EXPERIMENTAL HYPERTENSION

THE EFFECTS OF UNILATERAL RENAL ISCHEMIA COMBINED WITH INTESTINAL ISCHEMIA ON THE ARTERIAL BLOOD PRESSURE*

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Longcope and McClintock (1) determined the effects of constriction of the celiac axis and superior mesenteric artery of dogs by means of aluminum bands and found that neither cardiac hypertrophy nor hypertension followed the narrowing of these vessels. Blalock and Levy (2), by multiple stage operations, produced complete occlusion of the celiac axis, superior and inferior mesenteric arteries in survival experiments on dogs and reported that these procedures do not result in arterial hypertension. However, the blood pressure did not return entirely to the control level in approximately one half of the animals which survived following complete occlusion of the three main intestinal vessels, remaining elevated about 15 to 20 mm. Hg. This was considered to be of no significance but in view of later observations, it may be of importance.

The present experiments consist of a study of the effects on the blood pressure of unilateral renal ischemia in animals in most of which the three main intestinal vessels had been occluded previously.

Methods and Results

Dogs were used in all experiments. The blood pressure was determined by puncturing the femoral artery with a needle that was con-

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nected to a mercury manometer. The value obtained is approximately the mean blood pressure. The celiac axis, superior and inferior mesenteric arteries were occluded completely in multiple stage operations by the use of Goldblatt clamps.¹ In four experiments, unilateral renal ischemia was not produced until after the occlusion of these intestinal vessels had been rendered complete. In one experiment, due to an oversight, unilateral renal ischemia was caused before the inferior mesenteric artery was occluded. In the sixth experiment, intestinal and unilateral renal ischemia were induced simultaneously.

Since the experiments were few in number and since the procedures and results varied somewhat in the different studies, the protocol of each experiment is given in a moderate amount of detail. The two figures for blood pressure are the high and low values associated with the act of respiration.

Dog 1. Aug. 5, 1937, control blood pressure (needle puncture) 125–130. Aug. 5, incision left flank, Goldblatt clamps to celiac axis, one of $2\frac{1}{2}$ turns, to superior mesenteric artery $\frac{3}{4}$ of $2\frac{1}{2}$ turns. Slight temporary rise in blood pressure. Aug. 24, blood pressure 125–130. Aug. 25, $\frac{3}{4}$ additional turn of each clamp. Sept. 20, blood pressure 110–125. Abdominal incision, Goldblatt clamp to inferior mesenteric artery $2\frac{1}{2}$ of $3\frac{1}{2}$ turns. Oct. 23, blood pressure 142–152, incision left flank. Clamp on superior mesenteric artery had cut through artery, clamp came out when grasped. Clamp on celiac axis completely tightened. Nov. 4, blood pressure 160–166, abdominal incision, arterial pulsations could not be felt in intestinal vessels. Clamp on inferior mesenteric artery completely closed. The blood pressure the succeeding 2 months averaged approximately 150 mm. Hg. Jan. 14, 1938, incision left flank, Goldblatt clamp to left renal artery two of $3\frac{1}{2}$ turns. Jan. 19, blood pressure 210–215. The mean blood pressure which was determined every 2 or 3 days has remained at approximately that level. Aug. 3, blood pressure 205–215, incision right flank, the right kidney and renal vessels seemed entirely normal. Kidney possibly somewhat hypertrophied. Pulsations could be felt in arteries in mesentery of intestine but they were thought to be diminished. Jan. 31, 1939, blood pressure 215–225. Feb. 18, blood pressure 200–210. This dog lost weight during the process of occlusion of the vessels to the intestinal tract but has more than regained it since that time. Despite the fact that a clamp was applied to the renal artery of only one kidney, there has been a persistent elevation in blood pressure for almost 14 months. The blood pressure readings are recorded in Text-fig. 1.

¹ Furnished through the courtesy of Dr. Harry Goldblatt, Cleveland, Ohio.

Dog 2. Feb. 2 to Feb. 10, 1938, control blood pressure (needle puncture) varied from 105 to 130 mm. Hg. Weight 8.5 kg. Feb. 10, incision left flank, Goldblatt clamps to celiac axis, $\frac{3}{4}$ of $3\frac{1}{2}$ turns, to superior mesenteric artery, $\frac{2}{3}$ of $3\frac{1}{2}$ turns, to left renal artery $1\frac{1}{2}$ of $3\frac{1}{2}$ turns. A moderate rise in the blood pressure followed. Mar. 5, blood pressure 160–170. Incision left flank. Clamps on celiac axis and superior mesenteric artery each tightened $\frac{3}{4}$ turn, clamp on renal artery tightened $\frac{1}{4}$ turn. Mar. 16, blood pressure 150–165, inferior mesenteric artery doubly ligated and divided. Apr. 15, blood pressure 158–166. Apr. 19, blood pressure 130–138. Weight 8.2 kg. Apr. 21, clamps on celiac axis and superior mesenteric artery completely closed. Clamp on renal artery tightened $\frac{1}{4}$ turn. Apr. 30, blood pressure 175–185. The mean blood pressure continued to range

TEXT-FIG. 1. Dog 1. • = mean arterial blood pressure. CA, SM (1), partial constriction of celiac axis and superior mesenteric artery. IMA (1), partial constriction of inferior mesenteric artery. CA, SM (2), celiac axis and superior mesenteric artery completely occluded. IMA (2), inferior mesenteric artery completely occluded. RA, partial constriction of left renal artery.

between 170 and 240 mm. Hg, the usual level being about 195 mm. Hg. Nov. 16, blood pressure 182–188, incision left lower chest, supradiaphragmatic splanchnicectomy on left. Nov. 23, blood pressure 195–205. Dec. 2, blood pressure 190–200. Dec. 3, supradiaphragmatic splanchnicectomy on right. Dec. 5, blood pressure 205–215. Feb. 9, 1939, blood pressure 190–198. Ether, incision right flank. Right kidney and artery normal, incision closed. Feb. 11, blood pressure 190–200. Feb. 20, blood pressure 190–200. Weight 7.4 kg. It is now more than 10 months since the Goldblatt clamp on the renal artery was tightened the last time and the blood pressure has remained elevated. The blood pressure readings are given in Text-fig. 2.

Dog. 3. Feb. 25, 1938, weight 8.0 kg. Control blood pressure (needle puncture) 124–130. Incision left flank, Goldblatt clamps to celiac axis, $1\frac{1}{2}$ of $2\frac{1}{2}$ turns, to superior mesenteric artery $\frac{3}{4}$ of $3\frac{1}{2}$ turns. Slight temporary rise in blood pressure. Mar. 18, blood pressure 114–122. Incision left flank, $\frac{1}{2}$ turn to clamp on celiac axis and one turn to that on superior mesenteric artery. Temporary rise in blood pressure. Apr. 8, inferior mesenteric artery doubly ligated and divided. May 17, blood pressure 145–155. Incision left flank, the occlusion of the Goldblatt clamps on the celiac axis and superior mesenteric artery was made complete. Slight rise in pressure. June 14, blood pressure 140–145. Incision right flank, Goldblatt clamp to right renal artery $1\frac{1}{2}$ of three turns. June 20, blood pressure 190–196.

TEXT-FIG. 2. Dog 2. • = mean arterial blood pressure. CA, SM, RA (1), partial constriction of celiac axis, superior mesenteric artery and left renal artery. CA, SM, RA (2), constriction of these three vessels increased. IMA, ligation and division of inferior mesenteric artery. CA, SM, and RA (3), celiac axis and superior mesenteric artery completely occluded, constriction of left renal artery increased. Right and left splanchnectomy, supradiaphragmatic approach.

June 21, blood pressure 220–230. It is now more than 8 months since this single application of the Goldblatt clamp to the renal artery of one of the two kidneys, the blood pressure has remained elevated, the mean pressure ranging from 170 to 215 mm. Hg. Weight of animal 10.0 kg. The blood pressure readings are given in Text-fig. 3.

Dog. 4. Nov. 5, 1937, mean blood pressure 115–120. Incision left flank. Goldblatt clamp to celiac axis $1\frac{1}{2}$ of $3\frac{1}{2}$ turns, to superior mesenteric artery $\frac{1}{2}$ of $3\frac{1}{2}$ turns. Little if any alteration in blood pressure followed. Nov. 26, blood pressure 108–116, incision left flank, each clamp tightened $\frac{3}{4}$ turn. Dec. 16, blood pressure 122–130, clamp on inferior mesenteric artery $2\frac{1}{2}$ of $3\frac{1}{2}$ turns. Slight

rise in pressure followed. Jan. 3, 1938, blood pressure 138–144, incision left flank, clamps on celiac axis and superior mesenteric artery completely tightened. Jan. 11, blood pressure 142–146, lower abdominal incision, clamp on inferior mesenteric artery completely closed. No pulsations could be felt in mesenteric vessels. Jan. 24, blood pressure 128–134, incision right flank, Goldblatt clamp to right renal artery, $1\frac{1}{2}$ of $3\frac{1}{2}$ turns. Moderate rise in blood pressure. Feb. 10, blood pressure 175–180. Incision right flank, $\frac{1}{2}$ turn of clamp on renal artery. Feb. 14, blood pressure 204–210. Mar. 16, blood pressure 170–175. Incision right flank, $\frac{1}{4}$ turn of clamp on renal artery. Mar. 26, blood pressure 175–180. The mean blood pressure remained at approximately this level. July 2, blood pressure 175–180. July 7, blood pressure 155–160. Dog has developed discharging sinus

TEXT-FIG. 3. Dog 3. • = mean arterial blood pressure. CA, SM (1), partial constriction of celiac axis and superior mesenteric artery. CA, SM (2) increase in constriction of same two vessels. IMA, ligation and division of inferior mesenteric artery. CA, SM (3), complete occlusion of celiac axis and superior mesenteric artery. RA, partial occlusion of right renal artery.

right flank. Incision right flank. Enormous right kidney with marked pyonephrosis. Autopsy showed complete occlusion of right renal artery, celiac axis, superior and inferior mesenteric arteries. Left kidney and left renal artery appeared normal. The blood pressure remained definitely elevated for more than 5 months following constriction of the artery to one of the two kidneys. It began to decline when a severe pyonephrosis developed.

Dog 5. Weight 12.4 kg. Control blood pressure (needle puncture) 120–130 mm. Hg. Feb. 25, 1938, incision left flank, Goldblatt clamps to celiac axis $2\frac{1}{4}$ of four turns, to superior mesenteric artery $\frac{1}{2}$ of $3\frac{1}{2}$ turns. Feb. 28, blood pressure 156–162. Slow return of blood pressure to normal. Mar. 18, blood pres-

sure 110–120. Incision left flank, $\frac{3}{4}$ turn to clamp on celiac axis and $1\frac{1}{4}$ to clamp on superior mesenteric artery. Slight rise in blood pressure. Apr. 9, inferior mesenteric artery doubly ligated and divided. Slight rise in blood pressure. May 17, blood pressure 135–140, clamps on celiac axis and superior mesenteric artery completely closed. Very little change in blood pressure. June 9, blood pressure 130–135. Weight 11.9 kg. June 14, blood pressure 145–150. Incision right flank, Goldblatt clamp to right renal artery, two of three turns (pulsation obliterated at $2\frac{1}{4}$ turns). June 17, blood pressure 160–165. July 2, blood pressure 184–190, weight 11.8 kg. July 11, blood pressure 165–170. Incision right flank, kidney smaller than normal. Right main renal artery found to be completely occluded. Pulsations could be felt in ureteral vessels. July 15, blood pressure 165–170. The blood pressure varied during the succeeding 4 months between 140 and 180. Nov. 7, blood pressure 160–165, incision left flank, Goldblatt clamp to left renal artery, $4\frac{1}{5}$ of $2\frac{1}{4}$ turns. Nov. 12, blood pressure 190–195. Nov. 16, blood pressure 210–215. Dog looked sick. Incision left flank reopened, blood clot around clamp, clamp loosened. Nov. 21, blood pressure 230–236, N.P.N. 28. Marked elevation in blood pressure continued. Dec. 5, blood pressure 270–275. Dec. 12, weight 12.4 kg. Blood pressure 250–260. Given large dosages of phlorizin for 4 days at suggestion of Dr. Morton F. Mason in order to study its effect on the blood pressure. The pressure remained markedly elevated. Dec. 19, blood pressure 250–260. Dec. 24, blood pressure 235–245, animal appeared to be in good condition, good appetite. No abnormality noted except that eyes had been rather prominent for several weeks. Dec. 25, animal died, apparently rather suddenly. Autopsy revealed the following findings. Bloody fluid in both pleural cavities. The pericardium was filled with blood, most of which was clotted. The clot weighed 90 gm. There was a hemorrhagic area overlying the intrapericardial portion of the aorta with hemorrhage into a cavity which appeared to be between the adventitia and media of the wall of the aorta. There was a peculiar small defect overlying the left descending coronary artery. On one occasion it was thought that a small blood clot was squeezed from it but this could not be repeated. The kidneys were essentially normal in size, the left slightly smaller than the right. The left main renal artery was occluded. The lumen of the main right renal artery was occluded but there was a smaller artery which was patent. Hemorrhagic area just beneath the capsule of the left kidney. The celiac axis, superior and inferior mesenteric arteries were found to be completely occluded. The intestinal tract appeared to be essentially normal.

Dr. James Dawson of the Department of Pathology studied the microscopic sections and gave us the following report:

Examination of sections from the aorta shows that the wall of this vessel has been split. This is shown in Fig. 1. This splitting of the wall is seen in the outer third of the media. In general the coats of this vessel appear normal except for the blood filled space. There are, however, focal areas in which there is acute medio-necrosis associated with a polymorphonuclear leucocytic infiltration. This necrosis occurs in the outer portion of the media chiefly. Verhoeff elastic tissue

stains show little alteration in the elastic fibrils; there is questionable fraying but nothing more. The vasa vasorum in general have narrowed lumina; the degree of narrowing varies considerably but some are almost obliterated. This is shown in Fig. 2. This narrowing is due chiefly to intimal thickening. The split in the vessel wall generally is longitudinal for the most part but in some instances one sees clefts which run at right angle to the long axis of the vessel. These have extended through to the adventitia and within them as well as in the peri-adventitial stroma there is massive, fresh hemorrhage.

There is narrowing of the lumina of the smaller arteries and arterioles in the retina due to increase in thickness of media and intima. In the brain a few minute areas of softening are seen but there is little or no change in the vessel walls. The smaller branches of the coronary arteries show no definite change.

It is impossible to be certain of the sequence of events which transpired but it seems likely that obliteration of the lumina of the vasa vasorum, due to intimal thickening, led to necrosis of the media with the weakening of the wall; with the coexistent hypertension, rupture occurred and blood was forced into the vessel wall where it dissected along the media, finally escaping into the pericardium and leading to the death of the animal.

Dog 6. Male, weight 10.2 kg. Control blood pressure (needle puncture) 130–135. Feb. 22, 1938, incision left flank, Goldblatt clamp to celiac axis, $\frac{3}{4}$ of 3 turns, to superior mesenteric artery, $\frac{3}{4}$ of 3 turns. Feb. 25, blood pressure 140–146. Mar. 14, blood pressure 120–125, incision left flank, each Goldblatt clamp tightened $\frac{3}{4}$ turn. Mar. 25, weight 7.75 kg., blood pressure 110–115. Blood pressure remained at approximately this level. May 18, constriction of celiac axis and superior mesenteric artery was made complete. June 14, blood pressure 124–130, incision left flank, Goldblatt clamp to left renal artery $1\frac{1}{2}$ of $3\frac{1}{2}$ turns (occluded pulsation at $2\frac{1}{2}$ turns). June 16, blood pressure 150–155. June 20, weight 9.3 kg., blood pressure 140–145. June 25, clamp on left renal artery tightened $\frac{1}{4}$ turn. July 2, weight 8.81 kg. Blood pressure 130–135. Abdominal incision. Inferior mesenteric artery which was approximately twice the normal size was doubly ligated and divided. Very little alteration in the blood pressure. July 16, weight 9.27 kg., blood pressure 135–140. Incision left flank, kidney approximately one-fourth normal size. The clamp had cut through the artery. Its removal was followed by some bleeding, renal artery and vein ligation necessary in control of hemorrhage. No pulsations felt in ureteral vessels. Blood pressure slightly elevated for several days, return to approximately 135 mm. Hg where it remained. Oct. 20, weight 10.3, blood pressure 130–135. Nov. 7, incision right flank, Goldblatt clamp to right renal artery, one of $2\frac{1}{2}$ turns. Nov. 12, blood pressure 120–125. Dec. 12, blood pressure 140–145. Dec. 22, blood pressure 140–145, incision right flank, constriction of right renal artery increased by $\frac{1}{2}$ turn of clamp. Dec. 29, blood pressure 175–180. Jan. 9, 1939, blood pressure 215–225. Animal appeared ill, N.P.N. 71. Jan. 14, blood pressure 200–206. Animal appears well. Weight 10.4 kg. Feb. 4, blood pressure 205–215. Feb. 13, blood

pressure 220–225. Feb. 20, blood pressure 210–216. There was very little elevation in this animal until the second renal artery was constricted. It may be of significance that the Goldblatt clamp completely occluded the first renal artery.

DISCUSSION

It would appear to be more than a coincidence that a prolonged elevation in the blood pressure was observed in four of the six animals in which occlusion of the main arteries to the intestinal tract was followed by constriction of the renal artery of one of the two kidneys. As has been stated the pressure has remained definitely elevated for 14, 10, and 8 months respectively in three of the animals. The pressure declined in the fourth animal coincident with the development of pyonephrosis which was 5 months after the production of unilateral renal ischemia. The rise in pressure in the fifth animal was not so great and was not sustained as long. This may have been due in part to an accessory renal artery of moderate size which was found at the time of autopsy. It is interesting that this animal developed the most marked hypertension that we have observed following the induction of bilateral renal ischemia. Death was due to rupture of the intrapericardial portion of the aorta with resulting cardiac tamponade. There was very little elevation in the pressure in the sixth animal. It was found on exploration that the Goldblatt clamp had occluded completely the renal artery. In two of the four animals in which unilateral renal ischemia resulted in the most marked and sustained elevation in the blood pressure, the pressure was approximately 20 mm. higher before renal constriction than it had been prior to the production of intestinal ischemia. This may be an important factor in determining the response to renal ischemia. In general, the animals which exhibited the most marked rise in pressure associated with intestinal ischemia showed an even more marked elevation when unilateral renal ischemia was caused. This relationship could not be tested in one of the animals since intestinal and renal ischemia were induced simultaneously. A greater number of experiments are desirable and should be performed. The reasons for the relatively few experiments reported here are the high mortality rate associated with progressive intestinal ischemia, the technical difficulties associated with repeated exposure of the clamps, and the long time that it is necessary to observe these animals.

That the rise in blood pressure associated with unilateral renal ischemia was not due to the absence of a second kidney was shown by an exploratory operation in which the kidney and renal artery were palpated. Constriction of the intestinal vessels was not observed to reduce the calibre of the aorta with a resulting effect on the renal circulation. The operations for the purpose of inducing intestinal ischemia were all performed through an incision in the left flank. In the procedure of producing unilateral renal ischemia, the right and left sides were chosen an equal number of times. That the rise in blood pressure was not due to scarring of the renal pedicle associated with the operations on the intestinal vessels was shown by the absence of adhesions in the neighborhood of the right renal artery. Furthermore, we were unable to produce hypertension in previous experiments by injecting sclerosing solutions (sodium morrhuate) into and around the walls of the two renal arteries.

As stated, the prolonged elevation in blood pressure in four of these animals with unilateral renal ischemia would seem to be more than a coincidence. In a number of controls in which intestinal ischemia has not been present, we have not observed as lengthy and as marked elevations in pressure associated with unilateral renal ischemia. The usual finding is an elevation in pressure for 2 or 3 weeks followed by a return to the control level.

The following has been the experience of others. Goldblatt (3) stated, "It was shown in the original communication that hypertension of some degree follows the constriction of the main renal artery of only one kidney but that after a variable period the blood pressure tends to return to the original level. In some dogs the blood pressure remains elevated for a considerable period following unilateral renal ischemia. In one dog, the mean blood pressure remained at a higher level than normal for about nine months following the constriction of the main renal artery of only one kidney. During this time there was no impairment of renal function. After the removal of the kidney the blood pressure promptly fell to the normal level." The control pressure in this animal was approximately 135 mm. Hg and the pressure was approximately 180 mm. Hg 9 months following the production of unilateral renal ischemia. Goldblatt (4) stated subsequently, "In these and other studies, some of which have been reported, 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." In a personal communication (1938), Goldblatt states that the most common experience following unilateral constriction is an elevation in pressure which lasts from 2 to 6 weeks. Wood and Cash (5) have observed one dog in which the blood pressure remained elevated for 2 years following the production of unilateral renal ischemia. The animal was a very "nervous" male which weighed 27 pounds at the time that the right renal artery was constricted. Using their method for determining the systolic and diastolic pressures, the control figures were 148 and 54 mm. Hg. 2 years subsequently, the corresponding figures were approximately 200 and 83 mm. Hg. There had been a gain in weight of 10.5 pounds during this period. This may be of some significance. One of our animals has shown a considerable gain in weight. Elaut (6) produced hypertension by the Goldblatt method. He stated, "The hypertension is least pronounced and hardly exceeds 190 mm. Hg when the compression is limited to only one renal artery, the other remaining intact. It rapidly exceeds 200 mm. Hg if one compresses equally the two renal arteries." Verney and Vogt (7) report that the blood pressure was still elevated in one dog 104 days after unilateral renal ischemia had been induced. Fasciolo, Houssay, and Taquini (8) state, "Rise in blood pressure is obtained when ischemia of either or both kidneys is produced. If only one kidney is involved the blood pressure usually increases less and more slowly than if the two are involved; moreover, after a time it has a tendency to fall gradually to the normal level."

Additional confirmation of the rarity of a sustained elevation in the blood pressure following unilateral renal ischemia was obtained in the following additional observations. The first of these consisted of constricting partially one renal artery in each of five animals in which the two carotid and the two vertebral arteries had been ligated and divided previously. The latter procedure resulted in a moderate temporary elevation in the blood pressure. The production of unilateral renal ischemia was followed in four of the five animals by an elevation in blood pressure of about 35 mm. Hg which lasted for approximately 3 weeks. A rise in blood pressure of about 35 mm. Hg which persisted for 4.5 months, at which time the experiment was terminated, was noted in the fifth animal. The second observations consisted of producing unilateral renal ischemia in seven dogs after the pressure had returned to normal following ligation and division of the two common iliacs and the two subclavian arteries. There was no definite elevation in the pressure in one of these. There was an elevation in pressure of approximately 35 mm. Hg in four of these and it remained elevated for periods ranging from 3 to 8 weeks. The pressure of one of the animals rose approximately 50 mm. and remained

elevated for 11 weeks, at which time it returned to normal. The pressure of the seventh animal was elevated approximately 45 mm. for 3 months. It gradually declined after this time but did not quite return to the control level.

In one animal reported by Goldblatt (9), the splenic artery and both femoral arteries were greatly constricted at different times before the clamps were applied to the renal arteries, but no rise of blood pressure occurred until after the renal arteries were constricted.

That the non-ischemic kidney may be a factor in determining the blood pressure response to unilateral renal ischemia was shown by Blalock and Levy (10). In six of eight animals in which the blood pressure had returned to normal following the production of unilateral renal ischemia, removal of the sound kidney was followed by a re-elevation of the blood pressure. These findings have been confirmed by Verney and Vogt (7) and by Fasciolo, Houssay, and Taquini (8).

Various operations on the nervous system, even total sympathectomy (11), do not prevent the development of or abolish the hypertension that is associated with renal ischemia. It is evident that the renal ischemia cannot be altered by these procedures as long as the clamps remain applied. Bilateral supradiaphragmatic splanchnicectomy was performed on one of our animals with marked hypertension associated with intestinal and unilateral renal ischemia. No alteration in the blood pressure followed these procedures.

The cause for the unusually great and well sustained elevation in the pressure in most of the animals with intestinal and unilateral renal ischemia is not apparent. Even if one may for the moment liken occlusion of the large vessels of the intestinal tract to arteriosclerosis of the great vessels, it is well known that changes in the smallest arteries or arterioles are more closely correlated with hypertension than are lesions of the large arteries. A low blood pressure may be present in an individual with advanced arteriosclerosis. Extensive arteriosclerosis of the vessels of the gastro-intestinal tract is encountered very rarely. Occlusion of the large vessels to the intestinal tract at their origins from the aorta undoubtedly results in the opening up of many small vessels. This almost certainly results in an increase in the resistance to the flow of blood. This increase in resistance is apparently not great enough on its own account to cause a marked permanent elevation in the blood pressure, the disappearance being due

very likely to the opening up of collaterals. However, the small elevation in pressure which persisted in some of the animals following the induction of intestinal ischemia may be of more importance than we have assumed. Verney and Vogt (7) have shown recently that the perfused (non-ischemic) kidney liberates a substance which causes vasoconstriction of the vessels of the intestinal tract. The present conception of the hypertension associated with experimental renal ischemia is that a pressor substance (12, 13, 8) is formed in the kidney which causes increased peripheral vasoconstriction. It is possible that the explanation for our findings lies in an increased effectiveness of this hypothetical pressor substance due to an increase in the number of small vessels on which it may exert its effects. According to Poiseuille's law, the pressure varies inversely as the fourth power of the radius of a very small vessel. An extremely small increase in the tonus of a large area of arterioles suffices to cause marked hypertension. Goldblatt (4) has described thickening of the media of the arterioles with or without hyalinization of the intima in chronic hypertension due to renal ischemia. Child (14) has observed widespread changes in the arterioles, consisting of thickening of the walls with a decrease in the size of the lumina, and says that these alterations are most marked in the cardiac and mesenteric vessels. Unilateral renal ischemia may cause such changes in some of the smaller vessels conveying blood to the intestinal tract. This, however, is speculation as the animals which have had hypertension for long periods are still alive. It is interesting that one of our animals developed such marked alterations in the wall of the ascending aorta following the application of a clamp to the second renal artery that rupture of this large vessel occurred. This is the first time that this has been observed. Another possibility is that intestinal ischemia may in some way interfere with the development of collateral circulation to the ischemic kidney. Still another possibility is that intestinal ischemia may in some way interfere with the destruction of the pressor substance, if the evidence to the effect that such is formed in the ischemic kidney is correct.

Heymans (15) has called attention to a pressoreceptive mechanism located in the splanchnic area which has to do with the regulation of blood pressure and other functions. He states, "Experiments employing several different methods have permitted us, with the collaboration of Bouckaert, Farber, Hsu and Wierzu-

chowski, to show that in the dog deprived of carotid sinus, cardio-aortic, pulmonary and venous presso-sensitive zones, as in the spinal animal, the proprioceptive regulation of vascular zone still occurs, through presso-sensitive reflexes originating mostly from the vascular territory of the celiac and mesenteric arteries and secondarily from the territory of the thoracic arteries." It is possible that intestinal ischemia increases the responsiveness of this regulating mechanism to the effects of the hypothetical renal pressor substance.

Longcope and McClintock (1) examined at autopsy 46 patients in whom either the heart showed hypertrophy or the mesenteric artery and celiac axis were narrowed by arteriosclerotic processes, pressures from aneurisms, or from new growths. Of the 21 cases in which the splanchnic vessels were narrowed, only seven were associated with cardiac hypertrophy and in all seven cases a chronic nephritis coexisted.

The experiments reported confirm this observation in that intestinal ischemia alone does not result in a marked permanent elevation in the blood pressure.

SUMMARY

Unilateral renal ischemia superimposed upon intestinal ischemia has resulted in a prolonged elevation in the arterial blood pressure in a high percentage of the animals which were studied.

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EXPLANATION OF PLATE 43

FIG. 1. Hematoxylin and eosin. Photomicrograph of longitudinal section of aorta showing the split in the media and hemorrhage into the media and adventitia. $\times 30$.

FIG. 2. Hematoxylin and eosin. Photomicrograph showing vasa vasorum in media of aorta with narrowing of lumen due to thickening, particularly in intima. $\times 500$.

(Blalock *et al.*: Hypertension)