Aetiology of Multiple Sclerosis

SIR,—By using a new method, recently referred to in your columns¹ by Sir Macfarlane Burnet, we find that suspected idiopathic autoimmune disorders can be classified by statistical criteria into two categories. This division also corresponds, interestingly enough, to a fundamental anatomical distinction regarding the location of the target tissue.

In both categories it appears^{2,3} that the disease process is initiated in genetic carriers by a small number (from 1 to, perhaps, at least 12) of specific random events, the average rate of which is effectively constant in a given genotype, and in normal environments throughout post-natal life. Following Burnet⁴ we have suggested that these "random initiating events" are a form of somatic gene mutation in lymphoid stem cells, and that they trigger-off the growth of "forbidden clones." When such a disease affects both sexes we find the average rate of a specific initiating event in carrier females is either the same as or double that in carrier males, and we have so far found no significant departures from this "rule." An interval or "latent period" intervenes between the last random initiating event and the onset of symptoms or signs. It is here that the statistical distinction between the two classes of spontaneous autoimmunity is manifested.

The duration of the latent period is evidently governed, in part, by an endogenous defence mechanism directed against forbidden clones, and this is vulnerable to certain infective agents, certain drugs, and to mental stress.^{5,6-7} In one class of autoimmunity (inflammatory polyarthritis and systemic lupus erythematosus are classical examples), where the primary pathogen is probably a cell-bound (lymphocytic) autoantibody, defence is twice as efficient, on the average, in females as in males. For a given environment the average latent period in females is twice as long as in males.⁸ Defence is probably mediated through immunoglobulins,^{2,6-7} and in this class of disease gross abnormalities in these plasma proteins (for example, hypergammaglobulinaemia, rheumatoid factor, anti-nuclear factor) are common.

In the other class of suspected autoimmunity (multiple sclerosis, some peripheral neuropathies, and psoriasis are typical examples) the sex- and age-distributions show that the average latent period, in a given environment, is the same in males and females. We conclude that there is no sex-differential in the efficiency of the related endogenous defence mechanism. Furthermore, the target tissues (for example, central and peripheral nervous systems, and epidermis) are located behind a blood-tissue barrier and they are not normally infiltrated by small lymphocytes. There are various indications⁹ that the primary pathogen, or autoantibody, in these diseases is humoral (in some instances, at least, it appears to migrate with the α_2 -globulin fraction) and that it can diffuse through blood-tissue barriers. Disturbances in the immunoglobulins are generally inconspicuous in this class of disease—as Wright *et al.*⁸ confirm.

We therefore propose, in contradiction with your leader (20 February, p. 466), that multiple sclerosis may prove to be a

disturbed-tolerance autoimmune disease in which the primary pathogen is a humoral (non-immunoglobulin) autoantibody.—We are, etc.,

P. R. J. BURCH.
R. G. BURWELL.
N. R. ROWELL.

The University of Leeds,
The General Infirmary,
Leeds 1.

REFERENCES

- 1 Burnet, F. M., *Brit. med. J.*, 1965, 1, 338.
- 2 Burch, P. R. J., *Lancet*, 1963, 1, 1253.
- 3 Burch, P. R. J., *Brit. J. Psychiat.*, 1964, 110, 825.
- 4 Burnet, F. M., *The Clonal Selection Theory of Acquired Immunity*, 1959. Cambridge University Press, London.
- 5 Burch, P. R. J., and Rowell, N. R., *Lancet*, 1963, 2, 507.
- 6 ———, *Amer. J. Med.*, 1965, in press.
- 7 ——— and Burwell, R. G., *Quart. Rev. Biol.*, 1965, in press.
- 8 Wright, R., Morton, J. A., and Taylor, K. B., *Brit. med. J.*, 1965, 1, 491.

Oral Contraceptives and Liver Damage

SIR,—The communication on this subject by Dr. Antti Eisalo and his colleagues (15 August, p. 426) reports abnormal liver-function tests in every member of a small group of post-menopausal patients receiving 1–2 tablets of Lyndiol (5 mg. 17 α -ethynyl-oestrenol and 0.15 mg. 3-methoxy-17 α -ethynyl-oestradiol) daily. Similar changes have been noted by Drs. I. P. Palva and O. O. Mustala (12 September, p. 688) in post-menopausal patients receiving one tablet daily of Anovlar (4 mg. of norethisterone acetate and 0.05 mg. of ethinyloestradiol), which contains a different progestogen and a different oestrogen. On the other hand, Dr. L. I. Swaab (19 September, p. 755), Dr. G. Linthorst (10 October, p. 920), Dr. E. Rice-Wray (17 October, p. 1011), and Dr. E. T. Tyler (14 November, p. 1264) emphasize that large-scale, long-term investigations of premenopausal patients given Lyndiol or Conovid (5 mg. norethynodrel and 0.075 mg. mestranol) for contraception showed no evidence of liver dysfunction. We agree with these authors that Dr. Eisalo's report may reflect a different metabolism for these compounds in post-menopausal as opposed to premenopausal patients. We would, however, like to record our experience apropos of Dr. Rice-Wray's comment—"the evidence is insufficient to label this as a hepatotoxic effect," and Dr. Tyler's comment—"laboratory tests, *per se*, are not enough to prove a clinical diagnosis."

Since Dr. Eisalo's communication we have carried out routine liver-function studies and also liver biopsy in four post-menopausal patients receiving six tablets of Lyndiol daily in the treatment of breast cancer. In all cases there was a rise in serum glutamic oxalacetic transaminase and serum isocitric dehydrogenase levels well beyond normal, the changes in liver-function tests appearing after two weeks' drug administration. The serum glutamic oxalacetic transaminase level was above 200 units (Reitman-Frankel method; normal range 10–40 units) in all cases, the highest value being 450 units. The serum isocitric dehydrogenase values at this stage ranged from 77–165 units (normal range 3–10 units).¹ In addition, clinical jaundice was

noted in two patients associated with a serum-bilirubin level of up to 4.1 mg./100 ml. The alkaline-phosphatase and serum-protein levels remained normal in all cases.

Liver biopsy in all four patients showed parenchymal cell necrosis which was strictly limited to the centrilobular zones with accumulation of lipofuscin. In the two with raised serum bilirubin these areas showed also cholestasis in the hepatic cells and biliary canaliculi. In two cases where therapy was stopped after two months the abnormal levels in the liver-function tests fell to normal within two weeks of stopping in one case, but in the other, although reduced, have persisted for six weeks. In two cases where Lyndiol was continued beyond two months (currently six months in one case) the abnormal levels fell spontaneously while under treatment but did not return to normal.

We note that Dr. Eisalo found that the progestogen component of the drug (Lynestrenol or 17 β -hydroxy-17 α -ethynyl-oestrenol) given alone causes no changes in liver function whereas the oestrogen component (Mestranol or 3-methoxy-17 α -ethynyl-oestradiol) did so in one out of three cases. This is an interesting point, as Sherlock² has pointed out that steroids with an alkylated group at C17 are liable to induce some hepatic damage and cholestasis when given in sufficient dosage for prolonged periods. Both the progestogen and the oestrogen components of our drug possess this configuration.

Our experience therefore confirms Dr. Eisalo's findings, and in addition we have shown, by liver biopsy, the presence of hepatic impairment in four cases. We emphasize again that our patients were post-menopausal and were receiving six tablets daily.—We are, etc.,

BASIL A. STOLL.
J. T. ANDREWS.
R. MOTTERAM.
J. UPFILL.

Peter MacCallum Clinic,
Melbourne C.1, Australia.

REFERENCES

- 1 Bell, J. L., and Baron, D. N., *Clin. Chim. Acta*, 1960, 5, 740.
- 2 Sherlock, S., *Diseases of Liver and Biliary System*, 1963, 3rd ed., p. 307. Blackwell, Oxford.

Somatic Mutation

SIR,—In the second paragraph of his paper "Somatic Mutation and Chronic Disease" (6 February, p. 338) Sir Macfarlane Burnet writes, "For many years it has been recognized that . . . (for) . . . several types of cancer . . . if both age-specific incidence and age were plotted logarithmically the points fell on a straight line. This can be interpreted *only* on the assumption that the condition is determined by the random occurrence of events occurring with equal likelihood over the time-span being considered" (our italics). This, in our opinion, is not true.

The demonstration by Nordling¹ and Armitage and Doll² that the "random occurrence of events" hypothesis produces the required age-specific incidence pattern may be generalized as follows: Suppose that the probability distribution function of the age

of cancer in a cell (of the system under study) is $G(t)$ and that there are n cells "at risk." On the usual independence assumption we may then deduce the probability distribution function of age of appearance of the disease in the individual as^{3,4}

$$F(t) = 1 - [1 - G(t)]^n.$$

The age-specific incidence of the disease at age t will then be $f(t)/\{1 - F(t)\}$, where $f(t) = dF(t)/dt$. For large n , $F(t)$ will be virtually determined by the structure of $G(t)$ as $G(t) \rightarrow 0$.³ This can be shown to imply that any $g(t) [= dG(t)/dt]$ which behaves as a power of t for small $G(t)$ will produce the known age-specific incidence pattern.³

For example, both the following $g(t)$'s will produce the required age-specific incidence pattern:

$$(1) \quad g(t) = e^{-\lambda t} \lambda^r t^{r-1}/(r-1)!$$

$$(2) \quad g(t) = v_1^{\frac{1}{2}v_1} v_2^{\frac{1}{2}v_2} t^{\frac{1}{2}(v_1-2)/}$$

$$[B(\frac{1}{2}v_1, \frac{1}{2}v_2) (v_1 + v_2)^{\frac{1}{2}(v_1+v_2)}]$$

(1) is the model of r somatic mutations required in any order within a single cell where the mutations occur at a constant rate λ per cell per year, and (2) is the well-known F distribution on v_1 and v_2 degrees of freedom.

We carry no torch for any particular alternative theory but wish only to point out that no theory of carcinogenesis can be considered to be established solely on the basis of the mathematical relationship between incidence rates and age.—We are, etc.,

P. ARMITAGE.

London School of Hygiene and
Tropical Medicine,
London W.C.1.

R. DOLL.

M. C. PIKE.

M.R.C. Statistical Research Unit,
University College Hospital Medical
School,
London W.C.1.

REFERENCES

- ¹ Nordling, C. O., *Brit. J. Cancer*, 1953, 7, 68.
- ² Armitage, P., and Doll, R., *ibid.*, 1954, 8, 1.
- ³ Gumbel, E. J., *Statistics of Extremes*, 1958. Columbia University Press, New York.
- ⁴ Pike, M. C., *Biometrics*, 1965, in the press.

Retinal Detachment Centres

SIR,—Retinal detachments are fascinating and frustrating. The present rate of cure in a good centre should be in new cases 90%, including cases who have no operation because they are hopeless. Few regional consultants ever have the time that detachments require, nor opportunities to learn the necessary techniques to attain 90%, such as indirect ophthalmoscopy and the detailed examination of the ora. Indeed, after learning this last, one performs operations on the anterior segment with a new concern as to what its effects are on the posterior segment.

All surgeons desire either to operate successfully or pass the patient to a suitable centre. Detachment centres are excellent provided they have a head on whom the consuming fascination of detachment surgery has descended. Should his replacement not have this fascination that centre sinks to a utility level. Surgeons in the regional groups, where registrars and opticians are almost unknown, have geographical and administrative difficulties with waiting-lists which prevent more

than an occasional detachment operation. Where registrars are available in the region or teaching hospital, detachments commonly become their concern. This time-honoured method of solving a difficult problem has produced brilliant successes in the past, but the 90% results of a good detachment centre leave failures that require a research unit instead of a registrar.

A possible solution is for one surgeon, keen on detachments, in a group of surgeons to have two sessions of his contract set aside by mutual consent for detachment examination and operation. It could be arranged so that a colleague could operate on a particular detachment while the detachment surgeon does his clinic, an arrangement which could be mutually advantageous. Helpful discussions would follow with the interested surgeons in the nearest groups. The scheme may become important as the supply of ophthalmologists trained in detachments decreases. Further, one interested surgeon might handle cases for two groups by these modern methods, which allow the patients to be discharged in 10 days or less. The chance of better visual acuity after a successful first operation being greater than after the second operation will be taken advantage of in this scheme by using the new complicated methods first to ensure success. As the use of the laser increases (also in diabetes, etc.) and the price falls, these will become available to the groups and save much transport to light coagulation centres.

Ethically, either centres or this two-session idea seem theoretically to present difficulties due to our custom of practice. Indeed, a centre was proposed in 1947 but was shelved mainly for this reason. In fact, however, the consultants' desire for success is predominant and cases are now not uncommonly sent to those interested in detachments who manage as best they can.

Statistics for the country as a whole are not available, but hearsay suggests that one operable detachment in six is passed over while the remainder has a cure rate of 55% instead of 90%. Thus, at approximately 1 detachment in 7,000 in the population we have 7,000 in 50,000,000. A 90% cure rate with operation in all cases would give a cure to 6,300 cases with 700 failures. On the contrary, assuming that 1 in 6 are "thought unsuitable" for operation (1,166) and the failure rate in the remainder (7,000—1,166=5,834) is 45% (2,625) we have a failure rate of 1,166+2,625=3,791. This is a loss at present of nearly 3,800 eyes instead of 700.

Financially, the scheme would cost roughly £15 a week (two sessions). Discharge in 10 days instead of 20 would save £25 per case. Two patients can be examined and operated on in two sessions with a saving of £65. To the horror of the administrators, the least important figure of bed occupancy would fall—but the most important figure of turnover would rise, with a yearly saving of £1,250—i.e., almost enough to buy a laser. Further, approximately one-fifth have bilateral detachments and can become blind. If, say, one-tenth of the failures over the first 100 reach blind registration—i.e., one-tenth of 3,000, say 300—the country must supply £23,400 annually (£1 10s. each weekly), in itself a small thing compared with the personal tragedies.

Surgically, and financially, this scheme could improve administration, bringing fulfil-

ment of a frustrated dream to the detachment surgeon, relief to many and sight to thousands, and reduce the work of the teaching hospital with the inconvenience and transport difficulties involved.

In theory it is possible to arrange this type of scheme in one's own contract, but such a proposition is a delicate one to initiate and it is with the idea of promoting discussion which might result in such a change that this letter is written.—I am, etc.,

T. STUART-BLACK KELLY.

Bath Eye Infirmary,
Bath, Somerset.

Is Arterial Puncture Dangerous?

SIR,—In reply to Professor W. W. Mushin's letter (1 August, p. 310), we wish to describe one recent fatal complication, arising from the insertion of catheters into the femoral artery by the Seldinger technique, for the purpose of haemodialysis. Over 100 catheterizations had been performed before this accident occurred.

The case involved a man of 62 years of age, who had to be haemodialysed because of acute renal failure. The left femoral artery was punctured, and the Seldinger wire slipped in easily. The catheter was also inserted with ease, to a length of 8 in. (20 cm.), but on removing the wire no blood flowed back. Presumably the tip of the needle had come out of the lumen of the artery, and the wire and catheter had created an artificial track in the retroperitoneal tissues. The catheter was therefore removed and pressure was applied over the groin for five to ten minutes, after which time the external bleeding had stopped, although a subcutaneous haematoma the size of a walnut had been formed. This groin was not used again.

About half an hour later 2,000 U. of heparin was given and the dialysis commenced. Immediately the blood-pressure fell from 150 mm. Hg systolic to 100 mm. Hg systolic. The clotting time was kept at ten minutes throughout. The haematoma in the groin did not increase in size and there was no external bleeding from the skin incision in the left groin, which had not been sutured. Gradually, however, a tender mass appeared in the left flank. A continuous blood-transfusion of 4 pints (2.3 litres) of blood failed to maintain the pressure above 100 mm. Hg and so the dialysis was stopped prematurely after three hours. Subsequently the blood-pressure continued to fall in spite of administration of protamine sulphate and a further transfusion of 3 pints (1.7 litres) of blood over a period of two hours, and so it was decided to explore the vessel. At this stage we imagined that the Seldinger wire and catheter had pierced the artery wall high up in the abdomen, as there were no signs of bleeding in the groin.

At operation there was only the one puncture site in the femoral artery in the groin, about 1½ in. (4 cm.) below the inguinal ligament. But it was still bleeding. The blood had tracked upwards via the femoral sheath into the retroperitoneal tissues, forming a huge retroperitoneal haematoma. The vessel wall was intact throughout its course in the abdomen. The bleeding site was closed and the patient withstood the operation. However, he suffered from chronic asthmatic-bronchitis, and had needed steroids for several years: post-operatively he went into respiratory failure and died.

The femoral sheath is the apex of a fascial funnel composed anteriorly by the transversalis fascia and posteriorly by the ileopectineal fascia. It is a prolongation downwards of the fascia lining the abdomen. It therefore forms a natural channel for blood escaping from the femoral artery.