Analgesics and the Kidney

The clinical, pathological, and radiological features of the condition known as analgesic nephropathy are fairly well defined,¹ and there is little doubt that, since its recognition 20 years ago, it has increased in incidence.² Impressive epidemiological evidence associates the renal lesion with a history of analgesic abuse,³ and most physicians now assume that there is a cause-and-effect relationship between the two.

But there is a dearth of controlled observations which might be expected to establish beyond all doubt the existence of a definite relationship. The most convincing observation is that of A. F. Burry and his colleagues,⁴ who reported the results of 507 consecutive necropsies, in 106 of which they found the classical lesions of analgesic nephropathy. Subsequently the patients' drug histories, obtained from their relatives by a different observer, were compared with the necropsy findings, and a clear-cut relationship between analgesic abuse and renal disease was demonstrated. A recent paper by D. H. Lawson⁵ based on information collected by the Boston Collaborative Drug Surveillance Program apparently throws some doubt on the existence of this association. Nurses recorded a history of drug intake during the three months preceding the admission of 6,407 patients to medical wards. The patients were allocated to three groups according to whether they took analgesics regularly, occasionally, or not at all, and the incidence of abnormality of the urinary sediment and of diminished renal function in the three groups was compared. Though no significant differences were detected, the work does not allow the conclusion that there is no association between analgesic consumption and renal disease. The principal criticism is that the dose of analgesics consumed was not recorded, and there was no suggestion that even the regular consumers abused these drugs. Furthermore, the duration of the drug history was short, the persistence of the history takers in eliciting a history that is often concealed⁶ was not indicated, and only a small minority of the patients consumed analgesics containing phenacetin—a drug which on epidemiological grounds seems the most likely culprit.³

Thus the belief that analgesic abuse is associated with chronic renal disease remains unshaken. But controversy still rages over the nature of this relationship. K. G. Koutsaimanis and H. D. de Wardener³ have reviewed the extensive epidemiological evidence incriminating phenacetin, but the evidence has not found universal support possibly because phenacetin is seldom, if ever, consumed alone; it is usually taken in mixtures with salicylates, codeine, and caffeine. Experiments in man show that salicylates have a distinct effect on the kidney. L. F. Prescott⁷ found an increase in the urinary excretion of tubular epithelial cells which was greater during the administration of aspirin than phenacetin, and recently two groups have detected a reduction in glomerular filtration rate of 10% after oral⁸ and 30% after intravenous administration of salicylate.⁹ But it is questionable whether these findings have any relationship to the chronic renal damage that is associated with the consumption of several kilograms of analgesics over periods of years.

Numerous studies in rats¹⁰ have established that, in this animal, salicylates and salicylate-phenacetin mixtures both have a greater propensity to produce papillary necrosis than phenacetin alone and have pointed to salicylates as the principal offenders. But the fact that papillary necrosis is exceedingly rare in people who have abused salicylates alone must make this unlikely.³ In addition a high incidence of renal damage has been found in Swedish factory workers¹¹ who consumed analgesic mixtures containing phenacetin, phenazon, and caffeine but not salicylates. Priscilla Kincaid-Smith and colleagues¹² believe that the continued consumption of any analgesic including salicylates will prevent any recovery of renal function in a patient with established analgesic nephropathy and may allow renal function to deteriorate further. But this view too is not universally

¹ Taitz, L., and Harris, F., Acta Paediatrica Scandinavica, 1972, 61, 499.
² Taitz, L., and Byers, H. D., Archives of Disease in Childhood, 1972, 47, 257.
⁴ Bessette, J. L., Bulletin of the New York Academy of Medicine, 1971, 47, 579.
⁵ Abraham, S., and Nordsieck, M., Public Health Reports, 1960, 75, 263.
¹³ Heald, F. P., Practitioners, 1971, 206, 223.
accepted, and some workers\textsuperscript{13,14} consider that such patients may safely take small quantities of salicylates.

At present the balance of evidence still leads to the conclusion that excessive consumption of phenacetin is the principal factor in the development of analgesic nephropathy. This is not to deny that other factors, including the consumption of other analgesics, the presence of impurities in the phenacetin,\textsuperscript{15} individual variation in the metabolism of phenacetin,\textsuperscript{16} episodes of dehydration,\textsuperscript{17} and renal infection\textsuperscript{18} might all be important in potentiating this effect.

1 British Medical Journal, 1970, 4, 125.
2 Abel, J. A., Clinical Pharmacology and Therapeutics, 1971, 12, 583.

Site of Latent Herpes

Herpes simplex virus has a notable tendency to cause recurrent infections. This is an unusual property for a virus, since most give rise to a long-lasting immunity due to neutralizing antibody after primary infection. The immune response to herpes simplex is no different, but the antibody produced seems to protect against attack by the virus from outside the body and not against reactivation of virus already latent within the patient's tissues.

Most primary infections with herpes simplex virus are symptomless, but when accompanied by symptoms these usually take the form of acute gingivo-stomatitis.\textsuperscript{1} Rather surprisingly, the most common recurrent herpetic lesions—cold sores—do not usually appear at the site of the primary disease but at the muco-cutaneous junctions of lips or nose. Cold sores are provoked by a variety of stimuli such as common colds and sunlight, but nothing is known of the mechanism of reactivation. In addition, the site of latent herpes simplex virus has been a subject of some controversy and conjecture. Now evidence is mounting that the latent virus is in fact located in the trigeminal ganglion.

E. W. Goodpasture\textsuperscript{2} seems to have been among the first to suspect that herpes simplex virus spreads via the nerves\textsuperscript{3} from the primary lesions to become latent in the trigeminal ganglion. He suggested that virus might spread peripherally from there to cause recurrent infections. This view was supported by several reports\textsuperscript{4-7} that section of the posterior sensory root of the ganglion to relieve trigeminal neuralgia was often followed by an eruption of cold sores in the areas supplied by the sectioned sensory root. Cold sores did not follow section of either the motor root or the peripheral branches of the trigeminal nerve.\textsuperscript{8} Both ganglion cells and peripheral sensory fibres must therefore be intact for reactivation of virus to take place.\textsuperscript{9,10} This suggests that the virus is latent in the cells of the trigeminal ganglion and on reactivation spreads down one of the branches of the trigeminal nerve to cause lesions in the area of skin supplied by the branch involved. Attempts to isolate virus from the ganglion had until then been unsuccessful.\textsuperscript{11} Now F. O. Bastian and his co-workers\textsuperscript{12} and J. R. Baringer and Peggy Swoveland\textsuperscript{13} have independently managed to do this. Both used ganglia obtained postmortem and isolated herpes simplex virus by prolonged cultivation of the ganglia in vitro. Herpes simplex virus grows well in most types of cultured cell, with rapid production of a cytopathic effect, but was not detected in the cultures of ganglia until after 10 to 45 days. Bastian and his colleagues isolated virus from two of 23 patients tested, whereas Baringer and Swoveland achieved successful isolation from five of six patients examined. Only one of the latter five patients had a previous history of herpetic infection.

These results provide strong evidence that latent herpes simplex virus is located in the trigeminal ganglion. The fact that some of the patients had no history of recurrent herpetic lesions suggests that this need not be associated with viral reactivation and that patients not subject to recurrent herpetic lesions may also harbour latent virus. This agrees with epidemiological studies which have shown that normal people with no history of herpes occasionally shed herpes simplex virus in their saliva.\textsuperscript{14,15} It seems probable that the virus reaches the ganglion from primary lesions in the mouth via the peripheral nerves. After reactivation virus spreads down either the second or third branches of the trigeminal nerve to cause cold sores in the areas of skin supplied by the nerve round lips or nose. A similar mechanism may well operate in recurrent herpetic dendritic ulcer of the cornea.\textsuperscript{16}

In this instance the virus presumably spreads down the first branch of the trigeminal nerve. Many questions remain unanswered. Possibly the most interesting is the state of the latent virus in the ganglion. Is virus present in the ganglion cells as intact and infectious particles, or in the form of an incomplete provirus—perhaps integrated into the cellular chromosomes? Herpes simplex virus has been shown to be able to integrate at least a portion of its genome DNA into the chromosomes of cells in culture.\textsuperscript{14,17} Further work on the state of the latent virus will be awaited with interest.

1 Burnett, F. M., and Williams, S. W., Medical Journal of Australia, 1939, 1, 637.
3 Goodpasture, E. W., Medicine, 1929, 8, 223.
5 Cushing, H., American Journal of Medical Sciences, 1904, 127, 375.
9 Paine, T. F., Bacteriological Reviews, 1906, 24, 472.
17 Munyon, W., et al., Virology, 1972, 49, 683.