metry please, hydramnios; and what constituted a positive radiological correlation in such cases? The method used for scoring agreements in this study (stated simply as "whether the radiological interpretation agreed with the clinical diagnosis as stated on the request card") is not clearly defined (except when nothing was detected on a routine—no pathology suspected—request). Perhaps the author had accurate and specific clinical diagnoses in all cases, but this is not stated or implied. The reverse is actually implied when he refers to such diagnoses as vertigo or headache.

I was, in fact, impressed with the overall detection rate of 6.3% additional (unsuspected) significant chest lesions discovered (differently stated by the author, it is even more impressive—"more than one-fifth of all lesions detected in the chest . . . are not apparently suspected . . .") and almost 2% in the normal (routine) chests done. This is a high discovery rate in most present day surveys. Agreement with a specific clinical diagnosis (pulmonary tuberculosis, intestinal obstruction, fetal malformation, etc.) is quite different from radiological detection on examinations done for symptoms or signs (cough, abdominal pain, hydramnios, etc.). In the former, clear agreement or disagreement can be recorded and the contribution towards disagreement by each party can be known when the true lesion is discovered. The use of radiology for detection purposes when there is no firm clinical or pathological diagnosis must be appraised differently. Perhaps this difference helps to explain the wide agreement differences of 1.4% for skulls (rarely is a true clinical diagnosis given) and 54% for barium meals. (Frequently, a true diagnosis is given.) Other factors are undoubtedly important also as the author states.

The author admits "this method has obvious limitations as there is no final pathological diagnosis". He then goes on to assume the initial clinical diagnosis (although headache or vertigo hardly seem to be diagnoses) is the correct one, and considers the radiological diagnosis (such as no abnormality seen) wrong, if it does not agree, except when the clinician expected a normal result and the radiologist discovered a significant lesion. This situation is simply counted as an agreement for the radiologist as it is added to his other agreements for his total score; it is not counted as a disagreement for the clinician who suspected no pathology. True, this method has the merit of simplicity he notes, but it has no scientific merit. To then suggest that a parallel study of follow-up request cards showed the initial clinical diagnosis was repeated (as yet unpublished by the author) supports the view that it was, therefore, likely to be the correct diagnosis, is to accept the words of the Bellman in the *Hunting of the Snark*—"What I tell you three times is true." (Lewis Carroll).

The author also notes that "it is not possible in the present series to measure the clinical contribution to the low agreement percentage" that is, no pathological confirmation was obtained. In a study of this nature, as previously suggested, pathological diagnosis is essential; if the clinical contribution to misdiagnosis cannot be determined, how can the radiological? (Of course, the reverse assumption could have been made, that the radiological diagnosis was the correct one and disagreement was due to the clinical misdiagnosis.)

I strongly agree with the author's final statement that it is extremely important for the student to be taught the applications of diagnostic radiology, but such teaching must be based on studies with more scientific validity than this one.—I am, etc.,

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Experimental Infection of Man with Pig Whipworm

SIR,—*Trichuris suis*, the pig whipworm, has a worldwide distribution¹ as does the human whipworm *Trichuris trichiura*. Stoll² estimated that there were 355 million infected humans throughout the world. It is generally accepted that the two nematodes are distinct species. Dinnik³ demonstrated minor morphological differences, including the sizes of eggs and infective larvae and in chromosome numbers; others have failed to differentiate between the worm types.¹ The differences reported, however, are such that they would not be detected by routine medical and veterinary parasitological techniques.

Recently, an experimental self-infection of *Trichuris suis* was achieved in man (aged 23 years). A single oral dose of 1,000 infective eggs suspended in 10 ml of distilled water resulted in a patent infection detected by day 60. Five stool samples, two taken prior to infection and three during the next 40 days were negative for *Trichuris* eggs, using the formalin-ether concentration technique. The eggs used were harvested from the faeces of three naturally infected six-month-old farm pigs and were cultured to the infective stage in moist vermiculite at 26°C for 34 days. Concurrently, four pigs, aged 9 weeks, were infected successfully with eggs from this same harvesting and culture; 30,000 eggs were given in a single dose by mouth and maturation of the parasites occurred between 41 and 49 days. In the human experimental infection no symptoms of distress and no diarrhoea were experienced, and no pronounced alterations in the differential white cell count could be detected. The number of eggs in the faeces has remained constant at 20 eggs per gramme in the ten week period after maturation occurred, and 11% have embryonated in culture indicating the presence of both male and female worms; the usual embryonation rate of *T. suis* eggs from pig faeces is 84-86%.

A search of the literature has not yielded any previous reports of *Trichuris suis* experimental infections in man developing to maturation though Tukalevski,⁵ following a small dose of 87 infective eggs, isolated two larvae from his stool 19 days later. However, the dose was small and he discontinued stool examinations at 51 days.

The fact that this single human cross-infection was established with relative ease might suggest that the source of infection of some cases of trichuriasis in man could be the pig or its excreta, particularly in situations where man and pig have regular and close contact. It would be interesting to establish whether such an association exists. In the meantime, eggs from human cases of trichuriasis are being collected and processed in the hope of obtaining sufficient

numbers to attempt human to pig *Trichuris* infection.—I am, etc.,

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- 1 Beer, R. J. S., Taffs, L. F., Jacobs, D. E., Lean, I. J., and Curran, M. K., *Veterinary Record*, 1971, in press.
- 2 Stoll, N. R., *Journal of Parasitology*, 1947, 33, 1.
- 3 Dinnik, N. N., *Meditsinskaya Parazitologiya i Parazitarnye Bolezni*, 1938, 7, 907.
- 4 Schwartz, B., *Journal of Agricultural Research*, 1926, 33, 311.
- 5 Tukalevski, I. M., *Meditsinskaya Parazitologiya i Parazitarnye Bolezni*, 1940, 9, 444.

Recurrent Erythema Nodosum of Pregnancy

SIR,—Erythema nodosum is probably a hypersensitivity reaction characterized by inflammatory nodules in the dermis and subcutaneous tissue. It is regarded as secondary to a variety of underlying disorders, especially bacterial, fungals and viral infections and drug reactions, but may occur in pregnancy with no underlying cause found, as in the following case.

The patient's first pregnancy at 18 years of age was complicated by a rash of red, tender nodules over both her shins. This rash first appeared at 32 weeks amenorrhoea and fresh crops of nodules appeared regularly up to the time of delivery. After the normal delivery at term of a male infant weighing 3.5 kg, the rash began to fade and had disappeared completely by the end of the second week. Full investigation at the time failed to show an underlying cause.

One year later the patient's second pregnancy was similarly complicated by the same type of rash, over the same area, again from the 32 week onwards and fading after delivery of a male infant weighing 4.0 kg.

In each pregnancy the patient obtained the best relief by wearing elastic web bandages. These would appear to control the oedema around the nodules. No analgesia or corticosteroid treatment was required.—I am, etc.,

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Pyrexia and Dialysis

SIR,—The experience of Drs. P. J. A. Robinson and S. M. Rosen (6 March, p. 528) was shared by the Auckland Dialysis Unit in 1968. Over a four-month period 18 patients in a six-bed dialysis unit had 116 episodes of hyperpyrexia with rigors and hypotension in 519 dialyses. Several patients required hospital admission for intensive treatment.

A Biosystems MAKES machine supplied dialysate from a tank delivery system to Kiil dialysers. The tanks and lines were cleaned with Chlornox and formaldehyde 2%. The Kiil dialysers were built with wet cuprophane membranes, sterilized with 2% formaldehyde for six hours, drained, then flushed with two litres heparinized saline in the blood compartment, and tap water at 4 lb/in² (0.28 kg/cm²) for 30 minutes in the dialysate compartment. The dialysers were not shared between patients, new sterile blood lines were used each dialysis, and bacterial counts and culture samples were taken routinely from the emergent saline as the patient was connected to the dialyser.

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 m μ 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 Warden (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-Smith¹ 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,