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Correspondents are urged to write briefly so that readers may be offered as wide a selection of letters as possible. So many are being received that the omission of some is inevitable. Letters should be signed personally by all their authors.

Monoclonal theory of atheroma

SIR,—Your leading article on the monoclonal theory of atheroma (28 May, p 1371) is a timely reminder of the importance of the remarkable discovery made by Benditt and Benditt¹ four years ago. Their findings were confirmed by Pearson *et al*² and by Pearson *et al*.³ The facts are not in dispute. However, you raise certain objections to the interpretation of these experimental findings as evidence for a monoclonal origin of human atherosclerotic plaques. Concerning these objections, the following points are relevant:

(1) The demonstration by Benditt¹ that the mosaic patch size in the tunica intima of the human aorta is of the order of 10 cells makes it virtually impossible to suppose that the fibrous plaques in atherosclerosis are derived from the simultaneous proliferation of even a small number of adjacent cells.

(2) You say that "a group of cells may proliferate and then die. The few remaining cells may then proliferate again, and finally only a single enzyme phenotype may be present." This suggestion was made by Fialkow⁴ as a purely theoretical speculation. No evidence exists that such a sequence of events actually occurs. In such diverse experimental systems as the formation of the pseudo-intima lining fabric grafts of the baboon's aorta,⁵ the organisation of mural thrombi in the rat's aorta,⁷ and intimal thickening of the rabbit's aorta following mechanical removal of endothelium⁸ smooth muscle cells proliferated steadily until a new endothelial lining was formed. Thereafter the lesions neither pro-

gressed nor regressed. In view of these experimental findings Fialkow's speculation would require convincing experimental support before it could be taken seriously as an objection to evidence for the monoclonal origin of atherosclerotic plaques.

(3) You state: "Cells which divide rapidly gain advantage over others, and a single cell progeny may take over." If the cells of a mature lesion are the progeny of a single cell they are by definition monoclonal. What you describe may well occur, but we fail to understand what distinction you are trying to make.

(4) You refer to the suggestion by Thomas *et al* that one of the glucose-6-phosphate dehydrogenase (G6PD) alleles may be linked to genes that afford a selective advantage. Since lesions containing the A form of G6PD alone and the B form alone can occur in the same aorta, it would be necessary to suppose that the hypothetical locus on the X chromosome is situated at some distance from the G6PD locus and is frequently separated from the latter by somatic crossing-over. It would further be necessary to stipulate either that the crossing-over occurs at a very early stage of embryogenesis, prior to X-inactivation¹⁰ or else that the crossing-over is frequently accompanied by reactivation of genes derived from the inactive X. However, all the experimental evidence indicates that, even in the most genetically unstable systems, reversal of X-inactivation in somatic cells is extremely rare (see, for example, Kahan and De Mars¹¹); and, in any case, there is no evidence that

somatic crossing-over occurs with anything like the required frequency. Moreover, there is concrete evidence that such crossing-over does not occur between the G6PD locus and another locus at a distance from it on the X chromosome, namely, that for hypoxanthine guanine phosphoribosyl transferase (HGPRT).

Nyhan *et al*¹² studied a family in which four cases of Lesch-Nyhan syndrome had been identified. The two mothers of the affected boys were not only heterozygous at the HGPRT locus but also at the G6PD locus. An unexpected finding was that all the erythrocytes of these women were HGPRT-positive, although previous studies^{13,14} on clones of skin fibroblasts from mothers of boys with the Lesch-Nyhan syndrome had shown (as expected) that approximately equal numbers of HGPRT-positive and HGPRT-negative clones were obtained. Clearly among erythrocyte precursors there is selection against HGPRT-negative cells. In both these women this selection led to the erythrocytes showing only a single G6PD phenotype (in both cases type B) although skin fibroblasts showed the expected AB phenotype. Had there been significant somatic crossing-over between these loci, this result could not possibly have been obtained. In the small kindred examined by Nyhan *et al* meiotic crossing-over had occurred at least twice, indicating that the two loci were not closely linked. More recent work¹⁵⁻¹⁷ has shown that the two loci are separated by at least one-tenth and probably nearly one-sixth of the length of the X chromosome. This argument is reinforced by the consideration that erythrocyte precursors are among the fastest dividing cells in the body; and the argument would not be materially affected if it were supposed that the hypothetical advantageous locus is situated as far away from the G6PD locus as possible.

(5) Finally we have the paper by Thomas *et al*¹⁷ purporting to show that hypercholesterolaemic diet-induced atherosclerotic lesions in young swine are polyclonal. A group of pigs were injected with tritiated thymidine. Five were killed 15 days later and served as controls. The remaining eight were given a high cholesterol diet. Three were killed after 30 days and the remaining five after 60 days. Only one gross atherosclerotic plaque was found. This may well have been present before the start of the experiment. In addition "focal intimal cell masses" were found both in the control and in the cholesterol-fed animals. It would be rash indeed to assume that those in the treated animals were induced by the dietary treatment, though they may well have been exacerbated by it. In the absence of evidence that any of the lesions arose *de novo* during the course of the dietary treatment the autoradiographic findings reported provide no evidence about their clonality. In any case the interpretation of the results of this study is fraught with difficulties, depending as it does on predictions from an idealised theoretical model. In the complexities of an *in-vivo* situation such predictions might or might not be fulfilled.

If the objections raised in your leader are the most powerful ones that can be mustered against the monoclonal theory of atherosclerosis, its proponents need not worry unduly.

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¹ Benditt, E P, and Benditt, J M, *Proceedings of the National Academy of Sciences of the United States of America*, 1973, **70**, 1753.

² Pearson, T A, *et al*, *American Journal of Pathology*, 1975, **81**, 379.

³ Pearson, T A, *et al*, *American Journal of Pathology*, 1977, **86**, 657.

⁴ Benditt, E P, *Beiträge zur Pathologie*, 1976, **158**, 405.

⁵ Fialkow, P J, *New England Journal of Medicine*, 1974, **291**, 26.

⁶ Florey, H W, *et al*, *British Journal of Experimental Pathology*, 1962, **43**, 655.

⁷ Poole, J C F, Cromwell, S B, and Benditt, E P, *American Journal of Pathology*, 1971, **62**, 391.

⁸ Poole, J C F, *Advances in Experimental Medicine and Biology*, 1975, **57**, 237.

⁹ Thomas, W A, *et al*, *Experimental and Molecular Pathology*, 1976, **24**, 244.

¹⁰ Lyon, M F, *Proceedings of the Royal Society, Series B*, 1974, **187**, 243.

¹¹ Kahan, B, and De Mars, R, *Proceedings of the National Academy of Sciences of the United States of America*, 1975, **72**, 1510.

¹² Nyhan, W L, *et al*, *Proceedings of the National Academy of Sciences of the United States of America*, 1970, **65**, 214.

¹³ Migeon, B R, *et al*, *Science*, 1968, **160**, 425.

¹⁴ Salzmann, J, De Mars, R, and Benke, P, *Proceedings of the National Academy of Sciences of the United States of America*, 1968, **60**, 545.

¹⁵ Goss, S J, and Harris, H, *Nature*, 1975, **255**, 680.

¹⁶ Brown, J A, *et al*, *Cytogenetics and Cell Genetics*, 1976, **16**, 54.

¹⁷ Goss, S J, *Cytogenetics and Cell Genetics*, 1976, **16**, 138.

Royal College of Physicians and fluoridation

SIR,—Mr R V Mummery has criticised the report of the Royal College of Physicians, *Fluoride, Teeth and Health*¹ (21 May, p 1352) because it failed to quote Weaver's findings in 15- and 17-year-old schoolchildren and in young mothers in 1943-4 in adjacent high and low fluoride areas in County Durham and Northumberland.² These early observations, however, were based on small numbers—on 78 children aged 15 in the high fluoride area and in 11 in the control area, the corresponding numbers at age 17 being only 19 and 16.

Evaluation of the DMF score of the 100 mothers attending maternity and child welfare centres in each of the two areas is complicated by the unusually high fraction (73.9%) of the score that was contributed by missing teeth, suggesting, as mentioned by Weaver, that many had been the subject of dental clearance practices involving the extraction of some sound teeth prior to the fitting of dentures. Weaver's third paper,³ referred to by Mr Mummery, contained no new data.

In the few pages in the RCP report¹ devoted to a summary of the main evidence on fluoride and caries the main findings of only a few of the largest studies were specifically mentioned. Weaver's main study,⁴ which was prompted by J Irvine's observation that the "children evacuated to Westmorland from South Shields had remarkably good teeth—much better than those of the local children," was referred to by the RCP because it was the first study of dental caries in comparable high and low fluoride areas in Britain. This involved 500 children aged 5 and 500 aged 12 in each of the two areas and showed that at the age of 12 the number of DMF teeth in South Shields was 56% of that in the low fluoride town of North Shields. In the 30 years that have passed since these classic studies further similar studies involving much larger numbers of children and adults¹ have confirmed the dental benefits of water containing 1 mg of fluoride per litre and have also indicated that the benefits of drinking such water in childhood are lifelong.⁵⁻¹⁰ Indeed a recent study^{9,10} in York (low fluoride) and Hartlepool (high fluoride), towns not very far from Weaver's study area, involving over 4000 adults, bears local testimony to this conclusion. It is a pity that Weaver did not live to see the results of these subsequent studies.

Since the benefits of fluoride are not transitory, it is clearly inappropriate to refer to these simply as "caries-postponing," although it may also be observed that even "postponement" of some of the burden of any age-related disorder must amount to prevention in view of our limited lifespan.

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¹ Royal College of Physicians of London, *Fluoride, Teeth and Health*. London, Pitman, 1976.

² Weaver, R, *British Dental Journal*, 1944, **77**, 185.

³ Weaver, R, *Proceedings of the Royal Society of Medicine*, 1948, **41**, 284.

⁴ Weaver, R, *British Dental Journal*, 1944, **76**, 29.

⁵ Russell, A L, and Elvove, E, *Public Health Reports (Washington)*, 1951, **66**, 1389.

⁶ Englander, H R, and Wallace, D A, *Public Health Reports (Washington)*, 1962, **77**, 887.

⁷ Forrest, J R, *et al*, *Monthly Bulletin of the Ministry of Health*, 1951, **10**, 104.

⁸ Russell, A L, *Journal of Dental Research*, 1953, **32**, 138.

⁹ Murray, J J, *British Dental Journal*, 1971, **131**, 391, 437, 487.

¹⁰ Jackson, D, *et al*, *British Dental Journal*, 1973, **134**, 419.

Commitment to oncology

SIR,—The letters of Mr W H Bond and Dr S Dische (7 May, p 1214) bring to the surface an important issue for the future of oncology in the UK. They make unequivocal expressions of an objective, undoubtedly shared by others, that radiotherapists should have complete control of non-surgical cancer work with respect to both training and clinical practice.

To settle the dust it should be observed that the high standard of radiotherapy in the UK is well recognised, and, so far as I know, the

commitment of radiotherapists to oncology has not been questioned. What is questioned, as Dr Bond points out, is the "superior position of the radiotherapist as an authority on cancer." It isn't possible to answer this briefly and adequately, but perhaps the crux of it is that radiotherapy seems to have acquired, fairly or unfairly, the image of a discipline focused on current therapeutic practice at the expense of inquiry. Chemotherapy received tardy recognition by some radiotherapists, and Dr Bond's denigratory comments do little to promote confidence that one person can handle both successfully. Moreover, if a single specialty were as effective as Dr Dische suggests, would we not have seen British radiotherapy departments creating, rather than following behind, the recent advances in cancer treatment?

Training is indeed the central issue. The suggestion that there should be a single route with experience largely confined to radiotherapy departments backed up by a series of lecture courses and college examinations has little merit. It would allow radiotherapists to reproduce in their own likeness and would be admirable if the subject were completely ossified, but it's likely to drive the more able and original young people out of the country, or out of cancer work, with some speed. Medical oncology training takes 7-8 years' post-registration, and to substitute or add two years in radiotherapy would be unacceptable. Moreover, radiotherapy has already diminished in relative importance and it no longer provides a suitable foundation for training all future oncologists. Surely cancer problems are big enough to need clinicians with different training and different experience in clinical and research fields, and there is no reason why they should not work as equals within the same "oncology departments." In this medical oncologists will find common ground in Professor K Halnan's comments (14 May, p 1280), but the opportunity to replace retiring radiotherapists with medical oncologists is largely in the hands of radiotherapists.

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Modern treatment of eye injuries

SIR,—It is to be regretted that your contributor in an otherwise useful and informative leading article on the modern treatment of eye injuries (14 May, p 1237) should have seen fit to raise yet another reference to the eye as a "complex and delicate organ." It is almost certainly a truth that the eye is neither more complex nor delicate than any other part of the body. Indeed, the experience of many of those concerned with ocular trauma is what remarkably gross injury it can endure and yet retain or regain a surprisingly effective amount of function.

Over the years ophthalmologists have been attempting to disabuse not only the public but also the professions (who have, from fear and apprehension, been very wary and chary of ocular matters) of this error. When statements such as this again appear the programme of education and understanding takes a large leap backwards, undoing the pitiful forward gains of earlier years.

This in no way gainsays your leader's view that a reasoned, detailed, and painstaking