14049

Influence of Eosinophile Cells of Hypophysis on Kidney Function.

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White, Heinbecker and Rolf[1] reported that removal of the glandular division of the hypophysis in dogs resulted in a reduction of 50% or more in inulin and diodrast clearances and in maximal tubular excretion of diodrast at high plasma levels. These changes indicate a depression of renal blood flow and of renal tubular excretory capacity and were in evidence within 7 days after the removal of the glandular hypophysis. They have persisted under observation for a period of 2 years. It can be stated, therefore, that the glandular hypophysis exercises a humoral influence on the kidney. Evidence that the eosinophile cells of the hypophysis are responsible for this influence is presented in this paper.

Observations on the urea clearance of 5 patients with acromegaly revealed values of 130, 83, 135, 231, and 100%, respectively, of the normal standard. Three of these values are definitely above the upper limit of normal. An eosinophil tumor was found at autopsy in the first of these patients. The kidneys weighed 420 g. Microscopically the glomeruli and tubules were slightly hypertrophied. There was generalized arteriosclerosis of the renal vessels. Some increase in kidney size is a usual finding in acromegaly. Since eosinophil cell hyperplasia or eosinophil tumor formation has been found in all cases of acromegaly[2] coming to autopsy, the increase in renal function and in renal size observed in this disease perhaps may be attributed to hyperfunction of the eosinophil cells of the glandular hypophysis. The degree of secretory activity of the hypophysial tumor should be reflected in the extent of increase in renal function.

Winternitz and Waters[3] and White, Heinbecker and Rolf[4] have shown that in dogs a single remaining kidney fails to hypertrophy after removal of the glandular division of the hypophysis. If the eosinophil cell type is responsible for the renal hypertrophy associated with acromegaly, it seems probable that the failure of the kidney to hypertrophy after hypophysectomy is due to loss of the secretion of the eosinophil cells.

Kidney function studies by means of diodrast† and inulin clearances and by diodrast Tm determinations were carried out in 2 cases with signs and symptoms characteristic of Cushing's syndrome.

Case I was a 32-month-old white female child who showed obesity, hirsutism, abdominal striæ, hypertension, a suggestion of demineralization of the lower lumbar vertebræ, acne, enlargement of the clitoris, and a deep, hoarse voice. A mass was palpable in the left flank and an adrenal cortical tumor was found at operation.

Case II was a 33-year-old white female who exhibited obesity, hirsutism, abdominal striæ, hypertension, diminished dextrose tolerance, hypercholesterolemia, amenorrhea, and loss of libido. She, presumably, had the lesion more common in this disease.

The results of the renal function studies are shown in Table I. The technic employed for the 32-month-old child, as well as that for the adult, followed precisely that described by Goldring *et al.*[5] The range of values for the

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1 White, H. L., Heinbecker, P., and Rolf, D., *Am. J. Physiol.*, 1942, **136**, 584.

2 Bailey, P., and Davidoff, L. M., *Am. J. Path.*, 1925, **1**, 185.

3 Winternitz, M. D., and Waters, L. L., *Yale J. Biol. and Med.*, 1940, **12**, 705.

4 White, H. L., Heinbecker, P., and Rolf, D., PROC. SOC. EXP. BIOL. AND MED., 1941, **46**, 44.

† The diodrast used in these studies was generously supplied by the Winthrop Chemical Company.

5 Goldring, W., Chasis, H., Ranges, H. A., and Smith, H. W., *J. Clin. Invest.*, 1940, **19**, 739.

TABLE I.
Summary of Renal Function Studies in Two Patients Exhibiting Cushing's Syndrome and Hypertension.

	Case I Avg range	Case II	Normal range mean (Goldring *et al.*[5])	Normal mean (White *et al.*[14])
Diodrast whole blood clearance, cc/1.73 sq.m/min	964	687	718-1566 1115	
Diodrast[12] plasma clearance " " " "	470 (435-502)	374	455-921 669	497
Inulin[13] plasma clearance " " " "	95.2 (82-116)	77.6	92-179 131	
Diodrast Tm, mg iodine 1.73 sq.m./min.	34.3 (30.7-40.5)	39.9	36.6-72.0 51.6	44
Diodrast whole blood clearance / Diodrast Tm	28.1	17.2	16.0-29.5 22.3	
Diodrast plasma clearance / Diodrast Tm	13.7	9.4	10.2-16.7 13.4	11.3
Inulin clearance / Diodrast Tm	2.78	1.95	2.09-3.12 2.56	
Inulin clearance / Diodrast clearance	0.202	0.208	0.196	

diodrast clearances (4 periods); diodrast Tm determinations (3 periods); and inulin clearances (7 periods) obtained on the child, are included to demonstrate the comparative constancy of the measurements in consecutive periods, since the accuracy of such measurements in a young subject might be questioned. In a small child the factor necessary for correction of the observed clearance for comparison with clearance values in adults is quite large; in this child being 3.5, as calculated on the basis of difference in surface area. There are at present no data available on inulin and diodrast studies in normal children of different age groups with which these results may be compared directly. However, we have data on somewhat older children which suggest that this correction is valid for the measurements reported here. In addition, it has been established that urea clearances in normal infants[6] and in children[7] can be compared with those in adults by correcting the values for differences in surface area.

Analysis of the results showed that in the first case the renal blood flow, filtration rate, and renal tubular function were within the normal range. In the second case, the tubular function was in the lower range of normal but there was definite reduction in the renal blood flow. However, this change was not of the degree which follows removal of the glandular hypophysis in animals. The hypertension present in this case was of several years' duration and the diastolic pressure was fixed at a high level (120 mm Hg.). A depression of renal function as measured by inulin and diodrast clearances of a degree comparable with that found in this case has been observed by Goldring *et al.*[8] and by Findley *et al.*[9] in cases of essential hypertension. It is felt that

[6] Schoenthal, L., Laurie, D., and Kelly, M., *Am. J. Dis. Child.*, 1933, **45**, 41.

[7] Cullen, G. E., Nelson, W. E., and Holmes, F. E., *J. Clin. Invest.*, 1935, **14**, 563.

[8] Goldring, W., Chasis, H., Ranges, H. A., and Smith, H. W., *J. Clin. Invest.*, 1941, **20**, 637.

[9] Findley, T., Edwards, J. C., Clinton, E., and White, H. L., in press.

[12] Corcoran, A. C., and Page, I. H., *J. B. C.*, 1939, **127**, 608.

[13] White, H. L., and Rolf, D., PROC. SOC. EXP. BIOL. AND MED., 1940, **45**, 433.

[14] White, H. L., Findley, T., and Edwards, J. C., PROC. SOC. EXP. BIOL. AND MED., 1940, **43**, 1.

the normal renal function in the first case justifies the inference that structural kidney changes rather than a loss of trophic influence is responsible for the depression of renal function in the second case.

In cases exhibiting Cushing's syndrome, whether associated with an hypophysial adenoma, an adrenal tumor, or with neither, an invariable finding has been hyalinization of the basophil cells of the hypophysis.[10,11] We regard such a change as one which could only lead to a depression of secretory function of these cells. The finding of renal blood flow and renal tubular function within normal limits in our first case indicates that there was no lack of the humoral agent which normally acts to maintain a normal kidney function.

Again, therefore, the evidence seems to indicate that this humoral agent affecting kidney function is secreted by the eosinophil cells, which are histologically normal in all cases exhibiting Cushing's syndrome, rather than by the basophil cells. It is realized that more cases should be studied before final conclusions are drawn. It is hoped that this report will serve as a stimulus to others to obtain data on this subject.

10 Crooke, A. C., *J. Path. and Bact.*, 1935, **41**, 339.

11 Rasmussen, A. T., *Endocrin.*, 1936, **20**, 673.

14050

Action of Bacterial Toxins on Tumors. III. Some Biological Properties of Purified *Salmonella typhimurium* Endotoxin.

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We have postulated on the basis of a survey of tumor hemorrhage induction by 28 genera of bacteria,[1] and on a more recent extension of this survey,* that aside from immunological specificity the purified O antigens of gram-negative bacteria are probably similar both in toxic action and chemical type. This is consistent with the view, developed by Boivin and his school,[2] based on immuno-chemical investigation.

Morgan and Partridge,[3] working with *Shigella dysenteriæ* and *Salmonella typhi,* have demonstrated that antigenicity is conferred on the O antigen by the protein component (earlier designated by them as a "polypeptide"), but their most recent publication[4] leaves undetermined whether the toxicity of the antigen resides in the protein, the polysaccharide, or in a combination of the two.

The object of the present study was to determine whether the O antigen, following purification, retains activity in respect to: (1) lethality, (2) hemorrhage production in implanted tumors, (3) production of protective antibodies in mice. *Salmonella typhimurium* was chosen as a representative gram-negative possessor of the O antigen. The toxic material was tested for activity at 3 stages of the purification: (1) after acetone precipitation from concentrated culture, (2) after warm phenol extraction of the initial acetone precipitate, and (3) after various formamide treatments of the phenol extract.

Acetone Fraction (A). The toxic material used in this study was prepared from cultures

1 Zahl, Paul A., Hutner, S. H., Spitz, S., Sugiura, K., and Cooper, F. S., *Am. J. Hyg.*, 1942, **36**, 224.

* Abstracted in *J. Bacteriol.*, Jan., 1943.

2 Boivin, A., and Mesrobeanu, L., *Ann. Inst. Pasteur*, 1938, **61**, 426.

3 Morgan, W. T. J., and Partridge, S. M., *Biochem. J.*, 1940, **34**, 169.

4 Morgan, W. T. J., and Partridge, S. M., *Brit. J. Exp. Path.*, 1942, **23**, 151.