tubular cell excretion during the administration of drugs affecting rate of urine flow is therefore difficult to assess in the absence of other demonstrable nephrotoxic effects.

Dr. Gent and his colleagues suggest that the effect of caffeine on renal tubular cell excretion is due to its diuretic action. This does not seem to be the case in the study referred to,[2] since the mean urine flow rate during the control period was 45.8 ± 5.4 (S.E.) ml./minute, compared with 44.2 ± 3.4 ml./minute during treatment with caffeine. Moreover, renal tubular necrosis associated with markedly increased renal tubular cell excretion is known to occur in rabbits and dogs receiving repeated daily doses of caffeine. These changes were observed in dogs treated with caffeine in doses of only 40 mg./kg. daily.[3]

I do not think that the effects of frusemide on urinary cell excretion can be compared with those of analgesic drugs such as salicylates for several reasons.

1. There was no significant change in the rate of urine flow when 3.6 g. of aspirin was given daily.

2. The renal tubular cell response to this dose of salicylate was very much greater than that observed with frusemide. Thus the five-day mean tubular cell counts rose by a factor of 10 when aspirin was given, whereas only a threefold increase was noted with frusemide. In one volunteer receiving aspirin the excretion of renal tubular cells rose to 8,192,000 cells an hour—a 120-fold increase.

3. The renal tubular cell response to aspirin follows a characteristic pattern. After a latent interval there is a sudden dramatic rise, followed by a slower fall toward normal values, even though the drug is continued. An identical response with a dose-related latent period occurs in rats treated with mercuric chloride in doses sufficient to produce tubular necrosis. The sudden rise in cell excretion coincides with widespread tubular necrosis, and the slow fall is associated with lesser degrees of necrosis and rapid regeneration, despite the continued administration of mercury.[4] This typical pattern of response did not occur when frusemide was given, though the effects of larger doses are unknown. The fact that frusemide produced an immediate response is more in keeping with a mechanism related to the diuretic effects of this drug.

4. I do not know whether frusemide can cause tubular necrosis, but there is no doubt that such lesions can be produced in experimental animals treated with caffeine or salicylates. Renal tubular cell excretion does not seem to be increased following therapeutic doses of probenecid, penicillin, alpha-methyldopa, or cephaloridine (2 g. daily). On the other hand, large numbers of renal tubular cells have been observed in the urine of patients receiving potentially nephrotoxic antibiotics such as bacitracin, kanamycin, and colistin methanesulphonate.

As Dr. Gent points out, there are many problems still unsolved, and it is hoped that further studies will clarify the situation. Dr. S. T. G. Butterworth (23 November, p. 517) suggested that some of the small peroxidase-negative cells in the urine might be lymphocytes rather than tubular cells. This might very well be the case, and lymphocytes have been described in the urine during the rejection of renal transplants. However, the cells of the urinary sediment are often degenerate, and conclusive identification becomes very difficult with a routine method. Nevertheless, it is impossible to avoid the conclusion that the masses of peroxidase-negative cells appearing in the urine during experimentally induced tubular necrosis are derived from the necrotic tubules.

I am glad that Dr. Butterworth has drawn attention to the possible carcinogenicity of the 2:7 diaminofluorene used in our stain. I was not aware of this hazard when the original method was published, and precautions to avoid contact with the stain must be taken.—I am, etc.,

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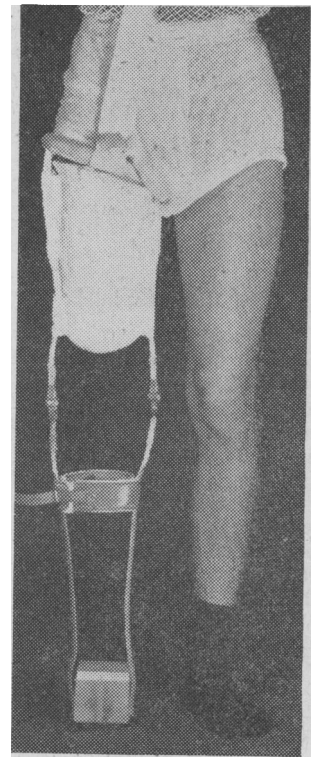
Through-knee Amputation

SIR,—The article by Mr. P. F. Early (16 November, p. 418) on through-knee amputation shows that this technique is becoming more recognized as advantageous, though its use is still limited by the shortcomings of the artificial limb makers. It is, of course, true that in traumatic amputations the precious skin around the knee is too often mangled, or is cut too short by inexperienced emergency surgeons, so that proper cover of the femoral condyles is not achieved. At the same time, in the case of ischaemic limbs the flaps are likely to be ischaemic too, so that only a small proportion of people can enjoy this stump. It seems a pity, therefore, that more attention is not devoted to the provision of the appropriate limb. A friction-loaded knee



joint, placed 1 in. (2.5 cm.) below the condyles, should not really cause a great deal of mechanical or cosmetic disturbance, in spite of the difference in the level of the knee joints. However, should this indeed be an insuperable obstacle, it is a very simple matter to shorten the femur by 2 in. (5 cm.) by an oblique resection in the upper middle third, immobilizing the femur with an adequately thick Küntscher nail. With the obliquity of the resection controlling rotation, it is possible for such a patient to start walking within a week of operation. The elevation of the condyles by 2 in. (5 cm.) does away with all the prosthetic objections.

One of the universal complaints about limb makers is the unconscionable delay between the amputation and the fitting of the limb. Under the modern development of applying in the theatre a plaster stump sock, delay even in the supply of a pylon is very irritating. It is certainly not a common experience to find that pylons are supplied in a few days, as suggested in point (3) at the end of Mr. Early's discussion. The picture suggests a method of getting round this problem, using a preoperatively supplied walking calliper with a locking knee hinge. Weight-bearing is shared with the calliper ring and it is important to ask for heavy-duty side bars to the calliper.—I am, etc.,

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Systolic Murmurs in the Elderly

SIR,—May I clarify a possibly misleading reference to one of my papers in the leading article on systolic murmurs in the elderly (30 November, p. 530)?

The findings in fact confirmed that aortic valve or ring abnormalities were present in most of the cases with clinically definite aortic murmurs. However, these were only 37 of the 173 patients studied, and in the remainder the examining physicians had not considered the murmurs as having definite aortic characteristics. Such cases are, however, still commonly diagnosed as "aortic sclerosis," but apparently more from traditional habit than clinical findings. It was in the latter group only that the high proportion of mitral abnormalities was observed, and to which the conclusion in your leading article refers.—I am, etc.,

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Screening for Cervical Cancer

SIR,—Dr. A. J. Lucas and others (30 November, p. 578) make a timely point in drawing attention to the payment of general practitioners for the taking of cervical smears only from women over 35 years of age.

In the north-east region of Scotland the general practitioners have responded well to the advice to take cervical smears from their healthy women patients. In 1962 only 3% (292) of cervical smears were taken by practitioners, whereas in 1967 40% (6,044) of the smears coming into the laboratory from women screened for the first time were from general practitioners. Fortunately these doctors do not appear to be limiting their smear-taking to the group for whom they will receive payment. This makes the attitude of the Ministry unreasonable and the screening commendable. The postal service initiated by the Ministry is most helpful.

Since our screening programme started unsuspected preclinical cases of cervical cancer have been detected at a rate of 0.3% below 30 years of age, but 0.81% between 30 and 35 years, and 0.85% between 35 and 40 years. Perhaps there was a case for