STUDIES ON EXPERIMENTAL HYPERTENSION

VII. The Production of the Malignant Phase of Hypertension*

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The experimental production of hypertension, accompanied or followed by the development of renal insufficiency and diffuse arteriolar hyalinization and necrosis (pale hypertension, one type, of Volhard (1), malignant hypertension of Keith, Wagener and Kernohan (2), malignant phase of essential hypertension of Fishberg (3)), has not hitherto been reported.

Methods

In a previous paper (4), the production of persistent hypertension in dogs by the constriction of the main renal arteries was published. This has also been accomplished in the monkey by the same method (5). In these and other studies, some of which have been reported (6–9), it has been found that when one renal artery is constricted adequately, the blood pressure rises in most animals and remains elevated for a variable period which lasts from weeks to months, but eventually returns to a lower, or even the original, level. In order to make the hypertension persist for years, it is necessary either to clamp the main artery of the other kidney or to remove the normal kidney. The removal of the normal kidney can be performed either at the time of the clamping of the main artery of the other kidney, or, more commonly, after the temporary hypertension due to constriction of one main renal artery has become established. The excision of the normal kidney, even after the temporary hypertension due to constriction of one main renal artery has subsided, results in a re-elevation of the blood pressure, which usually persists at a higher level than during the previous period. In most of the animals, when constriction of the main renal artery of both kidneys,

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or of the only kidney, is moderate, there is no consequent disturbance of renal function detectable by the usual studies of urine and blood, including urea and creatinine clearances, and the blood pressure remains elevated at various levels. In some of these animals the hypertension has persisted at a very high level for more than five years.

In the first paper (4) it was stated that when both main renal arteries were constricted severely at the same time, or with only a short interval between the two clampings, hypertension followed which was accompanied by severe disturbance of renal function. These animals developed typical clinical uremia which proved fatal after a variable period. Special mention was made in the first report (4)[1] of dogs 2-5 and 8-7, both of which developed severe hypertension and died due to renal insufficiency. In both dogs, at autopsy, petechiae were observed, mainly in the gastrointestinal tract, and urinary bladder.

The same gross lesions had been observed in several animals, before Nos. 2-5 and 8-7, during the period when the development of the clamp for the constriction of the renal artery was begun, but their nature was not recognized. No special significance was attached to these lesions, which were considered coincidental and probably infectious in origin, and they had not been examined microscopically at the time of the first report (4). Dog 8-7 had been dead about 36 hours in warm weather before it was examined. The tissue was useless for microscopic study. Subsequent study of the tissues of dog 2-5 revealed the nature of the lesion, but it was decided to delay making a report until a sufficient number of animals of this kind had been observed and studied to warrant conclusions about the exact nature and pathogenesis of the condition. Because it was soon found that severe constriction of both renal arteries proved rapidly fatal, and because the main purpose of the first investigation was to produce and study the pathogenesis of persistent hypertension, severe constriction of the main renal arteries of both kidneys was avoided. An interval of several weeks to months was allowed between the constriction of the two main renal arteries and it was frequently made moderate at first and later increased.

During the period from 1934–1936, the hemorrhagic lesions were again observed in three dogs. In dogs 1-33 and 2-37, the initial constriction of both main renal arteries had been made severe, with a short interval between the two clampings, as in dog 2-5. In dog 2-50, one main renal artery was first severely clamped, and, when the temporary hypertension was at its height, the ischemic kidney was removed. This was followed by prompt return of the blood pressure to the original level. After about 2 months of normal pressure, the main artery of the remaining kidney was severely constricted. The blood pressure became re-elevated and progressed rapidly to a very high level. Terminally, the mean blood pressure in the femoral artery, by the direct method, was more than 300 mm. Hg.

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[1] Goldblatt *et al.* (4), Text-figs. 5 and 6.

During the last 5 days of life, intraocular hemorrhage and bleeding from the anus developed and the animal was in uremia when it was killed. The chart of the blood pressure of this dog has already been published (8).[2] At autopsy, this animal had petechiae and larger hemorrhages in the esophagus, gastrointestinal tract, pancreas, diaphragmatic muscle and myocardium. The posterior chamber of both eyes was filled with blood.

When it was realized, as a result of the microscopic examination of the tissues of dogs 2-5, 1-33, 2-37 and 2-50, that the petechiae and larger hemorrhages were accompanied by the presence of severely degenerated, hyalinized and necrotic arterioles and that the extravasations of blood were probably due to rupture or destruction of these vessels, a deliberate attempt was made to produce the lesions by repeating the procedures used in dogs 2-5 and 2-50. It was thought at that time that the effect on the arterioles in both of these dogs might have been due to the previous sensitization of the arteriolar system to some substance circulating in the blood, as a result of the initial ischemia of one kidney, which was common to both animals.

During the past 2 years (1936–1938), the same clinical manifestations and gross lesions in the internal organs have been produced by various methods, in twelve more dogs. Common to all the methods have been hypertension and renal insufficiency due to severe reduction of the blood supply to the kidneys. In these dogs the experimental history varied. (For details, see the Summary of Experimental History at the end of this paper.) When the same procedures as in dog 2-5 were carried out on dog 3-35, there resulted the development of the same clinical manifestations and pathological lesions. When the same procedures as in dog 2-50 were carried out on dogs 2-67, 2-68, 3-05 and 3-39, all but 2-68 developed severe hypertension, renal insufficiency and the hemorrhagic lesions in various organs. Persistent hypertension and temporary moderate azotemia also developed in dog 2-68, but the renal insufficiency did not persist and the clinical signs of hemorrhages and pathological lesions of the arterioles (intraocular hemorrhage or bleeding from the intestine) did not develop. This animal is still living.

It was realized subsequently that sensitization of the arterioles is not a necessary condition for the development of the arteriolar lesions and hemorrhages, because they were observed in animals with hypertension and renal insufficiency due to the following procedures: (*a*) severe constriction of the main renal artery of one kidney followed, after an interval, by the removal of the normal kidney (No. 3-07); (*b*) unilateral nephrectomy followed by severe constriction of the main renal artery of the remaining kidney (Nos. 3-12, 3-16); (*c*) severe constriction of both main renal arteries at the same time (No. 3-41), and (*d*) severe constriction

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[2] Goldblatt (8), Fig. 3.

of the aorta immediately above the origin of the renal arteries in animals with one or both kidneys (Nos. 3-37, 3-59, 3-62, 3-63 and 3-65).[3]

The effects of the various procedures are illustrated by the individual histories given farther on.

Clinical Manifestations

In all the animals, during the terminal period, chemical examination of the blood revealed a great increase of urea, non-protein nitrogen and creatinine. Urea and creatinine clearance tests indicated great reduction of renal function. Some of the animals were anuric for several days before death. In all, the blood pressure was usually at a high level during this period, except a few hours before death, when it sometimes fell to a lower level. In most of the animals, the first clinical sign of the development of the malignant phase of the hypertension was bleeding from the anus. In two animals, the first sign of the onset of the condition was blindness, due to bilateral intra-ocular hemorrhage, and this was followed by the appearance of bleeding from the anus.

Gross Examination of the Tissues

In the gross, the only recognizable lesions were petechiae, some confluent, and some larger extravasations of blood. The distribution and severity of the lesions varied in different animals. In all, the gastrointestinal tract was affected in varying degrees. The petechiae appeared in all coats but were most prominent in mucosa and serosa. Next most common was the involvement of the pancreas and urinary bladder. Petechiae, and some larger extravasations of blood occurred in gall bladder, esophagus, brain, abdominal lymph nodes, heart (myocardium and epicardium), diaphragmatic muscle, eyes, suprarenals and gonads of some of the animals. In several of the dogs most of the organs mentioned showed these gross lesions. The organs in which no macroscopic hemorrhages were ever observed were the kidneys (except when associated with massive or localized infarction), skeletal muscles, skin, lungs, liver, thyroid and pituitary but, in some of these, hemorrhages were found on microscopic examination of the tissues.

[3] A preliminary report (10) of the production of prolonged hypertension by clamping the aorta above both renal arteries was made before the Central Society for Clinical Research, in Chicago, on November 5, 1937.

Microscopic Examination of the Tissues

In all the organs which showed macroscopic hemorrhages, and also in some of the organs in which they were not usually observed, in the gross, the microscopic pathologic changes consisted of degenerative disease of varying severity (hyalinization and necrosis) of the arterioles and fresh extravasations of blood into the tissue.

The most severe and most widespread lesions were found in all coats of the alimentary tract, with progressing severity from esophagus to rectum. The most severe lesions of arterioles were found in mucosa and submucosa. Pancreas, gall bladder, urinary bladder and spleen frequently showed severe hyalinization, with or without obvious necrosis, of the arterioles. The distinction between severe hyalinization and necrosis was often not very sharp. In the skeletal muscles, with the exception of the diaphragm, changes were not common and consisted of relatively slight hyalinization of the intima and thickening of the media in those arteries and arterioles that had been subjected to a long period of benign hypertension preceding the onset of the malignant phase. Actual necrosis of arterioles was not observed in the arterioles of skeletal muscles. In the lungs, the only vessels that showed the changes in some of the animals were the bronchial arterioles. The pulmonary arteries were not affected. The only other organs which did not show necrosis of arterioles were the kidneys (see pathogenesis).

The source of the petechiae and larger hemorrhages was not always clearly demonstrable. In many instances, they were obviously due to dissecting hemorrhage through the wall or to actual rupture of the necrotic arterioles. In or near some of the hemorrhages, no necrotic arterioles were found so that they appeared to be capillary in origin. The degenerative changes in the capillaries were not clearly demonstrable, but small hyalinized and necrotic masses were observed within many of these foci of hemorrhage which might represent degenerated capillaries. See Fig. 5.

The arteriolar degenerative lesions varied in nature and severity[4] (see Figs. 1–5). In some of the arterioles, there was some hyalin immediately beneath the endothelial lining of the intima which remained intact (Fig. 1). This hyalin stained yellow in Van Gieson preparations and was situated internal to the elastic lamina. In the smallest arterioles, in which the endothelium composed the entire intima, this accumulation of hyalin constituted a subintimal deposit. In some of the arterioles, the accumulation of hyalin was excentric, in others concentric, with partial (Fig. 2) or complete (Fig. 3) obliteration of the lumen. The lumen of some of the vessels remained normal while part of the entire thickness of the wall was necrotic (Fig. 4). In some entirely necrotic arterioles there

[4] Illustrations of these lesions were exhibited before the American Medical Association, Atlantic City, June 7–11, 1937, and at the Graduate Fortnight of the New York Academy of Medicine, New York, November 1–12, 1937.

was neither thickening of the wall nor reduction in the diameter of the lumen. Serial sections showed that different portions of the same arterioles could be relatively normal, partly or completely hyalinized, and partly or completely necrotic (Fig. 5), as Moritz and Oldt (11) have shown for human arteriolar disease. In larger arterioles, or small arteries, the lesion was mainly intimal, but, in some instances, even in the vessels of this size, the inner portion of the media was also affected. In the necrotic vessels, and even in some of the severely hyalinized arterioles, the elastica had defects or stained poorly but showed no reduplication (Weigert's method). Within the wall of some of the hyalinized or necrotic arterioles, red blood cells were present and some of these dissecting hemorrhages communicated directly with the lumen of the vessel and the extravascular blood. In no case was a deposit of blood pigment found, which would indicate repeated or old extravasations of blood. In all the tissues the hemorrhages were recent and indicated a terminal event. In none of the animals was there any intimal proliferation or reduplication of elastica in the arterioles and in none was there any indication that proliferation preceded hyalinization of the intima. In only one of the animals was there perivascular infiltration of polymorphonuclear leucocytes and lymphocytes around the necrotic arterioles of the intestine. This inflammation was probably due to coincidental infection.

Pathogenesis of the Arteriolar Lesions

Nothing is known about the pathogenesis of the arteriolar degeneration and necrosis which are found in many internal organs, but most frequently in the kidneys (3) and gastrointestinal tract (11), in human benign or malignant hypertension. The degenerative and necrotizing arteriolar lesions of the animals which have been described above are not distinguishable from those found in most cases of malignant hypertension in man (11) except that they are more severe and more widespread than in the latter. This indicates a greater susceptibility of the dog's arterioles to these changes. In human malignant hypertension, skeletal muscles and lungs also rarely show necrosis of arterioles, although hyalinization and other changes may occur in the muscles (12). The only striking difference between the lesions in man and dog is that in the latter the kidneys did not, while in the former they do very frequently show arteriolar necrosis. This discrepancy is easily explained and actually affords a clue to the pathogenesis of this lesion. In the animals, the intravascular pressure, within the kidney, is probably low, because the method involves the constriction of the main renal artery. In man, the intrarenal vascular tension is undoubtedly high, because there is sclerosis and

constriction of the preglomerular arterioles. In some of the larger vessels of the human kidney the lumen is also frequently narrowed, due to proliferation of the intima, but it has never been shown that the arterioles belonging to such vessels become necrotic. It may be that only those arterioles become necrotic that are subjected to the high bursting tension as well as to the hypothetical toxic substance or substances in the blood which result from the renal insufficiency. There are some human cases in which necrosis of small renal arterioles is not found. These may be cases in which the renal insufficiency is due to widespread intimal proliferation in the small arteries and large arterioles and not to the reduction in the caliber of the preglomerular arterioles. This may also account for the difference and point to one of the probable factors and necessary conditions in the pathogenesis of arteriolar necrosis and hemorrhage, namely, elevated pressure within these vessels. That the accumulation of chemicals in the blood is not by itself a sufficient condition for the production of the arteriolar lesions, is shown by the fact that bilaterally nephrectomized dogs that develop azotemia but no hypertension (5), do not develop the generalized hyalinization and necrosis of arterioles and associated hemorrhages in the organs. That hypertension alone is not sufficient to determine the formation of the necrotizing lesions of the arterioles is shown by the fact that animals that have had severe hypertension for more than 5 years, without accompanying significant disturbance of renal function, have not developed this lesion. That the lesions of the arterioles are not due to ischemia is shown by the absence of the lesions from the severely ischemic kidneys of the dogs and their presence in organs in which there is no preexistent ischemia. In the dogs, at least, the combination of hypertension and severe disturbance of renal function, with consequent accumulation of chemical substances in the blood, are at least two of the necessary conditions for the manifestation of the arteriolar necrosis and associated hemorrhages in various organs. Since the hypertension is not present within the intrarenal blood vessels of the animals with the main renal arteries or the aorta above the origin of the renal arteries constricted, the lesion does not manifest itself there. The same explanation (absence of local hypertension) probably applies to the absence of the lesion in the pulmonary arteries of man as well

as of animals. What the nature of the chemical substance or substances is that plays a part in the production of these lesions, is not elucidated by these investigations on experimental hypertension that have been carried out so far but they do show that hypertension, severe disturbance of renal function, and generalized degenerative changes, including severe hyalinization and necrosis, of the arterioles, all indistinguishable from those found in the malignant phase of hypertension in man, can be induced experimentally by pronounced reduction of the blood supply to the kidneys.

All of the investigations that have been carried out so far (6, 8, 9 and 13–31), on the pathogenesis of the type of experimental hypertension that is produced by constriction of the main renal arteries, whether or not accompanied by renal insufficiency, indicate that a humoral mechanism, in some way of renal origin, is the primary cause. Whether the "hypothetical effect substance" (8) has a pressor effect, by direct peripheral vasoconstriction, or acts indirectly, in conjunction with some other substance, perhaps a known hormone, or whether it produces the hypertension by neutralizing a hypothetical depressor substance is not known. Whether it is the same or a different substance that is responsible for the production of the necrotic arterioles is also not known. The disturbance of the circulation which results from constriction of the main renal artery, consists, in all likelihood, of reduction of the intravascular pressure in the entire renal arterial system and of intracapillary pressure within the glomeruli, and at least initial reduction of blood flow through these functioning components of the kidney. It is of great significance that the most severe lesions observed have been in animals that have had a fairly long period of hypertension before the period of renal insufficiency occurred. In these animals, the arterioles also showed a varying amount of thickening of the media due to thickening of the muscular layer. In the animals, the necrotizing lesion in organs other than the kidneys is therefore secondary to the renal insufficiency and the hypertension, and probably represents merely an acceleration of a degenerative process at least partly initiated by the hypertension.

The pathological changes in the blood vessels of animals that have had hypertension for years, without significant disturbance of renal

function, will be reported upon at a later date, when a sufficient number of animals will have been studied to warrant conclusions about the pathogenetic relationship between hypertension alone and any pathologic changes that may be found in blood vessels, especially the arterioles. The thickening of the media already observed in the arterioles of some of the animals in the malignant phase of hypertension has been observed in some of the animals whose tissues have been examined after a long period of benign hypertension and was probably due to the preexisting phase of benign hypertension. Pathological changes in the retinal vessels of animals with persistent hypertension have already been reported (7). The animal (3-8) that showed the most severe change (obliterative hyalinization of the intima) was one that had had hypertension for more than 4 years, with accompanying moderate impairment of renal function. A complete report of the pathological changes in the eyes of dogs with benign or malignant hypertension will be made later.

SUMMARY AND CONCLUSIONS

The production of the acute malignant phase of experimental hypertension has been accomplished in seventeen dogs.

The method used to produce this type of hypertension was the same as for the benign type (4), namely, constriction of the main renal arteries, or the equivalent, constriction of the aorta above the origin of both main renal arteries, but the constriction was especially severe.

The malignant phase in the animals was characterized by hypertension, terminal renal insufficiency and the development of petechiae and larger hemorrhages in many internal organs, especially the alimentary tract. These were due to dissecting hemorrhage through, or rupture of, the wall of severely hyalinized or necrotic arterioles, or rupture of capillaries. Hyalinization and necrosis of arterioles were more severe and more widespread in animals that had a period of benign hypertension before the onset of renal insufficiency. In animals with a previous long period of benign hypertension, thickening of the media also occurred in arterioles, with or without hyalinized intima.

Elevation of blood pressure (mechanical factor) and renal insufficiency (humoral factor) are at least two of the necessary conditions for the development of the necrotic arterioles and hemorrhages. Necrotic arterioles and hemorrhages have not yet been observed in animals that have had very high blood pressure for years without renal insufficiency, nor in animals with azotemia, due to removal of both kidneys, but without hypertension. Hyalinized retinal arterioles have been observed in dogs with persistent hypertension and with moderate or no disturbance of renal function. That ischemia is not the cause of the necrosis of the arterioles is shown by their absence from the ischemic kidneys of the dogs and their widespread presence in other organs that were not ischemic.

These experiments show that the necrotic arterioles and hemorrhages are secondary to and not the primary cause of the malignant phase of hypertension.

Summary of Experimental History of the Animals

(1927–1930).—This was the period of development of the clamp for the constriction of the renal artery. During this time, petechiae and larger hemorrhages were observed in the gastrointestinal tract and some other organs of several animals in which both renal arteries had been severely constricted by clamps of various kinds. The gross hemorrhagic lesions were interpreted at that time as of infectious origin and were not subjected to microscopic examination. In these animals no determinations of blood pressure or of chemical changes in the blood had been made. The only determinations of blood pressure that were being made during this period were on normal animals, to study the natural variations of pressure during a long period. Two of these animals are still living and have had hypertension for nearly 5 years, after having been observed during a normal period of 5 years.

(1930–1934).—During this period, the gross hemorrhagic lesions were observed in various organs, but mainly in the gastrointestinal tract, of three dogs. The results of early experiments were reported in 1932 (32).

No. 2-5. Short Haired, Female, Mongrel, 16 Kg.—Feb. 1, 1932. Normal period begun. During this period, the average systolic blood pressure[5] was 146 mm. Hg.

Apr. 2, 1932. Right main renal artery severely clamped. During the following 17 days the systolic blood pressure rose to a maximum of 180 mm. Hg.

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[5] In this publication, systolic blood pressure means blood pressure determined by the van Leersum carotid loop method.

Apr. 19, 1932. Left main renal artery severely clamped. Systolic blood pressure became progressively more elevated to a final level of 276 mm. Hg on the day of death. May 9, 1932, 3 days before death, became clinically uremic. Blood urea nitrogen 101 mg., non-protein nitrogen 135 mg., creatinine 6.5 mg. There was bleeding from the anus.

May 12, 1932. Died of renal insufficiency. At autopsy, there were petechiae and larger hemorrhages in the mucosa of the stomach, small and large intestine. Microscopically, in addition to the hemorrhages, there were severely hyalinized and necrotic arterioles in the mucosa, submucosa and muscularis of stomach and intestine, and some hyalinized arterioles in the pancreas.

No. 8-7. Mongrel, Female, 14 Kg.—Jan. 7, 1933. Normal period begun. Average systolic blood pressure during this period was 153 mm. Hg.

Apr. 12, 1933. Right main renal artery severely constricted (almost complete). During this period the systolic blood pressure reached 200 mm. Hg, then subsided to 170 mm. Hg.

Apr. 25, 1933. Left main renal artery severely constricted. The animal survived only 4 days. During this period the blood pressure rose progressively until it reached a systolic pressure of 300 mm. Hg on the day before death. During the last 2 days the animal was anuric and clinically uremic. B.U.N. 218 mg., N.P.N. 320 mg. There was some bleeding from the anus.

Apr. 30, 1933. Found dead. At autopsy, petechiae in the gastrointestinal tract and urinary bladder. The tissues were in poor condition, for the animal had been dead about 36 hours in a warm room. No microscopic examination of the tissues was made.

No. 1-33.—Nov. 27, 1933. Normal period begun. Average systolic blood pressure during this period was 155 mm. Hg.

Mar. 15, 1934. Left main renal artery severely constricted and a fish skin bag placed around the kidney to reduce the accessory circulation through the capsule. Maximum systolic pressure during this period was 200 mm. Hg.

Apr. 16, 1934. Right main renal artery severely constricted and the kidney encased in a fish skin bag. Blood pressure rose steadily to a systolic pressure of more than 300 mm. Hg for several days before death. On the day of death it fell to 220 mm. Hg. On that day the dog was in uremic coma, was vomiting bloody fluid and passing bloody fluid from the anus.

May 31, 1934. Killed with ether. At autopsy, there were petechiae and larger hemorrhages in the esophagus, stomach, intestine, pancreas, mesentery, myocardium and urinary bladder. Microscopically, these hemorrhages were associated with the presence of hyalinized and necrotic arterioles.

(1934–1936).—During this time the hemorrhagic lesions were observed in two more dogs following a period of hypertension and renal insufficiency.

No. 2-37. Short Haired Police, Female, 15 Kg.—Nov. 25, 1935. Normal period begun. During this period the systolic blood pressure was 174 mm. Hg.

Jan. 3, 1936. Splanchnic section and excision of lower four thoracic sympathetic ganglia on both sides. The blood pressure remained unchanged during this period; the average systolic blood pressure was 176 mm. Hg.

Jan. 21, 1936. The right main renal artery was severely constricted. The systolic blood pressure rose to a maximum of 210 mm. Hg during this period and then subsided.

Feb. 19, 1936. Systolic blood pressure 180 mm. Hg. Left main renal artery severely constricted. The systolic blood pressure rose to a maximum of 250 mm. Hg on Feb. 22, 2 days before death, when the B.U.N. was 109 mg., N.P.N. 138 mg. and Cr. 7.8 mg. On this day the animal was in clinical uremia, vomited bloody mucus and passed bloody material from the anus.

Feb. 24, 1936. The animal was found dead. At autopsy, petechiae and larger hemorrhages in the serosa and mucosa of the stomach and intestine, especially the large bowel, in the epicardium, myocardium, brain and leptomeninges. Microscopically, there were hyalinized and necrotic arterioles in the stomach and intestine. In the other organs the hemorrhages appeared to be of capillary origin.

No. 2-50. Long Haired, Female, Shepherd Collie, Young.—Apr. 4, 1936. Normal period begun. During this time the average systolic blood pressure was 150 mm. Hg and the direct blood pressure[6] was 134 mm. Hg.

May 14, 1936. The right main renal artery was severely constricted. The blood pressure rose during this period to a maximum systolic of 240 mm. Hg.

June 23, 1936. Right kidney was removed. The blood pressure fell promptly to normal, and remained down.

Sept. 3, 1936. The left main renal artery was severely constricted. The blood pressure rose again and became progressively higher until both direct and systolic pressures were more than 300 mm. Hg.

Oct. 12, 1936. B.U.N. 26.3 mg.

Oct. 14, 1936. The posterior chambers of both eyes were filled with blood. The eyeballs were tense.

Oct. 15, 1936. B.U.N. 83 mg. The animal was anuric and comatose. The direct blood pressure was 240 mm. Hg and the systolic pressure 270 mm. Hg. The dog was killed with ether. At autopsy, petechiae and larger hemorrhages were present in esophagus, stomach, small and large intestine, urinary bladder and pancreas. Microscopically, the arterioles in all these organs showed severe hyalinization and necrosis. This was most severe in the arterioles of the alimentary tract.

(1936–1938).—During this period a deliberate attempt was made to produce the arteriolar lesions by various methods, and they were also observed in other experimental animals. All of these methods had in common severe reduction of the blood supply to the kidneys.

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[6] In this publication, direct blood pressure means the so called mean blood pressure in the femoral artery, determined by inserting a needle connected with a mercury manometer directly into the femoral artery.

No. 2-67. Short Haired, Mongrel Bull, Female, Middle Aged, 13.6 Kg.—May 2, 1936. Normal period begun. Average direct blood pressure 135 mm. Hg. B.U.N. 15.7 mg., N.P.N. 33 mg. and Cr. 1.4 mg. per 100 cc.

May 28, 1936. Left main renal artery severely constricted. During this period the direct blood pressure rose to a maximum of 215 mm. Hg.

Feb. 23, 1937. Direct blood pressure 200 mm. Hg. B.U.N. 14.3 mg., N.P.N. 32.1 mg., Cr. 1.6 mg. Left nephrectomy. Blood pressure fell to normal in less than 24 hours and remained down.

Mar. 31, 1937. B.U.N. 17.3 mg., N.P.N. 33.3 mg., Cr. 1.7 mg. Direct blood pressure 140 mm. Hg. The right main renal artery was severely constricted. Direct blood pressure became re-elevated to a maximum of 230 mm. Hg.

Apr. 2, 1937. B.U.N. 24.3 mg., N.P.N. 92 mg., Cr. 2.4 mg. Direct blood pressure 205 mm. Dog vomiting, looked ill and muscles were twitching. Clamp on the right main renal artery was released completely, at 4:30 p.m.

Apr. 3, 1937. 9:00 a.m. Direct blood pressure 140 mm. Hg and remained down. B.U.N. 23.3 mg., N.P.N. 37.6 mg., Cr. 1.1 mg. Twitching stopped. Animal improved rapidly.

Apr. 23, 1937. 11:00 a.m. Direct blood pressure 140 mm. Hg. Right main renal artery reconstricted, severely. Direct blood pressure again rose to maximum of 200 mm. Hg. 3:30 p.m. Direct blood pressure 175 mm. Hg. Anuria. Animal ill. Vomiting. Clamp slightly released.

May 11, 1937. Became progressively more uremic. B.U.N. 133 mg., N.P.N. 194 mg., Cr. 6.0 mg. Vomiting bloody mucus and passing blood from the anus. Killed with ether. At autopsy, petechiae and larger hemorrhages in the esophagus, stomach, and small and large intestine, pancreas, epicardium, abdominal lymph nodes, pituitary and brain. In the right optic thalamus there was one zone of hemorrhage 0.5 cm. in diameter. Microscopically, these hemorrhagic lesions were associated with the presence of hyalinized and necrotic arterioles. The lesions of the arterioles were most severe in the gastrointestinal tract, pancreas and abdominal lymph nodes.

No. 3-05. Reddish Brown Male, Mongrel Hound, Middle Aged, 17 Kg.—Dec. 1, 1936. Normal period begun. The average direct blood pressure during this period was 138 mm. Hg.

Mar. 9, 1937. Left main renal artery severely constricted. After this the direct blood pressure reached a maximum of 215 mm. Hg on Apr. 5 and May 17, 1937.

Apr. 23, 1937. Direct blood pressure 190 mm. Hg. B.U.N. 10.5 mg., N.P.N. 24.5 mg., Cr. 1.2 mg.

May 25, 1937. Left nephrectomy. The direct blood pressure fell to 140 mm. Hg, in less than 24 hours, and remained normal.

June 28, 1937. Right main renal artery severely constricted.

July 2, 1937. Direct blood pressure rose to a maximum of 200 mm. Hg on this day.

July 3, 1937. B.U.N. 147 mg., N.P.N. 181.8 mg., Cr. 6.8 mg. The animal was comatose and died while the blood pressure determination was being made. At autopsy, petechiae and larger hemorrhages in the esophagus, stomach, intestine, pancreas, myocardium, diaphragmatic muscle, mesentery, omentum, brain and retroperitoneal lymph nodes, gall bladder and urinary bladder. Microscopically, these hemorrhagic lesions were associated with the presence of hyalinized and necrotic arterioles.

No. 3-07. Female, Police, Old, 26 Kg.—Dec. 1, 1936. Normal period begun. During this time the average direct blood pressure was 145 mm. Hg.

Mar. 15, 1937. Left main renal artery severely constricted. The direct blood pressure rose during this period to a maximum of 205 mm. Hg, on Apr. 19, and then began to subside.

Apr. 22, 1937. Direct blood pressure 170 mm. Hg. B.U.N. 22.0 mg., N.P.N. 41.4 mg., Cr. 1.7 mg. Right nephrectomy. The direct blood pressure rose again to 205 mm. Hg but dropped when the animal became seriously ill.

May 10, 1937. B.U.N. 271, N.P.N. 354, Cr. 8.4. In clinical uremia. Vomiting. Bleeding from anus.

May 11, 1937. Found dead. At autopsy, petechiae in the small and large intestine. Microscopically, these petechiae were associated with partly or completely hyalinized and necrotic arterioles, but the wall of most of these vessels was not thickened and the lumen was not decreased in diameter in the larger arterioles.

No. 3-12. Female, Short Haired, Mongrel, Young, 13.5 Kg.—Jan. 5, 1937. Normal period begun. During this period the average direct blood pressure was 146 mm. Hg.

Mar. 25, 1937. Left nephrectomy and partial suprarenalectomy. Two-fifths of the cortex alone of the left suprarenal was left. During this period the average direct blood pressure was 143 mm. Hg.

Apr. 13, 1937. Right suprarenalectomy and right main renal artery severely constricted.

Apr. 23, 1937. Animal died in uremia. The direct blood pressure during this period rose to a maximum of 220 mm. Hg. The N.P.N. on the day of death was 300 mg., Cr. 12.9 mg. At autopsy, there were petechiae in the esophagus, stomach and intestine. These were most severe in the lower part of the small intestine and in the large intestine. There were also petechiae and larger hemorrhages in the epicardium and myocardium. Microscopically, these lesions were associated with hyalinized and necrotic arterioles. The necrotic arterioles were most abundant in the sections of intestine.

No. 3-16. Police, Female, Young, 14 Kg.—Feb. 9, 1937. Normal period begun. The average direct blood pressure during this period was 125 mm. Hg.

Mar. 26, 1937. Left nephrectomy and partial left suprarenalectomy. About half of the cortex alone of this suprarenal was left, the medulla of this portion was destroyed. Average direct blood pressure during this period was 121 mm. Hg.

Apr. 28, 1937. Right suprarenalectomy. Right renal artery severely clamped. During this period the direct blood pressure reached a maximum of 225 mm. Hg 2 days before death. On May 23, the day of death, it was 215 mm. Hg. N.P.N. 74 mg. and Cr. 2.6 mg. At autopsy, there was a moderate number of discrete petechiae in the small and large intestine. Microscopically, these hemorrhagic lesions, especially in the mucosa, were associated with the presence of hyalinized and necrotic arterioles.

No. 3-35. Male, Chow, Young, 12.4 Kg.—Mar. 31, 1937. Normal period begun. Average direct blood pressure 127 mm. Hg.

July 29, 1937. Left main renal artery severely constricted. Direct blood pressure rose to 185 mm. Hg and then returned eventually to 145 mm. Hg. B.U.N. 19.5 mg., Cr. 1.5 mg.

Dec. 28, 1937. Right main renal artery severely constricted.

Dec. 31, 1937. Direct blood pressure 200 mm. Hg. B.U.N. 64.5 mg., Cr. 3.6 mg.

Jan. 1, 1938. Direct blood pressure 200 mm. Hg. B.U.N. 150 mg., Cr. 6.4 mg.

Jan. 2, 1938. At 11:00 p.m., the animal was in uremic coma and at 11:30 a.m. it was found dead. At autopsy, there were petechiae and larger hemorrhages in great abundance in the esophagus, stomach, small and large intestine, pancreas, gall bladder and urinary bladder, myocardium, diaphragmatic muscle and brain. Microscopically, these hemorrhagic lesions were associated with the presence of necrotic and hyalinized arterioles. Many of the arterioles had a thickened media.

No. 3-41. Collie, Male, 13.2 Kg.—Apr. 20, 1937. Normal period begun. The average direct blood pressure during this period was 126 mm. Hg.

Oct. 9, 1937. Both main renal arteries were constricted very severely at the same time.

Oct. 11, 1937. Direct blood pressure 208 mm. Hg. B.U.N. 96 mg., Cr. 2.8 mg.

Oct. 12, 1937. Direct blood pressure 220 mm. Hg. B.U.N. 150 mg., Cr. 5.4 mg. Passing blood from urethra and anus. In uremic coma. Vomiting.

Oct. 13, 1937. Found dead. At autopsy, petechiae and hemorrhages in the stomach, small and large intestine, brain (parietal lobe). Microscopically, in the stomach and intestine, these lesions were associated with hyalinized and necrotic arterioles, without much thickening of the wall or reduction of size of lumen. In the brain, the hemorrhage appeared to be of capillary origin.

Nos. 3-37, 3-59, 3-62.—In these dogs the aorta was greatly constricted immediately above the origin of both main renal arteries.

Nos. 3-63 and 3-65.—In these dogs, the right kidney was first removed and the aorta was severely constricted above the origin of the left main renal artery. Full details about these experiments will appear in a later paper with Dr. J. R. Kahn. In these five dogs, uremia developed, and, at autopsy, there were

petechiae in the gastrointestinal tract of all and in other organs of some of the animals. Microscopically, there were hyalinized and necrotic arterioles, most abundant in the intestinal mucosa and submucosa.

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EXPLANATION OF PLATE 36

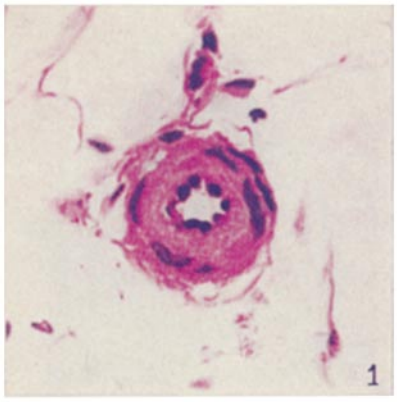
FIG. 1. Arteriole in submucosa of large intestine. Beginning subendothelial deposit of hyalin. Endothelium well preserved. Hematoxylin and eosin. ×265.

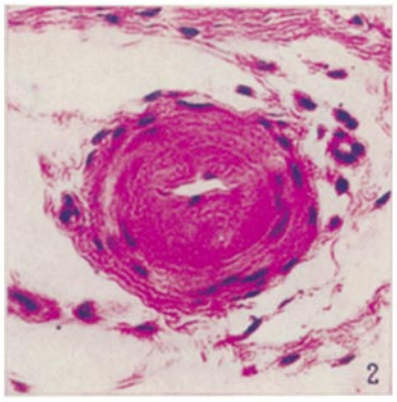
FIG. 2. Arteriole in submucosa of stomach. Obliterative hyalinization of intima, endothelium still recognizable but nuclei reduced in number and pyknotic. Hematoxylin and eosin. ×430.

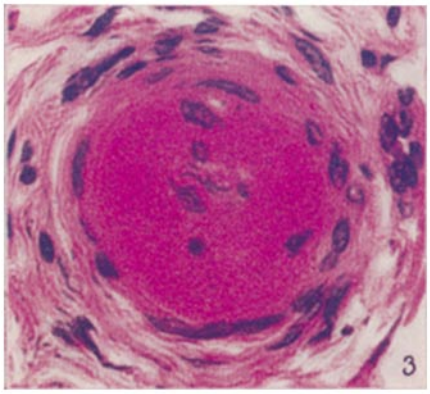
FIG. 3. Arteriole in submucosa of small intestine. Lumen completely obliterated by accumulation of hyalin containing a few pyknotic nuclei. Hematoxylin and eosin. ×430.

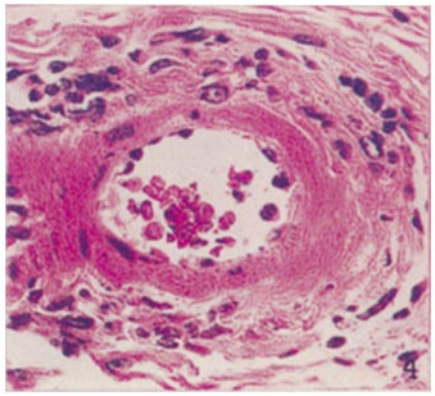
FIG. 4. Arteriole in submucosa of stomach. Portion of entire thickness of wall necrotic. Normal thickness of wall and lumen natural size. Hematoxylin and eosin. ×325.

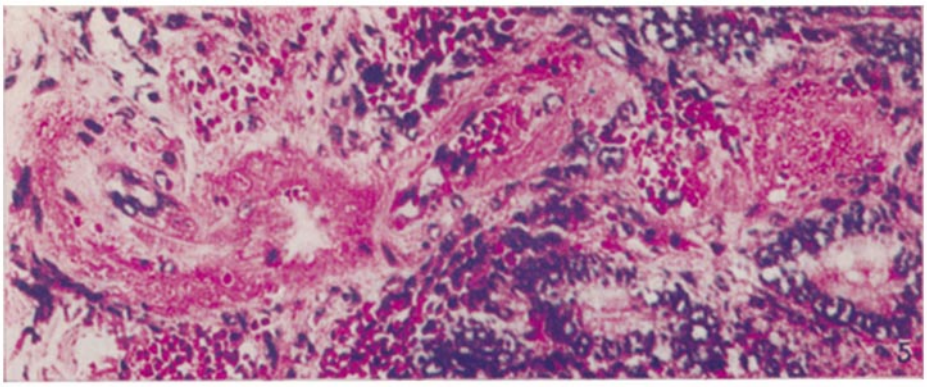
FIG. 5. Arteriole, cut longitudinally, in submucosa and mucosa of large intestine. Partly hyalinized, partly necrotic, with extravasated blood around it. A portion of the same arteriole, in the submucosa, immediately proximal to the part included in this figure, was entirely normal. Hematoxylin and eosin. ×255.











(Goldblatt: Hypertension. VII)