TREATMENT OF GANGRENE

SIR,—The interesting paper by Dr. Lassen and his colleagues (March 23, p. 606) contains one or two points of contention. The authors indicate that they themselves have reservations about the universal applicability of their technique in patients with peripheral vascular ischæmia.

In 4 of the 5 patients described the interval between the onset of ulceration and presentation was almost identical to the interval between presentation and healing. It could be suggested that the treatment therefore had no specific effect, but rather that it had been applied at the nadir of healing and that the course of therapy coincided with the natural resolution of the ulcer. In patient no. 4 the ulcers apparently appeared one week before admission to hospital and took twelve months to heal.

On the question of blood-flow it seems clear from the authors' observations that the induced hypertension was associated with an increase in flow through calf muscle. The relevance of this observation to skin blood-flow in the ischæmic area of the foot is not clear.

The ineffectiveness of vasodilator therapy in these patients is, as Dr. Lassen and his colleagues suggest, a matter of common knowledge. This may be, however, a function of the method of administration of the dilator drug rather than of the ineffectiveness of the drug. If a vasodilator substance is administered and fixed locally in the tissues, systemic hæmodynamic values remain largely unchanged, since the increased flow demand is restricted to fairly small volume of tissue. Indeed, we have shown that foot blood-flow may be strikingly increased for several hours after administration of a vasodilator substance by retrograde intravenous infusion.[1] The technique was originally described by Bier,[2] and revived as a technique for producing local anæsthesia in limbs.[3] Ardill et al.[4] described a similar manœuvre for obtaining vasodilator effects. The contention of Dr. Lassen and his colleagues that " vasodilator therapy of any form . . . is contra-indicated " is therefore an oversimplification of the problem.

From the clinical material presented, we feel that Dr. Lassen and his colleagues are entitled to make only three claims: (1) mineralocorticoids induce hypertension; (2) the treatment regimen relieved the pain associated with some ischæmic ulcers; (3) the regimen was associated with an increase in muscle blood-flow. In our opinion they have advanced little evidence that the observed healing was attributable to the induced hypertension.

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*** This letter has been shown to Dr. Lassen and his colleagues, who write as follows: " We agree that the healing of gangrene in any group of patients could be incidental to the treatment given. What makes us believe that we helped Nature in our cases was the demonstration that systemic (proximal) hypertension increased the distal (post-occlusive) blood-pressure and thereby increased the distal blood-flow in patients with chronic gangrene. The distal blood-pressure was evaluated by injecting histamine intramuscularly and using ^{133}Xe as the blood-flow indicator. Both the thus-measured maximal muscle blood-flow and the externally applied flow-cessation pressure rose during induced systemic hypertension. We have no information on changes in muscle blood-flow per se. Dr. Ledingham and Mr. Schraibman comment on retrograde intravenous injection of vasodilator drugs, but their observed increase in foot blood-flow does not necessarily mean that circulation in gangrenous skin areas also increased. We would like to know if ischæmic pain disappeared during the infusion. Acutely induced hypertension using systemic infusion of vasoconstrictor drugs (angiotensin or noradrenaline) regularly abolishes ischæmic pain within 1–2 minutes.[1,2] This striking analgesic action suggests that the concomitant rise in distal pressure allowed flow, and thus oxygenation, to increase in the critical skin areas."—ED. L.

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TRANSMISSION OF KURU TO MICE

SIR,—Kuru is a disease limited to the Fore linguistic group in the Eastern Highlands of New Guinea. Although from native memory it seems to have been present for some decades, its modern study dates from the description given by Gajdusek and Zigas,[3] who believed it to be genetic in origin, and there is no doubt that a strong genetic factor does govern susceptibility. However, Hadlow[4] drew attention to the pathological similarities between kuru and scrapie and made the seminal suggestion that efforts should be made to transmit kuru to laboratory primates. Gajdusek et al.[5] made the attempt in a wide range of animals and were successful only with the chimpanzee, in which many of the pathological changes are qualitatively similar to those of scrapie.[6] Encouraged, however, by the resemblance between the two diseases, further attempts have been made to establish kuru in the mouse starting from formalin-fixed human kuru brain and fresh second-passage chimpanzee brain (obtained through the kindness of Dr. J. D. Mathews of the Kuru Research Centre, Okapa, New Guinea, and Dr. D. C. Gajdusek of the National Institutes of Health, respectively).

10^{-1} suspensions of brain material in sterile isotonic saline solution (' Polyfusor ', Boots) were made by grinding in an ' M.S.E.' macerator. (The formalin-fixed material was subjected to a preliminary 48-hour wash in running water.) The suspension was clarified by spinning at 1500 *g.* for 10 minutes and then 2000 *g.* for 15 minutes. 0·05 ml. of supernate was injected intracerebrally into Swiss mice (reared in this laboratory). Passage was carried out after 23 days and repeated twice at intervals of 45 days. The last recipients were given 200 rads whole-body X-irradiation 18 hours before inoculation, the same dose after 13 days, twice more at monthly intervals, and again after a further 2 months, so that altogether 1000 rads were received over $4^1/_2$ months.

While similar experiments in which animals were irradiated without preliminary passage or passaged without X-irradiation have not given positive results to date, those animals which received the treatment outlined above developed clinical signs of scrapie in the case of the chimpanzee material. They were hunched with ruffled hair and stiff tails, and were easily pushed over. At necropsy the bladder was small and internal organs appeared normal. Brain and spinal cord, part of which was kept sterile for further passage, was fixed in formalin-ammonium-bromide, and stained by Cajal's method for astrocytes. Typical scrapie changes were seen: hypertrophy of astrocytes and microvacuolation. These changes extended throughout the brain and spinal cord. Similar pathological changes were present in the mice passaged with human kuru, but their clinical signs were much less clear. They tended to stand still for long periods (" drowsy state ") and were rather slow. Passages from these two groups of animals (all six of which in each case developed scrapie) are not yet completed.

Any experiments in which scrapie appears unexpectedly, if carried out in an institution which works with the disease, must be regarded with considerable caution,[7,8] and acceptance of the significance of such findings must necessarily wait upon independent confirmation. The procedure of rapid passage followed by X-irradiation of the final recipient is calculated to enhance the effect of even a small amount of

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contaminant, and further experiments are in hand to test what (known) degrees of contamination could give positive results, since such information does not seem to be generally available. Meanwhile the results are presented in the hope that they will be subjected to independent testing in units in which scrapie material is not (knowingly) handled.

I should like to thank Miss Greta Joyce for assistance in all stages of this work.

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DECREASED PROPERDIN ACTIVITY IN SWISS-TYPE LYMPHOPENIC AGAMMAGLOBULINÆMIA

SIR,—Several workers [1 2] have reported normal serum "properdin" activity in patients with agammaglobulinæmia (A.G.G.). Recent splitting of "agammaglobulinæmia" into several discrete syndromes [3 4] has led us to re-explore the serum-concentrations of this factor in a small group of patients with different forms of A.G.G.

Properdin, measured as outlined by Todd et al.,[5] represents an activity which is removed from serum by absorption with zymosan at 15–17°C; this is necessary to allow zymosan-induced inactivation of the classical third component of complement at higher temperatures.[6] Lately properdin has been characterised as a 5S β-globulin of 223,000 molecular weight which lacks immunoglobulin antigenic determinants and the complement component activities C'1q, C'1r, C'1s, C,4, and C'2.[7] Results of the present study are shown in the accompanying table. In confirmation of earlier investigations, normal

PROPERDIN, C'1q, AND HÆMOLYTIC C' ACTIVITIES IN AGAMMAGLOBULINÆMIA (A.G.G.)

Disease	Properdin*	C'1q†	$C'H_{50}$‡
Bruton-type A.G.G.	6	32	41
,,	6–8	32	33
,,	8	32	56
,,	8	128	38
Late-occurring A.G.G.	6–8	64	44
Swiss-type A.G.G.	<1	4	37
,,	3	8	26
Normal	6–8	128	65
,,	6–8	128	56
,,	8	128	60
,,	8	128	60
Childhood normal	6–8	64–256	33–65

* Units per ml.[5] † Agglutination units per 0·1 ml.[8] ‡ Units per ml.[9]

serum-properdin activity was observed in five patients with Bruton and late-occurring types of A.G.G., despite their extreme deficiency of immunoglobulins. However, serum-properdin concentrations were strikingly decreased in two patients with lymphopenic A.G.G. of the Swiss type.

In recent studies of the complement system in several A.G.G. syndromes, a somewhat similar alteration of the C'1q subcomponent of the C'1 macromolecule was observed: C'1q serum-titres were strikingly reduced in Swiss-type A.G.G. and only moderately reduced in the other A.G.G. syndromes, as shown by Gewurz et al.[8] and in the table. Normal or raised titres of complement components other than C'1[10] suggested that the C'1q abnormality derived from decreased synthesis. In-vitro investigations relating C'1 formation to the intestine,[11] and the regularly occurring intestinal damage in patients with A.G.G.,[12] particularly pronounced in Swiss-type A.G.G.,[13] suggested to us that lymphointestinal damage or abnormality might be the basis of the lowered C'1q titres; perhaps lymphointestinal alteration also relates to the decreased properdin activity in patients with Swiss-type A.G.G.

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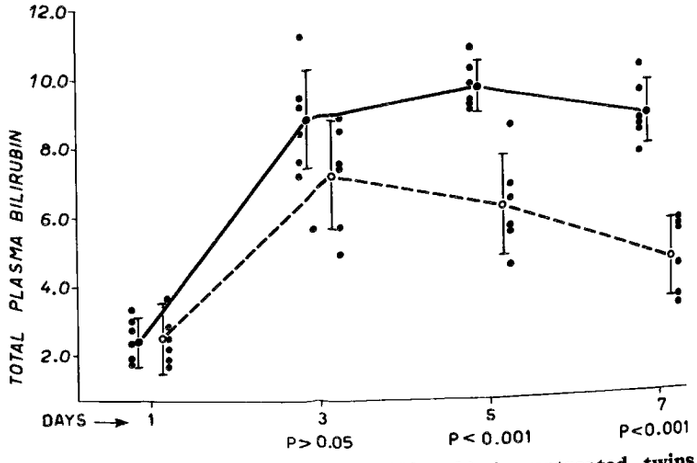
STIMULATING BILIRUBIN CONJUGATION

SIR,—It has been shown that newborn animals of some species do not develop hyperbilirubinæmia at birth and can handle bilirubin loads better than the low level of specific transferase would suggest.[14–16] This raises the question whether the low level of transferase explains human neonatal jaundice, even though it has been proved that diethylnicotinamide (a substance stimulating bilirubin-conjugating activity in liver slices of neonatal rabbits [17]) is effective in lowering bilirubin levels in newborn infants.[18] Uridine-diphosphate-glucose (U.D.P.G., 'Toxepase', Robin S.p.A.,



Plasma-bilirubin levels (mg. per 100 ml.) in untreated twins (●——●) and twins given U.D.P.G., 2·5 mg. per kg. per day (○– – –○).

Milan, Italy) treatment stimulates bilirubin-conjugating activity in mice infected with hepatitis,[19] and induces a lower bilirubin peak in the adult man after an intravenous bilirubin load.[20]

These results prompted us to investigate the effect of U.D.P.G. in human neonatal hyperbilirubinæmia. Considering the wide physiological scattering of bilirubin levels in newborn infants, twins only were investigated (all with Rh and blood groups compatible with their mothers). In most instances (6 of 9 pairs) 1 twin was treated and the other kept as a control. In 3 instances no treatment was given to either twin, to check similarity of the postnatal bilirubin serum-levels in twins. U.D.P.G. was administered intramuscularly, 2·5 mg. per kg., once a day from the first to the fifth day of life. Blood-samples

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