treating underlying disease or at affecting mood and an understanding emotional support.

Having said all this, one must still welcome the study by Bungay *et al* as a carefully executed and well presented account of the verbal aspects of the folkloric expression of the menopause in southern Britain and the pool of "middle-age symptoms" from which they are chosen.

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[2] Donovan JC. *Am J Obst Gynec* 1951;**62**:1281-91.
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Retroperitoneal fibrosis associated with atenolol

SIR,—There are many points raised in the two letters concerning retroperitoneal fibrosis and beta-blockers (26 July, p 311). For conciseness I will reply only to the main points raised, largely by using their figures and diagram. Quotations are from the letters.

I consider first the letter of Dr Winifred M Castle and others:

(1) "We feel that beta-blockers are no more likely than other antihypertensive agents to be associated with retroperitoneal fibrosis." Reports of retroperitoneal fibrosis to the Committee on Safety of Medicines (August 1980) total 30: eight with methysergide, 14 with beta-blockers, and eight with other drugs. In this last group of eight a total of 20 drugs are listed, 19 of which appear only once. Thus beta-blockers as a group predominate.

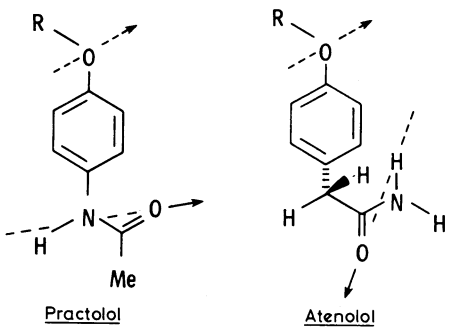
(2) They consider that retroperitoneal fibrosis occurs merely coincidentally with beta-blocker therapy and consider it "hardly surprising." On their figures, three cases are reported with 3 000 000 patient years of therapy for propranolol and four cases with 600 000 patient years of practolol and atenolol therapy, two compounds with some structural similarity. This distribution would occur by chance less than one in 50 times ($p < 0{\cdot}018$, Fisher's test). Thus some beta-blockers may be more likely than others to be associated with retroperitoneal fibrosis. (It should, however, be noted that pindolol was also taken in one of the two practolol cases.)

(3) While, as Dr Castle and her colleagues note, a number of patients have been transferred from practolol to atenolol with resolution of their "fibrosing oculomucocutaneous syndrome" they omit to say that the 14 patients reported by Zacharias[1] were described as having ocular and cutaneous lesions and *not* sclerosing peritonitis.

The letter of Dr F L Rose and Professor F Bergel contains three main points:

(1) "The mass of a drug substituent group has no accurately definable relationship to its biological activity." A drug-receptor interaction, in some respects, may be likened to a lock-and-key relationship, just as with an enzyme-substrate interaction. While not all Yale keys open all Yale locks I would suggest that the choice of a key of appropriate design and size increases one's chances of obtaining the desired (or, in the case of a drug side effect, undesired) result. Atenolol, practolol, and oxprenolol all provide keys of the same size.

(2) "The strong carbonyl (-C=O) dipoles of practolol and atenolol face different ways. . . ." With regard to atenolol, there is rotation about the two single bonds between carbonyl carbon and the point of attachment of the side chain to the ring. Rotation about these bonds causes the carbonyl dipole of atenolol also to face to the right, most easily seen with molecular models. The carbonyl oxygen sweeps out a volume in space as the bond rotates—hence the usefulness of the "nebulous



Practolol Atenolol

concept of associated electron clouds." There is little rotation about the carbonyl-nitrogen bond in either molecule. These bonds have partial double-bond character, similar indeed to the amide linkage in proteins. Viewing practolol from the reverse face of the benzene ring causes the dipole to be directed to the left, not the right. Unfortunately, calculations of most stable dipole directions in solution do not give information about dipole direction when bound to a receptor.

(3) The statement that the partition coefficient is "the important π factor determining biological activity in Hansch functions" is misleading. Many other factors are involved.[2] Thus oil-water partition coefficients for salicylamide and phenobarbitone are both 5·9, for barbitone 1·4, and for amidopyrine 1·3.[3] The reader may judge how well biological activity and partition coefficient correlate for these substances. Similarly, atenolol and oxprenolol have different partition coefficients but the common biological activity of beta-blockade. Partition coefficients in fact give more information about pharmacokinetic handling than biological activity.

Overall I do not share the confidence of Dr Castle and her colleagues that "the evidence to date is reassuring." Readers may judge for themselves whether there is a small cloud of suspicion overhanging beta-blockers in general, and perhaps some in particular, with respect to their association with retroperitoneal fibrosis.

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[1] Zacharias FJ. *Br Med J* 1976;i:1213.
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[3] Bowman WC, Rand MJ. In: *Textbook of pharmacology*. 2nd ed. Oxford: *Blackwell Scientific Publications*, 1980: 40-3.

Physical training and coronary risk factors

SIR,—Dr P E Moffitt (9 August, p 453) surely is justified in emphasising the difference between risk factors, as studied by Dr Antony W Sedgwick and others (5 July, p 7), and actual occurrence of coronary disease, if only because the media are so liable to get it wrong—as indeed happened in this instance. Moreover, it is doubtful whether there is particular point in further search for the mechanisms or pathways of a possible protective effect of exercise against coronary heart disease in the classical risk factors.[1] Interest has shifted to the training process itself[2]—for example, to thrombosis and lysis[3 4] and to the improvement in lipoprotein patterns with the rise of high-density lipoproteins.[5]

I hasten to add, however, that the middle-aged civil servants in our own study[6] did not engage in "violent" exercise. No marathons, all-in wrestling, judo, or karate, no rugger, not even squash. . . . The definition of *vigorous* exercise in leisure-time is that likely to incur peaks of energy expenditure of 31·5 kJ (7·5 kcal) per minute. The forms commonly taken, presumably enjoyed, and encouragingly associated with a low incidence of coronaries in eight and a half years of follow-up (recently completed) are swimming, tennis, brisk walking, running (jogging), hill climbing, keep-fit exercises, and the like.

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[1] Paffenbarger RS. In: Amsterdam EA, Wilmore JH, DeMaria AN, eds. *Exercise in cardiovascular health and disease*. New York: Yorke Medical Books, 1977:35-49.
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[6] Morris JN, Chave SPW, Adam C, Sirey C, Epstein L, Sheehan D. *Lancet* 1973;i:333-9.

Hyperlipidaemia advances and retreats

SIR,—As a general practitioner at present engaged in a research project to correct major risk factors for ischaemic heart disease in a random sample of one-third of our patients between the ages of 20 and 60, I find that the leading article on hyperlipidaemia (2 August, p 340) presents an extremely poor representation of the correct situation regarding the treatment of hyperlipidaemia.

While the subject is clearly controversial, it needs to be stated quite emphatically that even the authors of the report on the WHO clofibrate trial[1] were extremely puzzled by a number of anomalies in the trial. To state that the overall increased mortality outweighed the benefit for the person studied would appear to amount to a failure to recognise the basic problem experienced by any attempt to perform a double-blind randomised trial of a drug in a complicated multifactorial disease. When one looks carefully and critically at the failure of clofibrate to reduce the overall death rate in the treated compared with the non-treated hyperlipidaemic group, it will be noted that the excess mortality in the treated group was in fact in the disease category of malignancy. It will be further noted that the malignancies with the most significant difference between the two groups were, firstly, carcinoma of the bronchus and, secondly, the carcinomas of the oesophagus and stomach. If we add these two groups of malignancies together in the clofibrate group of patients, 26 patients died of these predominantly smoking-related carcinomas, whereas in the non-treated group only 15 patients died from these carcinomas.

The only conclusion which one could reach in the circumstances is that the investigators had, not surprisingly, found extreme difficulty in actually matching the smoking levels of the members of the two hyperlipidaemic groups. Since fatal myocardial infarction is relatively more common when it presents in smokers than in non-smokers,[2] it would seem that this discrepancy in the smoking levels in the two groups may also be the basic underlying reason why clofibrate reduced the non-fatal myocardial infarction by 30% but failed to influence the mortality rate of the two groups from myocardial infarction. In the circumstances it would be unwise to write off the use of clofibrate in hyperlipidaemia, as appears to have been the case, on the basis of the WHO trial, as quite clearly, attempting to assess a drug of this sort in a multifactorial disease throws extreme doubt on the validity of the trial one way or the other.

The end of the leading article on hyperlipidaemia was so vague in its recommendations for the physician that as an experienced worker in this field one was left wondering whether the article was based on actual experience of the problem of the primary prevention of arterial disease by

correction of known or suspected risk factors. There is clearly no magic formula, in my experience, which can be placed across the board and applied on a mass scale. There is, unfortunately, no alternative to the careful investigation of every patient on an individual level, correcting each risk factor presented, energetically, by the safest and most acceptable means for the patient. Clearly, the correction of hyperlipidaemia by all reasonable means must be included in any treatment programme for the prevention of atherosclerotic arterial disease. Unfortunately, all large multicentre trials that I have seen seem to fail in that they do not treat the whole patient, and for this reason grave doubt must be thrown on their validity in testing the concept of the primary prevention of arterial disease by studying one factor and seeking to match all other factors.

The review article by Professor Lewis (19 July, p 177) gives a clear and positive approach to the problem without leaving the physician with no guidelines to offer the patient.

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[1] A report from the Committee of Principal Investigators. *Br Heart J* 1978;**40**:1067-118.
[2] Royal College of Physicians of London. *Prevention of coronary heart disease*. London: Royal College of Physicians, 1976:21.

Social environment and relapse in schizophrenia

SIR,—Your leading article on social environment and relapse in schizophrenia (19 July, p 173) summarised the recent excellent work of the Medical Research Council Social Psychiatry Unit. It identified the value of medication and the importance of family life for the course of the illness. It lacked, however, a clear statement of the possible value of intervention in the family interaction processes to reduce excessive "emotional involvement, hostility, and dominance," which predisposes to relapse.

At least one methodologically adequate study in the United States suggests that family therapy may be useful,[1] and work in this country has examined some details of the pathological interactions.[2] The only family intervention explicitly suggested is removal of the patient from the family. As clinicians know, this is often unsatisfactory or unworkable. It is not unreasonable to think that sophisticated epidemiological research may clarify the value of family therapy techniques.

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[1] Langsley DG. *Am J Psychiatry* 1971;**127**:1391-4.
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What is "emergency"?

SIR,—I have no wish to play sword and buckler with my friend Mr W H Rutherford (26 July, p 308)—there might indeed be a casualty.

Shakespeare did *not* use the word casualty for the seriously injured—as a glance at a concordance will show.[1] Dickens's "casualty ward"[2] contained more than those injured. If Mr Rutherford knows of other references perhaps he will tell me.

In the sixteenth century casualty meant "a chance event" and it was used in this sense in the Rules and Orders of Newcastle Infirmary (1751).[3] In soliciting support, its founders[4] had drawn attention to the case of a poor woman, run over by the York Waggon, who lay in a public place for six hours before she received attention[5]; and so we have in the rules, repeated by other voluntary hospitals,[6] the phrase "casualties when patients are suddenly brought in." The use of the word casualty depended on the communal setting and the irregularity of timing, not the injury. The word casual, as "casual losses," not casualty, was used by the Army until much later than 1810.[7] Mr Rutherford is quite correct in quoting the *Lancet* reports of 1869. It was probably the interest being shown which prompted Robert Bridges to write his now famous account of the casualty-outpatient department at St Bartholomew's Hospital.[8] In reading this first-hand account we see that the work of Robert Bridges there was at set times and was that of a dispensary physician. The "casualties" were the third category of patients, many with far from trivial complaints, being treated by the house surgeons (and house physicians) in the corner of the room. Perhaps it was the realisation that in protesting about the number of his patients he was talking himself out of a job which made him turn to other, perhaps less frustrating, pursuits. In any case it was these patients whom all subsequent reports have tried to restrain. Mr Rutherford's "casual" patient never has been a problem; if he does not come with a flea in his ear he certainly leaves with one.

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[1] Bartlett J. *Concordance of Shakespeare*. London: Macmillan, 1927.
[2] Dickens C. *Sketches of Boz. The hospital patient*. London Gresham Publishing Co, 1860:180.
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[4] Hume WE. *The Infirmary, Newcastle upon Tyne*. Newcastle upon Tyne: Andrew Reid and Co, 1951:2
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[6] *Rules and Orders of Nottingham General Hospital*. Cresswell, 1781:15.
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[8] Bridges R. *St Bartholomew's Hospital Reports* 1878; **14**:167.

Factor VIII supply and demand

SIR,—Dr Peter Jones (21 June, p 1531) is to be congratulated for his perceptive analysis of what is a complex and fascinating topic. He is right to conclude that nothing can be achieved in our search for self-sufficiency in blood and blood products without considerable changes in the organisation of collection and processing of blood and in our attitudes to its optimum use. Dr Aronstam's cri de coeur (21 June, p 1532), though understandable, was somewhat one-sided in defining where the problems lay and how they could be solved. Perhaps it would be helpful to make the following comments:

(1) There is now sufficient evidence to support the view that the calculations made in 1975 of the future factor VIII requirements in the UK were a significant underestimate. This view is fully recognised by many colleagues in the UK Transfusion Services and current forward planning is cognisant of this fact.

(2) Considerable efforts are being made to secure a position in which sufficient plasma fractionation capacity, based in the United Kingdom, will be available to meet the anticipated demands for the future. It would be naive to conclude that the single major problem in this area is lack of finance. However, this and the other problems are being actively explored against a background assumption that the vital and sustaining quality of our voluntary blood donation services must be secured. None of these difficulties is insurmountable; but resolution will require much effort, improved organisation and business skills, active collaboration between all concerned, and a resolve to maximise flexibility and minimise unnecessary expenditure.

(3) Unlike Dr Jones, Dr Aronstam failed to mention a most important aspect of the problem of national self-sufficiency in blood products—the availability of plasma for fractionation. Although there are several outstanding exceptions, there is little doubt that unless those in charge of hospital blood banks are more successful in persuading clinical colleagues to use red-cell concentrates rather than whole blood in the management of the majority of routine hospital transfusions, the creation of major new plasma fractionation facilities will not be the salvation Dr Aronstam seeks. Each year many thousands of litres of fresh plasma are being directed away from fractionation in the United Kingdom, and it is increasingly clear that the key to preventing this loss is held by the medical profession. Here is an area in which Drs Jones and Aronstam and their colleagues can make a contribution now and in so doing reduce the necessity for the transfusion services to develop large-scale plasmapheresis programmes.

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Pre-eclampsia and eclampsia and change of paternity

SIR,—We appreciate that the printers' dispute in the spring has made a nonsense of the dates appearing on your numbers over several months. This presumably accounts for the fact that your leading article "Inheriting pre-eclampsia" (28 June, p 1557), which gives a generally excellent review of the current state of knowledge on immunogenetic possibilities and pre-eclampsia, fails to refer to the important short report from Nigeria by Mr Dozie Ikedife (5 April, p 985). This provides strong support for the idea that pregnancies by new consorts carry a higher risk of severe pre-eclampsia or eclampsia than that holding for multigravidas in general.

This information is very important in relation to immunogenetic ideas about the aetiology of this strange condition and underlines the value of collecting data from parts of the world where the condition is still relatively common. Retrospective studies in our own area[1] [2] showed that out of 34 201 deliveries there were 47 instances in which severe pre-eclampsia had occurred in multiparas who had normotensive pregnancies. Thirteen of these patients were found to have a change in paternity for the affected pregnancy compared with three matched controls.

The evidence is beginning to suggest that a pregnancy by a particular father gives the mother a degree of immunity to the condition in subsequent pregnancies by that father but that this does not cover pregnancies by other men. It would thus seem that pre-eclampsia