TUBULAR INSUFFICIENCY AND RENAL DWARFISM*

BY

G. FANCONI

From the Department of Paediatrics of the University of Zürich, and the Kinderspital, Zürich

(RECEIVED FOR PUBLICATION SEPTEMBER 2, 1953)

Taken as a whole, growth disorders may be attributed to various causes: (1) Lack of building material, especially proteins; (2) disturbance of neuro-hormonal regulation; (3) disorders of metabolism, e.g., in absorption in the intestine, transportation, assimilation or excretion; (4) non-response of the end-organs, i.e., bone and protoplasm in general. In this complex system of vital functions the kidney plays a prominent part because it is not only the organ of elimination for many metabolites, but, also, in its distal tubules, it is a most important seat (end-organ) of many chemical adjustments. If these adjustments fail the state of growth suffers in consequence.

The regulation of the metabolism of water, sodium chloride, calcium and phosphorus, dextrose and amino-acids, depends on the interplay of certain mechanisms (Fig. 1).

Mechanism of Growth and its Disorders

The diencephalon acts upon the end-organs directly or through the endocrine glands. The

FIG. 1.

* An Institute of Child Health Lecture given at The Hospital for Sick Children, Great Ormond Street, London, June 26, 1953.

hormones of the endocrine glands get into the extracellular fluid and influence the intestine, the storage organs and the kidneys. Chemoreceptors control the level of the chemical substances in the extracellular fluid and influence the diencephalon and the endocrine glands.

The individual members of this hierarchy of mechanisms are mutually dependent. A disturbance in the function of any one member is immediately counteracted by the others. It is often difficult, therefore, in any given case to locate the exact site of the disturbance.

The reabsorption of a large number of substances takes place in the tubules of the kidney in relation to the needs of the body as a whole. This adjusted reabsorption is described as facultative. There are good grounds for the belief that the reabsorption of each of the substances occurs at a different level in the tubule and is dependent on different mechanisms. Dextrose, amino-acids and part of the phosphate are reabsorbed in the proximal tubule. The reabsorption of the base equivalents (the economy of base and the production and excretion of ammonia) or of acid equivalents to maintain the acid base balance takes place in the distal tubule. The reabsorption of the main extracellular electrolytes, sodium and chlorine, as well as water, occurs throughout the whole length of the tubule, but mainly in Henle's loop.

This complex reabsorption process, obligatory as well as facultative, may be upset in one of two ways: the reabsorption may be excessive or insufficient. In the case of dextrose and amino-acids, normally completely reabsorbed, there is but one possibility, insufficient reabsorption causing renal glucosuria and amino-aciduria. For the other substances, however, instances of pathologically decreased and increased reabsorption are both known: (1) for water, on the one hand diabetes insipidus, on the other oliguria as in lipoid nephrosis; (2) for sodium chloride, on the one hand diabetes salinus renalis (salt-losing nephritis), on the other hand renal hyponatraemia as in Cushing's syndrome. (3) In phosphate diabetes (hypophosphataemic

vitamin D-resistant rickets) too little phosphate is reabsorbed, whereas in true and pseudo-hypoparathyroidism too much is reabsorbed. (4) Lightwood-Albright's tubular renal acidosis ensues if the reabsorption of inorganic bases is impaired. This may be due either to an insufficiency of H ions released from bicarbonate by carbonic anhydrase in the urine, or may be related to an insufficient formation of ammonia by the kidney.

In the literature various disorders related to an insufficiency of reabsorption at the level of the proximal tubule have been labelled Debré-de Toni-Fanconi's syndrome. Those related to an insufficiency of reabsorption at the level of the distal tubule have been called Lightwood-Albright's syndrome. These terms have caused much confusion and it would be better to use the more exact terminology 'proximal tubular or distal tubular insufficiency'. Darmady (personal communication) demonstrated in cases with insufficiency of the proximal tubules the cellular atrophy (narrow neck) in the proximal tubules by dissection of individual nephrons as well as in paraffin sections.

In practice, the diagnosis of tubular insufficiency is much more complicated, for the following reasons. First of all, the initial disorder does not always originate in the tubule itself, but may be located at another level of the hierarchy of regulatory mechanisms without any noticeable change in the symptoms, as for example in diabetes insipidus or hypoparathyroidism. For the regulation of water and sodium chloride the chief end-organ is the distal tubule. The osmoreceptor is probably located in the nucleus supra-opticus of the diencephalon. We have two groups or two hormones which control excretion in the tubules, a hormone from the posterior lobe of

the hypophysis, the adiuretin or pitressin, and the salt-hormone produced by the adrenals, and this depends on the A.C.T.H. excreted from the anterior lobe.

The same symptoms can be produced by disturbances at various places in the complicated system of regulation. For example, isothermia, that is, the impossibility to concentrate the urine, may be due to a primary insufficiency of the renal tubule or to a disturbance in the hypothalamic-pituitary system.

The second reason why diagnosis is complicated is that the disorders which affect the enzymes regulating tubular reabsorption (usually phosphatase and phosphorylase) may be generalized to a varying degree, with the result that the prominent symptoms are those of a generalized metabolic disorder such as cystinosis of the organs or glycogenosis of the liver.

Third, the disorder of reabsorption may extend simultaneously to several levels of the tubule and affect them in varying degrees (Table 1).

In the completely developed Debré-de Toni-Fanconi syndrome there is not only an insufficiency of the proximal tubule, but also a defective excretion of base equivalents, whereas excretion of ammonia is normal or slightly increased. There are, however, diseases like phosphate diabetes or renal glycosuria in which only one function of the proximal tubule is concerned. In the tubular renal acidosis of Lightwood-Albright not only the function of the distal tubule, but probably also the elimination of phosphate is altered. Indeed Latner and Burnard (1950) were able to show that an increase of the serum phosphorus improved the excretion of ammonia and the elimination of acid equivalents in the urine.

Thus a whole set of clinical pictures is derived from various such combinations. If we wanted to

TABLE 1
SOME EXAMPLES OF TUBULAR DISORDERS

Diseases	Whole Tubule		Proximal Tubule			Distal Tubule	
	Water	Na & Cl	Phosphates	Amino-acids	Dextrose	Base Equivalents	NH ³ Production
Diabetes insipidus normochloræmicus ..	—						
Diabetes insipidus hyperchloræmicus ..	—	+					
Lipoid nephrosis	+	+					
Diabetes insipidus occultus		+					
Cerebral hyperelectrolytæmia		+					
Diabetes salinus renalisis		—					
Hypercorticism		+					
Phosphate diabetes (Vitamin D-resistant Rickets)			—				
Renal glycosuria					—		
Debré-de Toni-Fanconi syndrome			—	—		—	?
True and pseudo-hypoparathyroidism			+				
Hyperparathyroidism			—				
Tubular renal acidosis (Lightwood-Albright)			?			—	—

Tubular reabsorption or NH³ production increased = +

Tubular reabsorption or NH³ production decreased = —

describe each combination of disturbed functions in the tubular or in the hierarchy of regulatory mechanisms as such, we would never come to an end. Diagnosis and therapy are better served if, instead of thinking in terms of rigid, strictly defined nosological entities, we reason functionally, seeking to locate and evaluate the seriousness of the disorder as completely as possible. In what follows we have tried to analyse some clinical entities by this functional method.

Forms of Diabetes Insipidus

TABLE 2

Factors (functions) regulating extracellular fluid

- (a) Tubular reabsorption of water.
(b) Tubular reabsorption of Na^+ and Cl^- .
(c) Adjustment of the osmolarity by the osmoreceptors.

<i>Clinical syndromes</i>	<i>Disturbed Function</i>		
Diabetes insipidus hyperchloraemicus	..	..	a, b, c
Diabetes insipidus normochloraemicus	..	..	a
Responsive to pitressin			
Non-responsive to pitressin			
Diabetes insipidus hyperchloraemicus occultus	..	..	b, c
Neurogenic hyperelectrolytaemia	..	..	c

It has always been evident that several forms of diabetes insipidus exist. In 1946 we drew attention to the fact that the various forms of diabetes insipidus could be differentiated according to the special functions which were upset in the excretion of water and NaCl (Fanconi, 1946). It is indeed possible to distinguish three such special functions which are not necessarily associated; (1) the regulation of tubular reabsorption of water, (2) the regulation of reabsorption of NaCl and (3) the adjustment of Cl and Na levels in the extracellular fluid, probably brought about by the osmoreceptors in the nucleus supra-opticus of the hypothalamus.

The first and second of these special functions are partly antagonistic, as an increase in the osmotic pressure of the extracellular fluid can equally well be counteracted by water retention, as by increased NaCl excretion. According to which of these three special functions is disturbed, the distinction can be made between the different forms of diabetes insipidus.

Hyperchloraemic Diabetes Insipidus.—The hyperchloraemic form of diabetes insipidus is mainly found when there is an important lesion of the hypothalamic-pituitary system. In this case all three special functions are upset and the diagnosis is easily made.

Normochloraemic Diabetes Insipidus.—In the normochloraemic form water excretion alone is upset, because the facultative reabsorption is insufficient in relation to the needs of the body as a whole. It is astonishing how the organism manages to maintain constant the osmotic pressure of the extracellular fluid despite considerable loss of water.

One cannot help thinking that a protective mechanism must come into play. During dehydration such a mechanism could bring about the storage, somewhere in the body, of NaCl in a dry (osmotically inactive) form. Mild cases of this form are difficult to distinguish from primary polydipsia as the limits are probably not clear cut. In any case we have observed several cases which, as they had a reasonable concentrating ability, appeared to be primary polydipsia but had later to be reclassified as diabetes insipidus. Veil (1920) was struck long ago by the fact that some of these cases did not respond to pituitrin, and in 1926 we described such a case in detail (Haymann and Fanconi, 1926). Such cases belong to the category of pitressin-resistant diabetes insipidus, named 'water babies' by American authors, a condition in which the disturbance probably occurs in the end-organ itself, namely in the kidney tubule.

Diabetes Insipidus Occultus.—There are also forms in which the first special function, that of water reabsorption, does not appear upset, as may be the case at the beginning of the disease with infants or at the end of the disease when the anterior lobe of the pituitary has been severely damaged by a tumour. We already suggested in 1937 that these forms should be called diabetes insipidus occultus (Fanconi, 1938).

For example, a 12-year-old girl was admitted to hospital with typical diabetes insipidus hyperchloraemicus, excreting daily 5 litres of urine of a specific gravity of 1005. The serum chloride was always high. But with the aggravation of the disease the diabetes insipidus gradually improved. The volume of the urine decreased to 500 ml., the specific gravity increased to 1020 and more, but the serum chloride increased more and more. Following a single dose of 7 gr. of sodium chloride by mouth, a test which was easily tolerated five months before, the child died three days later, with the chemical symptoms of salt-intoxication. We found a tumour of the brain, a glioblastoma multiforme of the hypothalamic region growing slowly and having infiltrated the posterior lobe of the hypophysis. The anterior lobe of the hypophysis did not seem to be affected, but it is very difficult to be sure that it was functionally unaltered.

We also had the opportunity of seeing two brothers, infants who later on developed typical diabetes insipidus hyperchloraemicus. In their infancy they had permanent fever without any detectable cause. The serum chloride level was very high. In both cases the fever disappeared when water was given or when the intake of salt was decreased. Although the serum chloride has remained high, the boys are still alive.

Neurogenic Hyperelectrolytaemia.—There is also a fourth form in which polyuria is always absent. Therefore it has nothing to do with diabetes insipidus. In 1946 we called this a special form of occult diabetes insipidus, but now we had better say with Cooper, 'neurogenic hyperelectrolytaemia', (Cooper and Crevier, 1952).

Children with this disease are continually at the limit of dehydration, with fever in the morning. They gain little or no weight, and present, therefore, a picture of severe, unyielding malnutrition. In our experience there are two forms, the one which is incurable and which is probably due to the lack or the destruction of the osmoreceptors, and the other, less severe, and probably due to the retarded development of the osmoreceptors. Children having the latter form are generally treated with all kinds of antibiotics that do nothing to bring down the fever. Only a salt-poor diet, plentiful in liquid, can improve the symptoms. After some years the mildly affected tolerate an ordinary diet. A mild hydrocephalus or a dilatation of the third ventricle as shown by pneumo-encephalography are signs of a primary cerebral disorder.

In one case the child presented certain kidney symptoms, a mild proteinuria and bacteriuria etc. Therefore we were not sure whether the condition was neurogenic hyperelectrolytaemia or renal acidosis (Lightwood-Albright). Indeed, in the beginning the child was not able to concentrate urine. One year later, this was possible. The response to ammonium chloride was completely normal and we could not demonstrate an insufficiency of the distal tubule, but the test was made when the child had already improved.

Debré-de Toni-Fanconi Syndrome

In a recent very important monograph (Bickel, Baar, Astley, Douglas, Finch, Harris, Harvey, Hickmans, Philpott, Smallwood, Smellie and Teale, 1952) Bickel considers cystinosis to be a necessary symptom and he proposes to call the cystine-storage disease with amino-aciduria and dwarfism Lignac-Fanconi disease, even though, at one time, Bickel himself published with me (Fanconi and Bickel, 1949) a case in which proximal tubular insufficiency was accompanied by liver glycogenosis but all signs of cystinosis were lacking. Bickel would now strictly differentiate this nosological entity from the Lignac-Fanconi disease. Proximal tubular insufficiency has also been described in adults (Dent, 1946, 1947, 1952; Lambert, de Heinzelin de Braucourt and Bruneel, 1953). In these cases there is no accumulation of cystine and an intake rich in phosphate and alkali has a definitely beneficial effect.

Weber from the Hungerlands Clinic (Weber, 1953) reports a case of cystinosis without any amino-aciduria or hypo-phosphataemia, or hyperphosphataemia, but which shows an insufficiency in the distal tubule. Moreover Bickel holds the opinion that amino-aciduria in the Lignac-Fanconi syndrome is a result of an overflow of amino-acids accumulated in the blood. In contradiction, as he has obtained very high amino-acid clearances, Dent has been able to show that in most cases it is a question of renal insufficiency. The task for future research will be to study the clearance of amino-acids, not as a whole, but individually as it is already known that each one has its more or less independent metabolism. The variations of the Fanconi syndrome will be better understood when we consider the various functional defects of the proximal and distal tubule as well as cystinosis as frequent but not indispensable symptoms. This view is stressed by the fact that the more the science of heredity advances, the more it shows that many special functions may be separately upset. It would be a step forward in scientific thinking if one reasoned less in terms of rigidly defined nosological entities and more in terms of special functions.

Renal Disease with Dwarfism

TABLE 3

A. Chronic glomerular and tubular insufficiency (non-protein nitrogen increased).

- (1) Congenital renal malformations with secondary interstitial nephritis:
 - (a) Without osteopathy (serum phosphorus normal)
 - (b) With osteopathy (serum phosphorus increased)
- (2) Primary and secondary chronic nephritis without malformations
- (3) Chronic renal (?) hypercalcaemia with osteosclerosis
- (4) Terminal condition of B.

B. Chronic tubular insufficiency (non-protein nitrogen and phosphorus not increased).

- (1) Diabetes salinus ('salt-losing nephritis') usually combined with A(1) or A(2)
- (2) 'Phosphatic diabetes' (Vitamin D-resistant rickets)
- (3) 'Amino-diabetes' (Debré-de Toni-Fanconi) with and without cystinosis
- (4) Renal hyperchloraemic acidosis with nephrocalcinosis (Lightwood, 1935, 1946; Albright, Consolazio, Coombs, Sulkowitch and Talbott, 1940; Albright, Burnett, Parson, Reifenshtein and Roos, 1946)
- (5) Renal hypochloraemic acidosis with late rickets (Boyd and Stearns, 1941, 1942)
- (6) Oculo-cerebro-renal syndrome (Lowe, Terrey and MacLachlan, 1952)
- (7) Osteopathia acidotica pseudorachitica (Fanconi, von Albertaini and Zellweger, 1948)
- (8) Nephronophthisis with primary tubular and secondary total renal insufficiency (Fanconi and co-workers)

'Renal dwarfism' is the title of my lecture. Not every renal disease causes dwarfism. For example, renal glycosuria and the chronic benign pyelitic or post-pyelitic hypertension described in our clinic does not do so (Fanconi, Rüegg and Dieterle, 1951). One of our patients, who is now 32 years old, has had a hypertension since the age of 10; at the age of 11 we found a very severe alteration of the fundus oculi. Fourteen years later the fundus

was normal and the young man is now very well, although the hypertension persists. In another case of benign post-pyelitic hypertension existing from the first year of life we found at the age of 19 years a unilateral dilatation of the calices of the pelvis as a scar of the infection during infancy. The serum chemistry of this girl was the opposite of that found in tubular renal acidosis as the alkali reserve was very high (77 vol. %) and the chlorine was normal or decreased (326 mg. %).

Furthermore the familial disease 'nephronophthisis', also described in our clinic, does not influence growth, at least not in the first period when the disturbance is only located in the distal tubule (Fanconi, Hanhart, von Albertini, Ühlinger, Dolivo and Prader, 1951).

I should like to draw your attention to congenital malformations with hyperphosphatemic osteopathia (Table 3, 1b), because in these cases we have frequently a combination with a renal hyperchloraemic acidosis and diabetes salinus renalis.

One of our patients, a boy of 16 years, had a very serious form of this disease. We observed him in our hospital at the age of 13 in 1937. As he had nephritis, we gave him a salt-free diet. After two weeks he presented all the symptoms of uraemia with symptoms of latent tetany. The level of serum chloride being very low, we fortunately decided to give him salt both orally and intravenously. The symptoms of uraemia disappeared very quickly. We made the diagnosis of diabetes renalis salinus and some months later we cautiously repeated the experiment with a salt-free diet. The child continued excreting chloride in the urine, he had lost the power of facultative reabsorption and the serum chlorine decreased, the general condition got worse and we were obliged after three weeks again to prescribe salt in the diet. Some days later he improved once more. The concentration of chlorine in the urine had decreased only a little during the salt-free period. To protect the body from too great a loss of NaCl the volume of urine decreased also. But this is a two-edged knife. By the reduction of the volume of urine it is not possible to excrete the scoriae of the metabolism and the azotaemia as well as the phosphaturia increases. With this experience we proved that we were really concerned with a salt-losing nephritis. Three years later the child died. The contracted kidney showed enlarged tubules with a very thin epithelium. We can well understand that the facultative reabsorption of NaCl corresponding to the needs of the whole body by such altered tubules is not more possible.

In this and other cases we find the signs of fibro-osteoclasia in the bones and in radiographs the signs

of secondary hyperparathyroidism. The phalanges show the typical subperiosteal bone reabsorption, the skull a granular atrophy. But in the metaphysis of the long bones we find also signs of renal rickets with proliferation of the osteoid tissue. This is probably not the consequence of the secondary hyperparathyroidism but of the acidosis.

This year we had the opportunity of making further observations on a boy 17 years old with the same disease. He excreted about 3,000 ml. of urine daily, day and night in the same quantity, and in the same low concentration. Other tests also demonstrated a complete isosthenuria. The analysis of the serum showed a certain degree of insufficiency of the glomeruli, and also of the distal tubule as in the Lightwood-Albright syndrome; that is, a marked chlor-acidosis. Unfortunately we could only make brief observations. The alkali therapy improved the hyperphosphataemia. Although the calcium level was very low, the kidney continued to excrete calcium. After treatment this excretion of calcium and also of the other kations Na and K decreased. The most striking point was the lowering of the phosphate level after the alkali therapy.

But alkali therapy is only possible if the glomerular function is sufficient. In another similar case we produced a very dangerous hyperelectrolytaemia by this therapy. The child died and we found in the bones a significant fibro-osteoclasia, a sign of secondary hyperparathyroidism. This case was sent to the hospital with the diagnosis of Cushing's syndrome, because the child was very fat. We spoke of a renal pseudo-Cushing syndrome. It is possible that chronic kidney disease causes a chronic stress. This could induce the adrenals to produce a larger amount of catabolic S hormones and so inhibit the growth and facilitate the deposit of fat.

To conclude we must try in these cases of nephropathy to avoid a loss of NaCl because of diabetes salinus renalis, and a loss of inorganic base because of the insufficiency of the distal tubule. But on the other hand we must also avoid hyperelectrolytaemia by giving too much salt and alkali. The fibro-osteoclasia and the osteomalacia can be cured by large doses of vitamin D, and in some cases dehydro-tachysterol may be tried.

The cases described by Schlesinger and his colleagues in London and in our clinic in Zurich (Fanconi, Girardet, Schlesinger, Butler and Black, 1952) prove that nephropathy with glomerular insufficiency can also produce chronic hypercalcaemia with osteosclerosis combined with a retardation of growth. In these cases the product of calcium and phosphorus in the serum is so high that an osteo-sclerosis must result.

Another form of renal retardation of growth is the phosphate diabetes with vitamin D-resistant rickets. We believe that this hereditary disease of the dominant type is the consequence of an insufficient reabsorption of phosphate in the tubules. This disease, which is not at all rare, must be treated with enormous doses of vitamin D.

Finally I must mention a case of renal osteoporosis without osteomalacia which represents perhaps a new type of nephropathy and for which we proposed the name of 'osteopathia acidotica pseudorachitica'. Treatment with vitamin D rapidly improved the osteopathy. The serum chemistry corresponds to that found in the Lightwood-Albright renal acidosis with the difference that the phosphatase is very high (Fanconi *et al.*, 1948).

With this exceptional case I wish to end my long lecture, in which I find that I have raised more questions than I have answers to give.

REFERENCES

Albright, F., Consolazio, W. V., Coombs, F. S., Sulkowitch, H. W. and Talbott, J. H. (1940). *Bull. Johns Hopk. Hosp.*, 66, 7.

- , Burnett, C. H., Parson, W., Reifstein, E. C. and Roos, A. (1946). *Medicine, Baltimore*, 25, 399.
- Bickel, H., Baar, H. S., Astley, R., Douglas, A. A., Finch, E., Harris, H., Harvey, C. C., Hickmans, E. M., Philpott, M. G., Smallwood, W. C., Smellie, J. M. and Teall, C. G. (1952). *Acta paediat., Uppsala*, 42, Suppl. 90.
- Boyd, J. D. and Stearns, G. (1941). *Amer. J. Dis. Child.*, 61, 1012.
- (1942). *Ibid.*, 64, 594.
- Cooper, I. S. and Crevier, P. H. (1952). *J. clin. Endocr.*, 12, 821.
- Darmady, E. M. Personal communication.
- Dent, C. E. (1946). *Lancet*, 2, 637.
- (1947). *Biochem. J.*, 41, 240.
- (1952). *J. Bone Jt Surg.*, 34B, 266.
- de Toni, G. (1933). *Acta paediat. Uppsala*, 16, 479.
- (1938). *Verh. dtsch. Kongr. inn. med.*, 50, 203.
- (1946). *Schweiz. med. Wschr.*, 76, 791, 829.
- (1953). *Dtsch. med. Wschr.*, 78, 85.
- Albertini, A. von and Zellweger, H. (1948). *Helv. paediat. Acta*, 3, 95.
- , Bickel, H. (1949). *Ibid.*, 4, 359.
- , Girardet, P., Schlesinger, B., Butler, N. and Black, J. (1952). *Ibid.*, 7, 314.
- , Hanhart, E., Albertini, A. von, Uhlinger, E., Dolivo, G. and Prader, A. (1951). *Ibid.*, 6, 1.
- , Rüegg, J. and Dieterle, E. (1951). *Ibid.*, 6, 281.
- Haymann, K. and Fanconi, G. (1926). *Z. ges. exp. Med.*, 51, 588.
- Lambert, P. P., de Heinzelin de Braucourt, C. and Bruneel, M. (1953). *Acta clin. belg.*, 6, 1.
- Latner, A. L. and Burnard, E. D. (1950). *Quart. J. Med.*, 19, 285.
- Lowe, C. U., Terrey, M., and MacLachlan, E. A. (1952). *Amer. J. Dis. Child.*, 83, 154.
- Lightwood, R. (1935). *Archives of Disease in Childhood*, 10, 205.
- (1946). *Proc. roy. Soc. Med.*, 39, 595.
- Veil, W. H. (1920). *Verh. dtsch. Kongr. inn. Med.*, 32, 134.
- Weber, H. (1953). *Helv. paediat. Acta*, 8, 348.