gest as an answer the two infections which are most akin to infantile gastroenteritis—namely, salmonella enteritis and bacillary dysentery.—I am, etc.,

A. G. IRONSIDE.

Department of Infectious Diseases,
Monsall Hospital,
Manchester 10.

Chemotherapy of Burkitt's Lymphoma

SIR,—An observation in the treatment of a patient with Kaposi's sarcoma led to my combining potassium iodide with cyclophosphamide in the treatment of Burkitt's lymphoma. The results to date suggest that potassium iodide potentiates the action of cyclophosphamide.

The Figure shows the survival curves for 24 cases of Burkitt's lymphoma, of which 23 were treated with cyclophosphamide alone and one with methotrexate; and for 10 cases given the combined treatment. Although sufficient time has not yet elapsed to be sure that the levelling out of the survival curve will remain at 65%, yet the difference is so great when compared with the 21% survival for the 24 cases that it would seem that potassium iodide may be a valuable adjuvant to cyclophosphamide in the treatment of this and other tumours. Clinically the recession of the growths is more rapid, and complete remissions have been seen with large and multiple tumours. Of the 24 cases 12 are stage 1 and 2, and 12 stage 3 and 4. Of the 10 cases five are stage 1 and 2, and five stage 3 and 4.

All the patients did not start treatment at the same time, and because of the intervals between entrance to the inquiry some of the patients have been under observation for a much longer time than others. In order to surmount this difficulty a life-table method of obtaining survivors has been employed.

Study of the available literature suggests that potassium iodide may inhibit cell glycolysis, rendering the cell membrane more permeable to cyclophosphamide.¹ But it is also noted that iodides activate dihydrofolic reductase in purine synthesis² and so it is felt that caution is called for, since potassium iodide administered alone may reactivate a tumour. I have therefore adopted the following treatment regimen. The dosage of oral cyclophosphamide is calculated at 40 mg. per pound (500 g.) of body weight. This is given at the rate of 300 mg. per day, and at the same time potassium iodide 600 mg. twice daily is given, but the administration of potassium iodide must cease the day before the total dose of cyclophosphamide is achieved. Concurrent leucocyte counts must

be performed, as there is frequently a sharp fall in these.

As my series is small and would take a long time to become large I am asking you to publish this letter so that others who may be interested in carrying out trials may do so without delay.—I am, etc.,

E. H. WILLIAMS.

Kuluva Hospital,
Arua, Uganda.

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Mononucleosis and Burkitt's Lymphoma

SIR,—I was interested in the medical memorandum by Dr. L. A. Price and Mr. D. Garfield Davies (5 April, p. 31), reporting a case of lymphosarcoma with a positive Paul-Bunnell test. Could this have been an atypical case of Burkitt's lymphoma?

Some authors feel that Burkitt's tumour is a form of lymphosarcoma.¹ Moreover, there is evidence to suggest that Epstein-Barr virus causes infectious mononucleosis in Britain and Burkitt's lymphoma in Africa. The reason for this is obscure, but the following explanation is suggested.

It is now well established that immunosuppression predisposes to malignant disease.^{2,3} In addition, it has also been noted that patients suffering from the coeliac syndrome have an increased incidence of lymphomata. Furthermore, these cases can often be identified by hypoproteinaemia and occasionally oedema.^{4,5} It may be that in malabsorption immunoglobulin synthesis is impaired, thereby leaving these patients unable to combat oncogenic virus or dispose of neoplastic cells. Such virus might attack the diseased bowel in the first instance, but extra-abdominal lymphomata have also been noted. In the case of Burkitt's tumour, it may be that African children, if not suffering from frank kwashiorkor and hypoproteinaemia, have at least an element of malnutrition leading to defective synthesis of immunoglobulin, which need not necessarily be quantitative. Again, Burkitt's lymphoma is unknown during the first year of life, when presumably these children still have passive immunity.

Finally, I would agree with your authors' explanation that their case is not a coincidence, but rather a true lymphoma presenting with a positive Paul-Bunnell test. At the same time it would be interesting to know how many other cases of lymphosarcoma have a positive Paul-Bunnell test in the very early stages of the disease. Certainly, in a recent case of reticulum cell sarcoma the Paul-Bunnell was negative some weeks prior to the correct diagnosis.⁶—I am, etc.,

W. S. B. LOWRY.

Royal Victoria Hospital,
Belfast.

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- ² *Lancet*, 1969, 1, 505.
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Diverticulosis of the Colon and Diet

SIR,—Mr. M. N. Morgan and Professor H. Ellis did not find diverticula in rats fed on a low residue diet for 50 to 70 weeks (5 April, p. 53) in contrast to the experience of Carlson and Hoelzel,¹ who found that such a diet produced the disease in rats in life-span studies. Their timely warning obviously was given so as to save other workers from terminating the existence of their experimental rats too soon, but it would be a pity if their letter fostered the belief that the clue to the causation of diverticular disease is most likely to be found in rats and animals. Furthermore, it is not true that the "aetiology of the disease is essentially unknown." The following facts are known:

Diverticular disease occurs in people who eat a low residue diet in which both flour and sugar are refined. The disease is not found in people living tribally who eat unrefined maize, but it appears in these people or their descendants if they change to a "civilized" diet lacking natural fibre. As would be expected in a disease which occurs in the latter half of life, this does not occur until after a latent period of some years.

Diverticulosis has been related to an increase in localized intrasigmoid pressures.²⁻⁴ These high localized pressures occur more easily in a narrow colon which is segmenting vigorously. A refined diet results in a more viscous stool that passes through the gut more slowly than the bulky stool of a high-residue diet. This can be proved by anyone who is prepared to eat either an unrefined diet or is willing to add unprocessed bran to his present diet. Is it not possible that this alteration in the faeces due to diet has an adverse effect on the intracolonic pressures, and hence leads to diverticula appearing in those who consume such a diet?

The incidence of the disease in England and Wales is increasing steadily since the beginning of this century, and, allowing for a latent period of about 40 years, this rise corresponds to the increased consumption of refined flour and sugar that has occurred in this country. The same is true of several other common diseases that attack civilized man.⁵

It is interesting to note that despite the fall in the mortality that follows perforated diverticulitis that resulted from the advent of the antibiotics, advances in anaesthesia, and better surgical management, the death rate from the disease steadily increased in England and Wales except for the years 1939-52.

FIG. 1.—Accrued death rate from diverticular disease in England and Wales, 1923-1966. From *Diabetes, Coronary Thrombosis, and Saccharine Disease*, by T. L. Cleave, G. D. Campbell, and N. S. Painter, reproduced by permission of John Wright & Sons Ltd., Bristol.

These were the war and postwar years when refined sugar was rationed and our bread contained more natural fibre.

The correction of colonic stasis by the addition of sufficient bran to the diet relieves the pain of diverticular disease.

Therefore, not only is there a great deal of evidence that a low residue diet causes the disease, but also that a high residue diet would prevent its appearance. Furthermore, the addition of roughage to the diet in the form of wholemeal bread and additional bran is of benefit even when the disease is already established and is causing symptoms.—I am, etc.,

NEIL STAMFORD PAINTER.

Manor House Hospital,
London N.W.11.

REFERENCES

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Transmission of *Trichomonas*

SIR,—Some of your correspondents have recently suggested that *Trichomonas vaginalis* is acquired by means other than sexual intercourse or sexual contact (12 April, p. 116, and 3 May, p. 315). None of them, however, puts forward a satisfactory alternative method by which the condition is commonly transmitted, nor have they produced any scientific evidence to support their statements.

Those who are familiar with the world literature on this subject will have no doubt that *Trichomonas vaginalis* is sexually transmitted in the majority of cases. At the First European Symposium on Trichomonal Infestations in Rheims in 1957 and at the First Canadian Symposium on *Trichomonas vaginalis* in Montreal in 1959 the majority of the delegates agreed that human trichomoniasis was usually transmitted by sexual intercourse and unanimous resolutions to this effect were passed at both meetings. The work of Chappaz¹ in France, Bauer² in Germany, Trussell³ in the United States, and Whittington⁴ in Britain has added very strong support to this view. Our own studies⁵ led us to the conclusion that the most frequent method of transmission of the parasite is by the sexual act, though in a small proportion of cases infestation may be acquired by other means.

It is frequently difficult to demonstrate the organism in men with the available methods of diagnosis. This is because the trichomonads are washed out of the urethra at each act of micturition and the total population of trichomonads in the lower genital tract is usually quite small at any time. Nevertheless, if modern diagnostic methods are used, including cultures and examination of the prostatic secretions as well as the centrifuged deposit of urine, the parasite can be found in male partners of women with trichomonal vaginitis in many cases.

It is well known that authentic cases of syphilis and gonorrhoea are sometimes acquired in a non-sexual manner and it is certain that occasional cases of *Trichomonas vaginalis* infestations occur from other

sources. This fact, however, does not invalidate the conclusion that trichomoniasis is transmitted sexually in the majority of instances.—We are, etc.,

R. D. CATTERALL.

Middlesex Hospital,
London W.1.

C. S. NICOL.

St. Thomas's Hospital,
London S.E.1.

REFERENCES

- 1 Chappaz, G., 1957, in *Les Infestations à Trichomonas*, Paris, Masson, p. 161.
- 2 Bauer, H., 1957, in *Les Infestations à Trichomonas*, Paris, Masson, p. 21.
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Immunity to Cancer

SIR,—Your leading article "Immunity to Cancer" (24 May, p. 461) and the paper by Dr. G. Hamilton Fairley (p. 467) give the impression that the detection of immune responses in cancer point irrefutably to the conclusion that the malignant lesion itself initiates these responses.

No consideration is given to the possibility that some of these autoimmune reactions may well be the cause of the malignant lesion by, as Burch¹ has suggested, removal, inhibition, or alteration of the differentiating factor within the cell. The finding that an inactivated vaccine, poliovaccine, administered parenterally shows a highly significant association with all forms of childhood malignancy² lends support to this aspect of Burch's theory in that poliovaccine is a known means of stimulating the lymphoreticular tissue to activity and hence possibly to autoaggressive activity. It may well be that many antigens and other carcinogens such as ionizing radiation are capable of similarly stimulating genetically susceptible lymphoreticular tissue, with subsequent neoplasia of a target tissue, and your explanation is not the only one that accounts for the immune antibodies.

Finally, it is a pity that the historical account of the development of the concept of immune mechanisms in cancer makes no mention of Green,³ who was one of the first to draw attention to such mechanisms.—I am, etc.,

MICHAEL D. INNIS.

Department of Pathology,
Princess Alexandra Hospital,
Brisbane, Australia.

REFERENCES

- 1 Burch, P. R. J., *Nature*, 1963, 197, 1145.
- 2 Innis, M. D., *Nature*, 1968, 219, 972.
- 3 Green, H. N., *British Medical Journal*, 1954, 2, 1374.

SIR,—The significance of Dr. G. Hamilton Fairley's learned review (24 May, p. 467) may not be that many tumours contain tumour-specific antigens against which the host is capable of reacting. The demonstration of such reactions is unconvincing, and new antigens are rarely found. Could it not be that the part played by the reticulo-endothelial system is more than a facet of an immune response to tumour growth? Instead of assuming malignancy is, with few exceptions, a potential characteristic of each and every cell with the reticulo-endothelial system reacting to malignancy in much the same way as it does to any other injurious process, we should consider whether this

unique system plays a greater part in the malignant process than hitherto suspected.

Until fairly recently such reticulo-endothelial malignancies as the leukaemias, myeloma, and Hodgkin's disease were excluded from most classifications of cancer, but now that these malignancies have been properly included with cancers in general we should consider whether this system requires further consideration in relation to all forms of cancer far beyond that of simple reaction. It has not always been assumed that malignancy was inherent in the specialized tissue cell, and in view of the very considerable part increasingly shown to be played by the reticulo-endothelial system and manifested by the studies of immunological procedures in cancer we should consider whether cancer in all its manifestations is not a form of pathological reaction similar to inflammation.

Because anaplasia and metaplasia are present in tissue cells it has been assumed that the cancer originates in these cells. Admittedly, there are difficulties. Some cells defy identification and some cancers defy classification, but we tend to identify the malignant process with the presumed cell of origin. The difficulties in this assumption go beyond those mentioned in the article and relate to tumours in general. It is not just why some circulating cancer cells survive and others do not and why reinjection of tumour cells does not, in the main, reproduce the tumour, but why so many so-called cultures of tumour cells, such as connective tissue sarcomas, return to normal adult cells when grown in vitro. The explanation of this unusual behaviour could be that either the cells are not malignant or that only a very few are. The tissue histiocytes and the free histiocytes, members of the reticulo-endothelial system, instigate fibroblastic reaction. Could the characteristic malignant changes in the tissue cells not be due to abnormal reaction of histiocytes liberating excess of trephones? It would account for the fibroblastic reaction, so often a feature of growths, as well as the abnormal tissue response. But, above all, it could account for the confusing results obtained with most tumour cultures and implantations, and explain the significant successes in these fields with cancerous conditions of the reticulo-endothelial system. Subject only to the rules of immunity, the experimental transmission of leukaemia in mice has been accepted, and lymphoblastic lymphoma has been reproduced by inoculations from Burkitt's lymphoma.¹

The proposal that all cancers originate in the multipotent reticulo-endothelial system and not just leukaemia, lymphomas, endotheliomas, reticulosarcomas, etc., has fascinating possibilities beyond being a convenience in classification. It would explain the vagaries of the circulating "cancer" cell, the reason why some metastases regress and others do not, and the loss of differentiation in metastases. It suggests why stimulation of the reticulo-endothelial system retards some growth, and why some tumours regress after the intravenous and intraperitoneal injections of spleen cells, but above all it relates the malignant process to a disorder of or an aberrant form of the inflammatory and repair processes, something that has been suspected and postulated for a very long time.—I am, etc.,

J. A. BARCLAY.

Edinburgh.

REFERENCE

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SIR,—Dr. G. Hamilton Fairley in his Goulstonian lecture (24 May, p. 467), in referring to the recent isolation of a herpes-like virus from some cell cultures of Burkitt's lymphoma, states, "This appears to be the