Extensive studies were done on the bacteriology of the tap water, the dialysate from the supply tank onwards, and the patient's blood. The rigors were not related to bacterial counts in blood, tap water, dialysate, or Kiil fluid, nor to the type of organism detected; nor were they related to the state of the Kiil boards, the rubber gaskets, the procedure of removing formalin, or the techniques of sterilizing dialysers and the supply system.

The problem was solved when the emergent saline from the dialyser blood compartment was searched for protein instead of viable bacteria. Spectrophotometric examination detected a protein peak at 278 mμ from this fluid, and none from tap water, dialysate, or the sterilizing solutions used. The concentration of this protein correlated with the severity of the rigors in different patients. Search back to the initial preparation of the membranes revealed a fluctuating bacterial count in the tank in which they were washed. Bacteria adhering to the membranes were efficiently killed by formalin, but inadequately washed off the membranes by the saline flush.

As soon as dry membranes were used to build the dialysers, the numbers of and episodes of hyperpyrexia were markedly reduced and in the following 4,160 dialyses, only 49 unexplained pyrexias have occurred.

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Salicylates and Papillary Necrosis

SIR,—Dr. T. W. Steele's (31 October, p. 306) main criticism of our paper (5 September, p. 559) is that we should adopt a more objective approach to the question: are salicylates responsible for renal damage in man?

In reply to the specific points in his letter about the effects of diuretic substances, we deliberately did not apply statistics to the group shown in Tables III and IV because we did not like to add up results in the different small groups. If, however, Dr. Steele feels that statistics should be applied the fact that 31 of 80 rats in the dehydrated groups fed on aspirin-containing mixtures developed papillary necrosis compared with 6 of 40 in the rats on a constant water diuresis and aspirin-containing mixtures shows a highly significant difference ($P<0.005$). If the groups of rats in Table IV which were dehydrated but given acetazolamide and sodium bicarbonate are compared with dehydrated rats in Table III the difference is again significant ($P<0.025$). The diuretic action of caffeine should if anything diminish the effects of dehydration in the groups in Table III. In fact the only group in Table III which approaches significant difference from the other small groups is the A + C group ($P<0.1>0.05$)—with Yates correction). This together with the fact that the dose of aspirin is higher in the A + C group compared to the A + P group suggests that "caffeine may reduce the nephrotoxicity of aspirin" as we state in our discussion (5 September, p. 559).

Most of Dr. Steele's points relate to our discussion in which we drew attention to the association between renal damage and aspirin intake in man. We did not claim that this proved anything. The mere fact that papillary necrosis has been reported in patients who are said to have taken only aspirin is of interest. No such data are available for phenacetin in man, but nonetheless it is very widely believed that phenacetin causes papillary necrosis in man. What more objective approach is possible in man? A long term epidemiological study is in progress in Switzerland. This may be the right line of approach but is a doctor entitled to let his patients continue to take tablets and observe deterioration in function over many years until papillary necrosis develops when he can demonstrate that the analgesics which they are taking produce papillary necrosis in animals?

Perhaps the recent demonstration that salicylates are concentrated within the renal papilla will carry more weight with physiologically inclined nephrologists.[1] Dr. K. G. Koutsaimanis and Professor H. de Wardener (17 October, p. 131) seemed to attach great importance to Bluemle and Goldberg's observation that *N*-acetyl-*p*-aminophenol (paracetamol) is concentrated in the papilla. We are inclined to look at things more from the morphological point of view and are more impressed when we see necrosis than by a concentration gradient in the papilla of an animal.

The last paragraph of Dr. Steele's letter implies that in demonstrating that salicylates produce papillary necrosis in rats we were not adopting an objective approach to the question: do salicylates cause papillary necrosis in man? While this may be so animal experiments form the basis of testing all new drugs and the Dunlop Committee or any similar body would be unlikely to accept a new drug in 1970 if it produced papillary necrosis in over a third of the animals tested. Should we then adopt quite different methods of testing old drugs and new drugs?

We think that the fact that salicylates will produce papillary necrosis in animals, and that phenacetin in the same dose will not, is at least suggestive that salicylates contribute to the development of papillary necrosis in patients who take aspirin, phenacetin, and caffeine and aspirin, paracetamol, and caffeine mixtures.—We are, etc.,

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[1] Gault, M. H., Abstract, American Society of Nephrology, 1970, p. 28.

Phenacetin Nephropathy

SIR,—The choice of the title "Phenacetin Nephropathy" rather than "analgesic nephropathy" in our paper was deliberate (17 October, p. 131). We avoided the term "analgesic nephropathy" for two reasons. The first is that in our opinion the facts now overwhelmingly incriminate phenacetin as the cause of analgesic nephropathy. It is therefore misleading to continue to use the term analgesic nephropathy. Secondly the use of the term analgesic nephropathy unjustifiably includes other analgesics such as caffeine and codeine against which no accusations have so far been made that in the absence of phenacetin they may cause papillary necrosis in man. For instance, Nanra, Fairley, and Kincaid-Smith[1] have pointed out that codeine phosphate is not harmful, even to patients known to have papillary necrosis due to phenacetin-containing analgesics.

We are astonished that Dr. L. F. Prescott (21 November, p. 493) continues to support his hypothesis that aspirin causes papillary necrosis in man. In our paper we reported that the consumption of aspirin in Great Britain in 1967 was 3,020,000 kg and that during the same year the consumption of phenacetin was 540,000 kg. Therefore the annual consumption of aspirin ingested without phenacetin is of the order of 2,000,000 kg per year.

Nevertheless, this annual avalanche of aspirin has yielded only two possible victims with papillary necrosis (Dr. R. M. Murray and others 27 February, p. 479). On the other hand, extrapolating from our own experience of 18 patients suffering from phenacetin nephropathy in seven years we concluded that the total incidence of new patients presenting with phenacetin nephropathy in England and Wales is unlikely to be much less than 500 per year. After perusing these figures, Dr. Prescott comes to the conclusions that "Although abuse of mixed analgesics is associated with papillary necrosis, it is most unlikely that phenacetin itself plays a major aetiological role. The salicylates and pyrazolones taken with it are much more likely to be the culprits". For our part we have been so impressed by the almost total lack of any evidence that in man aspirin causes papillary necrosis that, like Dr. R. M. Murray (and others), we advise our patients suffering from phenacetin papillary necrosis to take aspirin, if their need for analgesic continues after they have ceased taking phenacetin-containing tablets. The improvement in these patients' health and renal function upon stopping the ingestion of phenacetin-containing tablets has been the same as those who stopped taking all forms of analgesics.

We feel that Dr. P. Kincaid-Smith's views' are close to our own. Nevertheless she continues to support the contention that, in addition to phenacetin, aspirin and some other analgesics may also cause papillary necrosis in man. She mentions that she has seen patients with phenacetin papillary necrosis who have had a severe deterioration of renal function shortly after the patients have returned to taking large quantities of non-phenacetin analgesics. In support of this view, Dr. Murray and colleagues report that an unstated number of their patients in whom papillary necrosis developed while ingesting phenacetin-containing tablets had a continued deterioration of renal function subsequently if they continued to take the same tablets from which, however, phenacetin had now been removed. This, of course, is not evidence that papillary necrosis is due to non-phenacetin analgesics. It can only be put forward as evidence that in a patient with phenacetin papillary necrosis the ingestion of such tablets may cause a deterioration of renal function. On the other hand, this suggestion contrasts with our own experience which has been mentioned above. It also contrasts with the findings of Dr. Murray and his colleagues themselves, who reported that "No difference in prognosis could be found between those who abstained from analgesics entirely and those who took small doses of paracetamol or aspirin when necessary". It must also be pointed out that the patients described by Dr. Nanra and colleagues and Dr. Murray and colleagues already knew that their kidneys had been partially destroyed by the ingestion of phenacetin-containing tablets. Patients with phenacetin nephropathy are well-known to conceal their habit and to underestimate their ingestion of phenacetin, particularly when they suspect that their doctor is trying to relate this ingestion to their symptoms. We would suggest that it is very probable that these patients' statement that they subsequently ingested non-phenacetin-containing drugs was probably untrue,

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