References and Notes

1. A. M. Kuris, *Q. Rev. Biol.* **49**, 129 (1974). Kuris reviews data that suggest a close similarity between parasitic castrators and parasitoids. He concludes that castration phenomena may be important components of population regulation for many marine organisms. Regulation of hosts will not be discussed here.
2. E. O. Wilson and W. H. Bossert [*A Primer of Population Biology* (Sinauer, Stamford, Conn., 1971)] name Eq. 1 after Euler. See also L. B. Slobodkin [*Growth and Regulation of Animal Populations* (Holt, Rinehart & Winston, New York, 1961)] and J. M. Emlen [*Ecology: An Evolutionary Approach* (Addison-Wesley, Reading, Mass., 1973)] for derivation and discussion. Emlen calls Eq. 1 perhaps the most important basic equation in ecology.
3. Pathological effects of trematode parasites in mollusks are reviewed in C. A. Wright, *Helminth. Abstr.* **35**, 207 (1966); T. C. Cheng, *Pac. Sci.* **22**, 141 (1968). Trematode-infested mollusks in laboratory culture have been found to have higher mortality rates than uninfested ones; see J. R. Uzmann, *J. Parasitol.* **39**, 445 (1953); R. H. Millar, *Nature (Lond.)* **187**, 166 (1963); C.-T. Pan, *J. Trop. Med. Hyg.* **14**, 931 (1965); M. Howell, *Trans. R. Soc. N.Z.* **8**, 221 (1967). M. R. S. Negus [*Parasitology* **58**, 355 (1968)] believes that many biochemical effects of trematode parasitism in mollusks are similar to those found in starving mollusks.
4. Supported by NSF grant GA-33438. I thank A. M. Kuris and W. Chang for discussions and the Shephards for providing retreat.

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Reciprocation of Renin Dependency with Sodium Volume Dependency in Renal Hypertension

Abstract. *An angiotensin II inhibitor was administered to rats with two-kidney Goldblatt hypertension. The inhibitor produced a marked drop in blood pressure after 5 weeks but no significant change after 15 weeks of hypertension. However, even after 15 weeks of hypertension, following sodium depletion by either diuretics or a low sodium diet, the animals again became renin dependent as readministration of the inhibitor induced a significant fall in blood pressure. The data indicate that two-kidney Goldblatt hypertension is initially renin dependent but subsequently becomes sodium volume dependent in a way similar, although more protracted, to that already described for one-kidney Goldblatt hypertension.*

Experimental renovascular hypertension exhibits two different pathophysiologic patterns: The two-kidney Goldblatt hypertension (one renal artery clipped with the contralateral kidney left untouched) has been considered typical of renin-angiotensin dependent hypertension in both the initial and the established phase. Elevation of renin and angiotensin II in the plasma has been demonstrated in this model (*1*) in the established phase; at this time the blood pressure can be lowered by the administration of antibodies to, or blockers of, angiotensin II (*2*).

In contrast, the one-kidney Goldblatt model (one renal artery clipped with the contralateral kidney removed) shows only an initial transient renin dependent phase of a few days duration (*3–5*), but then becomes sodium volume dependent in the established phase (*5*) with normal plasma renin and angiotensin II levels and no blood pressure response to blocking agents of or antibodies to angiotensin II. During this phase, sodium deprivation converts hypertension to an overtly angiotensin II dependent type (*6*).

Our study was designed to investigate whether a similar change from a renin dependent to a sodium dependent mechanism occurs with time in the two-kidney Goldblatt model and whether this status can also be reversed by sodium depletion.

A silver clip was placed on the left renal artery of male Wistar rats weighing 140 to 150 g; the right kidney was left untouched. Three groups of animals were studied and all received initially a regular Purina rat chow diet (sodium content 0.22 meq/g). The blood pressure was measured twice weekly by means of the tail microphone method.

The animals in group 1 ($N = 5$) were maintained on the above diet and examined 4 weeks after the clipping. The animals were anesthetized with ether, the femoral vein was cannulated with a PE 10 catheter for the infusion, and the external iliac artery was cannulated with a PE 50 catheter for blood pressure monitoring. Arterial pressure was monitored with a Sanborn pressure transducer. After the animals recovered from the anesthesia, they were kept in a semirestrained position. At the end of a 30-minute control period, the pressure response to an intravenous dose of 100 ng of angiotensin II was determined. Subsequently, [sarcosine^1, alanine^8]angiotensin II (Eaton Laboratories), a highly specific competitive antagonist of angiotensin II (*7*), was infused at a rate of 9 g/min for 60 minutes. After the infusion was discontinued, the blocking effect of the inhibitor was tested by an injection of 100 ng of angiotensin II. The animals were killed 3 hours later when the blood pressure had risen to that observed before the infusion.

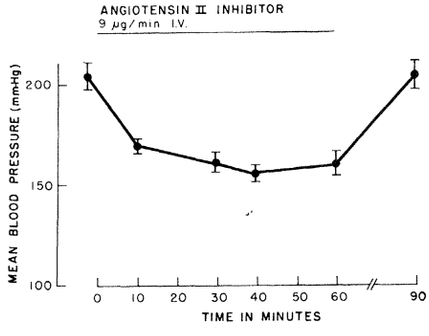

Fig. 1. Blood pressure response to angiotensin II blockage 4 to 5 weeks after the clipping of one renal artery; *I.V.*, intravenous.

The rats in group 2 ($N = 6$) were cannulated 14 to 15 weeks after they were clipped, and the same protocol was followed as described for the animals in group 1. After their recovery from the initial infusion, the animals were maintained in a semirestrained position for another 24 hours, during which time they received an intravenous injection of furosemide (2 mg) and were fed a low sodium diet (*8*) with free access to tap water. Urines were collected, and Na and K determinations made in order to calculate Na and K excretion over a 24-hour period. After this period of sodium depletion, the antagonist infusion was repeated.

The rats in group 3 ($N = 8$) were also kept for a period of 14 to 15 weeks on the regular salt diet. Eight days prior to the experimental treatment they were placed on the low sodium diet, and the antagonist was infused at the end of the 8-day period. Five of these animals were housed in metabolic cages (Acme), and sodium and potassium balance studies were carried out as described (*9*).

In the animals of group 1 (which were kept on the regular salt diet), 4 weeks after clipping, the angiotensin II inhibitor produced an immediate and progressive fall in blood pressure with a decrease of 36.6 ± 4.8 (mean $\pm$ S.E.) mm-Hg after 10 minutes ($P < .01$) and a maximum decrease of 44.0 ± 6.2 mm-Hg after 60 minutes ($P < .01$) (Fig. 1).

In the animals of group 2 (which were also on the regular salt diet), 14 to 15 weeks after clipping the mean of the blood pressures in the controls was similar to that of group 1, but the angiotensin II inhibitor produced no significant change in blood pressure. The maximum decrement in blood pressure was 3.1 ± 3.6 mm-Hg after 60 minutes ($P < .5$) (Fig. 2a). Subsequently, sodium depletion was induced by 24 hours of low salt diet and intravenous injection of 2 mg of furosemide; the resulting loss of sodium was 2.1 ± 0.4 meq, and the net loss in weight was 49.0 ± 7 g, but there was no change in the blood pressure. A second dose of the inhibitor then produced a marked fall in blood pres-

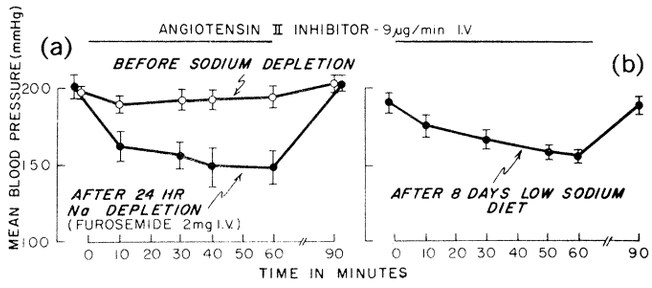

Fig. 2. (a) Blood pressure response to angiotensin II blockade 15 weeks after the clipping of one renal artery, before and after sudden sodium depletion. (b) Blood pressure response to angiotensin II blockade 15 weeks after the clipping of one renal artery and after the animals were deprived of dietary sodium for the 8 days preceding testing.

sure by 43.0 ± 7.6 mm-Hg ($P < .01$) after 10 minutes and a maximum fall of 55.0 ± 10.3 mm-Hg after 60 minutes, a similar response in pressure to that seen in group 1.

In the rats of group 3, 14 to 15 weeks after the animals were clipped and after they had been placed on a low sodium diet for 8 days prior to test, the angiotensin II inhibitor induced a significant fall in blood pressure of 28.1 ± 4.2 mm-Hg ($P < .01$) at 10 minutes and a maximum fall of 46.4 ± 6.4 at 60 minutes ($P < .01$) (Fig. 2b). Balance studies in five animals showed a mean sodium loss of 2.8 ± 0.3 meq after the final 8-day period. However, the body weight showed only a transient fall during the first 2 to 3 days, but then rose slightly toward the end of the 8-day period on a low sodium diet (428 ± 9 g as compared to the initial weight of 420 ± 10 g).

These experiments indicate that the two-kidney Goldblatt model of renovascular hypertension, often considered a typical model of renin dependent hypertension, is subject to a change in its mechanism, presumably resulting from changes in the sodium metabolism. Thus, infusion of the angiotensin blocker produced a lowering of blood pressure at 4 weeks, confirming that at this stage the hypertension is renin dependent (*2*). However, 10 weeks later the response to the blocker became negligible, indicating that angiotensin no longer appeared to play a role in the maintenance of the high blood pressure and that sodium retention with ensuing volume expansion was probably the main operating mechanism. Sodium depletion over a period of hours by the use of diuretics alone did not cause any fall in the blood pressure, probably because of stimulation of renin release, as suggested by the dramatic fall of blood pressure when infusion of the angiotensin blocker was repeated. More gradual sodium depletion of the same magnitude, achieved by dietary salt deprivation over a longer period, had the same effect of reinstituting the renin dependency of the hypertension.

This sequence of events in two-kidney Goldblatt hypertension thus resembles that already described in the one-kidney Goldblatt model (*6*). Both models exhibit a renin dependent early phase followed by a volume dependent phase later on, during which a latent role for renin can still be exposed by sodium deprivation. In the two-kidney model this transition occurs in several weeks and may be attributed to the presence of a normal contralateral kidney, which at first excretes sodium freely in reaction to the raised systemic blood pressure. However, the continuing exposure of this initially normal kidney to raised arterial pressure, perhaps combined with elevation in the circulating renin level, may produce secondary vascular damage in this kidney and lead to impaired sodium excretion, to volume expansion, and then to suppression of renin release from the clipped kidney (*10*); at this point removal of the clipped kidney no longer normalizes the blood pressure (*11*). In the one-kidney model a considerable loss of total renal function occurs immediately, resulting in a decrease of capacity for sodium excretion and thus earlier sodium retention (*4*).

A similar mechanism may be applicable in renal and even certain forms of essential hypertension in man. According to this hypothesis, patients exhibiting "normal" or even low renin levels might have actually had an elevation of renin levels earlier, which could have produced subtle kidney damage sufficient to sustain the hypertension with the subsequent lesser or latent participation of renin. In this regard, essential hypertensive patients with low renin levels have been found to be older than essential hypertensive patients with normal renin levels (*12*).

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Insulin-Unresponsive Tissues Respond To Superactive Insulin-Like Material

Abstract. *Insulin-like material prepared from insulin-Sepharose stimulates glucose oxidation by isolated diaphragm of C57Bl/6J ob/ob mice, but insulin does not. This material is much more effective than insulin on epididymal fat tissue from these mice. Insulin-like material and insulin are equipotent on the corresponding tissues from lean littermates.*

It has been reported (*1*) that soluble insulin-like material (ILM) can be produced by treating insulin-Sepharose with bovine serum albumin solution, and that the material solubilized in this manner elicits unusual insulin-like responses from mammary epithelial cells. The ILM exerts a greater stimulatory effect than insulin does on the accumulation of α-aminoisobutyric acid by mammary cells from pregnant