The kidney in myeloma

"The tube contains urine of very high specific gravity. When boiled it becomes rather opaque. On the addition of nitric acid, it effervesces, assumes a reddish hue, and becomes quite clear, but as it cools, assumes the constellance and appearance which you see. Heat relieves it. What is it?"...

So wrote Dr Thomas Watson in 1845 to Henry Bence Jones about the urine of Thomas Alexander McBean, drawing attention to one of the most characteristic abnormalities of multiple myeloma.

Over half of all patients with myeloma develop renal insufficiency and it is the second most common cause of death (after infection). A raised blood urea concentration at presentation is the single most important pointer to a poor prognosis.

The causes of renal impairment in myeloma are many, and any one patient is unlikely to have a single cause. Those factors most usually mentioned include infection, hypercalcaemia, hyperuricaemia, hyperviscosity, Bence Jones proteinuria, Fanconi’s syndrome, plasma cell infiltration of the kidney, amyloidosis, and glomerulosclerosis.

Renal failure is strongly associated with an excess of immunoglobulin light chains in the urine. Light chains are normally filtered by glomeruli and then reabsorbed and catabolized by cells in the proximal tubule—a physiological mechanism designed to deal with the small amounts of free light chain produced by normal people. The large amounts produced in myeloma, however, are toxic to renal tubular cells. In animals, injecting large amounts of light chain causes acute renal damage associated with the formation of casts and tubular atrophy; and studies of slices of rat kidney incubated with light chains have shown inhibition of the adenosine triphosphatase dependent sodium pump and of gluconeogenesis and metabolism of sodium iodohippurate in tubular cells.

Yet despite this toxicity some patients excrete large quantities of free light chains for long periods without any damage to their renal tubules. Apparently some light chains are more toxic than others. Two groups have shown that renal damage in myeloma correlates with the presence of urinary light chains with a high isoelectric point (pl) 1, 2. Such light chains are more likely to precipitate in the acid urine of distal tubules to form casts; but attempts to alkalinize the urine with oral bicarbonate in a large series of patients had no effect on survival. This finding may merely show the difficulty of alkalinizing the urine.

The casts in the urine of patients with myeloma are characteristic, having a waxy, laminated structure surrounded by reactive, syncytial giant cells, with occasional renal cells embedded in the matrix. Such casts usually indicate renal failure, and it was once thought that they caused the damage in myeloma kidney by obstructing individual nephrons. As many as a third of patients with myeloma, however, have no kidney casts, 3, 4, 5, and they are more likely to be the consequence of renal damage than its cause.

The sequence of events in myeloma kidney begins with insidious damage to the proximal tubular cells by filtered light chains. This is present in virtually all patients with urinary light chain concentrations of over one unit per litre whether or not glomerular function is impaired. As a result tubular reabsorption of light chains is reduced, increasing their final concentration in the urine. Tubular damage may be compounded by other factors such as hypercalcaemia, hyperuricaemia, and nephrotoxic antibiotics. Against this background individual episodes of dehydration and infection lead to tubular atrophy. As nephrons are lost each individual tubule carries an increasing load of light chains resulting in the formation of casts—possibly owing to the interaction of cationic light chains with the anionic Tamm-Horsfall mucoprotein.

Patients who present with renal failure commonly do so after a recent precipitating event, usually infection or dehydration. Prompt treatment with rehydration, antibiotics, and regimens to lower the calcium and urate concentrations— together with short term dialysis if necessary—will often restore renal function. The eventual outcome depends on whether or not the tumour responds to chemotherapy.

In patients who have urinary light chains but who are not yet in renal failure a fluid intake of three litres a day is likely to prevent deterioration of renal function. The exception to this happy prognosis is renal amyloidosis, which causes glomerular lesions as well as interstitial damage. Although individual patients have responded to intensive chemotherapy, in general even experimental treatments have been unsuccessful in this condition. Nevertheless, though systemic amyloidosis in myeloma is usually rapidly lethal, its progression is sometimes slow; it is well worth persevering with treating the myeloma and the renal failure with supportive measures short of long term dialysis.

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Safety of lasers

Uses are now being found for lasers in all aspects of medicine, but ophthalmology remains the specialty making the most demands on this new technology. After Meyer-Schwickerath showed the value of retinal photoocoagulation back in the 1950s using xenon arc, lasers were quickly found to have advantages in the management of diseases primarily affecting the vascular systems of the retina and choroid. In particular, several large scale clinical trials have conclusively shown the value of photoocoagulation with the argon laser as a treatment for proliferative diabetic retinopathy. Virtually all eye units in Britain now undertake laser treatment of diabetic and other ischaemic retinopathies as well as some forms of macular disease.

More recent advances have been the use of trabecucloplasty in the chronic open angle glaucomas and laser iridotomy for some forms of closed angle glaucoma; the more widespread use of the krypton laser; and the Nd:YAG (near infrared) laser, which is proving a valuable alternative to intraocular surgery in several conditions affecting the anterior segment of the eye. The place of other lasers—such as the “Excimer” or carbon dioxide—ophthalmology has to be established, though carbon dioxide lasers are used widely in plastic surgery and gynaecology.

Most clinical applications of laser energy depend on the destructive effects produced by the absorbance of the laser energy in the target tissue. Clearly great care must be taken to avoid inadvertent exposure outside the target.

The American National Standards Institution established guidelines for the use of lasers in 1980, and these were followed by the British Standard Institution in 1983. Laser products are classified from 1 to 4 depending on the power output, only class 1 being inherently safe; classes 3 and 4 require medical surveillance. The concept of the maximum permitted exposure for direct ocular exposure was introduced in terms of radiant exposure (J/m²) or irradiance (W/m²) at the cornea. This value is well below (roughly two orders of magnitude) the level necessary to produce an ophthalmoscopically visible retinal lesion within 24 hours—the defined threshold lesion. Damage may, however, be produced at much lower levels, and the maximum permitted exposure should not be understood as marking the dividing line between safe and dangerous levels. The maximum permitted exposure for skin need not be so stringent.

A report produced by the DHSS last year stated that a “laser controlled area” should be established around any laser in use if there is any risk of the maximum permitted exposure being exceeded in that area. The design of most ophthalmic lasers is such that the beam emerging from the laser tube is very well collimated. Passage of the beam through the delivery system alters this. Typically the laser is attached to a slit lamp or operating microscope and the beam is focused through an optical system converging towards a focal point and diverging thereafter. In some systems—for example, the endolasers used during vitreoretinal surgery—delivery is through a fibre optic and a diverging beam emerges. In both cases the beam irradiance will fall below the maximum permitted exposure at some distance from the delivery system. This distance, the nominal ocular hazard distance, is the crucial measure for any assessment of the protection of medical and paramedical staff working closely with lasers.

The DHSS guidelines for controlled areas imply that the nominal ocular hazard distance is known for each laser device. In practice, however, some manufacturers cannot supply this information, but a recent paper has shown that it may be calculated with a relatively simple technique which is capable of precise results and is reproducible. In commonly encountered clinical settings the risk area may extend nearly 30 m from the delivery point. Usually, therefore, the whole of the room or operating theatre needs to be designated a laser controlled area, and staff working or moving within that area need protection.

These immediate risks are straightforward to define. We know far less about possible risks to laser operators from long term use. Some anecdotal evidence suggests that ophthalmologists who spend many hours a week using a laser may have reduced central visual acuity, abnormal colour perception, and other features indicating possible macular damage. Possibly some of the early apparatus exposed doctors to risk through inadequate shielding, but this is not so for the modern laser. Nevertheless, a young ophthalmologist may expect to spend 40 years in photoocoagulating procedures, and we do not know whether he is exposing himself to risk. There may be a case for screening, at regular intervals, all those surgeons intending to use lasers frequently. At least they should be well placed to provide such screening facilities.

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