Letters to the Editor should not exceed 500 words.

Neuroparalytic Accidents with Poliovaccines

SIR,—Your leading article, "Neuroparalytic Accidents with Poliovaccines" (1 August, p. 264) refers to the need for work on "neuroallergy." We believe that the aetiology of such phenomena and perhaps also central nervous system (C.N.S.) disease in infections with poliovirus and arboviruses may lie in a different type of antigen-antibody reaction in the C.N.S.

Some virus infections (e.g., herpes simplex, adenoviruses in tonsils) persist although the host has circulating antibody. Such latent infections are often difficult to demonstrate because when infected tissue is ground up the antibody in it neutralizes the freed virus. Thus the failure to isolate viruses from cases of "neuroallergy" does not necessarily prove their absence.

We have recovered viruses of the Russian spring-summer (R.S.S.) complex from liver, muscle, and C.N.S. tissues of monkeys and patients with homologous circulating antibody. Our studies of patients with R.S.S.-complex infections have shown that when antibody is present in the blood it may also be found in the cerebrospinal fluid (C.S.F.) and therefore in the tissue fluids of the C.N.S., but that its time of appearance there varies from very soon after it is detectable in the blood to at least two to three weeks later.

Gleiser *et al.*¹ and Berge *et al.*² showed in animals that a virus infection of the C.N.S. caused a much more vigorous inflammatory response in the C.N.S. if homologous antibody was administered at a critical time during the infection. Experiments we have made with another virus tend to confirm this. Seamer *et al.*³ showed that mice given virus subcutaneously before intracerebral infection 1-3 days later died earlier than those given intracerebral virus only. The earlier dose of subcutaneous virus probably leads to a more rapid antibody response during the course of the C.N.S. infection.

Virus appears to reach the C.N.S. during viraemia and serum antibody becomes detectable at the time when vigorous virus multiplication is occurring in the C.N.S. If the antibody reaches the C.N.S. at some critical time in relation to virus multiplication antigen-antibody reactions occur and may be associated with an inflammatory response. This

may present as an encephalomyelitis, but might also be responsible for initiating long-term changes such as demyelination. Conditions which cause antibody to reach the C.N.S. earlier than normal may increase the risk—e.g., cold and increased blood-CO₂ tension increase the permeability of the "blood-brain barrier."⁴ Concurrent disease may have a similar effect: when tick-borne fever occurs concurrently with louping ill in sheep there is an increased probability of encephalitis due to the latter.⁵

Clinical encephalitis or poliomyelitis occurs just when serum antibody is becoming detectable, and it may be significant that the early lesions are perivascular. Clinical disease is rare in relation to infection rates and perhaps occurs only in individuals in whom antibody reaches the C.N.S. at the critical stage of virus multiplication. Where the C.N.S. infection remains latent and antibody arrives late demyelinating lesions may be engendered. C.N.S. diseases following live-virus vaccination or the virus exanthemata can be explained along similar lines. Their greater rarity may be because virus less often reaches the C.N.S.

The mechanism whereby antibody causes inflammation is not clear. Possibly the antigen-antibody reactions lead to immediate hypersensitivity or to an Arthus-type phenomenon, or delayed hypersensitivity with its similar timing may be the basis.

The object of this letter is to draw attention to a hypothesis more susceptible, perhaps, to clinical and laboratory investigation than "neuroallergy."—We are, etc.,

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Leukaemia and Phenylbutazone

SIR,—Sixteen cases of acute leukaemia occurring in association with phenylbutazone therapy have been reported. The latest report (27 June, p. 1707) by Dr. G. F. Thorp was of a 56-year-old woman with a painful left ankle who was given 300 mg. daily for 17 days (no haematological assessment prior to therapy). Two weeks after treatment the patient developed bruising, and investigation then revealed the diagnosis of acute leukaemia. Locomotor symptoms are a frequent accompaniment of acute leukaemia. Silver-

stein and Kelly¹ reviewed 450 patients and found such symptoms predominating in 7.7%. Single-joint involvement occurred in 6% and the lower extremities were involved most commonly. This was probably the underlying factor in the case reported and phenylbutazone therapy was coincidental.

The following is an additional case:

A 58-year-old man injured his back 35 years ago. In November 1962 he had an exacerbation of back pain treated with phenylbutazone, 100 mg., four times daily for seven days. In

March 1964 he had a further episode of back pain radiating to the right hip and knee and accompanied by paraesthesiae over the right second and third toes. An x-ray showed degenerative disk disease with posterior disk protrusion at L4/L5 level. The patient was given 100 mg. of phenylbutazone four times daily for seven days. Two weeks later the patient developed spontaneous bruising, and upon subsequent investigation a diagnosis of acute myeloid leukaemia was made.

Phenylbutazone has also been reported to produce thrombocytopenic purpura, agranulocytosis, leukaemoid reaction, and aplastic anaemia. The latter is a preleukaemic condition, and it is reasonable to assume that an agent with a broad spectrum of toxicity to the bone-marrow could also induce leukaemia. Against this theoretical possibility one must balance the coincidental use of phenylbutazone therapy for symptoms of an undiagnosed leukaemia, coincident disease, or pre-existing symptoms aggravated by haemorrhage or infiltration. Perhaps all cases with locomotor symptoms requiring more than rest, heat, and salicylates should have a pretreatment smear and differential, haemoglobin, and white count.

Court-Brown and Doll² demonstrated the leukaemic effect of x-ray therapy of the spinal column in patients with ankylosing spondylitis. Since that time phenylbutazone therapy has been used extensively for this condition. Has the incidence of leukaemia changed? These patients may offer a yardstick for the leukaemogenicity of phenylbutazone.—I am, etc.,

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Anticoagulants for Strokes

SIR,—In addition to the use of hypotensive agents Dr. John Marshall recommends anticoagulants in the management of "little strokes" (1 August, p. 304). May I suggest that the theory behind this procedure is no less questionable than its practice is precarious.

It is all very well to maintain that hypertensive cerebrovascular catastrophe tends to follow an exclusive pattern either of infarction or haemorrhage in any individual. But it is a little difficult to understand why a single minor thrombosis should offer any guarantee against subsequent bleeding. And if the theory should fail some patient may well succumb abruptly with a nasty headache.

Recorded surveys and personal experience suggest that this is all too likely to happen. And, in fact, in order to see the danger fully illustrated one has to look no further than the figures given in another of Dr. Marshall's own papers. Earlier this year¹ he described the results of induced hypotension in patients who had "recovered from a cerebrovascular accident judged on clinical grounds to have been due to a non-embolic cerebral infar-