over 140 mm. Hg on the basis of recordings every fifteen minutes or less. A steady increase in dosage was necessary and the patient died after twenty-one hours, having had a total of approximately 70 mg. of adrenaline. For almost the whole of that period the required B.P. level was maintained, but the pressure always dropped precipitately during the brief periods when the drip was discontinued.

Autopsy showed no cardiac infarction and no unusual or severe renal lesions. A small cerebral cyst, filled with altered blood, was present in the parietal region on each side.

Through the kindness of the research department of Messrs. May and Baker Ltd., the hexamethonium-bromide content of the last three urine specimens collected was examined. In the last twenty-four hours of life only two catheter specimens, totalling 13 ml., were obtained, together containing 7·5 mg. of the drug; previous specimen twenty-seven hours before death contained 55·2 mg. There was no methonium in the vomitus, which had a chloride content of 352 mg. per 100 ml.

We wish to stress that this patient, under careful supervision in hospital, entered an irreversible, progressive, and fatal hypotensive state after an oral dose of hexamethonium bromide smaller than those which she had previously taken without alarming or consistent reduction in the B.P. Further, no progressive fall in the initial morning B.P. had occurred to suggest a cumulative effect. Indeed, the high chloride content of the copious vomitus (260 oz.) makes it questionable whether death was due simply to sympathetic blockade. Earlier use of adrenaline might have averted the fatal outcome, but continuous therapy for twenty-one hours was unavailing.

We have reason to believe that this is not the only tragedy which has occurred with the methonium compounds, and we doubt whether it is justifiable for these substances to be used at all outside a hospital. Disasters are probably inevitable in the early stages of experience with any new and potent drug, but the course of hypertension is so unpredictable, particularly in women, and the response to hexamethonium bromide has been so unreliable in our experience, that we do not propose to use these drugs again except for patients in whom a relatively early death appears inevitable with any other form of medical treatment.

West Herts Hospital, Hemel Hempstead.

C. HIRSON
A. R. KELSALL.

SPINAL ANÆSTHESIA

SIR,—The arguments of your annotation last week justify disuse of spinal anæsthesia for merely securing abdominal relaxation. Unfortunately the considerable prejudice against it, especially in obstetrics, has prevented its use in conditions where there is increasing reason to think it valuable. Evidence of its efficacy in eclampsia and anuria is being sporadically reported, and Hingson has provided a long list of successes. In interpreting his method of Pavex caudal analgesia it becomes clear that he aims at a "denervation" of the kidney and at avoiding a fall of blood-pressure meanwhile. In eclampsia low spinal block is equally effective. The meagre fall of blood-pressure herein ensuing cannot be held responsible for the improvement. It is reasonable to assume that these two almost similar procedures have a common target. In the Hingson technique it is the kidney directly. In the other the same organ is indirectly involved by interruption of a uterorenal reflex. No other explanation comes to mind. Shorr's work on V.E.M. and V.D.M. would explain postoperative shock through the mediation of the kidney, and should be an incentive to the anæsthetist to devise methods of insulating that organ from stimulation during major surgical procedures. Here again caudal anæsthesia is the goal. The decline in the practice of spinal anæsthesia will blur a new horizon needlessly.

London, W.1. J. SOPHIAN.

PROPHYLAXIS AGAINST TETANUS IN BURNS

SIR,—In his review of burns and their management (Feb. 24, p. 460), Mr. Clarkson advises that "Anti-tetanus serum should certainly be given in all cases," and he suggests that active immunisation of the whole population should be seriously considered. He bases this advice on the fact that Dupuytren mentioned the risk of tetanus in burns over 100 years ago, and on Dr. Altemeier's report to the recent Washington Conference of "an incidence of contamination by tetanus organisms of 3% in routine smears from primary burns." I have looked up Dr. Altemeier's published work on the bacteriology of traumatic wounds (two papers, one of which mentions 13 burns) but I have found nothing to support the idea that true tetanus bacilli frequently contaminate these latter injuries. I did not hear Dr. Altemeier's statement in Washington, but I think it unlikely that he would rely on "routine smears" for the positive identification of tetanus bacilli.

However, quite apart from this evidence, I wonder how often Mr. Clarkson has encountered, or heard of, tetanus as a complication of burns in this country? I have no doubt it may occur occasionally but in the course of 8 years' contact with burned people (about 6000 cases) I have not experienced it. I realise that there are likely to be other injuries in the event of an atomic "incident" over this country, and active immunisation of the population might well be worthy of consideration in connection with them; but I question whether we should inflict yet another injection, and the risk of serum sickness, on those who have only burns.

Farnham Royal. LEONARD COLEBROOK.

EXPERIMENTAL GLOMERULONEPHRITIS

SIR,—Heymann and Lund,[1] Solomon et al.,[2] and Pressman et al.,[3] using improved methods, have confirmed the glomerular origin of the antigen that gives rise to nephrotoxic serum. In consequence the observation by us of the nephrotoxic effect of anti-rabbit-stomach serum was unexpected.

We immunised ducks by intraperitoneal administration of antigen prepared from rabbit stomach, and injected intravenously into the rabbit the serum thus obtained. A pathological process ensued which clinically and histologically resembled closely acute and subacute glomerulonephritis in man.

The manifestations of nephritis, which appeared after a latent period averaging six days, were: albuminuria, microscopic hæmaturia, cylindruria, hypertension, water retention, and occasionally anuria. These manifestations developed in the course of a few days; and this sudden onset reminds us of anaphylactic reactions. The animals either recovered or died of uræmia. It seems remarkable that experimentally, as in man, uræmia is preceded by hyposthenuric polyuria.

Necropsy usually revealed a large white kidney; among 12 animals we found only 1 granular kidney. In 3 cases we found multiple bleeding gastric erosions, but peptic ulceration had not developed.

Histological examination showed that in some cases virtually all the glomeruli were affected; and the pathological changes were diffuse. In the glomeruli could be discerned the specific capillary reaction accompanied by local anæmia that characterises the disease in man. The loops, despite occasional extreme dilatation, did not contain red blood-cells. These peculiar empty loops recalled Froehlich's *Plasmablicke*,[4] which is a local anaphylactic phenomenon. In the exudative phase the dilated cavity of the glomerular capsules was filled with albumin; in the proliferative phase the size of glomeruli was almost doubled, owing to endothelial

1. Heymann, W., Lund, H. Z. *Science*, 1948, **108**, 148.
2. Solomon, D. H., Gardella, J. W., Fanger, H., Dethier, F. M., Ferrebee, J. W. *J. exp. Med.* 1949, **90**, 267.
3. Pressman, D., Hill, R. F., Foote, F. W. *Science*, 1949, **109**, 65.
4. Froehlich, A. *Z. Immunforsch.* 1914, **20**, 476.

proliferation. In certain places the loops and capsule adhered; elsewhere half-moon formation appeared.

As a control two rabbits were given two intravenous injections of 20 ml. of normal duck-serum. The animals have been observed for eight weeks, during which no abnormality has become evident.

From these findings we conclude that the glomerulonephritis described is a specific process, the pathogenesis of which is to be found in an antigen-antibody reaction; and that the rabbit stomach contains what may be called "heterotopic antigens," identical with those in the glomeruli. In the duck these heterotopic antigens evoke specific nephrotoxic antibodies.

Our experience does not refute Masugi's [5] theory of the specific origin of nephrotoxic nephritis; and it provides additional evidence of the allergic origin of the disease in man. Our findings do, however, show that not only kidney antigens but also heterotopic antigens can give rise, by an immunological process, to glomerulonephritis.

Further details of this work are to be published in *Acta medica hungarica*.

Medical Department, Szeged University, Hungary.

ARTUR HÁMORI
FERENC OLÁH.

CORONARY DISEASE AND MODERN STRESS

SIR,—Dr. Stewart (Dec. 23) gives the following comparison of occupational groups with regard to death from coronary disease:

Agricultural workers	32
Coalminers below ground	40
Banking and insurance officials	183
Anglican clergy	218
Physicians and surgeons	368

He says that these figures are remarkable and significant. No doubt they are; but what is their significance? He suggests that the differences are proportional to the degree of mental stress in the classes mentioned. Are they not just as likely to be inversely proportional to the amount of physical work done by the classes concerned? At the present time agricultural workers do more work than any of the other classes mentioned. Physicians and surgeons do the least. They rarely even walk. Some clergy and some banking and insurance officials do. If one postulates that physical work is a preventive of coronary-artery disease, then the figures quoted by Dr. Stewart fit in perfectly. This hypothesis would also agree well with Dr. Stewart's statement that members of primitive races are immune but lose their immunity when subjected to civilised life. He says that two main influences are brought to them by civilisation, unfamiliar stress and increased richness of diet. But as Dr. Percy Stocks points out (Feb. 10) there is also a third factor—a decrease in physical effort.

It is also in favour of this hypothesis that the differences in physical work are a known factor, whereas the differences in mental stress are merely a suggestion put forward by Dr. Stewart. I wonder whether the manual workers have as little mental stress as he imagines. When we start weighing other people's mental stress we are apt to fall into error. Does the manual worker as he feverishly turns over the evening paper to see if the second leg of his double has come up in the 4.30 experience more or less stress than the doctor who lies awake at night wondering if he can afford to send his son to his old school? Who knows?

I have put forward one hypothesis which I think fits the facts given us by Dr. Stewart as well or better than his modern-stress theory. There are of course other hypotheses which would fit his facts just as well, but it is not necessary to elaborate them, for my purpose has been to show that the identification of sufferers from coronary disease as the selected victims of modern stress may not be as reasonable as Dr. Stewart suggests.

In an effort to prevent this letter from being entirely destructive, I put forward rather hesitantly some personal speculations.

I think that long periods of hard physical labour continued over a long time are bad for the cardiovascular system, and if carried to the extreme degree will cause serious cardiovascular degeneration. In these cases the coronary arteries tend to be calcified. On the other hand, absence of physical activity tends, I think, to produce degenerative changes in the coronary arteries, and this degeneration shows itself in the formation of atheromatous patches.

It seems to me that hard physical work for relatively short periods may have a protective effect on the coronary arteries. We know that hard physical exercise greatly increases the flow of blood through the coronary arteries, and it may be that this increased flow benefits the condition of the arteries. We know also that hard physical exercise produces considerable movement of the diaphragm, and this seems bound to affect the coronary circulation.

I know well the dangers of putting forward unsubstantiated hypotheses to solve medical problems, and in this case I have taken the risk for two reasons—(1) because we have had little help from the scientific investigators, and (2) in the hope that further investigations may be made. There are two simple investigations which might throw some light on this problem: a comparison of the incidence of coronary-artery disease in scholastic teachers and physical instructors; and a careful investigation of the condition of the coronary arteries in racehorses, particularly a comparison between those which continued in training till they were aged and those which were retired to stud as three-year-olds.

Houston, Renfrewshire. EDGAR RENTOUL.

BACTERIAL VARIANTS PRODUCED WITH CHLORAMPHENICOL

SIR,—In the interesting articles by Dr. Voureka in your issue of Jan. 6 there are three points on which I should like to comment.

(*a*) The only mention Dr. Voureka makes of the type of urine specimen she examined is in connection with case 2, in which "samples of mid-stream urine were plated." She does not say how the other specimens of urine were obtained, or whether her patients were men or women, and one wonders whether this intricate and detailed work may not have been carried out on organisms not representative of those causing the initial infections in the patients' urine; for non-catheter specimens are notoriously misleading.

(*b*) Dr. Voureka stated that, when *Bact. coli* D433 was exposed to chloramphenicol alone, no stable atypical colonies were obtained throughout the experiment. "It was then thought that special conditions in the body might have influenced the production of these forms. . . ." She draws an analogy between the effect *in vitro* on *Bact. coli* D433 exposed to both chloramphenicol and a specific antiserum and the effect obtained when she carried out her painstaking cultural investigation on urines of patients with *Pseudomonas pyocyanea* and coliform infection. This might be an unfortunate analogy, for another worker in the same laboratory, W. H. Hughes,[1] has emphasised that cases with urinary infections develop no agglutinins: he made use of this observation in recommending that vaccine therapy should be followed by chemotherapeutic agents, when a chemotherapeutic agent by itself would not produce a cure. Therefore I assume that Dr. Voureka's cases probably had no agglutinins in their serum to produce an effect analogous to her *in-vitro* experiments on *Bact. coli* D433. Except for

5. Masugi, M. *Beitr. path. Anat.* 1933, 91, 82; *Ibid*, 1934, 92, 429.

1. Hughes, W. H. *Proc. R. Soc. Med.* 1943, 36, 477. Paper (unpublished) read at Summer meeting, 1948, of the Pathological Society of Great Britain and Ireland.