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EXPERIMENTAL STUDIES ON PERIPHERAL ARTERIAL EMBOLISM IN DOGS. ※

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Introduction

In spite of the fact that the clinical importance of peripheral arterial embolism has been considered for many years, however, reports concerning the experimental works on peripheral arterial embolization is scarce. Evidently, it is difficult to make the emboli experimentally and embolized it in certain arteries without traumatizing the adventitial layer of these arteries.

The materials used in our study for occlusion is non-radiopaque non-toxic and has been found accidentally during the study of the pain-conducting path-way in extremities of dogs. Our study was directed to embolized the systemic peripheral arteries of the body and observed the clinical, pathological, histochemical, and electrophysiological changes in these organs.

The latest study on peripheral arterial embolization was by S. J. Dencker 1953, who prepared the cellulose sponge with fine poleres impregnated with a mixture of lead acetate and glue. The above material suspended in heparinized physiologic saline was injected into the left ventricle of the heart and resulted the multiple emboli of the body. The animal survived only from one to three minutes in this case.

In our experiment, 10% of raw rubber mixed into the several mediums (benzol, petroleum benzine, carbon tetrachloride, paraffium liquidum etc.), and added lead monoxide for rentgenological evaluation. Injecting of this rubber solution results a complete embolization of the peripheral arteries.

Preparation of rubber solution

Multiple pieces from raw rubber measuring approximately $0.5 \times 0.5 \times 0.5$ m.m. in size were prepared and mixed into the following medium; 99% benzol, ether, petroleum benzin, carbon tetrachloride, paraffium liquidum and under temperature of 20 to 30 degree celsius until the rubber have been dissolved completely. It may apper

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slightly smoky soon after the solution is prepared but it will clear after 10 to 20 hours with white precipitate. The clear part of solution was used. The time required for this procedure depend on the kinds of the mediums used. Usually, benzin dissolves the rubber most shortly while ether takes two days or more days longer at times.

Lead monoxide was added to this solution at the rate of one to ten when an angiographic study was made.

Technique

Small amount of this rubber solution can be injected with a 1/1 or 1/4 needle and syringes if the arteries are either palpable (e.g. femoral, popleteal, or brachial arteries) or easily exposable (e.g. pancreatic, hepatic, gastric or renal arteries). The technique used mostly in our experiments was digital compression peripheral to the site of injection and this results the embolization of arteries in the area above digital compression.

The injection of rubber solution the tensity of digital compression peripheral site of injection will occluse the arterioli or the capillar arteries. In cases of deep vesseles (e.g. coronary artery or portal vein), rubber solution was injected under fluoroscopy with a fine angio-catheter.

Usually, 0.1 to 0.3 c.c. of rubber solution is enough to make the occlusion in most arteries but in the portal system, as much as 2.0 to 3.0 of rubber solution is required to interrupted the circulation. In cases of mesenteric, renal or pancreatic arteries, the amount of the rubber solution require is more less. The inner space of the needle is filled with rubber solution and simply pushed out with physiologic saline in the syringe. Same technique was applied when arterial catheterization was performed.

Experimentals

Healthy adult mongrel dogs, weighing from 8 to 10 kilograms were used for this experimental study. Anesthesia was obtained by subcutaneous injection of 2% morphine hydrochloride in doses of 0.2 c.c. per kilograms of body weight.

(A) Internal carotic artery.

Using sterile surgical technique, an incision was made in the lateral site of the trachea to expose the internal carotic artery. Using a small hypodermic needle on a syringe, 0.5 c.c. of rubber solution was forced into the lumen of this artery. No significant hemorrhages occurred after the needle was withdrawn from the artery, if a few minutes of digital compression is applied.

Flexion of the head to the opposite side, whining, unconsciousness and cramps of extremities followed soon after injection. Whining, cramps of extremities and unconsciousness recovered 6 hours after injection of rubber solution, but flexion of head and paralysis of the extremities remained unaltered.

Two dogs used for this series and both died within two days. Several areas of

softning (encephalomalacia) in the cerebrum of injected site was noted but the interesting point is that the same change was found in the cerebellium of the opposite side of the injection. It may be considered that the rubber solution flew with the blood stream of the basilic artery. The above cases resembles to the innervation of the cerebrum and the cerebellium. It is one of the most interesting phenomenon in this series.

Injection of a minimal amount of the rubber solution (less than 0.1 c.c.) after alternation of the body position resulted the embolization in certain arteries. (Fig. 1) showing the occlusion of the area of frontal lobe and blindness of the right eye followed. Necrosis of the iris and the ciliary body, opaque lense and diffuse edema of the fundus were observed in this case.

When a minimal amount of the rubber solution was used, the animal usually lived well over 14 days, but no observations over two days were done in this series.

(B) External carotic artery.

By using same technique as in the cases of the internal carotic artery, rubber solution was injected into the lumen of the external carotic artery. Injection of less than 0.1 c.c. of rubber solution were not satisfactory for gross observation, but injection of over 0.5 c.c. of rubber solution resulted with serval changes. (Fig. 2) is a case of embolized mandibular artery. The tooth in embolized side were dried, black and pulpas showed opaque hyperemic changes. Also noted small ulcers in the mucosa in the mouth which resembled to cellulitis of the oral base.

(C) Left ventricle of the heart.

Injection of 0.5 c.c. of the rubber solution into the left ventricle through the chest wall results the occlusion of the left internal carotic artery, the coronary artery and infarction of the kidneys. Embolization in the other site followed next to the above arteries. The reason for this order is not clear. (Fig. 3) and (Fig. 4).

(D) Coronary artery.

After exposure of left common carotic artery, a specially designed heart catheter was inserted to the ostium of the aorta. Rubber solution is injected through the inner tube. At the tip of the outer tube, there is a fine rubber balloon. (Fig. 5). Under fluoroscopy, a catheter inserted to the ostium of aorta and injected the mercury through the outer tube to the rubber balloon until it obstructed the ostium of the aorta with mercury filled balloon. Rubber solution was injected quickly through inner tube during heart diastole. After confirmation of the coronary occlusion by the rubber solution under fluoroscopy, the catheter was removed from the artery. Sutures and digital compression were given for prevention of hemmorrhage after this procedure.

0.1 c.c. of rubber solution was injected into the coronary artery. In this case, the animal died 20 minutes after injection. (Fig. 6) and (Fig. 7). The animals have been managed to kept alives for 24 to 48 hours recently but for further study on chronic coronary occlusion and myocardial infarction, they should kept alive much longer. Further study of this program must be required.

Electrocardiographical evaluation was done in this series and it will be reported

in the following paper.

(E) Stomach.

It has been known that there are no significant changes in the stomach except for a slight hemorrage in the gastric mucosa even though the four main arteries of the stomach (left and right gastric arteries, left and right gastroepiploic arteries) are ligated.

Remarkable changes (e.g. diffuse inflammation, necrosis and perforation sometimes) were noted in the stomach after injection of rubber solution into the arteries of the stomach.

Minimal amount of rubber solution (0.5 c.c.) was injected into the small arteries directed toward the wall of the stomach results the ulcer formation 24 to 48 hours later. At least three of thease arteries will have to be occluded for such ulcer formation. (Fig. 8) and (Fig. 9)

Numerous experimental methods for production for gastric ulcer has been reported ("licotodium" is most well known), however, there are no methods which produces it so quickly with steady results as in our method.

(F) Mesenteric artery.

Diffuse progressive necrosis of the intestine is produced by injection of 0.5 c.c. of the rubber solution into the mesenteric artery and animals died within 24 hours. Animals survives longer when a smaller amount of the rubber solution (less than 0.1 c.c.) is used. Nausea and vomiting commenced within 24 hours and they finally die with symptoms of ileus and acute peritonitis due to perforation of the intestine between the 3rd and the 5th day. In these cases, the necrosis of the intestine is limited to 10 c.m. in length. (Fig. 10) and (Fig. 11).

Mass ligation of the mesenteric vessels usually do not produce necrosis of the intestine but it occer when both end of the intestine are ligated. Necrosis of the intestine have been easily produced by our method.

Microscopic picture was taken 2 hours after injection of rubber solution into the mesenteric artery shows complete occlusion of the arterioli in the intestinal wall. (Fig. 12).

After rubber solution was injected into the mesenteric artery bathed in Ringer's solution (opened the abdomen in the special bath which filled about 38 degree celsius of Ringer's solution added oxigen), and the movements of the intestinal muscles were observed by kymograph. Movements of the longitudinal and transversal muscles were both increased as soon as rubber was injected into the mesenteric artery, but it gradually slowed down and the longitudinal muscle stopped 15 minites after the injection being by the transversal muscle one minite later. Few drops of acetylcholine added to the Ringer's solution will help restart the intestinal movement, but 30 minutes after the injection, no movements were recorded completely.

In this series, our study was also directed to the electrophysiological evaluation. After ligation of the mesenteric nerve, the peripheral site of this nerve's fibres were separated and the afferent action potentials were conducted from the nerve fibres. Many

of the afferent spikes were recorded as soon as mesenteric artery was occluded. 15 minutes after the injection of rubber into the mesenteric artery, it suddenly decreased and it disappeared completely after 15 minutes and 30 seconds. Such special gradational changes of the spikes suggests that the functional receptor in the intestine are limited to 15 minutes in this caces. It may be considered that the automatic function of the intestine will disappeare 15 minutes after the injection of the rubber solution into the mesenteric artery but still react to external stimuli for 30 minutes after the mesenteric occlusion. The intestine will become to necrosis gradually over this petiod.

(G) Pancreatic artery.

Rentgenogram of the pancreatico-duodenal arteries is shown in (Fig. 13). Rubber solution has been injected into the superior and inferior pancreatico-duodenal arteries.

The main stem of the superior pancreatico-duodenal artery runs in the parenchym of the pancreas supplying the superior portion of the pancreas and sending the branches to the duodenum. The inferior pancreatico-duodenal artery, which ramificated from a branch of superior mesenteric artery, supplies the inferior portion of the pancreas and a part of the duodenum. It was technically difficult to embolized the arteries supplying the pancreas exclusively because of its anatomic relationship but we have succeed to embolized these arteries without damaged to the duodenum.

Separate and expose the artery which supplies the pancreas and then inject 0.1 c.c. to 0.2 c.c. of the rubber solution into this artery. After 48 hours, there were well marked fat necrosis of the omentum and the mesenterium. The pancreas were completely necrotic, edematous, hemorrhagic and sometimes fibropurulent.

When large amount of the rubber solution were injected (0.5 c.c.) the change such as edema and induration spread to the mucosal surface of duodenum. The changes which was noted in several places, not only limited in the pancreas were considered to be dued to the autolysis of the pancreatic parenchym. Such phenomenon are seen quite often clinically.

The rubber solution was also injection into the pancreatic duct and compared with these of the artery. (Fig. 14) is a case of pancreatic arterial occlusion. The pancreatic lobule displays central necrosis with the acini at the peripherary living. In the case of pancreatic duct occluded, the islands of the necrosis spreaded to the whole lobulus (Fig. 15). Same changes were seen in the ribo-nuclear staining.

Many clinical and experimental studies have been reported for the genesis of acute pancreatic necrosis, but non have adequate explanations for this etiology. Since Pauman, in 1862, injected small particles of wax into the pancreatic artery, numerous experimental studies evauatling the genesis of the pancreatic necrosis put special emphasis to the vascular factor. Smyth (1940) and Ishikawa (1944) produced pancreatic necrosis by injecting mercury into the pancreatic artery. In their case, the embolization also results to the branches supplying the duodenum and also the emboli were not occluded the small arterioli or capillar arteries because of its high surface tension and large granule.

On contrary in our study, the arterioli and the capillar arteries were completely embolized and the pancreatic necrosis were produced without invading the duodenum.

We have been continueing to study on experimental embolization of the pancreatic artery as a one of the etiologic factor of the acute pancreatic necrosis which is still under progress and it may be well considered.

(H) Portal system.

Injection of 0.1 c.c. to 0.5 c.c. of rubber solution into the portal vein results incomplete occlusion in the arterioli of the lobulus of the liver, but when a large amount of rubber is injected (more than 1.0 c.c.), portal hypertension, ascitis and mild jaundice are resulted.

No remarkable changes were noted in the liver, spleen or other organs in this series.

(I) Hepatic artery.

On the other hand, injection of 0.1 c.c. of the rubber solution into the hepatic artery produced marked jaundice immediately but the ascitis was mild. Cirrhotic changes of the liver and spleen resembling hepatic intoxication were noted and the animals died within 24 hours. (Fig. 16).

(J) Kidney.

Injection of a large amount of the rubber solution into the renal artery results the diffuse necrosis of the kidney by 2nd day. After 3 to 4 days of the injection, empyema of the kidney developed and finally died on 6th day. (Fig. 17).

Necrosis was limited to one-third of the kidney when less than 0.1 c.c. of the rubber was injected into the renal artery. (Fig. 18). Alubuminuria and hematuria started on 5th day. Cyirinders in the urinary sediments and hypertension were observed in later stage. The animals were killed within 14 day. The rubber emboli in the glomerulus and its necrosis are shown in (Fig. 19) and (Fig. 20).

(K) Pelvis of the kidney and ureter.

0.1 c.c. of the rubber solution was injected into the pelvis of kidney or ureter. Both end of injected areas were clamped prior to the rubber injection and was released 5 minutes after the rubber was forced into the pelvis or ureter.

Within 5 to 7 days, occlusion of pelvis and ureter resulted and these resembled the clinical pictures of calculi in these organs, such as hydronephrosis, dilatation of ureter above the obstructed areas. (Fig. 21) (Fig. 22) and (Fig. 23).

(L) Femoral artery.

The leg was clamped above the knee with tuorniquet and 0.5 c.c. of the rubber solution was injected into the femoral artery. As soon as the injection was completed the dog cried, and the stiffness and coldness of the affected leg followed immediately. After recovering from anesthesia, the dog would bend that knee and cripple (Fig. 24). Rentgenogram immediately after the injection of the rubber solution shows a complete occlusion of the femoral artery. (Fig. 25). The rubber emboli still remains 40 minutes after the injection. (Fig. 26) and (Fig. 27). By the 7th day of this series,

the embolized leg becomes completely gangrenous. (Fig. 28) and (Fig. 29).

Injecting benzin or ether into the femoral artery without mixing the rubber also resulted crying, coldness and stiffness of the leg immediately but these recovered 6 hours after injection. No crippling or gangrene of the leg were remained.

In ligation or resection of the femoral artery not resulted the specific circulatory disturbance other than crippling of few days. The numerous collateral vessels develops on the 2nd day as shown in (Fig. 30).

Injection of the rubber solution into the femoral artery without clamping the leg produces complete occlusion of small arteries of the peripheral site of the leg. (Fig. 31). The rubber still remained in arterioli and capillar artery even two weeks after the injection, untill leg became gangrene and fell off. (Fig. 32) and (Fig. 33).

Summary

(1) Experimental embolism was produced in the several arteries using special rubber solution as the emboli. Raw rubber were mixed into several mediums (ether, benzin, benzol, paraffine etc.) and lead monoxide was added into this solution for rentgenological evaluation.

(2) The above rubber solution were injected into the several arteries through needle or catheter and an occlusion of these arteries were produced.

(3) Brain, coronary artery, pancreas, kidney, liver, portal vein, stomach, intestine and femoral artery were studied and experimentally encephalomalacia, blindness, coronary occlusion, pancreatic necrosis, hydronephrosis, infarction of the kidney, ascitis, hepatic jaundice, portal hypertension, gastric ulcer, perforation of the stomach and intestine were produced.

(4) Our studies were directed not only to embolized several arteries systemically but to observed these organs from the clinical, pathological, histochemical and electrophysiological standpoints.

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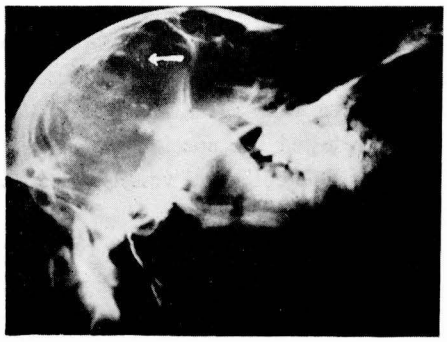
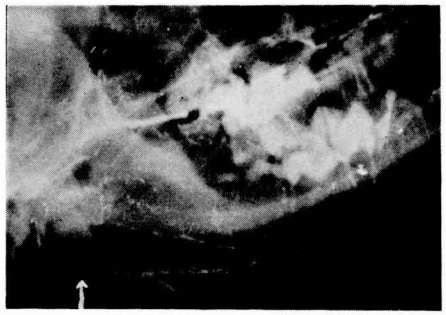
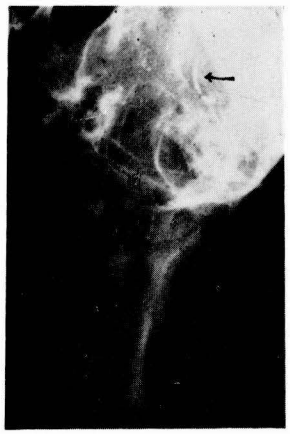


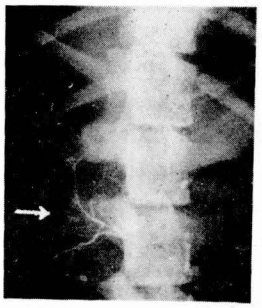
(Fig. 1) Occlusion in the area of frontal lobe following the injection of the rubber into the internal carotic artery.



(Fig. 2) Embolization in mandibular artery after injection of the rubber into the external carotic artery.

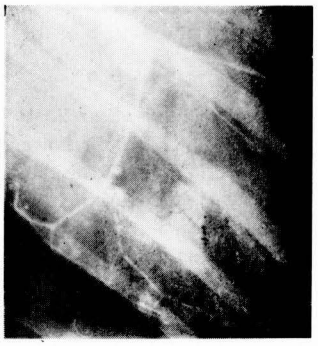


(Fig. 3) Rubber occlusion in left internal carotic artery after injection of rubber into the left ventricle of heart.

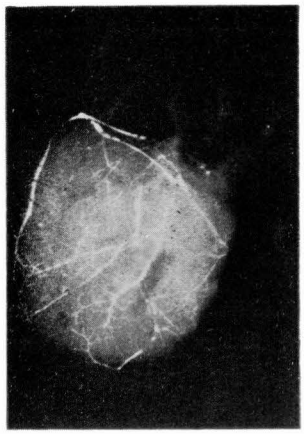


(Fig. 4) Kidney was infarcted after injec- of rubber into the left ventricle of heart.

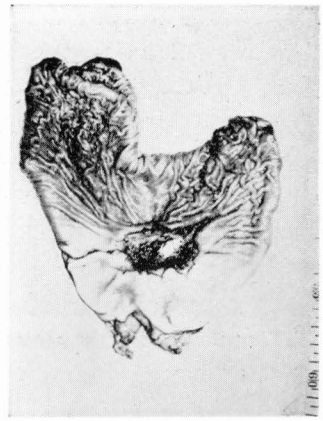
(Fig. 5) Specially designed heart catheter for study of coronary occlusion.



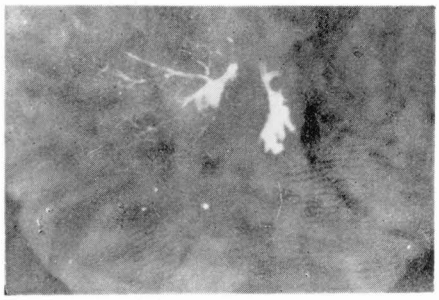
(Fig. 6) Soon after injection of rubber solution into the coronary artery using heart catheter.



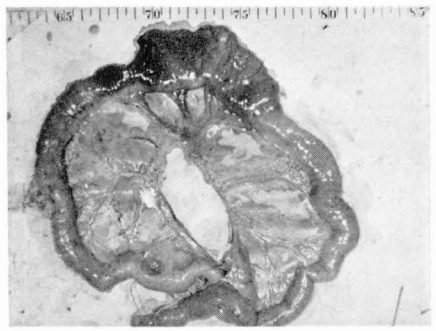
(Fig. 7) 20 minutes after injeccion of 0.5 c.c. of rubber solution into the coronary artery.



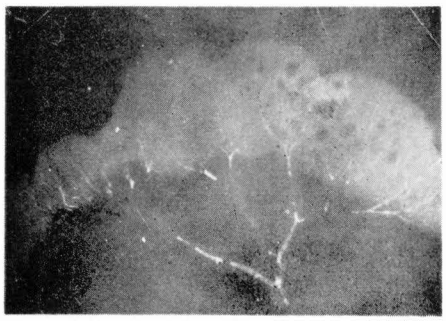
(Fig. 9) Ulcer formation after 24 hours injection of the rubber into the small arteries of the stomach.



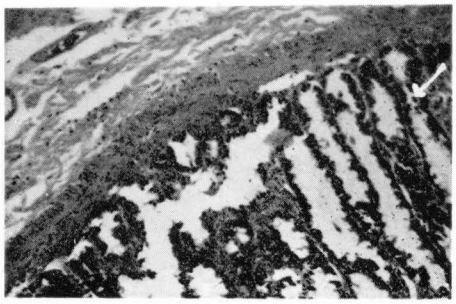
(Fig. 8) Rentgenogram of 24 hours after injection of the rubber solution into the gastric arteries.



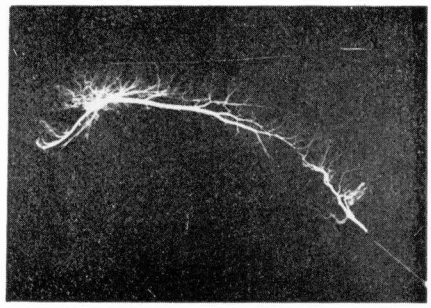
(Fig. 11) The intestine shows necrosis 24 hours after injection of the rubber into the mesenteric artery.



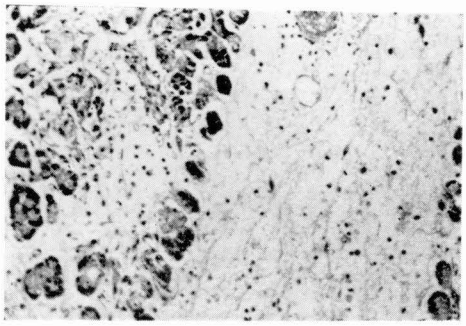
(Fig. 10) Rentgenogram, 24 hours after injection of the rubber into the mesenteric artery.



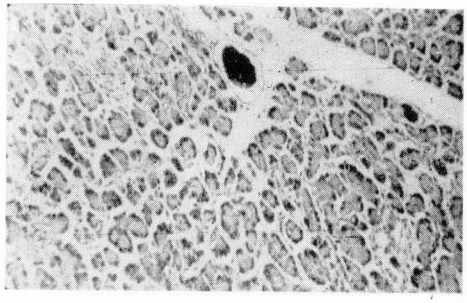
(Fig. 12) Rubber occlusion of the arterioli in wall of small intestine.



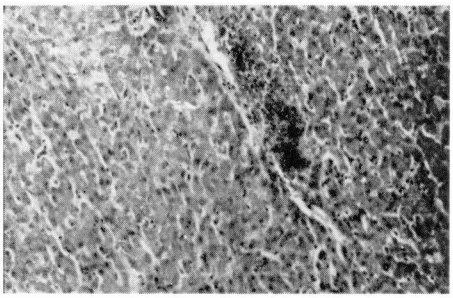
(Fig. 13) Rentgenogram of the pancreaticoduodenal arteries.



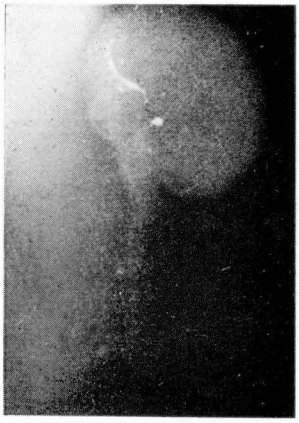
(Fig. 14) Central acinal necrosie of a pancreatic lobule 48 hours after injection of rubber into the pancreatic artery.



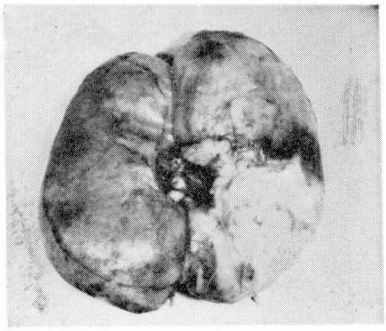
(Fig. 15) Necrotic islands spreaded in pancreatic lobule, 48 hours after injection of the rubber into the pancreatic duct.



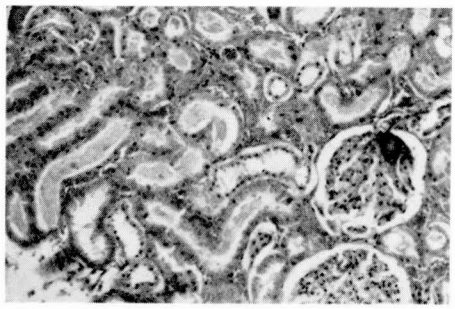
(Fig. 16) 24 hours after injection of the rubber into the hepatic artery.



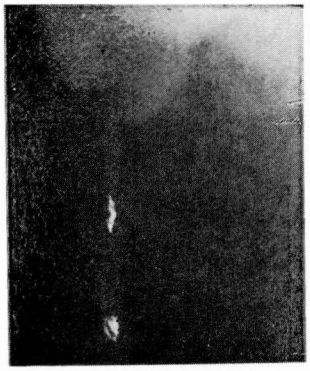
(Fig. 17) Rentgenogram of injected rubber with lead monoxide into the renal artery.



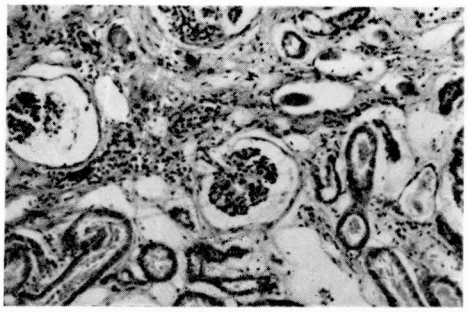
(Fig. 18) Kidney infarction followed to rubber injection into the renal artery.



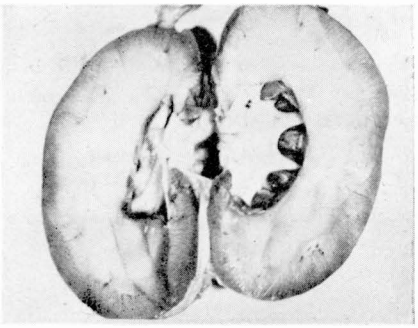
(Fig. 19) Rubber emboli in the glomerulus and arterioli of the kidney.



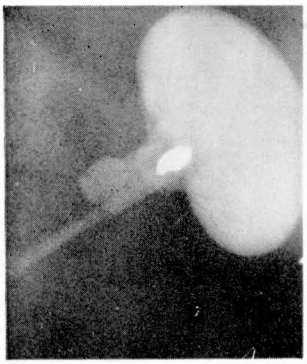
(Fig. 22) Ureteral occlusion with dilatation.



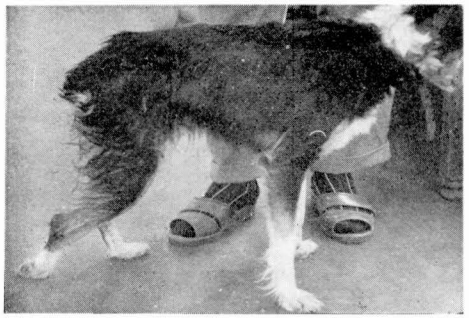
(Fig. 20) Partial necrosis of the glomerulus 24 hours after injection of the rubber solution into the renal artery.



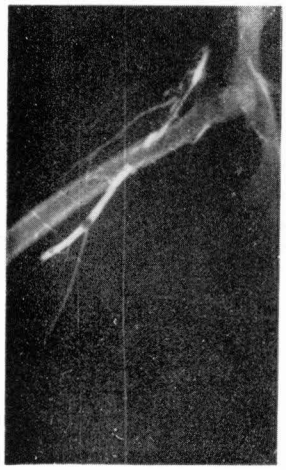
(Fig. 23) Pelvis of the kidney shows marked dilatation followed rubber occlusion.



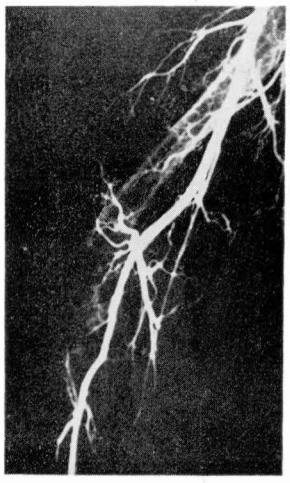
(Fig. 21) 14 days after injection of lead mixed rubber into the pelvis of the kidney.



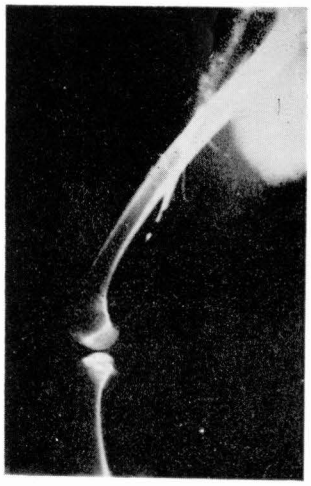
(Fig. 24) Cripple of leg after injection of rubber solution into the femoral artery.



(Fig. 25) Rentgenogram of rubber occlusion in femoral artery.

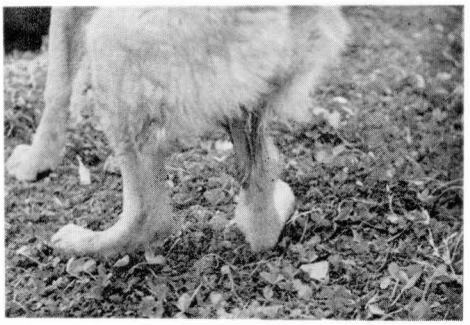


(Fig. 26) Normal rentgenogram of femoral artery in dog.

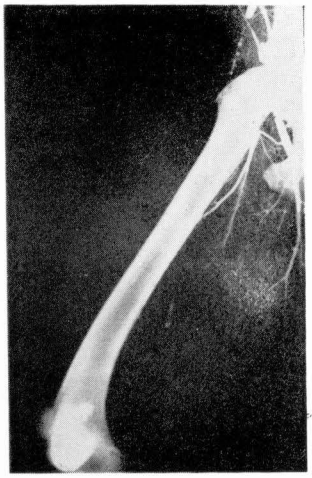


(Fig. 27) Moljodol arteriogram 40 minutes after injection of rubber solution into the femoral artery.

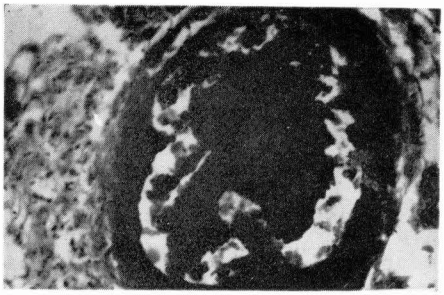
(Fig. 28) Gangrene of the leg followed to rubber occlusion of the femoral artery.



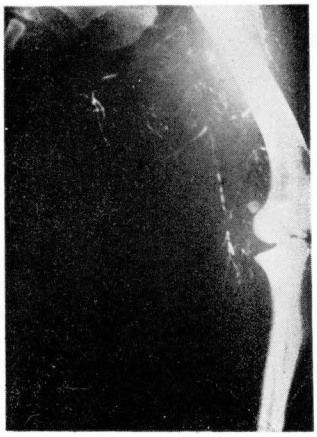
(Fig. 29) Gangrene of the leg followed to rubber occlusion of the femoral artery.



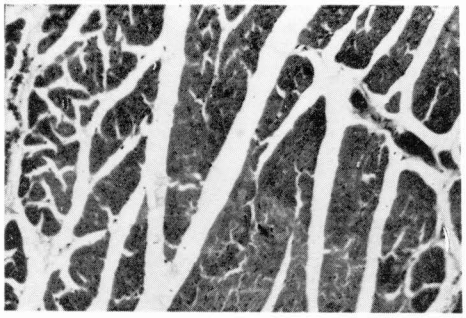
(Fig. 30) Collateral vessels develeped two days after resection of femaral artery.



(Fig. 32) Microscopic picture of rubber emboli in artery.



(Fig. 31) Rubber occluded in the arterioli in leg.



(Fig. 33) Rubber emboli in arterioli in muscle.