oids having a profound influence on protein metabolism. Factors which influence the rennin inhibitor predominantly further implicate the steroid hormones. The association of estrogens with certain benign breast hyperplasias is well known and the significance of stimulated estrogenic or androgenic activity in healing fractures has been demonstrated by Albright and co-workers.[7] Rennin inhibitor may increase also in many of the psychoses which have been shown by Pincus and Elmadjian[8] to exhibit diminished adrenal response to stress. The unexpected finding that a high percentage of the hypertensive and allergic groups have abnormal rennin inhibitor levels is of interest but difficult to interpret. Studies to determine the direct effects of steroid hormone administration on the proteolytic enzyme inhibitors are being undertaken.

Pregnancy is usually accompanied by a pronounced elevation of both inhibitors in the mother's circulation. In contrast, the cord blood of the newborn is high only in rennin inhibitor, while the other is very low.

A study of malignancy by this method reveals a characteristic but fluctuating picture, the host doing well clinically when the rennin inhibitor only is elevated, as occurs early, or at intervals in the course of the disease, but failing rapidly when the chymotrypsin inhibitor rises very high and rennin inhibitor drops to low levels (unpublished data). Obviously, it would be impossible to diagnose malignancy by these methods since an increase in inhibitor of either proteolytic enzyme is not specific for cancer. The inhibitor concentrations are profoundly influenced by radiation therapy and surgical excision, and thus a low percentage of abnormal inhibitor levels was noted in treated cases. Repeated observations on the serum inhibitors in cases with neoplasm may prove to be of considerable prognostic value and may indicate when further treatment is required as well as the effectiveness of the treatment given. This appears to us to be the chief value of the method as applied to the cancer patient. This aspect of the problem is being extended at the present time.

*Summary.* Methods are described for the determination of chymotrypsin and rennin inhibitors in serum. The many physiological and pathological conditions which influence their concentration are discussed.

[7] Albright, F., Bloomberg, E., and Smith, P. H., *Trans. Assn. Am. Phys.*, 1940, **55**, 298.

[8] Pincus, G., and Elmadjian, F., *J. Clin. Endocrinol.*, 1946, **6**, 285.

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## 17121. A Comparison of Total Body Water as Determined by Antipyrine and Desiccation in Rabbits.

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A method for determining total body water which employs the volume of uniform distribution of antipyrine, an analgesic drug, has been described recently.[1] Further support for the antipyrine method is presented in the present paper which records the values for total body water estimated by the antipyrine procedure and the values obtained by actual desiccation of the experimental animals.

*Experimental.* Four rabbits were injected intravenously with 60-240 mg of antipyrine according to body weight (approximately 100 mg/kg). Blood samples were drawn from each animal at 50, 75 and 100 minutes following the administration of the drug. The zero time plasma concentration (the concentration at the time of injection if uniform distribution

[1] Soberman, R. J., Brodie, B., Hollander, V., Levy, B., Axelrod, J., and Steele, J. M., *J. Biol. Chem.*, 1949, **179**, 31.

TABLE I.
Comparison of Total Body Water in Rabbits Determined by Antipyrine and Desiccation.

| Rabbit | Weight (g) | Total water: Antipyrine (cc) | Antipyrine (% body wt) | Desiccation (cc) | Desiccation (% body wt) | Difference in (%) |
|---|---|---|---|---|---|---|
| 1 | 1782 | 1330 | 74.6 | 1350 | 75.8 | —1.2 |
| 2 | 1846 | 1270 | 68.8 | 1285 | 69.6 | —0.8 |
| 3 | 660 | 501 | 75.8 | 481 | 72.9 | +2.9 |
| 4 | 1172 | 912 | 77.8 | 902 | 77.0 | +0.8 |

TABLE II.
Antipyrine in Tissues of Rabbit 50 Minutes After Intravenous Injection.

| Tissue | Water (%) | Antipyrine in wet tissue (γ/g) | Antipyrine in tissue water (γ/ml) | Tissue water antipyrine / Plasma water antipyrine |
|---|---|---|---|---|
| Plasma | 92.0 | 39.6 | 43.1 | 1.00 |
| Heart | 73.7 | 30.5 | 41.3 | .96 |
| Liver | 72.0 | 33.2 | 46.1 | 1.08 |
| Muscle | 73.0 | 31.2 | 42.8 | .99 |
| Kidney | 78.6 | 33.1 | 42.1 | .97 |
| Lung | 71.6 | 31.1 | 43.5 | 1.01 |

was instantaneous and if none of the substance had been metabolized) is calculated by plotting the plasma levels on semilogarithmic paper as a function of time and extrapolating the straight portion of the time concentration curve (50, 75 and 100 minutes) to the time of injection. The value for total body water is obtained by dividing the amount administered by the plasma water level at zero time.

$$\text{Body water (liters)} = \frac{\text{Amt of drug injected (mg)}^{1}}{\text{Plasma water level (mg/L)}}$$

After the last blood sample had been drawn, the animals were weighed and sacrificed. The total animals were ground, and the final mass was then spread over large evaporating dishes and placed in a vacuum desiccator at a temperature of 85°C for a period of 5-7 days until constant weight had been achieved.

Since the rabbit, unlike a human, degrades antipyrine at a rapid rate (approximately 40% an hour), it appeared possible that the falling blood level indicated plasma degradation and not the concentration of antipyrine in the entire body. Accordingly, the distribution of antipyrine in the tissues of a fifth rabbit at the end of 50 minutes was determined. The water content of the tissues was determined by drying to constant weight at 100°C. The concentration of antipyrine in the tissues was measured and then calculated in terms of tissue water. The antipyrine is estimated directly in the plasma filtrate after deproteinization with zinc hydroxide. Sodium nitrite is added and the resulting 4-nitroso antipyrine measured in a spectrophotometer at 350 mu.[2]

*Results.* Comparison of the values obtained for total body water by antipyrine method and desiccation indicates close agreement between the two methods, thus confirming that antipyrine can be used as a measure of total body water (Table I).

The data of Table II demonstrate that the ratio of concentration of antipyrine in the tissues to that of plasma is one. Thus, the plasma concentration reflects the level of antipyrine in the entire body.

*Summary.* The close agreement obtained for the values of total body water by the use of the antipyrine method and desiccation, indicates the validity of this procedure for the purpose of measuring total body water.

[2] Brodie, B., Axelrod, J., Soberman, R. J., and Levy, B., *J. Biol. Chem.*, 1949, **179**, 25.

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## 17122. Arterial Hypertension Produced by Experimental Stenosis of the Thoracic Aorta.

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Arterial hypertension has been produced in dogs by stenosis of the thoracic aorta. The hypertension is sustained and has many of the characteristics of that observed in coarctation of the aorta in man.

*Materials and methods.* The method of producing permanent and prolonged stenosis of the thoracic aorta in dogs, described in detail elsewhere,[1] consists in the substitution of a section of lucite tubing for a segment of the aorta. This tube is designed to reduce turbulence by making the bore hourglass in shape. In the dogs used in this experiment, the tube was 3.7 cm long with 3 mm as the narrowest diameter. The lumen of the aorta was reduced in the dogs in this group approximately 75 to 85%.

Blood pressure records were obtained by direct puncture of the femoral or carotid arteries and measurement of the pressure with either a mercury or Hamilton manometer. From the records obtained with the Hamilton manometer, the systolic and diastolic pressures were calculated. Mean pressures were obtained either from estimations with the planimeter of the area under the pulse waves, or read directly from the mercury manometer. All blood pressure determinations were made with the animals under nembutal anesthesia, 27 mg per kg of body weight.

*Results.* There were 11 of 16 dogs that survived the operative procedure. Six of the 11 died at intervals of 7 days to 3 weeks after operation, 4 dying because of spastic paralysis of the lower part of the body. Of the 5 animals that survived for longer than one month, 4 are still living. One dog died at the end of 4 months from unknown cause. The remainder are still living at intervals of 4 to 14 months after stenosis of the aorta.

The changes in the blood pressures in these animals has followed, in all instances, a definite pattern as demonstrated in Table I. The femoral mean pressure has shown a drop after operation that persisted in some animals for as long as 7 days; but by the 14th day the pressure returned to normal. After 2 weeks the femoral mean pressure increased above the normal. The carotid mean pressure increased by the end of the first week to levels well above normal, and by 14 days reached hypertensive levels. The mean pressures in both the femoral and carotid increased during the next 3 months. After this time there was in the 2 dogs observed for one year, a decrease in the mean pressure both above and below the constriction, but the pressure still remained in the hypertensive range. The results with 5 animals are tabulated in Table II.

Recordings of the blood pressure with the Hamilton manometer have shown a large increase in the pulse pressure above the constriction and a decrease below. The diastolic pressures both above and below the constriction have increased along with the rise in the mean pressure.

*Discussion.* The experiments described here show that severe arterial hypertension can be produced in dogs by stenosis of the thoracic aorta. The various mechanisms that contribute to the elevation of the blood pressure are not evident from these results. It has been suggested that the hypertension in coarctation of the aorta is renal in origin.[2] Though the blood flow to the kidneys is not recorded in these experiments, it is interesting to note that for only about 14 days was the mean pressure below the constriction lower than the normal. After this interval there was a progressive rise in the mean pressure. On the other hand, there was a diminution in the

[1] Sealy, W. C., and McSwain, George H., *Surgery*, in press.

[2] Rytand, D. A., *J. Clin. Invest.*, 1938, **17**, 391

TABLE I.
Experimental Hypertension. Blood pressure changes associated with stenosis of the thoracic aorta in the dog.

| Days after constriction | Blood pressure in mm mercury Femoral Mean | Femoral S/D | Blood pressure in mm mercury Carotid Mean | Carotid S/D |
|---|---|---|---|---|
| Normal | 127 | 165/108 | 126 | 149/110 |
| 6 | 45 | 45/45 | 138 | 161/116 |
| 16 | 133 | 151/121 | 158 | 200/137 |
| 30 | 157 | 181/135 | 190 | 233/149 |
| 40 | 169 | 184/154 | 197 | 236/162 |
| 124 | 176 | 199/167 | 238 | 292/198 |

S = Systolic. D = Diastolic.

TABLE II.
The Blood Pressure Changes Associated with Experimental Coarctation of the Aorta in Dogs.

| Animal No. | Normal blood pressure Femoral M | Femoral S/D | Carotid M | Carotid S/D | Duration of aortic constriction, mo. | Last recorded blood pressure Femoral M | Femoral S/D | Carotid M | Carotid S/D |
|---|---|---|---|---|---|---|---|---|---|
| 14 | 118 | | 124 | | 14 | 133 | 144/123 | 158 | 185/130 |
| 16 | 128 | | 130 | | 5 | 196 | | 222 | |
| 22 | 134 | | 140 | | 13 | 154 | 170/137 | 193 | 241/160 |
| 29 | 127 | 165/108 | 126 | 149/110 | 4 | 176 | 199/167 | 238 | 292/198 |
| 31 | 125 | 157/107 | 161 | 184/146 | 3 | 162 | 170/157 | 239 | 299/199 |

M = Mean pressure. S = Systolic. D = Diastolic.

pulse pressures below the constriction that persisted. This might be interpreted as evidence for renal origin of the hypertension as suggested by Kohlstaedt and Page.[3]

The substitution of a rigid narrow tube for a section of the aorta would alter the characteristics of the pulse waves above and below the constriction; but this would not explain the marked elevation of the blood pressure that occurs in experimental stenosis of the aorta.

*Summary.* 1. By stenosis of the thoracic aorta in dogs, arterial hypertension can be produced above and below the stenosis.

2. This type of experimental hypertension has many of the characteristics observed in the hypertension occurring in coarctation of the aorta in man.

[3] Kohlstaedt, K. G., and Page, I. H., *J. Exp. Med.*, 1940, **72**, 201.

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