(5) No patient should be woken before 7.30 am. The traditional grounds for starting their day earlier are no more or less valid than those used to exclude women from all-male colleges and medical schools.

Longer term, the educational changes that will be needed include a review of nursing and medical curricula to correct the balance between their scientific and experiential components. A new subject should be introduced into the curriculum: the social and psychological determinants of interactions between health professionals and patients, including harmful forms of care-giving and their causation. Both the qualifying examination (SRN, MB, BS, etc) and the specialist examinations (FRCS, MFCM, MRCP, MRCPsych, etc) should include obligatory questions on these topics. Departments for the study of staff-patient relationships will be needed in medical and nursing schools, and they might be funded perhaps by the royal colleges, the Patients' Association, the TUC, and the Institute of Health Service Administrators. The significance of grief, illness, admission to hospital, and surgical procedures should be discussed in general textbooks, and, for example, accounts of conditions such as glaucoma, emphysema, or colostomy should include their effects on the patient and his family, and on his nurse and doctor.

Conclusions

The practical measures I have suggested will bring comfort to the patient and boost his morale; but they will not be enough unless there are also changes of bias in educational aims and understanding of the power and range of the factors that determine patient care.

The achievement of these objectives might seem a daunting task, but to do nothing means turning a blind eye to behaviour that falls short of acceptable levels at times, has a damaging effect on professional wellbeing, and places an added burden on patients. As doctors we are no different from our patients despite our efforts to prove otherwise, so that enlightened self-interest—if nothing else—should provide a powerful incentive towards improving the quality and consistency of care.

References

- ¹ Kyle, D, *British Medical Journal*, 1969, **1**, 246.
- ² Mackintosh, J P, *British Journal of Hospital Medicine*, March 1978, p 282.
- ³ Royal Commission on the NHS, *Patients' Attitudes to the Hospital Service, Research Paper No 5*. London, HMSO, 1978.

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Today's Treatment

Drug induced diseases

Drug-related disease and the kidney

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The effects of drugs on the kidney can show themselves clinically in only a few ways. Some drugs may have more than one effect, and genetic predisposition may determine which renal syndrome or sign may occur first. No list of drugs can be totally exhaustive with respect to renal toxicity, and therefore in any patient presenting with renal disease awareness of this possibility is of major importance. It is difficult to quote figures about the incidence of overall renal drug toxicity, which varies from country to country. In Britain analgesic nephropathy is responsible for about 5% of cases of end-stage renal failure, whereas in Australia the figure is nearer 21%. For the nephrotic syndrome drugs account for 1-2% of all cases. Whether a drug induces renal toxicity may depend on total dosage given, duration of such exposure, and whether there was pre-existing renal impairment. For those patients who need drugs known to have a nephrotoxic potential monitoring of either serum

concentrations—for instance, gentamicin—or evidence of developing renal damage, such as gold, penicillamine, and amphotericin B, is clearly important.

Acute nephropathy (acute renal failure)

The number of drugs capable of causing an acute nephropathy seems limitless. Drugs may be responsible for between 20-30% of acute renal failure cases. Acute nephropathy may present as (1) acute tubular necrosis (direct tubular toxicity), (2) acute renal arteritis, (3) acute glomerulonephritis, (4) acute interstitial nephritis, or (5) acute tubular obstruction (acute intrarenal obstruction). Drugs incriminated aetiologically for (1) include penicillins; gold; aminoglycosides (for instance, gentamicin, kanamycin, neomycin); metals such as the mercurials, bismuth, antimony, and copper; solvents such as carbon tetrachloride, tetrachloroethylene; and glycols; and other drugs such as salicylates, amphotericin B, cresol; and finally items such as snake venom and mushroom toxins; for (2) anticonvulsants, penicillins, sulphonamides, thiazides, and intravenous amphetamines (drug abuse); for (3) sulphonamides, penicillin, and hydrallazine; for (4) phenindiones, sulphonamides, ampicillin, rifampicin, para-amino salicylic acid, metals (gold and bismuth), thiazides, and phenylbutazone; and for (5) cytotoxic agents used in the treatment of reticuloendothelial proliferative disorders and tumours leading to hyperuricaemia and precipitation of urate within tubular lumina, methotrexate

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crystallisation in the distal nephron, sulphonamide crystalluria, precipitation of radio-iodinated contrast media (particularly in patients who are dehydrated, the elderly, those with myeloma, and those with pre-existing renal disease), intravenous xylitol used as a component in parenteral nutrition regimens leading to oxalate crystalluria, and finally drugs causing haemolysis in glucose-6-phosphate dehydrogenase deficiency—for example, antimalarials, quinine, sulphonamides, and nitrofurantoin. Rifampicin can cause haemolysis per se and subsequently acute renal failure.

Renal vascular lesions leading to impaired renal function

Such renal involvement will depend on which size of vessel is affected first, varying from glomerular capillaries causing glomerulonephritis to interlobular arteries causing a more generalised pan-nephropathy to larger vessels still causing infarctions. The vascular lesion in turn may be due to (1) an interstitial nephritis (direct toxic effect), (2) immune complex damage, (3) allergic reactions causing lesions similar to spontaneous polyarteritis nodosa, and (4) as part of a drug-induced lupus erythematosus (LE)-like syndrome.

INTERSTITIAL NEPHRITIS (direct toxic effect)

Interstitial nephritis is really part of a pan-nephropathy, and drugs incriminated in producing this syndrome include the penicillins, sulphonamides, anticoagulants (such as phenindione), ampicillin, rifampicin, methicillin, and the thiazide group of diuretics.

IMMUNE-COMPLEX GLOMERULONEPHRITIS

If gold and penicillamine have been taken the renal lesions may be due to the formation of immune complexes. Immuno-fluorescent and electron microscopic techniques have shown immune complexes on capillary glomerular basement membranes. Similar renal lesions have occurred after treatment with sulphonamides, rifampicin, and methicillin.

ALLERGIC REACTIONS

The renal lesions in allergic reactions are histologically similar to the spontaneously occurring polyarteritis nodosa. Drugs held responsible for such appearances include sulphonamides, penicillins, iodides, and phenytoin sodium.

AS PART OF A DRUG-INDUCED LE-LIKE SYNDROME

Renal involvement is less often seen with drug-induced LE syndrome (about 6%) than with the spontaneous form of the disease (about 60%). Furthermore, withdrawal of the offending drug may lead to a spontaneous resolution of the renal disease. The mechanism of drug-induced LE syndrome is not clear, but some evidence suggests a genetic predisposition via the genetically controlled rate of liver acetylation dependent on the enzyme acetyltransferase. Thus individuals may be divided into "slow" and "fast" acetylators. The drug-induced LE syndrome occurs more commonly in slow acetylators, and implicated drugs include hydralazine, procainamide, and isoniazid. Interestingly, antinuclear factor is more commonly found in slow acetylators of isoniazid. Other drugs that have been incriminated, but less often, are the penicillins, sulphonamides, para-amino salicylic acid, streptomycin, anticonvulsants such as phenytoin and ethosuximide, propylthiouracil, contraceptives, and the hypotensive drugs such as reserpine and methyldopa.

Drug-induced nephrotic syndrome

Two principle mechanisms operate here either via immune complex formation or direct toxic effects, principally on the tubules. Often, though not invariably, the renal lesion resolves on drug withdrawal. Although some drugs—for example, gold and penicillamine—cause this by immune complex formation they have more than one mode of causing the syndrome—sometimes by direct toxic effects on renal tubules (for instance, gold). Other drugs thought responsible include the mercurial compounds, anticonvulsants—for instance, troxidone—and hypoglycaemics such as tolbutamide, phenindione, and probenecid. The newer tetracyclines are not incriminated in the production of the Fanconi syndrome.

Analgesic nephropathy

An important and well-recognised cause of chronic renal failure is the abuse of analgesics, particularly those containing phenacetin. It is important to make this diagnosis by careful insistent history taking for if discovered and the patient can be persuaded to stop taking the drugs, renal function will at least stabilise or sometimes improve. Patients vary considerably in their susceptibility to developing renal damage after analgesic abuse. No absolute minimal intake to cause the syndrome is known, though there is some agreement that about 2 kg of the offending drug needs to have been consumed over a period of at least two years. Phenacetin has generally been regarded as the main offender in European and Scandinavian countries, though in Australia aspirin is coming increasingly under suspicion. In Australia analgesic nephropathy is second only to glomerulonephritis as a cause of end-stage renal failure needing regular haemodialysis treatment, and accounts for 20% of patients on their National programme. When aspirin-phenacetin-caffeine compounds are being taken it is difficult to apportion responsibility between the ingredients in such compounds as to the main cause.

Drugs causing uraemia by interfering with protein metabolism

The best-known drug in this category is tetracycline or oxytetracycline, and it is especially likely to occur in elderly patients with known or unsuspected renal disease. Tetracycline can cause gastrointestinal symptoms if high serum concentrations occur resulting in anorexia, nausea, vomiting, and diarrhoea leading to salt and water depletion accentuating any degree of pre-existent renal failure. Tetracycline, however, also inhibits the incorporation of amino-acids into protein synthesis, thus the amino-acids are deaminated with increased urea production rate leading to a rise in blood urea concentration and negative nitrogen balance. Steroids, corticotrophin, and tetracosactrin may all lead to a divergence of the urea:creatinine ratio by increasing protein breakdown. Also, overenthusiastic use of nitrogen source solutions in intravenous feeding regimens can cause a similar divergence.

Retroperitoneal periureteric fibrosis

Some cases of retroperitoneal periureteric fibrosis characterised by an extra renal obstructive uropathy have been related to methysergide. Other drugs have also been incriminated, such as hydralazine, ergotamine, diuretics, and methyldopa. The mechanism whereby these drugs cause this fibrosis is not known.

Drugs, altered metabolism, and nephropathy

Hypokalaemia

Hypokalaemia may result from laxative abuse, diuretics, carbenoxalone, excessive liquorice consumption, and amphotericin B.

tericin B treatment. The effects on the kidney are impairment of renal concentrating ability and later a characteristic histological vacuolation lesion of the renal tubular cells. In severe cases a nephrogenic diabetes insipidus syndrome may occur. Kidneys showing the typical hypokalaemic histological lesion are more susceptible to infection with the risk of supervening chronic pyelonephritis.

Hypercalcaemia

Hypercalcaemia may occur with the milk-alkali syndrome and occasionally from excessive intake of vitamin D. As with hypokalaemia there is an early impairment of renal concentrating ability and histologically the basement membranes become thickened and calcified. Depending on duration of exposure to the offending drug, later nephrocalcinosis may appear with associated chronic renal failure.

Rarely, acute hypercalcaemia after massive ingestion of vitamin D or after cytotoxic treatment for bone metastases occurs, leading to acute renal failure. Such a crisis demands intravenous neutral phosphate, haemodialysis, steroids, and withdrawal of the offending drug. Remember that the half life of vitamin D is measured in months and not hours.

Again fairly rarely renal stones may develop if drug-induced hypercalcaemia or hypercalciuria or both has been prolonged. This may be associated with the milk-alkali syndrome, prolonged steroid treatment, analgesic nephropathy, acetazolamide, and excessive consumption of Worcester sauce.

Urate

In addition to the well-known acute urate nephropathy after treatment of reticulosos, occasionally non-radio-opaque urate stones may develop after prolonged use of probenacid or thiazide diuretics. These drugs should also be avoided during the cytotoxic treatment of malignant disease, otherwise the risk of tubular urate precipitation is increased.

Silicon

Rarely, reports have appeared of opaque silicon dioxide stones occurring after excessive consumption of magnesium trisilicate in patients with peptic ulceration symptoms.

Hypovolaemia, hypervolaemia, and renal impairment

Some drugs may cause salt and water depletion through effects on the gastrointestinal tract, such as anorexia, nausea, vomiting, and diarrhoea. Thus depending on a patient's individual susceptibility, and this is more likely in the elderly and those with pre-existing renal disease, many drugs, particularly antibiotics such as tetracycline and ampicillin, have this propensity. Thus hypovolaemia causing hypotension leads to impaired renal perfusion causing uraemia or an accentuation of chronic renal failure. At other times overzealous use of diuretics such as frusemide, ethacrynic acid, and bumetanide (particularly in the elderly) causes a worsening of existing renal failure or its precipitation by excessive renal loss of salt and water.

Conversely, it is worth emphasising that some drugs because of their associated sodium content can cause hypervolaemia and accentuation of hypertension with the risk of further renal damage. These include the antibiotics ampicillin, carbenicillin, cephalothin, chloramphenicol, erythromycin, methicillin, oxacillin (sodium content of previous drugs mentioned range from 2.4-4.7 mmol/g), penicillin G (1.7 mmol/million units), heparin (1.5 mmol/10 ml), and sodium polystyrene sulfonate (67 mmol/15 g).

Antidiuretic hormone (ADH and the kidney)

Some drugs may cause a significant impairment of renal concentrating ability, either through direct toxic effects or via secondary effects, such as hypokalaemia or hypercalcaemia. Drugs incriminated in this way include amphotericin B, lithium salts, analgesics, and, rarely, out-of-date tetracycline.

There is also the syndrome of inappropriate antidiuretic hormone secretion, which may be drug induced. Drugs reputed to do this include cyclophosphamide, carbamazepine, chlorpropamide, thiazide diuretics, clofibrate, metformin, and vincristine.

Drug combinations

Certain drugs are associated with a high incidence of nephrotoxicity. Cephaloridine is such an example, and its nephrotoxicity potential is enhanced by concurrent use of diuretics, such as frusemide. Similarly, cephalothin nephrotoxicity is enhanced by concurrent use of gentamicin. The known nephrotoxicity of gentamicin is enhanced by concurrent use of frusemide. Mention has already been made about avoiding concurrent use of potent cytotoxic agents with other drugs known to cause hyperuricaemia and tubular urate precipitations. Thus whenever possible drug combinations where individual components have known nephrotoxicity should not be used unless no alternative is available. If they must be used, however, then renal function must be monitored and drug serum concentrations measured.

Impaired renal function and drug toxicity

The foregoing has been concerned with the effects of drug toxicity and specific induced renal damage. It must be emphasised, however, that impaired renal function itself can bring about an increased rate of drug toxicity systemically if drug doses are not suitably modified or attention paid to the degree of renal impairment. Thus the anaemia or uraemia can be accentuated by inappropriately high doses of cytotoxic agents such as azathioprine, chlorambucil, or cyclophosphamide used for treating various immunologic renal diseases. The use of drug combinations must be carefully considered, for although satisfactory in normal patients they may be less so in those with impaired renal function. Thus using combinations of cimetidine, frusemide, co-trimoxazole, and azathioprine in renal transplant patients needs to be carefully monitored. Drugs with a known high potassium content or the ability to cause potassium retention (such as triamterene and spironolactone) should be used with caution, if at all, in such patients.

Metabolic encephalopathy can be caused by drugs such as phenobarbitone, diazepam, and flurazepam in renal failure patients. Likewise, doses of anaesthetic agents must be suitably tailored. The use of hypotensive agents must be carefully monitored in patients with impaired renal function. For although initially blood pressure control may be satisfactory, if renal function did deteriorate at the same hypotensive dosage then renal hypoperfusion will occur with accentuation of renal damage from accumulation of the hypotensive agent.

Conclusion

The potential effects of drugs on the kidney are very variable, and a constant awareness of the possibility of drug-induced renal disease is of paramount importance. Many clinical syndromes seen by nephrologists may be related to or caused by a drug or its metabolites in the face of altered renal function. The importance of being aware of the possibility of drug-

induced renal disease is that often by simply withdrawing the offending drug renal function can be salvaged or at least progression halted. Although it is not possible to monitor the renal function of all patients receiving many of the drugs referred to, those with a known high nephrotoxic potential should not be used unless no alternative is available and appropriate monitoring facilities can be used. Drug combinations increasing nephrotoxicity potential should be avoided.

Since the effects of drugs on the kidney are varied any evidence of impaired renal function during the course of drug treatment should be queried as to its relation to drugs being used. Thus impaired renal concentrating ability, impaired renal acidification ability, the presence of an abnormal urine microscopic deposit, the presence of proteinuria, or the overt deterioration of renal function (serum creatinine and blood urea concentrations rising) can all be due to drugs as individual

manifestations or as a complete profile. As drugs with known high incidence of nephrotoxicity are removed from the therapeutic armament it can be certainly envisaged that new ones will appear that will still have nephrotoxicity, and thus the physician must always be on his guard.

Bibliography

- Bennett, W M, Plamp, C, and Porter, G A, *Annals of Internal Medicine*, 1977, **87**, 582.
 Bisset, G W, and Jones, N F, in *Recent Advances in Renal Disease*, 1, ed N F Jones. London and Edinburgh. Churchill Livingstone, 1975.
 Curtis, J R, *British Medical Journal*, 1977, **2**, 242 and 375.
 Mitchell, J R, et al, *American Journal of Medicine*, 1977, **62**, 518.
 Nanra, R S, *Medical Journal of Australia*, 1976, **1**, 745.
 Nickas, G M, *Arizona Medicine*, 1976, **33**, 577.
 Silverblatt, F J, *Urologic Clinics of North America*, 1975, **2**, 557.

MATERIA NON MEDICA

Caribbean journey

Her face, topped with a full head of close-curved silver hair, was calm as the trio waited in the cool corridor. She wore a faded communion dress, which looked both tawdry and incongruous, on her frail aged frame. It was, however, the best the nuns could provide for this important journey.

Outside the noon sun baked the open courtyard with its parched rectangle of grass. The bus, a converted truck, with multicoloured timber frame, approached in a cloud of dust, and the two nuns accompanying the old woman looked relieved that their hasty telephone call had achieved the necessary detour. With a rumble the bus entered the courtyard across the buckled cattle-grid and almost disgorged its mountainous roof load of fruit, vegetables, and various livestock while swinging around the grass rectangle. The merry banter of the passengers continued as the driver descended and approached the trio. The elder of the nuns moved into the bright sunlight to meet the driver, and following a brief discussion and transfer of papers he returned to the bus. Mayhem ensued as the passengers and driver of the packed bus remonstrated and argued over their ability to take on yet another passenger. With much grumbling, baggage and passengers shuffled around the bench seating, and the old woman quietly embarked.

The bus departed in a cloud of dust and noise, the driver irritated by the callousness of his commuters. How else was the old woman, impoverished throughout life, going to make this last trip but on the only bus to her village that day.

The death certificate grew damp in his shirt pocket as he sweated and strained to negotiate the pot-holes in the dirt road.—K B QUEEN (registrar in urology, Newport, Gwent).

Black is white

Traditionally, all villages are supposed to harbour an individual of especially disreputable disposition, perhaps a poacher, anyway, a character with hidden depths, who during the day lives an apparently blameless life—maybe he's the postman or a farmhand. In a fishing village where I once lived it was the sexton, usually seen in his corner at the pub with his pipe and pint and knowing gaze twinkling over a blue veined, bulbous nose. His murky past featured a debt to the local parish council, incurred for repairs to the harmonium he had "borrowed" from the church hall to provide music for an impromptu party on his boat. The party went too well and the boat capsized. Fortunately the harmonium floated ashore and was not too expensively damaged. A glimpse of his hidden depths was given by the way he discharged the debt, making tactical use of an unexpected opportunity in a way that would not have disgraced a Wellington or a Montgomery.

One day a carthorse from one of the cliffside farms disappeared, and its fate was revealed by a fresh bite out of the cliff, which had crumbled away under the unfortunate beast's weight as it had been grazing too near the edge. Sure enough, the carcass was lying below on the beach: a sad end for a fine black mare. Disposal was a problem: the beach was accessible only from the sea, and it was not feasible to hoist the body back up to realise its remaining value as horseflesh, so the farmer asked the sexton to bury it. After a suitable fee was agreed,

the sexton set off in his boat at dusk to deal with the corpse. Instead of burying it, however, he towed it out to sea and dumped it on his way to some doubtlessly nefarious nocturnal engagement.

There was a bit of a storm in the night and on his way back to port in the early morning the sexton was perturbed to see that the horse had been washed ashore again in more or less the same place. He did not want to lose his burial fee, and his nimble wit soon suggested a plan. He nipped ashore, painted the corpse white with some paint he'd been meaning to use on the boat, and continued on his way.

The talk in the pub that evening was all about the second horse, which no one seemed to own. After a few days, when the corpse was still there, large as life but rather less fragrant, the sexton offered to bury it—on payment of a fee larger than usual because of the fragrance. Eventually the town council bowed to public opinion and put up the fee, and the sexton, suppressing a smile, did his job.

By coincidence, the council's fee was enough, with the farmer's contribution, to pay the repair bill for the harmonium—with just a little over for a tin of white paint.—A C MARTIN (GP vocational trainee, Hong Kong).

The fallen idol

One's credibility as a parent is always under challenge these days. It used to be so simple. Everyone knew what was right and that it would be rewarded, just as wrong would get its just deserts. Yet after last Friday even I sense such immutable laws are not without their exceptions.

A house call came during the mid-afternoon. The twinge of disappointment that this pensioner had not rung in the morning presaged a whole constellation of emotions I was to feel before the day was out.

For convenience I took my 18-year-old daughter's Mini, drove to the old man's house, parked outside, and strode across his tiny lawn—all actions I had done monthly for 15 years, and all quite unexceptional. I went in, wrote his prescription, passed a pleasantry or two with his wife, and took, I swear on a pile of MIMS, no more than four minutes. On emerging, there was the car—gone. Disbelief, anger. The keys had been left in it. Always had been—monthly for 15 years. "Tried to make it easy for them, Sir?", was all the policeman could say. Guilt, chagrin. What had I always told my daughter about the keys? Recriminations and raised voices. I knew I was wrong. A stolen car was what I deserved; my rationalisations mocked me.

Late that night the police reported the Mini's recovery. Surely a dented wing and the theft of the contents was, by the proper order of things, the least I could expect. At the station there it stood, unmarked; the rugs, jumper, riding boots, all intact. But, surprise, surprise, there on the back seat beneath the rug was a transistor radio and a newish set of joinery tools. "They are in your locked car, so they must be yours," was the deadly logic of the constable, snapping his report book closed.

By breaking my own rules and leaving the keys in the car I had gained about £200 worth of goods. By retaining those which are not ours, my daughter argues, we have helped to soothe the pain and suffering we had experienced. By claiming the goods the thief would admit to the crime. By retaining them we are now thieves, even though we had a constabulary nod.

Whatever the moral of the story, I know my grip as the custodian of the household's rectitude has been loosened for ever.—JAMES H LEAVESLEY (general practitioner, Perth, Western Australia).