Today's Treatment

Diseases of the urinary system

Drug-induced renal disorders: II

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Apart from acute nephropathy (see part I), drugs may induce a wide variety of other conditions that affect the kidney.

Drug-induced lupus erythematosus

Many drugs may produce a syndrome closely resembling spontaneous systemic lupus erythematosus (SLE). Those most commonly implicated are hydralazine, isoniazid, and procainamide.

Drugs less commonly implicated include the following.

Antimicrobials—sulphonamides, penicillins, tetracycline, streptomycin, and para-amino salicylic acid;

Antithyroid drugs—methylthiouracil and propylthiouracil;

Anticonvulsants—phenytoin, methoin, primidone, troxidone, and ethosuximide;

Antihypertensives—reserpine and methyl dopa;

Oral contraceptives;

Miscellaneous drugs—griseofulvin, phenylbutazone, and practolol.

The mechanism of drug-induced SLE is not clear, but genetic predisposition may be important. Hydralazine, isoniazid, and some sulphonamides are metabolised by acetylation in the liver. The rate of acetylation by the enzyme acetyltransferase is genetically controlled; some people are "slow" acetylators and others "fast." Drug-induced SLE develops more commonly in phenotypically slow acetylators of hydralazine and antinuclear factor is more commonly found in slow acetylators of isoniazid.

Clinically, renal involvement is usually less common in the drug-induced as opposed to the spontaneous form of SLE. About two-thirds of patients with spontaneous SLE have renal disease, but the incidence falls to about 20% in hydralazine-induced SLE and to about 2% in procainamide-induced SLE. Drug-induced SLE may be reversible on withdrawal of the drug, but this is not always so.

Drug-induced nephrotic syndrome

Several unrelated drugs can produce a nephrotic syndrome, which is usually but not always reversible on withdrawing the offending drug. These include inorganic and organic mercurials, gold salts, penicillamine, paramethadione, troxidone, tolbutamide, perchlorate, probenecid, and phenindione.

The mechanism of drug-induced nephrotic syndrome seems to vary. With penicillamine, however, fluorescence microscopy has disclosed deposits of immunoglobulins and complement components along the glomerular capillary basement membranes, suggesting that the underlying mechanism includes deposition of immune

complexes with the drug presumably acting as a hapten. Similar changes have been reported in some cases of gold-induced nephrotic syndrome while others have shown tubular damage with no evidence of immune complex deposition in the glomeruli, suggesting that in some cases at least gold has a direct toxic effect on the renal tubules. Gold salts produce various nephrotoxic effects including depression of the glomerular filtration rate, sometimes resulting in uraemia.

Drug-induced retroperitoneal fibrosis

Drug-induced retroperitoneal fibrosis is a curious condition in which extensive and progressive fibrosis occurs most commonly in the retroperitoneal space affecting and obstructing the ureters with a resulting obstructive uropathy, which may cause acute or chronic renal failure. The ureteric obstruction is due to replacement of the muscular walls of the ureter by fibrous tissue, although the lumen itself is not occluded and, paradoxically perhaps, it is usually quite easy to pass a ureteric catheter up the obstructed ureter from the bladder. Other structures may be affected by this fibrotic process, including the inferior vena cava and aorta. In addition, the process may occasionally occur elsewhere—for instance, in the mediastinum, liver, and thyroid gland. Several drugs have been incriminated in this condition, particularly methysergide but also ergotamine, dihydroergotamine, hydralazine, dexamphetamine, and methyl dopa. In many cases, however, no particular drug can be blamed. The underlying pathological mechanism is not known.

Localised fibrosis and stricture formation in the wall of the ureters have also been attributed to chronic analgesic abuse.

Analgesic nephropathy

Analgesic nephropathy is now a well-recognised form of chronic renal disease and an important cause of chronic renal failure. The basic pathological lesion is papillary necrosis. The mechanism would seem to be damage to, and occlusion of, the vasa recta leading to ischaemic necrosis of the papillae. Renal tubules passing into a necrotic papilla are obstructed, and this leads to secondary atrophy of the obstructed nephrons with resulting changes in the overlying renal cortex, which have in the past been referred to as "chronic interstitial nephritis." Analgesic nephropathy is particularly prevalent in Switzerland, Scandinavia, and Australia. Phenacetin has generally been regarded as the drug responsible, although most patients have taken the phenacetin with a number of other mild analgesics, particularly aspirin, codeine, amidopyrine, and phenazone. It is therefore difficult to be sure whether it is the combination of drugs or phenacetin alone that is the cause. It is interesting that there have been only isolated reports of papillary necrosis due to chronic abuse of aspirin or paracetamol alone. Paracetamol is particularly interesting since it is the principal metabolite of phenacetin. Chronic analgesic abuse is often associated with chronic laxative abuse, and the combination may be responsible for papillary necrosis. Analgesic nephropathy is dose-related, and by the time that it is recognised patients have usually taken more than 2 kg of phenacetin over many years and sometimes much more than this. In Britain phenacetin has been obtainable only on prescription for the past few years, and it will

be interesting to see whether the incidence of analgesic nephropathy falls as a result of this. In Scandinavia, phenacetin has been obtainable only on prescription since 1961, and the incidence of analgesic nephropathy has decreased.

Clinically, analgesic nephropathy may be difficult to diagnose unless every patient with chronic renal disease is questioned, sometimes repeatedly, about drug intake. The reasons for taking these large amounts of analgesic mixtures are often obscure and take place against a background of psychiatric illness. Patients may often deny or fail to mention taking analgesics. A history from a close relative may be revealing. In Australia particularly there is a close association between analgesic nephropathy and peptic ulceration, but this has not been a feature of cases reported in Britain.

The clinical syndrome may include polyuria, polydipsia, and nocturia due to a renal-concentrating defect. There may be a sodium-losing tendency, and hypertension tends to be a late complication. Attacks of renal colic or of haematuria due to sloughing of necrotic papillae may occur, and there may be sterile pyuria. The plasma urate may be high for the degree of renal failure and secondary gout may occur. Many patients present with unexplained severe chronic renal failure. The intravenous pyelogram may be normal even if papillary necrosis is present but usually the kidneys are reduced in size with caliectasis. Less commonly, but diagnostically, calcified triangular papillae or detached papillae surrounded by contrast medium and lying free in the calices may be seen. The tendency for the affected papillae to calcify may be related to the fact that these patients may also have an impaired acidifying ability and a reduced urinary citrate excretion. Diagnosis may be made rarely by detecting necrotic papillae in the urine, which has to be strained through a piece of cloth or gauze, or occasionally on renal biopsy. Haemolytic anaemia with Heinz bodies and methaemoglobinemia may also be produced by phenacetin, and the passage of dark brown urine (in the absence of haemoglobin or its derivatives) with the property of reducing silver nitrate solution in the cold has been reported. Phenacetin derivatives may also be detected in the urine by using simple chromatographic techniques.

Analgesic nephropathy is an important diagnosis to make because if the patient can be persuaded to stop taking the drugs then deterioration in renal function can be halted and sometimes partially reversed.

Complications of analgesic nephropathy, apart from those already mentioned, include ureteric obstruction due to blockage of the lumen by dislodged necrotic papillae or calcified papillae acting as calculi or to localised ureteric fibrosis. The development of transitional cell tumours of the renal pelvis in patients with analgesic nephropathy has been reported. Others have described associated cerebral cortical atrophy in some patients with analgesic nephropathy.

In the differential diagnosis chronic radiological pyelonephritis with caliectasis and cortical scarring must be included, and there seems to be little doubt that in the past many cases of analgesic nephropathy have been incorrectly labelled as chronic pyelonephritis. Indeed, it may be difficult to distinguish between the two in advanced cases, and they may coexist. There are also other causes of papillary necrosis to be considered, including acute pyelonephritis (rarely and particularly in diabetes), obstruction of the urinary tract (especially when associated with infection), renal tuberculosis, and sickle-cell anaemia and trait.

Drugs increasing protein breakdown

The glucocorticoids such as hydrocortisone, prednisone, ACTH, and tetracosactrin (Synacthen) can all produce an increase in protein breakdown, which results in a rise in blood urea concentration and a lesser rise in plasma creatinine concentration, particularly in patients with underlying renal failure. These drugs can all increase the degree of clinical uraemia.

Hypovolaemia due to saline depletion

Hypovolaemia due to saline depletion may be produced by drugs in various ways. Many drugs have gastrointestinal side effects such as anorexia, nausea, vomiting, and diarrhoea, and all of these may result in saline depletion. This, if severe, may result in acute renal failure due to hypovolaemia, hypotension, and a reduced renal blood flow. This complication is particularly important if it occurs in patients with underlying renal failure because their urinary sodium conservation may be impaired and they are consequently more vulnerable to saline depletion. A vicious cycle may be set up, the

worsening renal failure leading to further vomiting that in time results in further saline depletion, and so on.

Overenthusiastic use of diuretic drugs, particularly the powerful loop diuretics such as frusemide, may also cause hypovolaemia due to excessive urinary loss of salt and water and result in acute renal failure or worsening of existing renal failure.

Nephropathy due to potassium deficiency

Potassium deficiency may be produced by various drugs, including laxative abuse, diuretics, prolonged steroid treatment, carbenoxolone, excessive consumption of liquorice, and, rarely, breakdown products of tetracycline, amphotericin-B, and massive sodium penicillin treatment. Although the correlation between plasma potassium concentrations and total body potassium is not good, symptoms do not usually arise unless the plasma potassium concentration is below 2.5 mmol(mEq)/l. An initial selective impairment of renal concentrating ability may occur, resulting in thirst and polyuria. There may also be muscular weakness, lethargy, depression, and constipation. With plasma potassium concentrations below 2.0 mmol/l, a generalised flaccid paralysis may occur and, rarely, tetany and respiratory failure. The myocardium becomes more sensitive to cardiac glycosides, and deaths from cardiac arrhythmias may occur if the patients are also taking digitalis.

The most important long-term effect of potassium deficiency is on the kidneys. There is a characteristic tubular lesion with vacuolation of the cells of the collecting ducts and elsewhere throughout the tubular epithelium. Initially, the selective impairment of renal concentrating ability may produce a nephrogenic diabetes insipidus. The kidneys in chronic potassium deficiency are more susceptible to infection, and chronic pyelonephritis may result. Renal failure may also develop and progress to terminal uraemia if the potassium deficiency is not recognised and corrected in time. Clinically, severe chronic potassium deficiency leading to renal failure is most commonly seen in patients with chronic laxative abuse.

Nephropathy due to hypercalcaemia

Drug-induced hypercalcaemia may occur with vitamin D intoxication or abuse and in the milk-alkali syndrome. Characteristic changes occur in the renal tubules with thickening and calcification of the basement membranes. In the early stages a relatively selective impairment of renal concentrating ability may occur producing thirst and polyuria sometimes amounting to a nephrogenic diabetes insipidus. If prolonged the hypercalcaemia and hypercalciuria may lead to diffuse nephrocalcinosis and progressive impairment of renal function until severe renal failure is produced. There may be an associated pruritus and a band keratopathy due to deposition of calcium in the cornea. Renal stones may also be produced.

Occasionally an acute hypercalcaemic crisis may occur (similar to that which may occur rarely in primary hyperparathyroidism) due to vitamin D poisoning or occasionally during the treatment of skeletal metastatic cancer with cancer chemotherapy. In this condition the serum calcium may rise rapidly to levels of 5 mmol/l (20 mg/100 ml) or more. Clinically there may be an initial polyuria followed by dehydration, oliguria, and acute renal failure. There may be acute abdominal symptoms with pain, recurrent vomiting, and severe constipation. Muscular weakness, drowsiness, mental confusion, and a psychosis may also develop. Unless the severe hypercalcaemia is controlled, death may follow from uraemia. Management will mean recognition of the cause and withdrawal of the offending drug (vitamin D). Acute dialysis may be needed to tide the patient over the period of acute renal failure and also to help lower the serum calcium concentration. Prednisone treatment is also effective in lowering the serum calcium concentration in vitamin D poisoning and in the milk-alkali syndrome. Calcitonin has also been used in the management of hypercalcaemia due to vitamin D poisoning.

Renal stones

Calcium-containing stones may be induced by a wide variety of drugs including prolonged steroid treatment, milk-alkali syndrome due to excessive consumption of indigestion mixtures containing alkali and calcium and milk for peptic ulceration, vitamin D intoxication, treatment of skeletal metastatic cancer with cancer chemo-

therapy or hormones, analgesic nephropathy, and excessive consumption of Worcestershire Sauce. Acetazolamide produces an alkaline urine with low citrate content, and this may result occasionally in calcium-containing calculus formation.

Thiazide diuretics and probenecid can occasionally cause the formation of non-opaque urate calculi, and these may also be formed during the treatment of reticuloses, when there may be a tremendous breakdown of tumour nucleoprotein with excessive formation of urate.

Opaque calculi formed of silicone dioxide have resulted rarely from the excessive consumption of magnesium trisilicate for peptic ulceration.

Urate nephropathy

In addition to the occasional production of urate calculi as a result of drugs, acute renal failure may result from an acute hyperuricaemic crisis during the treatment of malignant disease (particularly lymphomata) by cytotoxic drugs, radiotherapy, or both. Serum urate concentration rapidly rises to high levels, sometimes as high as 30 mg/100 ml as a result of rapid breakdown of neoplastic cells releasing large amounts of nucleoprotein, which in turn is metabolised to urate.

The urinary excretion of urate is greatly increased and is precipitated in the renal tubules, resulting in an intrarenal obstructive uropathy and acute renal failure. This potential hazard of cancer chemotherapy is now well recognised, and allopurinol may be given prophylactically. If it is diagnosed before acute renal failure is established an alkaline diuresis should be established to wash out the tubules and minimise further urate precipitation. If acute renal failure is established dialysis treatment may be necessary, but there may be some slow recovery of renal function once the hyperuricaemia is controlled.

Impaired renal concentrating ability

Some impairment of renal concentrating ability will be found in any renal disease severe enough to cause appreciable nitrogen retention. There are several renal disorders, however, in which there may be selective and particular damage (at first) to the medulla, resulting in a selective impairment of renal concentrating ability when the glomerular filtration rate may still be normal or only slightly reduced. This will be associated with an impairment in the renal response to antidiuretic hormone (ADH). Clinically there may be polyuria and polydipsia, sometimes severe enough to justify the term "nephrogenic diabetes insipidus" or "pitressin-resistant diabetes insipidus."

Some of these disorders are directly or indirectly drug-induced and include: potassium deficiency, hypercalcaemia, analgesic nephropathy, deteriorated tetracyclines (anhydro-4-epitetracycline), demethylchlortetracycline, methoxyflurane, lithium salts, and amphotericin-B.

Syndrome of inappropriate secretion of ADH

The syndrome of inappropriate secretion of ADH consists of hyponatraemia and reduced plasma osmolality together with a urine osmolality usually exceeding that of the plasma. Despite hyponatraemia, urinary sodium excretion often exceeds 50 mmol(mEq)/day. There is no oedema and fluid depletion is absent. The condition is produced by continuous release of ADH inappropriately to the plasma osmolality, and it occurs in the absence of renal or adrenal disease. The clinical features are due to water intoxication and include lethargy, apathy, nausea, vomiting, headache, irritability, disorientation, increasing confusion, convulsions, and coma. The relaxation phase of tendon reflexes may be prolonged as in myxoedema, and in severe cases tendon reflexes may be absent with extensor plantar responses. Mild hypothermia may occur. The syndrome may easily be confused with several neurological disorders. Inappropriate ADH secretion has several causes. Perhaps the most well-known is that occurring in association with various tumours, particularly carcinoma of the lung, in which arginine vasopressin has been identified in tumour extracts. There are many other causes, however, including drug-induced cases. Drugs that have been incriminated in this syndrome include chlorpropamide, thiazide diuretics, carbamazepine, vincristine, cyclophosphamide, clofibrate, and metformin. The

mechanism of the drug-induced variety of this syndrome is not clear, but there is conflicting evidence that in some cases the drugs stimulate in some way an increased release of ADH (chlorpropamide, carbamazepine, clofibrate, and vincristine).

Management of the syndrome is basically reduction of water intake. In clinically severe cases intravenous frusemide to promote a diuresis together with sodium and potassium replacement have been used. Lithium carbonate has been used to inhibit the action of ADH, and demethylchlortetracycline has also been advocated. Both these drugs can produce selective impairment in renal concentrating ability and consequently resistance to the action of ADH on the kidney.

Urinary tract neoplasms and drugs

Mesothelial tumours of the renal pelvis have been reported in patients with analgesic nephropathy. There is a high incidence of papilloma, carcinoma, or both, of the renal pelvis, ureter, or bladder in patients with Balkan nephropathy, and recent evidence suggests that this condition may be due to a nephrotoxin—that is, contamination of local foodstuffs by nephrotoxin-producing fungi (*Penicillium verrucosum* var *cyclopium*).

Occupational exposure to chemicals in the dyestuffs and rubber industry is well known to be associated with bladder cancer. 2-Naphthylamine mustard has been used to treat Hodgkin's disease and leukaemias and has resulted in bladder tumours.

Drug-induced radiological changes can lead to confusion in diagnosis. Thus severe intrarenal bleeding due to anticoagulants can cause renal enlargement and caliceal deformity so that the intravenous pyelographic appearance may mimic that of a hypernephroma. Aminocaproic acid used in some haemorrhagic disorders can also cause a renal pseudotumour due to the presence of blood clots in the renal pelvis, which may cause obstruction and temporary loss of function.

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ONE HUNDRED YEARS AGO Among the causes of that kind of Bright's disease known as granular kidney, mental anxiety and prolonged distress take a high, if not the chief, place. A middle-aged person, man or woman, will come to us complaining that he is no longer active and eager for work, but is unaccountably languid and heavy; that he has of late become liable to dyspnoea; and that, especially after mental anxiety, attacks of this dyspnoea may come on even during hours of repose. The physician will then find the flesh falling and the complexion fading, the pulse growing tense and the heart enlarging; the urine varying widely in quantity, of low gravity, and often slightly albuminous. Now, if he inquire into the preceding history of such a patient, he will very commonly find that carking care or bitter and long sorrow has set its mark upon his life. It is impossible to prove this statement by the reading of cases; my statement is one which must be tested by others, and must stand or fall by the general voice. But I may say that I am even myself surprised to find how fully my belief is borne out by the comparison of my own cases. During the last two years, I find I have made notes of thirty-five cases of granular kidney occurring in private practice, and I find a marked history of mental distress or care, or both, in twenty-four of them. As a result of such causes, indeed, I find that granular kidney follows more frequently than degeneration of the brain or spinal cord, and far more frequently than primary failure of the heart's muscle. (*British Medical Journal*, 1877.)