CLIOQUINOL CAUSES ATAXIA IN RATS

SIR,—Repeated oral administration of clioquinol to dogs,[1,2] cats,[2] and a monkey[3] caused neuropathy similar to subacute myelo-optico-neuropathy (SMON), strongly suggesting that clioquinol is the cause of the disease. By contrast, rats and mice, the usual animals for toxicity testing, did not show such neurological effects. The reason was thought to lie in the fast metabolism of these animals, which meant that high plasma levels of clioquinol were hard to maintain. On analysis of mesenteric venous plasma we find that in rats much of the clioquinol is conjugated with glucuronic acid during passage through the intestinal wall,[4] while the rest is metabolised mainly in the liver. We have therefore studied routes of administration other than oral.

Clioquinol was ground with polysorbate 80 and mixed with water in a mortar to become a fine suspension, which was intraperitoneally administered to rats. On injection of less than 200 mg/kg, the plasma concentration of clioquinol decreased rapidly. With 400 mg/kg, however, the concentration reached about 20 μg/ml and fell slowly indicating prolonged retention of clioquinol in the abdominal cavity.

When rats were injected intraperitoneally with 400 mg/kg clioquinol daily, they became ataxic within a week, first in the hind legs then in the front legs; neck movement was almost unchanged. The picture resembled that of SMON; further, during administration of clioquinol, the rats had the green faeces and sometimes the green urine seen in SMON. Physical and pathological examinations are in progress.

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PLATELET AGGREGATION IN PATIENTS USING FEVERFEW FOR MIGRAINE

SIR,—The herb feverfew is becoming increasingly popular as a prophylactic treatment for migraine. Collier et al.[5] found that a phosphate buffer extract of feverfew leaves caused the inhibition of prostaglandin (PG) production (peak inhibition 58% ± 5·5 SEM with 5 μl/ml) but this extract did not inhibit cyclo-oxygenation of arachidonic acid. Makhjeja and Bailey[6] found that microlite quantities of phosphate buffer extracts of leaves completely inhibited aggregation of human platelets produced by ADP, collagen, or thrombin, but not that caused by arachidonic acid. Their extract did not block the cyclo-oxygenase enzyme either but completely inhibited human phospholipase A_2 activity in vitro. They concluded that the anti-platelet activities of feverfew were due to phospholipase inhibition and suggested that this also explained the efficacy of the plant in migraine, arthritis, and asthma. Although of pharmacological interest these observations may not be relevant to migraine patients taking feverfew since we have shown that their platelets readily aggregate to ADP and thrombin.

Ten patients who had taken feverfew for from 3·5 to 8 years were invited to donate a sample of blood for standard platelet aggregation studies, and dose-aggregatory response curves to ADP, thrombin, serotonin, and the stable PG endoperoxide 11α,9α-epoxymethanoprostaglandin H_2 (U46619, kindly provided by Dr J. Pike, Upjohn Company, Kalamazoo, Michigan) were obtained. The platelets of all patients on feverfew aggregated characteristically to ADP and thrombin and these responses seemed indistinguishable from those of platelets from four control patients who had stopped taking feverfew at least 6 months before attendance at the clinic. The threshold for initiating the aggregatory response to U46619 appeared to be increased in several patients taking feverfew especially after 4 or more years' continuous daily consumption. Aggregation of platelets in response to serotonin was also greatly attenuated in plasma of feverfew takers and only occurred when high doses were used.

It seems likely therefore that the results from the addition of aqueous extracts of feverfew to healthy platelets found by Makheja and Bailey are not applicable to the clinical situation. Whether or not feverfew possesses anti-serotonin activity that would account for its apparent efficacy in migraine remains to be established.

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MATHEMATICS AND MEASLES

SIR,—In your editorial of July 31 (p. 248) you discussed the work of Fine and Clarkson which showed that "the transmission parameter [of measles] has not fallen in the years since the introduction of measles vaccine, suggesting that the total number of susceptible people in the country has not changed despite immunisation programme". In Hamburg we investigated the influence of measles immunistion on children entering school.[1] Of 19 661 children entering school in 1968 (only 1% being immunised with killed measles vaccine) the parents claimed that 59% had already had measles. Of 12 793 children entering school in 1979 37% had been immunised against measles but only 34% of the total had a history of measles. Thus the transmission of measles virus among the immunised cohort of children was evidently decreased.

The conclusion of Roden and Heath (cited in the editorial)—that the proportion immune among older children has probably fallen as a result of the immunisation programme—is supported by our data from Hamburg. We found this trend in a comparative study of the measles hospital admissions rate in 1960–73 and 1974–80 (Allerdist H, Erdmann C, Ehrengut W, unpublished). In the former period, by the age of 5 years 75% of the patients had already had measles; in the latter period, this percentage was reached only by the age of 7 years. At the same time the hospital admissions per year dropped from 221 measles patients (1960–73) to 116 (1974–80). In relation to the total of Hamburg children under 11 years, the ratio was 1 case per 1186 in 1960–73 versus 1 case per 1836 in 1973–80. Thus the benefits of measles immunisation are quite clear.

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HEPATITIS B INFECTION IN HAEMOPHILIA

SIR,—We have just completed a series of studies similar to the one reported by Dr Rickard and colleagues from Sydney (July 17, p. 146). During the period 1971–79 we assessed hepatitis B infection in 56 patients with haemophilia A by repeated measurements of serum levels of HBsAg, anti-HBs, and anti-HBc. We find that the incidence of hepatitis B infection is approximately 8% per annum—identical to that found by Dr Rickard in his patients in Sydney. Furthermore, as in the Australian patients, the highest incidence was in severe haemophiliacs, who used large amounts of blood products. By 1979, 88% of our severe haemophiliacs had evidence of previous hepatitis B infection. We have not been able to demonstrate any reduction in the frequency of infection during the period of our survey. Both Dr Rickard's study and ours have

1. Tateishi J, Ikeda H, Saito A, Kuroda S, Otsuki S. Myeloneuropathy in dogs induced by iodoxyquinoline. *Neurology* 1972; **22:** 702–09.
2. Tateishi J, Kuroda S, Saito A, Otsuki S. Experimental myelo-optic neuropathy induced by chioquinol. *Acta Neuropath* 1973; **24:** 304–20.
3. Tateishi J, Saito A, Kuroda S, Otsuki S. Pathological findings of a monkey orally administered with oxyquinoline. *Med Biol* 1971; **83:** 313–15.
4. Koraki H, Yamamura Y, Tanimura Y, Tamura Z. Absorption and metabolism of chinoform in the rat intestine. Annual Report of SMON Research Commission 1981; 295–99.
5. Collier HOJ, Butt NM, McDonald-Gibson WJ, Saeed SA. Extract of feverfew inhibits prostaglandin biosynthesis. *Lancet* 1980; ii: 922.
6. Makheja AN, Bailey JM. The active principle in feverfew. *Lancet* 1981; ii: 1054.

1. Mai U, Ehrengut W. Impfschutz und Kinderkrankheiten in der Anamnese von Hamburger Schulanfängern. *Hamb Ärztebl* 1981; **35:** 40–42.

therefore demonstrated that haemophiliacs are still at high risk of hepatitis B infection despite the introduction of screening techniques by the Blood Transfusion Service to detect HBsAg in individual donor plasmas. It is possible that more sensitive methods will reduce the risk in future.

These results are of great interest because both the Sydney and Edinburgh patients have been treated predominantly with cryoprecipitate prepared from individual voluntary blood donations. They might therefore be expected to have a lower incidence of hepatitis B infection than haemophiliacs who have received commercial factor VIII concentrates prepared from large plasma pools. The very high prevalence of hepatitis B markers in our patients with severe haemophilia suggests that the use of cryoprecipitate instead of factor VIII concentrates does not protect against infection. Prospects for haemophiliacs in this regard, however, must now be brighter with the potential for immunising patients against hepatitis B. Furthermore, if true hepatitis-free factor VIII concentrates become generally available, then protection against not only hepatitis B but also, non-A, non-B viruses may become a reality.

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ACETYLCHOLINE RECEPTOR ANTIBODY TESTS BY POST

SIR,—The acetylcholine receptor (AChR) antibody test has greatly assisted the investigation of patients with myasthenia gravis. However, in most countries the test is available in only a few laboratories.

To try and overcome the problems of storage and dispatch of frozen or refrigerated samples to such specialised laboratories we have tested the stability of AChR antibodies in blood samples dried on paper.

Antibody dried on paper had enhanced heat stability (half-life 12 days compared with 12 h in liquid samples at 60°C). At room temperature the antibody is stable for at least 2 weeks. The antibody can be readily eluted from paper which permits the assay to be done with the same sensitivity and reproducibility as for liquid serum samples. These results suggest that the assay can be done on a few drops of whole blood, dropped onto paper and posted to a specialised laboratory.

This method of storage and dispatch of blood samples may be applicable to other antibody tests, making complex tests available to many areas of the world lacking local specialised laboratory services.

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Commentary from Westminster

Think Tank's Thoughts on the Welfare State

THE search by the Social Services Secretary, Mr Norman Fowler, for a way out of the protracted and bitter dispute over pay in the National Health Service has been made no easier this week by confirmation that some powerful elements of the Government are keen to abolish the N.H.S. altogether. The health unions, the T.U.C., and the Labour Party, already locked in combat with the Government, have been further committed to confrontation by news of a study from the Government's Central Policy Review Staff, the so-called think tank. This study, circulated to Cabinet Ministers and then leaked to the Press by one of them, explores possible routes towards a drastic reduction in public spending. In effect it considers how the Welfare State might be dismantled by the Government. Unless that is achieved, says the report, over half of Britain's gross domestic product will go on public spending each year for the forseeable future—and that would only just keep the machine ticking over weakly, as it is now.

The N.H.S., the C.P.R.S. ventures, would be phased out fairly rapidly, and individuals would insure themselves for treatment privately. A compulsory minimum level of insurance could be introduced, to prevent people under-insuring. "Hotel" fees for a stay in hospital, fees for visiting a doctor, and much higher prescription charges combined with fewer exemptions are also mooted in the C.P.R.S.'s grand design. More than a third of public spending on health would thus be saved.

The study is nothing if not radical. It proposes, for instance, that all higher education should cease to be state-funded and that just 300 000 students a year would get state scholarships; all other students would have to find from their own resources the probable £12 000 cost of a three-year course. The Government would be ready to lend aspiring students the cost of their education—at the market rate of interest, naturally.

The future set out for the N.H.S. is exactly the future which Mr Fowler has been at great pains to reject since he took office. He shelved similar suggestions made by the Department's own Working Party on Alternative Finances for the N.H.S. He told the Social Services Committee of the Commons that this was "not a road down which the Government intends to go". It is not surprising, then, that the Cabinet saw a small-scale revolt when the Chancellor, Sir Geoffrey Howe, proposed a detailed Cabinet examination of the C.P.R.S. report. All the "wet" Ministers insisted that the study was so misconceived as to be not worth discussing. Blocked, but not defeated, Sir Geoffrey is now mulling the matter over. He is not the C.P.R.S.'s only champion in the Cabinet. The Prime Minister herself, Sir Keith Joseph, (Secretary for Industry), and the former Social Services Secretary Mr Patrick Jenkin are among those who insist that the Government's long-term success hinges on bigger spending cuts than anything so far contemplated.

Soon after the C.P.R.S. study was leaked, and two weeks after the crucial Cabinet meeting, the Treasury Secretary, Mr Leon Brittan, returned to the theme. In a speech which had plainly been discussed with Sir Geoffrey, Mr Brittan pointed out that the Government could offer the voters no hope of a sustained tax-cutting programme (on which platform it was, after all, elected in 1979) unless the growth of public spending were greatly slowed down: "Radical options have not been ruled out. The whole area of Government expenditure has to be re-examined to see if we can identify ways in which we might reverse the past inexorable rise in public expenditure". Mr Brittan criticised those who refuse to face uncomfortable facts.

The Social Services Secretary, it appears, belongs to that category. The day after Mr Brittan spoke, Mr Fowler told a symposium at the Office of Health Economics that he wanted to "take this opportunity to state firmly once more this Government's commitment to the N.H.S". He repeated his promise to Parliament last July that the Government has no plans to change the present system of financing the N.H.S.

An internecine ideological battle is now raging in the Cabinet. On one hand the wets, or traditionalists, say they