the formation of $\beta_2$-M amyloid. Formation of radicals by activated neutrophils in the synovia may locally produce radicals. One could speculate that radicals make proteins susceptible to the action of proteases, thus causing fragmentation of native $\beta_2$-M and favouring amyloid fibril formation. Nevertheless, so far this attractive idea is based only on in vitro studies and evidence for the role of hydroxyl radicals from in vivo studies is eagerly awaited.

Can one predict the risk of $\beta_2$-M amyloidosis? Recent clinical studies showed that (1) elevated plasma levels of $\beta_2$-M, (2) long duration of dialysis, and (3) advanced age are risk factors for amyloidosis. It is unlikely that accumulation of native $\beta_2$-M, i.e. the amyloid precursor alone, is the crucial event, since no difference in the plasma levels of $\beta_2$-M is found between dialysis patients with and without amyloidosis. Such absence of a difference would be compatible with the idea that it is modification of the precursor protein that triggers amyloid formation. But if so, what triggers modification? Resolution of these issues is required before appropriate therapeutic strategies can be developed.

**References**


**The tragic paradigm of Chinese herbs nephropathy**

C. van Ypersele de Strihou¹ and J. L. Vanherweghem²

¹University of Louvain Medical School, Cliniques Universitaires St-Luc; ²Université Libre de Bruxelles, Hôpital Erasme, Brussels, Belgium

**Introduction**

Subacute renal failure leading a young woman to renal replacement therapy within a few months is a sad, though rare, reality of nephrology practice. Puzzlement is added when biopsy discloses a most unusual lesion that triggers amyloid formation. But if so, what triggers modification? Resolution of these issues is required before appropriate therapeutic strategies can be developed.

Whether the recently described epidemic of Chinese herbs nephropathy (CHN) [1] will spread to a significant extent is as yet unknown, although recent reports suggest that similar cases have been encountered abroad. Still, this dramatic experience teaches us a series of lessons well beyond the tragedy affecting now over 80 young women. It is certainly our responsibility to make sure that as much as possible is learned, not only to avoid the repetition of such catastrophes but also to use the possible clues revealed by CHN to understand the pathogenesis of renal interstitial sclerosis and, possibly the links between renal destruction and carcinogenesis.

**Chinese herbs nephropathy**

The clinical picture of CHN is characteristic: virtually all affected patients are women aged 23–65 years.
Blood pressure is initially normal in over half of them. Anaemia is often present and more severe than might be anticipated from the degree of renal failure. Proteinuria is mild and of tubular origin. The urinary sediment is unremarkable. Renal failure is usually not suspected and, when present, discovered only by routine blood testing. All patients have in common attendance at the same slimming clinic and the consumption between 1990 and 1992 of pills containing two Chinese herbs, namely Stephania tetrandra and Magnolia officinalis. Despite the interruption of this treatment, progression of renal failure is usually relentless over a period of a few months to a few years and has already led half of these patients to renal replacement therapy, and eventually a few to renal transplantation.

The pathological aspects include an intense, paucicellular, interstitial fibrosis with a corticomedullary gradient, atrophy and loss of tubules, a relative sparing of the glomeruli and focal, irregular thickening of interlobular and afferent arterioles [2,3]. More worrying is the discovery in nephroureterectomy specimens of extensive cellular atypias of the urothelium extending from the papilla to the ureterovesical junction [2]. In one patient these atypias evolved into microinvasive urothelial carcinoma [4]. A similar case has been observed by one of us (JLV).

The fibrotic process may extend beyond the kidneys as demonstrated by an intense periureteral fibrosis in a young woman [5] and by a marked submesothelial fibrosis of the peritoneal membrane in two patients with an attendant alteration of peritoneal permeability [6]. Puzzling is the observation of aortic insufficiency in approximately one-third of the patients.

**Its cause**

The subacute course of the disease and its clear link with a slimming regimen prescribed by a single team of physicians strongly suggested a toxic aetiology. The fact that renal failure developed only in patients given between 1990 and 1992 a slimming pill whose content had been modified in 1990 by the substitution of a previously innocuous mixture of fucus extracts, laminaria and pancreas powder, by two Chinese herbs, Stephania tetrandra and Magnolia officinalis, circumvented the search of the culprit to these latter Chinese herbs. Phytochemical analysis of the capsules quickly eliminated the possibility of adulteration by known toxic compounds. In contrast the alkaloid derived from Stephania tetrandra could not be identified, suggesting that this herb might have been replaced by another, more toxic vegetable [1]. This hypothesis was substantiated by Pui-Hay But [7] who demonstrated the presence of Aristolochia fangchi in a batch of Chinese herbs imported in Belgium, a finding subsequently confirmed by Van Haelen et al. [8]. Aristolochic acid might thus be the offending drug: it is indeed a powerful nephrotoxic substance endowed, in addition, of mutagenic potential [9]. It should not be forgotten that the broad name of aristolochic acid covers a large number of different though related molecules. Still, the fact that Chinese herbs, originating from batches imported at the same time, have been utilized for the same purpose, without apparent untoward effects raises the possibility of a synergistic effect of toxic herbs with some of the other compounds included in the slimming cure.

**Its relationship with other renal disease**

This unfortunate series of observations raises important questions. The analogy between CHN and Balkan endemic nephropathy (BEN) might provide a clue to the cause of the latter disease [2]. Both conditions share the same unusual histological picture of severe paucicellular interstitial fibrosis with focal vascular lesions due to endothelial cells' swelling. Both lead to cellular atypias and malignant transformation of the urothelium [2,4]. Both finally exhibit a tubular proteinuria confirming a primary tubular damage. This similarity lends support not only to a toxic origin of BEN but also to a common aetiological factor, aristolochic acid. The role of the latter compound in BEN had been previously considered but not fully investigated. Still, the two diseases differ by the rapidity of evolution: a few months to a few years in CHN versus several years in BEN. This difference may relate to the amount of ingested aristolochic acid.

After interruption of the toxic slimming pills, CHN runs a relentless course even if serum creatinine was initially normal. Nitrosourea-induced interstitial nephritis may follow a similar pattern [10]. Consideration of both diseases might reveal some common determinants of delayed destruction of the kidney.

More broadly, the story of CHN calls the attention on the role of unsuspected herbal remedies in the aetiology of renal disease. Two cases of severe renal failure eventually requiring dialysis treatment have been attributed in Toulouse (France) to Chinese herbs, including the dubious Stephania tetrandra, prescribed as slimming agents [11]. Another as yet unreported case has been observed in London after the utilization of Chinese herbs in the treatment of eczema [A. Rees, personal communication]. Interestingly, a case of Fanconi syndrome with tubular proteinuria has been reported from Japan in a patient taking a complex mixture of Chinese herbs for slimming purposes [12]. Herbal remedies also cause acute tubular necrosis in African areas where they account for up to 35% of all cases of acute renal failure [13]. Incriminated herbs include Securidaca longepedunculata, Euphorbia matabalensis, Crotalaria laburnifolia [14] and Callilepis laurtea [13], prescribed mainly by witch doctors for impotence or other forms of sexual dysfunction, menstrual abnormalities, constipation [15].

**Public health issues**

The Chinese herb disaster also raises issues for both public health authorities and our Western society.
First of them is the place of alternative medicines, including traditional Chinese medicine in a society driven to expect from medicine not only cure but total happiness. On the one hand society is ready to try medicine before a mediatico-popular jury on the basis of rumour or dubious consumer magazines reports, rather than pay attention to the painstaking, though probably less appealing, double-blind studies involving thousands of patients. On the other hand the same society nurtures therapeutic approaches devoid of scientific basis, including acupuncture, herbal treatment, heat therapy and therapeutic massage.

This tolerance has even gained access to distinguished medical journals: in the Canadian Medical Association Journal, a freelance writer [16] explained very seriously that Western philosophy 'believes that humans are quite separate from nature' whereas in the East 'human body and mind and their environment are approached as a whole'. The alternative medicines derived from the latter philosophy, she continues, although derided by the medical establishment, are fortunately, much better accepted by 'allied health professionals such as nurses and physiotherapists' who 'are more open-minded about these less well-known health cure options such as traditional Chinese medicine'.

The Chinese herbs disaster emphasizes the medical profession's constant responsibility to remind the general public that the cornerstone of 20th Century medicine and its success remains the critical evaluation of every therapeutic modality. As La Bruyère aptly put it more than three centuries ago 'Quacks' recklessness and their gloomy successes give credence to medicine and to physicians: if the latter let die, the former kill'. The establishment of an office of alternative medicine as part of the NIH in 1991 to evaluate alternative medical practices is a first step in the right direction.

Western medicine relies on a critical evaluation of both benefits and side-effects of accepted drugs. The therapeutic efficacy of various Chinese herbs is often wanted. Although it has been suggested in some indications such as adult atopic dermatitis [17], it rests for many others on broad, undocumented statements derived from the so-called century-old wisdom of Chinese medical practice. Needless to say that ancient Western European medical wisdom has claimed similar benefits for the now long abandoned practices of bleeding and cathartic enemas. In the case of CHN no documented evidence supports the claim that the two incriminated herbs have any slimming effect. More insidious is the widespread belief that herbal remedies are devoid of side-effects; it is derived from the myth that nature is beneficent.

The lack of official regulations on herbal remedies in many countries stems from this illusion: 'natural products' are expected to be harmless; phytotherapy appears thus preferable to conventional medicine. The public should be reminded that most poisons utilized from Greek antiquity (Socrates' hemlock) until more recent times in Africa and Asia are derived from plants. Similarly many of our most potent (and dangerous) drugs from digoxin to cyclosporin originate from plants. The Chinese herb nephropathy as well as the many diseases originating in herbal remedies draws the attention of public health authorities to the necessity to submit these substances to the same scrutiny as common drugs prior to their release for medical use.

Lastly, the fact that an error in the delivery of the herbs is probably the cause of the CHN epidemics emphasizes the need to implement a rigorous control of the composition of herbal remedies. The ordeal of our patients would be completely wasted if drastic steps are not taken in these areas.

Conclusion

Our observations clearly demonstrate the aetiological role of toxic compounds in the genesis of renal interstitial disease and in the development of malignancies. The hypothesis that kidney disease as well as some carcinomas are caused by as yet unrecognized toxic substances has already yielded important insights into drug-induced nephropathies and analgesic-induced nephropathy with urothelial tumours etc. Many more are yet to be discovered. Only tedious, unglamorous, and undramatic detective work will sometimes uncover the clue that breaks open a case. In 'A case of identity' the dumbfounded Dr Watson says 'You appeared to read a good deal upon Mrs Sutherland which was quite invisible to me'. Sherlock Holmes replies: 'Not invisible but unnoticed, Watson. You did not know where to look and so you missed all that was important'.

References

Nephrological and moral aspects of physical torture

N. Lameire and E. Vermeersch

Renal Division of the Department of Internal Medicine and the Department of Philosophy, State University Gent, and University Hospital, 185 De Pintelaan, Gent, Belgium

Rhabdomyolysis, myoglobinuria and acute renal failure have been known to follow massive crush injury. Although in the past the non-specific clinical syndrome of muscle pain, weakness, and brown urine was called Meyer–Betz syndrome [1], the full-blown clinical picture first came to the attention of the nephrologist from the classic description of the crush syndrome in patients injured during the bombing of London in 1940–1941 [2].

Much of the pathogenesis of rhabdomyolysis has been clarified by careful observations in exertional and metabolic rhabdomyolysis and has been extensively reviewed [3,4]. The early management of the often severe traumatic shock and prophylaxis of acute renal failure in traumatic rhabdomyolysis have recently been discussed by Better and Stein [5]. Although earlier studies have suggested that myoglobin released from injured muscle cells is a nephrotoxin per se, there is at present little evidence to support this notion [4]. Similar to haemoglobin, myoglobin has been infused intravenously and, as long as urine flow is adequate, it is difficult to demonstrate any harmful effects on renal function. However, in dehydration or shock where the urine is highly concentrated, and especially if the urine is acidic, some investigators have found evidence of nephrotoxicity. Associated with low renal blood flow, decreased glomerular filtration rate, back-leak of filtrate, intratubular obstruction by myoglobin and/or by haemoglobin, together with release of proteases or vasoactive kinines from injured skeletal muscle cells may probably directly damage the kidney [3,4].

Shock and severe dehydration were probably the 'setting' of the patients described in this issue by Malik et al., who developed acute renal failure following rhabdomyolysis caused by extensive traumatic muscle injury and haemolysis due to physical torture.

This paper makes both the readers and reviewers very uncomfortable, first of all because of the moral aspects, which will be commented on later, but also because of the pathophysiological lessons that we can learn from it on post-rhabdomyolysis and/or haemolysis-induced ARF.

The editor and the reviewers have hesitated some time to discuss these 'scientific aspects' of the paper. We remember the recent discussion [6] on the Schaltenbrand experiment, performed by Georg Schaltenbrand, one of Germany's most eminent post-war neurologists, who tried to establish a viral aetiology for multiple sclerosis. He and his co-workers administered intracisternal injections of cerebrospinal fluid from monkeys with a spontaneous encephalomyelitis in several mentally ill individuals. We of course agree with the comments recently formulated by Seidelman [7] on these experiments: 'What needs to be published and studied today is not the scientific data from the experiment but a recounting of the consequences of ethical compromise where human life and dignity become secondary to personal, professional, scientific, and political goals'.

The reasons that we do discuss some of the medical aspects of Malik et al.'s paper are twofold: first, the authors themselves were absolutely not involved in the torturing of the victims. Second, we feel they should be congratulated for the courage to publish this and a previous paper [8] on this subject.

Malik et al. divide the 34 ARF patients in three groups; a first group of 21 patients with only myoglobinuria, a second group of 10 patients with combined myoglobinuria and haemoglobinuria and a third group (n = 3) with only haemoglobinuria. All patients were severely dehydrated, because they were denied fluids and food during their captivity and they all presented severe acidosis and/or hyperkalaemia. In both groups with haemoglobinuria, all patients had undergone 'falanga' torture, where severe beating of the soles of the feet is done. This torture technique is practised worldwide, especially in the Middle East [9] and apparently also in Kashmir. Only those who had undergone falanga showed evidence of haemoglobinuria. The authors speculate, probably correctly, that direct mechanical damage of the red blood cells within the microcirculation of the soles of the feet explains the haemolysis and resulting haemoglobinuria, a mechanism that also may explain the well-known march...