the use of corticotrophin after thymectomy in one and splenectomy and thymectomy in the other. The pathogenesis of this condition remains obscure, but these various results of treatment are compatible with the concept that thymectomy may result in the removal of an inhibiting humoral factor, so allowing normal erythropoiesis to take place either spontaneously or under the influence of steroids.

Summary

A case of benign thymoma and red-cell aplasia is described. Thymectomy did not produce a haematological remission, but normal erythropoiesis occurred later during treatment with prednisone. The patient's plasma did not inhibit erythropoiesis when injected into normal rats.

We are indebted to Dr. W. Phillips, under whose care this patient was admitted; to Dr. J. D. P. Graham for assistance with the animal experiments; to Mr. R. G. Wood for help with the isotope studies; and to Mr. D. M. E. Thomas and Dr. R. M. E. Seal, of Sully Hospital. Facilities for doing the experimental studies were made available to one of us (G. S. K.) during the tenure of a Research Fellowship in Medicine in the Royal Infirmary, Cardiff.

REFERENCES

- Barquet Chediak, A., Fuste, R., and Vazquez Rosales, G. (1953). *Arch. Hosp. univ. (Habana)*, **5**, 27.
 Belcher, E. H., Gilbert, I. G. F., and Lamerton, L. F. (1954). *Brit. J. Radiol.*, **27**, 387.
 Chalmers, J. N. M., and Boheimer, K. (1954). *Brit. med. J.*, **2**, 1514.
 Humphreys, G. H. II, and Southworth, H. (1945). *Amer. J. med. Sci.*, **210**, 501.
 Lamerton, L. F., Belcher, E. H., and Harriss, E. B. (1956). *Proc. roy. Soc. Med.*, **49**, 863.
 Loeb, V., jun. (1956). *J. Amer. med. Ass.*, **160**, 1319.
 Matras, A., and Priesel, A. (1928). *Beitr. path. Anat.*, **80**, 270.
 Ross, J. F., Finch, S. C., Street, R. B., and Strieder, J. W. (1954). *Blood*, **9**, 935.
 Soutter, L., Sommers, S., Relman, A. S., and Emerson, C. P. (1957). *Ann. Surg.*, **146**, 424.

ROLE OF OSMOTIC DIURESIS IN IMPAIRMENT OF CONCENTRATING ABILITY IN RENAL DISEASE

BY

E. J. DORHOUT MEES, M.D.

*From the Medical Department, University Hospital,
Utrecht, The Netherlands*

It has been suggested by Platt (1952) that the loss of "concentrating power" (osmotic ceiling), which is so constant a feature of chronic renal insufficiency, might be, at least partly, due to osmotic diuresis. He pointed out that in nephropathies there often is anatomical as well as functional evidence of increased activity per nephron. Osmotic diuresis may be constantly present in these conditions, not only as a result of elevated blood levels of solutes—for example, of urea—but also by an increased filtration rate per nephron.

Direct proof of this attractive hypothesis has not yet been given. Several authors (Nickel *et al.*, 1953; White and Rubin, 1954; Bull, 1956) have reported a linear relationship between flow and load in their patients, which they regarded as an argument for the presence of osmotic diuresis. This, however, is not conclusive, because such relationships may also be observed under normal conditions—for example, during a concentration test (McCance, 1945) or during maximal water diuresis (Schoen, 1957).

To determine whether and to what extent osmotic diuresis is responsible for the loss of concentrating power in a particular patient, his flow-load relations must be compared with those of normal people.

In normal man, during acute experiments and maximal antidiuretic hormone activity, osmotic diuresis is characterized by a certain relation between urine flow and concentration (Rapoport *et al.*, 1949). In most cases this relation can be expressed by the formula:

$$\frac{C_u}{C_p} = \frac{V + A}{V} \dots\dots\dots \text{Formula 1}$$

where C_u and C_p represent total osmolar concentration in urine and plasma, V the urine flow, and A a quantity of water which if added to the urine would make it iso-osmolar with the plasma. This factor A has been called "water economy" (West and Rapoport, 1950) or "negative free water clearance," and reaches a maximum which is designated as T^cH_2O by Smith and his school. When, at a certain flow, this maximum has been reached it can thus be calculated:

$$T^cH_2O = V \left(\frac{C_u}{C_p} - 1 \right) \dots\dots\dots \text{Formula 2}$$

In order to investigate the question to what extent osmotic diuresis is present under conditions of everyday life in renal patients, we have established the "flow-load relation" in these patients during maximal antidiuresis with and without additional osmotic loading and compared the results with those obtained in normal people under the same conditions.

Materials and Methods

All patients were submitted to a standard concentration test and to a mannitol infusion. These experiments were often done in succession. When we were afraid that severe fluid deprivation would not be well tolerated, thirsting was reduced to 12 hours and a pitressin-tannate-in-oil injection was given in addition, to provide for maximal antidiuresis. Mannitol was infused as a 15% solution in amounts varying from 75 to 150 g., during one to one and half hours. After the infusion was finished, urine was collected in portions of 100–200 ml. by spontaneous voiding, in at least four successive periods. Osmolarity was measured by freezing-point determination according to the Johlin (1931) principle. For calculation of the T^cH_2O we used the average "water economy" (formula 2) from all periods during which serum mannitol concentrations were at least 350 mg. per 100 ml.

The subjects were divided into four groups. Group 1 consisted of 10 normal persons. One of these subjects (No. 1 in the Table) was examined several times in different circumstances. The flow-load relation curve thus obtained was used as a standard with which the results obtained with the other individuals were compared.

In group 2 the data were collected from nine patients with probably chronic nephritis, and in group 3 from five patients in whom predominant tubular damage could be expected—two with hypercalcaemia whose history is reported elsewhere (Dorhout Mees, 1957); two with tubular necrosis 32 and 28 days respectively after the beginning of anuria; and one with unexplained renal diabetes insipidus. Group 4 is a miscellaneous group, including two patients with one kidney, one with renal vein thrombosis, and two others in whom renal impairment of undetermined origin was found accidentally.

Results

The Table gives a survey of the data obtained. The $\text{T}^2\text{H}_2\text{O}$ value was calculated as the mean of at least four measurements. For the "standard person" (No. 1) this value was calculated as the mean of 34 determinations, obtained during four experiments. These experiments were done under conditions of different salt intake, while the load was once in urea and three times in mannitol. The $\text{T}^2\text{H}_2\text{O}$ values showed considerable variations (from 3.9 to 6.6) in the various experiments. The mean value of 5.7 was arbitrarily chosen as a standard reference to which the $\text{T}^2\text{H}_2\text{O}$ values of the others, normals as well as patients, were related.

In column 4 this relation is given as a factor (k) by which the $T^{\circ}\text{C}_2\text{H}_2\text{O}$ value should be multiplied to make it equal to 5.7.

The last three columns (5, 6, and 7) give the urine/plasma (U/P) osmolar maximum during thirsting, the urine volume at which this was reached, and the time of dehydration used. For graphical representation of the flow-load relation it seemed more appropriate to relate

the urine osmolar concentration $\left(\frac{\text{load}}{\text{flow}}\right)$ with urine

flow instead of the load itself, and to express total urine osmolar concentration by the osmolar urine/plasma ratio.

In the Chart the mean of all observations and the control limits of the "standard person" are given as

Data Obtained from the Four Groups

Subject	Diagnosis	Sex	TcH ₂ O	Factor k	U/P Osmolar Maximum	Urine Volume During Max. Conc.	Hours of Dehydration (Conc. Test)
<i>Group 1</i>							
1	Normal	M	5.7	1	4.1		
2	"	M	6.1	0.93	4.0	0.50	18
3	"	M	5.1	1.12	3.6	0.20	20
4	"	M	5.3	1.07	4.1	0.42	16
5a } 5b }	"	F	{ 4.9 4.7	{ 1.16 1.21 }	3.6	0.5	20
6	"	M	5.7	1	3.4	0.32	22
7	"	M	5.2	1.10	3.5	0.28	20
8	"	M	6.0	0.95	4.1	0.39	19
9	"	M	6.0	0.95	3.7	0.35	24
10	"	M	5.4	1.06	3.8	0.45	24
<i>Group 2</i>							
A	Chronic nephritis	M	2.5	2.3	2.2	0.38	24 + P
B 1 } B 2 }	"	F {	{ 1.6 1.4	{ 3.6 4.1	2.4	0.62	24
C	"	M	1.5	3.8	2.1	0.16	26
D	"	F	0.16	35	1.4	0.5	30
E	"	M	0.5	11.4	1.2	0.7	14 + P
F	"	M	0.4	14	1.3	0.22	19 + P
G	"	M	1.1	5.2	2.2	0.55	19 + P
H	Acute neph., recovering	M	3.2	1.8	2.5	0.44	26
I	Chronic nephritis, dubious	M	2.9	2.0	2.6	0.45	24
<i>Group 3</i>							
J 1 } J 2 }	Hyperparathyroidism	F {	{ 1.7 1.1	{ 3.4 5.2 }	1.9	0.32	26
K	Vit. D intox.	F	1.1	5.2	1.55	0.54	25
L	Tubular necr.	F	1.9	3.0	1.45	0.36	20 + P
M	"	M	1.5	3.8	1.5	1.55	17 + P
N	Renal diab. insip.	M	0.65	9	1.8	1.4	24 + P
<i>Group 4</i>							
O	Renal vein thrombosis	F	1.1	5.2	1.8	0.40	20 + P
P	Hypoplasia of one kidney.	M	3.1	1.8	3.3	0.25	20 + P
Q	Hypertension	M	4.4	1.3	2.3	0.7	20 + P
R	Nephrectomy Unknown (nephrothiasis?)	M	4.0	1.4	2.8	0.3	24
S	(Hypertension)	M	2.7	2.1	2.2	0.35	36

the drawn line and the dotted lines respectively, showing a flow-load relation which is similar in shape to that obtained by Rapoport *et al.* (1949), though not quite identical with it.

In order to compare flow-load relations observed in the other persons with this particular flow-load relation,

Maximal urine concentration at low urine flows related to corresponding flows, after "correction" of the latter by factor k.
For further explanation see text.

we have multiplied the diuresis values of each person by the above-mentioned factor k , which results in a displacement of the point in a horizontal level in the Chart. For the sake of simplicity in the Chart only one point of each patient is shown. For this point we chose the observation during which the highest urine concentration was measured—that is, the left-hand end of each curve.

As an example we demonstrate the procedure on patient O, whose $T\dot{C}H_2O$ was nearly constant (1.1 ± 0.06) during six observations. During the first period a U/P osmotic concentration ratio of 1.34 was found, the urine production being 3.2 ml./min. This is represented by point a in the Chart. After multiplication of the urine flow value with factor k (5.2 in this case) the point is displaced to the right. It is clear that it will coincide with the drawn line (point b), as factor k was given just that value that would make flows in the range where $T\dot{C}H_2O$ is reached (i.e. water reabsorption is maximal) identical with those produced by the standard person at the same urine concentration. When the urine flow (0.40 ml./min.) observed during the highest U/P ratio (1.8) is multiplied by factor k_1 , point c (representing this low urine flow) is also displaced to the right, which results in point O—that is, not on the “standard curve.”

It is obvious that in the hypothetical case the renal tissue of the standard person could be reduced in amount but remain qualitatively normal in all respects, all the points from the regression curve would be displaced to the left, the different urine flows being reduced in a constant proportion. Multiplication of the flows with the reverse of this factor would again reproduce the original line. In the case of patient O and of the other patients, there cannot be found any one factor that would make the flow-load relations identical with those of the standard person in the entire flow range.

Discussion : Theoretical Considerations

The renal capacity for active water reabsorption seems to be limited by two factors—the osmotic ceiling at low flows and a volume transportation capacity (T^cH_2O) at high flows.

So far it is assumed that $T^{\circ}H_2O$ indicates a renal tubular function and that one can speak in terms of $T^{\circ}H_2O$ for each nephron. The findings that $T^{\circ}H_2O$ is influenced by the state of hydration (Epstein *et al.*, 1957a) and the protein intake (Epstein *et al.*, 1957b) are not in contradiction with this assumption. More difficult to explain are the divergent values found during sodium (Ladd, 1951) or mercurial (Grossman *et al.*, 1955) diuresis and after loading with mannitol (Zak *et al.*, 1954). Curiously enough, this fact has not attracted much attention.

The occasional reports of hypotonic urines in osmotic diuresis during hydropenia (Mudge *et al.*, 1949; Zak *et al.*, 1954; Anslow and Wesson, 1955), and the observations of De Wardener and del Greco (1955) suggesting hypotonicity in the proximal tubules, throw further doubt on the "classic" theory. If the attractive views of Wirz (1957) are true, revision of many theoretical constructions will be necessary. Even then, however, it is to be explained why in many instances the value of the $T^{\circ}H_2O$ remains so constant.

As Bull (1956) stated, it is not possible to compare experiments in different individuals, as the number of nephrons is unknown and there may be various degrees of glomerular and tubular hypertrophy, which complicate experimental approaches.

This matter may nevertheless be simplified by stating that flow-load relation is a question of balance between excreted load and faculties of renal water reabsorption. If osmotic diuresis is substantially depressing urine concentration, it is more specifically a question of balance between excreted load and $T^{\circ}H_2O$. It is obvious that comparison of results obtained in different persons is hampered by the differences in this $T^{\circ}H_2O$ value.

In order to obtain the same relation between load and $T^{\circ}H_2O$ for all persons, the "correction factor" k was introduced, making the $T^{\circ}H_2O$ (whatever may be its physiological significance) equal to that of the standard person.

In this way, flow-load relations at high flows are arbitrarily made to coincide, and if the only difference between the subjects would have been a different amount of (qualitatively normal) renal tissue, flow-load relations at lower flows would also fall into the same range.

It is clear that values of the other normal people show close agreement with the standard regression line, whereas those of the patients (with one exception) fall to the left and below this line.

If osmotic diuresis were the only factor limiting urine concentration, there is no reason why the concentrations at the "corrected" urine flows would not reach normal values. It appears, however, that most of our patients were not able to reach as high a concentration gradient between urine and plasma as were the normal people, at a same relation between excreted load and maximal water reabsorption capacity.

This fact, indicating that the osmotic ceiling was relatively more depressed than could be accounted for by osmotic diuresis, may, however, not be a proof of tubular cell damage. It may be that normal functioning of the concentrating mechanism is possible only in the presence of a normal renal architecture and is readily disturbed by scarring, occlusion of blood vessels, and the presence of non-functioning tubuli, as can be expected from Wirz's conceptions. It was expected that patients with one normal kidney would have a normal osmotic ceiling, if correction was made for osmotic diuresis.

This was indeed the case in patient Q, but not in patient R. Perhaps there are still other reasons for loss of concentrating power. We sometimes observed that, at the end of osmotic diuresis experiments, a more concentrated urine was produced (at higher loads) than during dehydration with minimal load.

Summary and Conclusions

Measurements were made of maximum urine osmolar concentration, $T^{\circ}H_2O$, during mannitol loading and mannitol clearance in normal people and in patients with several forms of renal disease. The results are discussed in the light of the hypothesis that constant osmotic diuresis may be responsible for diminished urine concentration in renal disease.

It is concluded that the loss of "concentrating power" cannot be accounted for entirely by the effect of osmotic diuresis in patients with chronic glomerulonephritis or other disturbances. Specific damage to tubular function seems to be of more importance.

The significance of the $T^{\circ}H_2O$ concept is critically discussed. It is suggested that disturbance of tubular water reabsorption reflects not only tubule cell damage but also disturbance of renal architecture.

REFERENCES

- Anslow, W. P., and Wesson, L. G. (1955). *Amer. J. Physiol.*, **180**, 605.
 Bull, G. M. (1956). In *Modern Views on the Secretion of Urine* (Cushny Memorial Lectures, 1956), edited by F. R. Winton, p. 256. Churchill, London.
 De Wardener, H. E., and del Greco, F. (1955). *Clin. Sci.*, **14**, 715.
 Dorhout Mees, E. J. (1957). *Acta med. scand.*, **157**, 199.
 Epstein, F. H., Kleeman, C. R., and Hendrikx, A. (1957a). *J. clin. Invest.*, **36**, 629.
 ———, Pursel, S., and Hendrikx, A. (1957b). *Ibid.*, **36**, 635.
 Grossman, J., Weston, R. E., Borun, E. R., and Leiter, L. (1955). *Ibid.*, **34**, 1611.
 Johlin, J. M. (1931). *J. biol. Chem.*, **91**, 551.
 Ladd, M. (1951). *J. appl. Physiol.*, **3**, 603.
 McCance, R. A. (1945). *J. Physiol. (Lond.)*, **104**, 196.
 Mudge, G. H., Foulks, J., and Gilman, A. (1949). *Amer. J. Physiol.*, **158**, 218.
 Nickel, J. F., Lowrance, P. B., Leifer, E., and Bradley, S. E. (1953). *J. clin. Invest.*, **32**, 68.
 Platt, R. (1952). *Brit. med. J.*, **1**, 1313.
 Rapoport, S., Brodsky, W. A., West, C. D., and Mackler, B. (1949). *Amer. J. Physiol.*, **156**, 433.
 Schoen, E. J. (1957). *J. appl. Physiol.*, **10**, 267.
 West, C. D., and Rapoport, S. (1950). *Amer. J. Physiol.*, **163**, 159.
 White, A. G., and Rubin, G. (1954). *Proc. Soc. exp. Biol. (N.Y.)*, **86**, 30.
 Wirz, H. (1957). In *The Neurohypophysis*, edited by H. Heller, p. 157. [Colston Papers, vol. 8.] Butterworth, London.
 Zak, G. A., Brun, C., and Smith, H. W. (1954). *J. clin. Invest.*, **33**, 1064.

Turkeys, ducks, and pigeons have now joined parrots on the danger list of public health as transmitters to man of a generalized virus infection known as psittacosis or ornithosis. Ninety-eight species of birds (57 of them belonging to the parrot and parakeet family) have been found to be naturally infected with this disease, which is by no means always benign in man, since until recently it killed 2.6% of its victims. With modern antibiotic treatment the number of deaths has been considerably lowered. . . . Epidemics have been reported from many countries, including the U.S.A., Canada, Czechoslovakia, Austria, the U.S.S.R., Germany, etc. So far as is known, the disease has never been contracted from eating diseased birds. Addition of tetracycline compounds to poultry feed has been successful in eradicating the infection from a few parakeet-breeding aviaries, but the results with pigeons and turkeys have been less promising; it is hoped, nevertheless, that a suitable chemotherapeutic method can eventually be developed (Dr. K. F. Meyer, *W.H.O. Bulletin*, Vol. 20, No. 1, 1959).