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-

tion." Of 16 patients (12 treated and 4 controls) six, if not seven, had died from haemorrhage, and only three from coronary or cerebral thromboses.

One may well wonder how anticoagulant therapy could have helped those who were to suffer fatal bleeding. Indeed it is not unreasonable to suppose that the treatment that he now advocates might have added substantially to the number of those who died in this way. Medicine, like war, often presents "an option of difficulties." Before adding to them, in the complex matter of cerebrovascular disease, it might be as well to find out a little more about some of those problems that are already sufficiently evident.—I am, etc.,

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REFERENCE

- ¹ Marshall, J., *Lancet*, 1964, 1, 10.

M.O.H.s may find it difficult to provide several weeks' compensation for food-handlers who are "contacts or potentially infected" if they follow your advice to exclude them from work. Do you mean also that the housewife with a case in the household should do no cooking? Exclusion from school or food-handling is wise for a contact with any illness during the incubation period, and it should cover a period without symptoms which sometimes intervenes before jaundice or dark urine appears.

There is need for an authoritative and succinct guide to measures for preventing the spread of infection in households. G.P.s and health visitors and public health inspectors could use it to give useful—and the same—advice to worried housewives, who are usually ready to do the right thing.—I am, etc.,

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ALLAN M. MCFARLAN.

Treatment of Rheumatic Fever

SIR,—In your recently published trial where phenylbutazone was compared with aspirin (Drs. G. Will and W. R. Murdoch, 1 August, p. 281), the parameters used were fever, sedimentation rate, and joint pain and swelling. In a Further Report of the Rheumatic Fever Committee, July 1957, it is pointed out that these are the weakest diagnostic criteria for rheumatic fever.¹ They occur in many other conditions where phenylbutazone is already established as therapeutically useful. It is not unexpected, therefore, that phenylbutazone should provide clinical improvement in these acute manifestations when they occur in rheumatic fever. It would be interesting to know if the incidence of more specific rheumatic manifestations such as nodules or chorea was different in the two groups studied, and also, if possible, whether the severity or duration of carditis was affected in any way.

The occurrence of fresh signs and symptoms reported in the trial in the aspirin-treated cases may well be due to fluctuating blood-salicylate levels, and it would be necessary to know that this level was adequate at the time of the flare before ruling the drug as less efficient than phenylbutazone. Drs. Gerhard Levy and L. F. Hollister (1 August, p. 286) point out that the size and frequency of the maintenance dose of salicylates could be determined accurately only if the rate of elimination is known. Phenylbutazone, on the other hand, rapidly reaches a plateau level in the blood which is maintained for at least 24 hours,² and this smoother effect may, in fact, be the only difference between the two groups.

It is possible that phenylbutazone may be of some use in the treatment of prolonged rheumatic activity or persistent pericardial pain where these have failed to respond to aspirin and where some authorities would now use steroid. Fluid retention, although this was not reported in any of the phenylbutazone-treated cases, does occur with this drug, and must surely be contraindicated where cardiac failure is present.—I am, etc.,

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REFERENCES

- ¹ Royal College of Physicians of London. Further Report of Rheumatic Fever Committee, July 1957, p. 9.
² Hart, F. D., and Burley, D., *Brit. med. J.*, 1959, 1, 1087.

Lung-function Tests

SIR,—I am grateful to Dr. B. M. Wright (18 July, p. 190) for his support and I am pleased to know he feels the term "indirect M.B.C." no longer fulfils any useful function. There is already such a profusion of terms and abbreviations in respiratory physiology that it is essential to avoid duplication.

Having made a plea for the correct use of words (27 June, p. 1708), I find I have erred to a limited extent in this respect myself and I acknowledge Dr. Wright's mild strictures. Of course ventilatory capacity depends on many factors of which airway resistance is only one. May I plead some extenuation in that the original clinical trial conducted by Drs. Kennedy and Thursby Pelham was carried out in subjects with obstructive airway disease, and I think Dr. Wright will agree that the only method of objectively measuring a change in airway obstruction in a manner appropriate to their study necessitates the measurement of airway resistance.

Finally, I agree that the measurement of airway resistance in poliomyelitis and spondylitis is not likely to be helpful, but this does not apply to "unilateral pneumonectomy," as so many subjects who have had this operation also have obstructive airway disease. May I add in passing that I trust Dr. Wright's use of the term "unilateral pneumonectomy" does not lead the neophyte into believing there is a bilateral procedure!—I am, etc.,

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W. K. C. MORGAN.

SIR,—In his letter (27 June, p. 1708) Dr. W. K. C. Morgan questions the objectivity and validity of the indirect M.B.C. test for the assessment of the ventilatory capacity. He then asks, "Why not use the direct measurement?"

When the maximum breathing capacity is measured directly with an individual blowing in and out of the spirometer this index is very dependent on the co-operation of both the individual and the personality of the observer, and this direct measure is also subject to other variables, such as the rate of breathing.¹ However, the indirect M.B.C. is less dependent on these variables and hence is more objective. In the indirect M.B.C. test the rate of breathing is theoretically standardized, and the test requires very little in the way of patient co-operation. It is, of course, essential that the individual takes a full inspiration, and, provided this is done, the test is highly reproducible if recorded graphically on a fast-revolving kymograph, when invalid spiograms can be easily detected and rejected.² It is for the above reasons that the indirect M.B.C. or the F.E.V. has largely replaced the direct M.B.C. over the past 10 years.

Of course both the F.E.V. and the indirect M.B.C. are derived from the same spiogram. The F.E.V._{0.75} or the F.E.V._{0.1} are expressed in litres whilst the indirect M.B.C. is expressed in litres per minute, the only difference being a correction factor. We prefer to express our measure of the ventilatory capacity in litres per minute and hence use the term indirect M.B.C., which is the same unit used for other dynamic measures such as resting ventilation and exercise ventilation.

Dr. Morgan suggests other tests might be more appropriate for the assessment of change

Infectious Hepatitis

SIR,—Your leader (11 July, p. 69) stressed the difficulty of controlling outbreaks of infectious hepatitis. You recommended careful hand-washing before meals and after defaecation. Why not also improvements in W.C. hygiene (your leader, 13 June, p. 1523), and paper towels for drying hands and food utensils, and the proper use of an effective disinfectant?

Microbiologists in their laboratories and surgeons in the operating theatre use disinfectants on their hands as well as thorough washing. I hope we shall be told what Aberdonians did when they MacQueened their hands to rid them of typhoid bacilli. One press photograph showed a bowl of disinfectant on a shop counter. In the home a bowl or bottle of disinfectant beside the hand-basin would reinforce the plea to wash hands well.

Mothers with an infectious child in the home are prompted by advertisements to buy a disinfectant from the grocer and pour it down the drain. They should get better advice about the right disinfectant and the right way to use it. For poliovirus some virologists have suggested to me a detergent-iodine complex. This might be active against hepatitis virus and other intestinal viruses as well as bacteria. Active immunization may be useful in controlling infectious hepatitis when a vaccine is available, but it will not be practicable against all the increasing horde of intestinal pathogens nor much use in an epidemic of a disease with a short incubation period. Passive immunization, as you noted, has its limitations. There is therefore every reason to devise means to block the routes from intestine to mouth.

M.O.H.s will welcome the suggestion (Dr. P. W. Bothwell, *Brit. med. J.*, 20 June, p. 1634) that hepatitis virus might be transmitted in tinned foods infected outside their area, but they had better heed your injunction that the probability is that the source was an infectious food-handler. Viruses do not grow in the absence of living cells and infective doses in foods are likely to be irregularly distributed. Much shoe-leather epidemiology is needed to incriminate foods as the vehicle of such infections, and it is rarely possible to obtain laboratory confirmation, so that sceptics refuse to accept the field-worker's conclusion.