artery closed in the human subject by firmly adherent thrombi.

Hyperaemia of infarct explains the circumstance that at an early stage from 10 hours, and from that time onwards, have an increasingly abundant finely granular transudate in the glomerular capsule and interstitial tissue (Interstiten). Ribbert thinks that the materials which form this transudate are derived from the blood mass itself. Most authors hold that this transudate owes its origin to a penetration of the infarct by a fluid from the normal parts. In
the central parts of the infarct nuclei becomes fainter more rapidly at first when circulation is best and transudation is active, and very slowly later when circulation is stopped. The circulation is more active at the edge of the infarct and transudation is greater and consequently the nuclei rapidly disappear.

The transudate also flows naturally into the tubules and in them it is coagulated in the form of fibrin. The presence of fibrin can easily be proved by Weigert's method. The amount of fibrin is, on an average, not great, but varies in different cases. The hyperaemia and transudation at the beginning explain the prominence of the infarct at first.

The paling of the infarct:

This is not at all due to, or only partly due to, the outflow of blood from the infarct. Microscopic examination after 24 hours, shows the meshes of the glomeruli, and many of the interstitial vessels still filled with red blood corpuscles, but these have lost their colour. The paling of the infarct begins about the 16th hour, and is due to an extraction of the red corpuscles under the influence of the exudate. This process is supposed also to take place when the infarct is originally haemorrhagic.
The loss of colour means that circulation has stopped. The collaterals can, at this period, still be injected partially under a high pressure. The injection reached only the small interstitial vessels and did not enter the glomeruli.

Observations teach that the renal infarct is rich in blood, but not haemorrhagic during the greater part of the first day.

The zone of cellular infiltration:

At 10 hours it is not visible microscopically but is undoubtedly present and forms a boundary between the hyperaemic zone and the infarct proper. The vessels of the red zone are packed full of blood and contain more multinucleated corpuscles than normal. These are found in greatest numbers next the central necrosed parts. They are hidden from the naked eye at the 10th hour by the hyperaemia. At 16 hours the mass of leucocytes has become greater, and the zone which they form is wider. Some vessels appear to be quite filled with white corpuscles. Close to the central mass they are so numerous that they compress to a great extent, the tubules. They are even squeezed for a short distance between the necrosed canals of central mass itself.

A similar cellular zone is formed around the island or strip of tissue, before described, between
the cortex and medulla.

At the surface of the infarct the zone takes longer to form. At 16 hours the zone at the surface is similar to the zone at the sides of a ten hour infarct. At 24 hours it is definitely formed, but it is substantially less marked than the lateral zones. It lies $\frac{1}{2}-1$ m.m. under the capsule, the hyperaemic zone intervening.

The capsular supply: The slowness of formation of a superficial cellular zone is due to the very small capsular lateral supply. This is not able to keep the tubules next the capsule from dying, although the connective tissue is nourished. This disproves the importance of the capsular arterial supply, which some hold. It is different in case of the capsular veins, for if the renal vein be slowly and completely obliterated these dilate and fulfil its function and no changes worth mentioning are produced in the organ.

The collection of cells in the capillaries, and also their energetic emigration, leads to compression of tubules and helps to stop any blood supply going to the central mass of the infarct.

The cause of the cellular infiltration is the action of dead tissue upon the vascular system. The result
is universally viewed as an inflammatory process and is not caused merely mechanically for hyperaemia and sometimes haemorrhage is present. Haemorrhage in man is variable. Sometimes there is none: in other cases haemorrhages of considerable extent occur.

**Functions of the cellular infiltration:**

Collateral circulation is limited and is ultimately stopped and so total necrosis is hastened. The leucocytes have little to do with the absorption of dead material. They break up quickly and nuclei crumble. The total cellular emigrated mass is gradually reabsorbed. It is considerably reduced in 6 days, and has quite disappeared by the 14th day.

**Fatty Degeneration:**

In the tubules, the interstitial tissue and certainly in the protoplasm of the vessel endothelium, there are very fine fat droplets in 16 hours. Their size and number gradually increase and by the 3rd day their amount and size are so great that on staining with osmic acid the interstitial tissue appears engrained (Gekornt) black. The connective tissue cells and leucocytes are also affected, the latter only slightly even in the inner half of the cellular infiltration. Fatty degeneration did not
reach an intensity worth speaking of in experimental infarct. Also in man I have seen only slight degeneration limited to single tubules and limited areas of endothelium in the edges of many infarcts.

The degeneration is always most marked in the outmost zone. It is less marked in the hyperaemic zone and never is found beyond the cellular infiltration of typical infarcts. In the smallest infarcts fat droplets are found in the interstices of the central parts, but in these there is not total necrosis in the centre. These small infarcts show a red centre and are bounded by a grey white edge.

The outmost zone:

After 2 days the nuclei of the connective tissue are enlarged, and here and there in mitotic division. After 3 days the interstices are much broadened and cellular. On the 6th day a large-celled connective tissue is present, which is composed of developed spindle and emigrated cells, and contains capillaries with large endothelium. Mitosis is not rare. This development of connective tissue occurs most rapidly at the lower edge of the cortical infarct, in the region of the collateral paths, which supply most blood. It takes place more slowly at the sides and hardly at all under the capsule. From this one gathers the slight importance of the capsule capillary anastomosis.
The growing connective tissue together with vessels now pierce the necrotic part. The larger the infarct the longer time is required for entire penetration. Very little connective tissue succeeds in reaching the central parts of large masses. In the small and smallest infarcts it is different. In 14 days they are penetrated by connective tissue and are rich in cells. The cells of the affected part take part in the process. These are altogether healthy or only in part altered.

The fate of tubules which are not entirely necrotic:

They are present in the proliferating connective tissue and are shut up in the scar. They are lined by bright cubical peculiarly differentiated epithelium devoid of function (entbehrendem). Their presence is partly explained by the fact that the intercalary segment, the loop and straight tubules are spared in the necrosis. At the edge of the outmost zone convoluted tubules, which do not belong to the infarct tissue are entangled in the connective tissue growth. (4) Those undergo degeneration; their epithelium loose their differentiation and become like that of the straight canals.

Foa (5) explains the change in another way. He thinks that the granular dull protoplasm, which includes the inner section, takes part in the formation
of cylinders, while the bright external section remains. Ribbert has not convinced himself of this, and has always found the inner edge of the cell definitely marked off from the cylinders. Ribbert has never observed a pushing off of protoplasm or cylinders being formed from it, and therefore concludes, that there is a change in the cell as a whole which degenerates to a simpler form. In consequence of this, in connective tissue mass, tubules, similar to the straight tubules, are found. Similarly at the edges of human infarcts, where there is increase of connective tissue, the urine canals present have all got clear epithelium. New formation of epithelium occurs in the hyperaemic and outer zones. Mitosis is not uncommon. Either single cells or cells in small sections have died. There is often in the tubules a central dull mass of the original epithelium with new formed cubical cells between the central mass and the membrana propria. These cubical cells may be looked upon as newly formed and pushed into the necrotic part. Foa has spoken of the same. It is difficult to say how far degeneration may go. It is certain that it is without significance for the function of the organ. It may be questioned whether the new formation arises from the epithelium of the convoluted tubules, as the
necrosis always affects a whole system. Mitosis
is never seen in the epithelium of the convoluted
tubules but only in the clear cells, most of all
in those of the straight tubules.

Ribbert has found straight canals pushed into
an infarct from its deep surface and reach nearly
to surface. The lining epithelium was cubical, and
mitotic figures were seen. These were in-growths
from the straight canals of the preserved part. In
man I have found tubules in extensively necrosed
areas which arose from underneath the mass, and were
similar to the gall ducts which one meets with in
cirrhosis of the liver.