

established. Several metabolic products of T3 and T4 in the urine which have not yet been identified might crossreact with the antibody.

(2) The increase of apparent T3 in thyrotoxic patients could be due partly to an increase in T4 breakdown products. It is remarkable that the T3 excretion-rate in patients with T3 thyrotoxicosis had a considerable overlap with the normal range, whereas plasma-T3 levels were significantly raised in all cases.

(3) T3 excretion is decreased in renal insufficiency, probably because of reduced glomerular filtration, though the contribution of the kidneys itself to T3 excretion is not yet clear.

Considering all these points, we do not see any diagnostic advantage in measuring T3 excretion instead of plasma-T3 levels. Rather, there are several additional sources of error and several as yet unclarified factors. We are not convinced that measurement of T3 excretion-rate will be of special benefit in cases of uncertain thyroid hyperfunction. In our opinion plasma-T4, thyroxine-binding index, and T3, the thyrotrophin-releasing-hormone test, and a ^{99m}Tc-scintigram are sufficient to clarify nearly all thyroid disorders.

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CIRCULATING LEVELS OF IgE IN PATIENTS WITH CANCER

SIR,—Jacobs et al. (Nov. 18, p. 1059) claim to be the first to study IgE levels in cancer. May we therefore draw your attention to our own study on precisely this subject,¹ where we investigated in addition to IgE levels also skin reactions to grass-pollen antigens, which are prevalent allergens in this country. We found that 65 cancer patients had rather lower IgE levels and fewer positive skin reactions than 50 unselected normal controls—i.e., our IgE results are similar to those obtained by Jacobs et al. by the same method (radial immunodiffusion^{2,3}) while our skin-test results appear to be in agreement with the results of Gabriel et al.⁴ However, 48 age-matched non-cancer surgical patients in the same wards as the cancer patients gave results almost identical to the cancer patients, both in IgE levels and in skin-prick tests. None of our subjects had been treated with cytotoxic drugs. The data given by Jacobs et al. do not include an age-matched control.

The paper contains some further superficially plausible but erroneous statements.

(1) IgE is certainly not absorbed to "tissue cells sensitised with allergen", but to mast cells and basophils which have special receptors for IgE,^{5,6} quite unrelated to allergens—a moreover most heterogeneous lot.⁷ Allergens themselves are in fact most mobile substances spreading rapidly throughout the body, quite in contrast to IgE.⁸ IgE antibodies are of course Dale's "sessile" anaphylactic antibodies.⁹

(2) There is no shred of evidence that interaction with IgE antibodies ever leads to cell lysis and there is certainly no

equivalent of red-cell lysis by IgM antibody for the cells in the presence of complement. Even the release of histamine, &c., from basophils triggered off by the interaction of allergens with IgE antibodies fixed to them turns out to be an active secretory process and not lysis.^{10,11} If IgE antibodies played any part in tumour rejection it would have to be via an anaphylactic expelling mechanism as contemplated in nematode infestations^{1,12-14} and not via tumour-cell lysis.

(3) Lastly, the numbers along the ordinate of the figure published by Jacobs et al. should read 1, 2, 3, 4, and 5 in place of 10, 100, . . . and 100,000.

The discrepant results given by their two methods in half their cancer patients, and interpreted by them as being due to a tumour-derived factor interfering with IgE/anti-IgE interaction, are highly intriguing; it is, however, difficult to see how an inhibitory factor could have evolved for a completely artificial in-vitro system which has no equivalent in the contemplated in-vivo system; or is it suggested that an inhibitor for IgE/anti-IgE interactions would also inhibit the fundamentally rather different interaction of (hypothetical) IgE antibodies with the corresponding (hypothetical) cancer allergens?

The apparently so high IgE levels have so far been demonstrable only by an inhibition assay—i.e., in what may be called a "negative" way. Confirmation in some positive way is urgently required.

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* * * We showed this letter to Mr Jacobs and his colleagues, and their reply follows.—ED. L.

SIR,—We are very grateful to Dr Augustin and Mr Chandrasa for bringing to our attention their excellent communication.¹⁵ We apologise for not having referred to this work, which we missed despite an extensive survey and contact with organisations and specialists in the IgE field. The statement that "the present study is the first, of which we are aware, involving the assay of circulating IgE levels in a large number of patients with cancer" is still true to the extent that we studied a much larger number of subjects using an analytical technique capable of detecting values below the normal range. The failure of Dr Augustin to find significantly low IgE levels in their cancer patients, in contrast to our findings,¹⁶ may relate to the lack of sensitivity of radial immunodiffusion as compared with radioimmunoassay, or to a difference in the severity of the disease in their subjects. Our paper also remains, as far as we are aware, the first study in which it has been postulated that neoplasms secrete an inhibitory material. However, attention should certainly be drawn to their important preliminary data on lymphocyte transformations and the effect of *B. pertussis* in inhibiting tumour formation in mice.

Certainly IgE is not absorbed to tissue cells sensitised with allergen, an error mistakenly left in the text by one of the authors (J. L.). However, IgE is found free in the circulation and on the surface of basophilic granulocytes,^{17,18}

1. Augustin, R., Chandrasa, K. D. *Int. Archs Allergy*, 1971, **41**, 141.
2. Rowe, D. S. *Bull. Wld Hlth Org.* 1969, **40**, 613.
3. Augustin, R. in *Handbook of Experimental Immunology* (edited by D. M. Weir); p. 42-1. Edinburgh (in the press).
4. Gabriel, R., Dudley, B. M., Alexander W. D. *Br. J. clin. Pract.* 1972, **26**, 202 (cited by Jacobs et al.).
5. Ishizaka, T., DeBernardo, R., Tomioka, H., Lichtenstein, L. M., Ishizaka, K. *J. Immun.* 1972, **108**, 1000.
6. Sullivan, A. L., Grimley, P. M., Metzger, H. *J. exp. Med.* 1971, **134**, 1403.
7. Augustin, R. *Excerpta med.* 1972, International Congress Series 235-II, 9.
8. Spies, J. R., Bernton, H. S., Chambers, D. C. *J. Allergy*, 1960, **31**, 175.
9. Dale, H. H. *J. Pharmac. exp. Ther.* 1913, **4**, 167, 517.

10. Lichtenstein, L. M., Osler, A. G. *Proc. Soc. exp. Biol. Med.* 1966, **121**, 808.
11. Lichtenstein, L. M. *J. Immun.* 1971, **107**, 1122.
12. Augustin, R., Ridges, A. P. in *Immunity to Protozoa* (edited by P. C. C. Garnham, A. E. Pierce, and I. Roitt); p. 296. Oxford, 1963.
13. Ogilvie, B. M. *Nature*, 1964, **204**, 91.
14. Ogilvie, B. M. *Immunology*, 1967, **12**, 113.
15. Augustin, R., Chandrasa, K. D. *Int. Archs Allergy*, 1971, **41**, 141.
16. Jacobs, D., Houri, M., Landon, J., Merrett, T. G. *Lancet*, 1972, **ii**, 1059.
17. Tada, T., Ishizaka, K. *J. Immun.* 1970, **104**, 377.
18. Ishizaka, T., Debernardo, R., Tomioka, H., Lichtenstein, L. M., Ishizaka, K. *ibid.* 1972, **108**, 1000.

and can be presumed to be readily available throughout the body. The word "log" was included in the ordinate on the figure due to the mistake of another author (T. G. M.). We would not feel confident in concluding, should it be found that IgE plays a part in tumour rejection,¹⁹ that it is not as a result of causing lysis, as suggested by Ure.²⁰ The idea of an anaphylactic expelling mechanism as contemplated in nematode infestation^{21,22} does not necessarily have relevance when applied to tumour rejection, nor to the presence of IgE in the kidney in some patients with nephrotic syndrome,²³ in the thyroid of some patients with thyrotoxicosis,²⁴ or in rabbit immune-complex disease.^{25,26}

Our experiments showing the presence of an IgE inhibitor can hardly be termed negative, since the inhibitor was found in approximately 50% of advanced untreated cases of a wide variety of cancers we studied, the remainder having significantly lower IgE values than normal; furthermore, where inhibitor was found in the circulation of operable patients the level close to the tumour was always found to be higher. In addition, other studies have been performed. Thus a more sensitive radioimmunoassay (measuring 0.3 units per ml.) has demonstrated that IgE from cancer sera behaves differently from IgE found in allergic sera; an enriched inhibitor fraction has been eluted from 'Sephadex' columns in a position corresponding to a molecular weight of 50,000; and reacting a sephadex coupled IgE with ¹²⁵I-labelled anti-IgE confirms the existence in untreated cancer sera of an inhibitor that could be either a multivalent antigen or an antibody.²⁷ The only other clinical condition in which we have demonstrated the existence of similar inhibitor is in pregnancy.

There now seems enough evidence from our own, Dr Augustin's, and much other work to justify thinking of IgE in relation to cancer and various clinical conditions, in addition to allergy.

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SIR,—Jacobs et al. have reported serum-IgE levels of more than 100,000 units per ml. in approximately half the patients with untreated neoplasms when determined by radioimmunoassay, but IgE levels were undetectable by single radial immunodiffusion. This discrepancy led these workers to conclude that there was an inhibitor present in the serum of these cancer patients which interfered with the combination of anti-IgE and IgE in immunological tests. It would have been logical then to confirm the function of this serum inhibitor by doing the following additional experiments: to determine the inhibitory capacity of these special sera in the radioimmunoassay of serum IgE of normal and allergic subjects; to find out if these sera also interfere with IgG, IgA, and IgM levels by single radial immunodiffusion; and to determine the in-vivo inhibitory capacity of these sera in the reversed cutaneous-anaphylaxis test. Injection of anti-human-IgE to the skin of monkeys caused increased vascular permeability locally, as evident by the extravasation of the injected

dye such as Evans' blue.¹ If these special sera can inhibit this reversed type allergic skin reaction, it would indicate that the inhibitor present in these sera is active in vivo as well as in vitro.

If the report of Jacobs et al. is confirmed, it may have important implications in allergy and oncology.

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LIQUOR LICENSING

SIR,—It is regrettable that Dr Howorth (Dec. 30, p. 1426) should seek to quarrel with your very sensible editorial on the Erroll committee report (Dec. 16, p. 1297), relating as it does to the control of alcohol, the commonest drug of addiction.

He points to the rise in the consumption of alcoholic drink in the United Kingdom over the past 20 years, but he apparently elects to ignore the growing problem of alcoholism which, as recent inquiries have shown, is by no means confined to the meths-drinkers of "skid-row", but is also alarmingly prevalent in the board-room and on the shop floor and is certainly not unknown among our own profession.

I should like to draw his attention to the very cogent message in the article by Dr. Griffith Edwards² on Public-health Implications of Liquor Control. "Such evidence as there is, however, tends to suggest that the control of the environmental conditions of drinking—and in particular, the availability and the price of alcoholic drinks—may be all-important in checking the incidence of alcoholic addiction and problem drinking. Considerations of the public-health aspects of the drinking laws must override both the personal moral view which declares that drinking is inherently reprehensible and the alternative view which sees loosening of controls and increase in competition as intrinsically worthy aims." He goes on to say: "Since we are not able to manipulate personality and produce a race with no neurosis, the only realistic method of exerting a benign influence on the prevalence of alcohol addiction is by control of the environmental conditions of drinking, and it is the availability element that remains the prime candidate for control. . . . There is, in fact, evidence to support the hypothesis that abnormal-drinking rates are high in countries where alcohol is readily available . . ." (my italics).

For Dr Howorth to talk about "the more leisurely era of gracious living" shows some ignorance about the social history of this country since before the turn of the last century. It would indeed be regrettable if the clock were "put back" to the conditions that prevailed in this country before the 1914-18 legislation and the Licensing Act of 1921. A trade which spends £20 million per annum in pushing its product is not particularly concerned about the effects on the nation or on its economy.

As a profession we should be as concerned to restrict the subtle advertising on television and in the Press (especially the glossy magazines) as we were to ban the advertising of cigarettes. Indeed, this course has been suggested by some Members of Parliament. Increased facilities for the consumption of alcohol cannot but be reflected in a further increase in alcoholism and in increased casualties on the roads, as well as by the adverse effect on the "public health" in its widest sense.

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19. Bartholomaeus, W. N., Keast, D. *Nature*, 1972, **239**, 206.

20. Ure, D. M. J. *Scott. med. J.* 1969, **14**, 51.

21. Augustin, R., Ridges, A. P. in *Immunity to Protozoa* (edited by P. C. C. Garnham, A. E. Pierce, and I. Roitt); p. 296. Oxford, 1963.

22. Ogilvie, B. M. *Nature*, 1964, **204**, 91.

23. Gerber, M. A., Paronetto, F. *Lancet*, 1971, **i**, 1097.

24. Werner, S. C., Wegelius, O., Fierer, J. A., Hsu, K. C. *New Engl. J. Med.* 1972, **287**, 421.

25. Henson, P. M., Cochrane, C. G. *J. exp. Med.* 1971, **133**, 554.

26. Cochrane, C. G. *ibid.* 1971, **134**, suppl. 75.

27. Lundquist, U. Personal communication, 1972.

1. Ishizaka, K., Ishizaka, T. *J. Immun.* 1968, **100**, 554.

2. *Lancet*, 1971, **ii**, 424.