thrombin, a common pathway may be involved in the release reaction caused by all these stimuli.

Summary. Phenylbutazone inhibits thrombin-induced platelet aggregation and the release of platelet constituents but this effect can only be demonstrated with low concentrations of thrombin. The action of thrombin on fibrinogen is not affected by phenylbutazone.

1. Hovig, T., Thromb. Diath. Haemorrthag. **9**, 264 (1963).

2. Mustard, J. F., Glynn, M. F., Nishizawa, E. E., and Packham, M. A., Federation Proc. **26**, 106 (1967).

3. Packham, M. A., Warrior, E. S., Glynn, M. F., Senyi, A, S., and Mustard, J, F., J. Exptl. Med. **126**, 171 (1967).

4. Packham, M. A., Nishizawa, E. E., and Mustard, J. F., Biochem. Pharmacol. Suppl. **171** (1968).

5. Evans, G., Nishizawa, E. E., Packham, M. A., and Mustard, J. F., Blood **30**, 550 (1967).

6. Haslam, R. J., Nature **202**, 765 (1964).

7. Evans, G., Packham, M. A., Nishizawa, E. E., Mustard, J. F., and Murphy, E. A., J. Exptl. Med. **128**, 877 (1968).

8. Glynn, M. F., Movat, H. Z., Murphy, E. A., and Mustard, J. F., J. Lab. Clin. Med. **65**, 179 (1965).

9. Mustard J. F., Hegardt, B., Rowsell, H. C., and MacMillan, R. L., J. Lab. Clin. Med. **64**, 548 (1964).

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Effects of Subtotal Nephrectomy on Renal Hypertension* (33491)

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On the assumption that renal hypertension is due to relative renal ischemia and increased renin release, it has been suggested that reduction of renal mass—by restoring a proper balance between renal blood flow and renal mass and by reducing the number of cellular complexes responsible for renin formation—might reverse the course of hypertension (1, 2). Results have been inconclusive, however (1–6). In some experiments, remission of hypertension was attributed to establishment of a secondary circulation (3). On the other hand, in those in which hypertension persisted (4, 5), it was not proven to be still dependent on renal mechanisms. The purpose of the present investigation was to study sequentially the effects of partial and total resection of clipped kidneys on blood pressure and to correlate the data obtained with renal renin.

Methods. Female Sprague-Dawley rats weighing 155–165 g were made hypertensive by unilateral clipping of the renal artery with and without contralateral nephrectomy. In experimental series 1, one kidney was clipped and the other was left untouched. After stabilization of pressure, hypertensive animals were evenly divided according to blood pressure levels into 3 groups. Part of the clipped kidney was surgically removed in group 1 and excluded by a ligature in group 2. Animals of group 3 were sham-operated. After 35 days, all animals of group 2 and 6 of group 1 were killed; clipped kidneys were resected in the remaining animals of group 1 and in those of group 3. The experiment was terminated on day 42. The number of surviving animals in each group was 14, 6, and 8, respectively.

In experimental series 2, the contralateral kidney was removed at the time of renal artery clipping. Hypertensive animals were also divided into 3 groups and treated as in the first series. Twenty-six days later, kidneys were unclipped in all groups, but not removed, so as to avoid renoprival hypertension. At the end of the experiment, on day 49 there were 6, 8, and 6 rats in each group, respectively.

All operations were performed under ether

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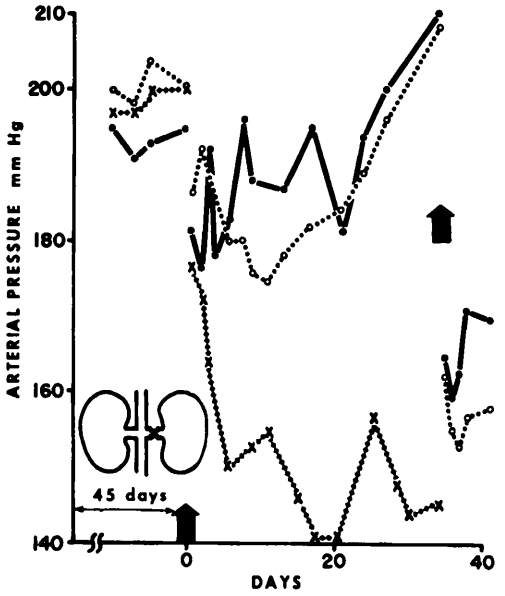

FIG. 1. Blood pressure changes in hypertensive rats: at first arrow the clipped kidney was partially resected in group 1, (O); ligated in group 2, (x); and subjected to a sham operation in group 3, (●); at second arrow the clipped kidney was excised in groups 1 and 3.

anesthesia. A silver clip was used to constrict the renal artery. Renal mass was reduced by excising one or both poles during clamping of the renal pedicle. Bleeding was stopped by compression of the kidney with fingers. Exclusion of a portion of the kidney approximately equal to that removed surgically was done by a ligature with heavy thread. In sham-operated rats, clipped kidneys were decapsulated while being temporarily ischemic. Blood pressure was measured from the tail by sphygmography using an E and M recorder. Pieces of kidneys removed at surgery and at autopsy were weighed and frozen for determination of renin by direct assay in nephrectomized rats (7).

Results. Expt. 1. Renal manipulations performed at zero time on hypertensive animals caused an initial fall in pressure of about 20 mm Hg (Fig. 1). Arterial pressure later fluctuated and then rose above original hypertensive levels in animals subjected to subtotal nephrectomy (group 1) and in those which were sham-operated (group 3) but continued to decline to normotensive levels in rats with ligated kidneys (group 2). Subsequent excision of clipped kidneys in groups 1 and 3 caused a sharp fall in pressure, with complete remission of hypertension in most of the animals; only one rat remained severely hypertensive. In one representative animal, the following ranges of pressure were observed: 190–200 mm Hg prior to subtotal nephrectomy, 200–225 mm Hg after left subtotal nephrectomy, and 100–140 mm Hg after left total nephrectomy. Thus, renal ligation caused remission of hypertension while surgical reduction of the mass of the clipped kidney had no significant effect. These results are supported by heart weights. In the 6 animals of group 1 killed 35 days after left subtotal nephrectomy, heart weights (expressed as percentage of body weight) averaged 453 ± 33 mg. This value is significantly greater ($p<0.001$) than 314 ± 18 mg in animals of group 2 which became normotensive. After removal of the clipped kidney, heart weights decreased averaging 348 ± 39 mg in group 1 and 342 + 37 mg in sham-operated group 3; only the former value is significantly above normal ($p<0.05$).

The amount of renal tissue removed by surgery averaged 304 ± 68 mg in group 1, thus representing approximately 44% of the total mass, since weight of the clipped kidney in sham-operated group 3 averaged 683 ± 217 mg. Clipped kidneys in these 2 groups were relatively free of adherences and could be easily dissected out. By contrast, kidneys of group 2 which had been ligated, were imbedded in fibrous tissue; they were uniformly atrophic with fibrosis at the site of the ligature. On day 35, clipped kidneys averaged 369 ± 60 mg in group 1 and 290 ± 182 mg in group 2, while contralateral kidneys averaged, respectively, 1580 ± 320 mg and 1320 ± 190 mg. It is to be noted that although weights of clipped kidneys were similar in group 1 and 2, only animals of group 2 were normotensive. Seven days after removal of the clipped kidney contralateral kidneys averaged 1402 ± 187 mg in group 1 and 1395 ± 172 in group 3. These results indicate that after unilateral clipping, the contralateral kidney undergoes considerable hypertrophy so that subsequent partial or

TABLE I. Renal Renin and Arterial Pressure at Time of Partial Surgical Nephrectomy (A) and 35 Days Later (B).

Renin content of clipped kidneys (units/g)			Blood pressure (mm Hg)		
A	B	Difference	A	B	Difference
112	114	+2	200	180	−20
55	57	+2	180	230	+50
50	54	+4	190	155	−35
18	25	+7	200	220	+20
36	45	+9	200	215	+15
35	44	+9	195	230	+35
49	62	+13	205	220	+15
50	100	+50	185	230	+45
47	135	+88	200	200	0
33	18	−15	205	230	+25
80	62	−18	190	190	0
49	22	−27	230	200	−30
94	39	−55	200	190	−10
112	27	−85	215	220	+5

total removal of the clipped kidney has little effect.

Renin content in pieces surgically removed from clipped kidneys averaged 64 ± 33 Goldblatt units/gm; 35 days later it averaged 46 ± 25 units in the remaining part. The difference is not statistically significant ($p>0.05$). Renal renin in the contralateral kidney averaged 2.7 ± 0.9 units on day 35 and 3.9 ± 3.2 units 7 days after removal of the clipped kidney. In animals of group 2 which became normotensive, renal renin in the whole clipped kidney, including the ligated part, averaged 19.6 ± 9.8, and in the contralateral kidney 2.8 ± 1.9 units.

Data in Table I show absence of relationship between renin concentration and levels of arterial pressure at the time of, and 35 days after, surgical reduction of the renal mass: rats with the same severity of hypertension had either low or high renal renin. A lack of relationship is also noted between changes in pressure and in renal renin following reduction of the renal mass.

Expt. 2. In hypertensive rats with a lone clipped kidney, surgical reduction of the renal mass (group 1) caused a slight and transitory fall in pressure followed by a return to preoperative levels (Fig. 2). The same changes occurred in the sham-operated group 3. In animals of group 2, ligation of the kidney had insignificant effects on blood pressure. By contrast, removal of the clip caused in these 3 groups a sharp fall amounting to about 60 mm Hg, followed by stabilization at lower but still slightly hypertensive levels. When rats were killed 23 days later, heart weights in the 3 groups were within the normal range, averaging, respectively, 323 ± 60, 294 ± 21, and 300 ± 32 mg/100 g of body weight. Thus, these results demonstrate that surgical reduction of the renal mass and ligation of the kidney did not reverse the course of hypertension at a time when its maintenance was still mainly dependent on the kidney.

Amounts of kidney removed surgically averaged 324 ± 76 mg. Final kidney weights in the 3 groups were similar, averaging 1410 ± 233 mg in group 1, 1358 ± 216 mg, including 229 mg for the part excluded by the ligature in group 2, and 1432 ± 83 mg in group 3. The ligated kidneys again showed many adhesions, but, unlike the first experimental series, were not atrophic.

Renin content in group 1 averaged 10.1 ± 5.4 units at the time of subtotal nephrectomy and 6.8 ± 2.4 units 23 days after re-

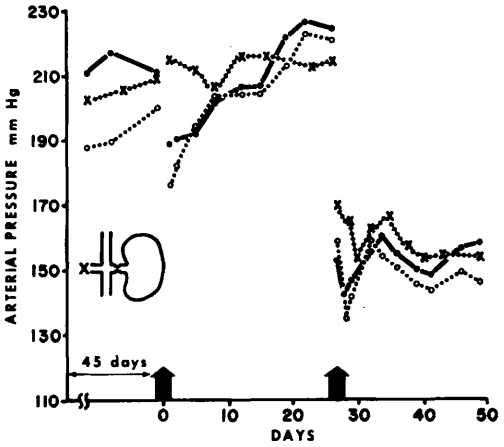

FIG. 2. Blood pressure changes in hypertensive rats following at first arrow partial nephrectomy in group 1, (●); renal ligation in group 2, (x); and sham operation in group 3, (○); and at second arrow removal of the clip in the 3 groups.

moval of the clip. These are not significantly different from 10.8 ± 7.4 obtained in control group 3. In group 2, renin content averaged 6.4 ± 6.8 units in the part distal to the ligature and 4.2 ± 1.3 units in the remaining portion; variability in the distal part likely reflects differences in amounts of degenerated tissue.

Discussion. These experiments demonstrate that reduction of the mass of a clipped kidney does not significantly interfere with the course of hypertension. Whenever there was a fall in pressure it was transient and also occurred in sham-operated rats. Although the same results have been reported in dogs (5), and rats (4), we further demonstrated that at the time of partial nephrectomy, the hypertension was still reversible and dependent on renal mechanisms. Our findings contradict, however, the results of others, particularly Schlegel and Okamoto (2), who showed that reduction of the mass of the clamped kidney causes a sustained fall in pressure and suggested this procedure as a possible cure of hypertension. Their conclusions were based on studies on 5 dogs. Hypertension was not severe, as evidenced by pressure gradients in the renal artery and heights of the pressure. Since partial nephrectomy was performed from 2 to 6 weeks after clamping, hypertension was still labile. Such animals are sometimes known to become normotensive for no apparent reason. In the experiments of Donohue, who claimed to have confirmed in rats the results of Schlegel and Okamoto (6), blood pressure levels ranged between 107 and 130 mm Hg 1 month after clipping. It is doubtful whether such animals can be considered hypertensive.

Schlegel and Okamoto (2) have interpreted their results by suggesting that hypertension results from an imbalance between renal blood flow and renal mass and that this imbalance is corrected by partial nephrectomy. It may be that this situation had been realized in their experiments. The kidney contralateral to the clamped kidney was removed at the same time as clamping. We know that compensatory hypertrophy can take place in spite of a clamp (8): even in the absence of a decrease in renal blood flow (9), a relative ischemia may have occurred. They did not demonstrate, however, that it played a pathogenic role. Indeed, most of the evidence is against this interpretation. First, it is generally agreed that ischemia per se is not a determining factor in hypertension. Second, hypertension can develop when clamping is delayed until the hypertrophy due to contralateral nephrectomy is almost completed (5); renograms and clearances are unaffected by clamping or partial nephrectomy (5). Third, as demonstrated here in rats, the size of the clipped kidney is decreased, and not increased, when the contralateral kidney is not removed; in a similar situation in dogs, renal blood flow remains generally normal (9).

Subtotal removal of the renal cortex has been suggested as a means of reducing the number of juxtaglomerular apparatus responsible for the formation of renin, hence to cause remission of hypertension (1). In many instances animals had renal insufficiency (4), so that whenever pressure remained elevated, the participation of renoprival factors could not be excluded. It has been generally observed that hormonal deficiencies can be obtained only by almost complete removal of an endocrine gland; such a drastic procedure on the kidney would be fatal. Although the source of renin was reduced by up to ⅔ by partial nephrectomy, the amounts left in the remaining part were still considerable and probably sufficient to maintain hypertension (9). In the absence of relationship between renin content and pressure, it is not known what constitutes the minimal amount of renin compatible with hypertension. On the other hand, increased amounts of renin can be associated with normal pressure. Weights of, and renin concentration in, clipped kidneys were the same following a renal ligature or partial nephrectomy, but hypertension was remitted in the former situation and persisted in the latter.

Although attempts to reduce renal mass by necrosis were unsuccessful, we found that renal ligation caused remission of hypertension in rats with one clipped kidney and one contralateral untouched kidney. The clipped kidney was atrophic and enclosed in a tight

capsule. It is very likely that the ligature exerted a compression, not only locally but on the whole kidney, through a tightening of the unruptured renal capsule. Local tissue reaction may have also contributed to this effect. This sustained compression resulted in gradual atrophy of the clipped kidney, remission of hypertension, and compensatory hypertrophy of the contralateral kidney. The situation is similar to the one resulting from a loose ligature placed on the aorta between the origins of the two renal arteries in very young rats; during growth, the left kidney gradually atrophies without hypertension (10). On the other hand, when the contralateral kidney is removed, stimuli for compensatory hypertrophy are strong enough to overcome this atrophy. In an endocrine kidney, excretory function is restored by contralateral nephrectomy (8).

Summary. Surgical reduction of the mass of a clipped kidney does not alter the course of hypertension, whether a contralateral untouched kidney is present or not, while subsequent removal of the clip or excision of the kidney usually causes remission of hypertension. These observations do not support the view that hypertension is due to an imbalance between flow and mass, which can be corrected by reduction of renal mass. Constriction of the clipped kidney by a ligature causes a gradual renal atrophy and remission of hypertension only when the contralateral kidney is present. There is no relationship between renal renin and pressure levels.

1. Sonder, P., Acta Pathol. Microbiol. Scand. Suppl. **105**, 183 (1955).

2. Schlegel, J. U. and Okamoto, S., J. Urol. **86**, 27 (1961).

3. Fischermann, K., Acta Pathol. Microbiol. Scand. **43**, 373 (1958).

4. Bing, J., Acta Pathol. Microbiol. Scand. **47**, 287 (1959).

5. Blaufox, M. D., Campbell, J. C., Utz, D. C., and Owen, C. A., J. Surg. Res. **3**, 281 (1963).

6. Donohue, J. P., J. Urol. **95**, 658 (1966).

7. Masson, G. M. C., Kashii, C., Panisset, J. C., Yagi, S., and Page, I. H., Circulation Res. **14**, 150 (1964).

8. Omae, T. and Masson, G. M. C., J. Clin. Invest. **39**, 21 (1960).

9. Bounous, G. and Schumacker, Jr., H. B., Surg., Gynecol. Obstet. **114**, 415 (1962).

10. Robert, A., Rev. Can. Biol. **13**, 3 (1954).

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