subjects' figures and tried to represent them graphically, purporting to present a degree of precision that does not exist. The points on the graph in both groups give the appearance of representing mean concentrations on most days of the cycle in all subjects, whereas one point may represent the progesterone level in only one subject, and be joined to that of a totally different subject on the next day. The findings that the authors considered to be most significant, between days 10 and 12 premenstrually, may represent only single readings in three subjects. Additionally, the graph shows the high level of progesterone in symptomatic subjects compared with the asymptomatic group during the immediate three premenstrual days, whereas the table indicates the reverse.

In contrast to these authors, at least eight publications, including those of Bäckström,^{3,4} have discussed an imbalance between oestradiol and progesterone in the second half of the cycle or reported an absolute lack of progesterone in a much greater number of subjects. Mr O'Brien and his colleagues do not report oestrogen levels in their paper, and so we do not know whether a relative deficiency of progesterone actually exists. It has been further suggested⁵ that the obvious cause of premenstrual syndrome is a change in plasma hormone values from the time of ovulation. Changes in progesterone levels from high after ovulation to low premenstrually are certainly claimed by the authors, the high levels preceding changes in mood; could it be, therefore, that administration of progesterone from around the time of ovulation to menstruation would flatten this variation and relieve symptoms?

Irrespective of the aetiology of premenstrual syndrome the most effective therapy should be employed. Although Sampson's study² of progesterone versus placebo showed no difference, a suppository or pessary was used, the treatment period was short, and the number of patients was small. Perhaps the most work and the best results to date have been reported for dydrogesterone,⁶⁻¹⁰ which is orally active—although there is still need for further study and much work is under way.

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¹ O'Brien PMS, Craven D, Selby C, Symonds EM. *Br J Obstet Gynaecol* 1979;**86**:142-7.

² Sampson GA, Jenner FA. *Br J Psychiatr* 1977;**130**: 265-71.

³ Bäckström T, Cartensen H, Sodergard R. *J Steroid Biochem* 1976;**7**:473-6.

⁴ Bäckström T, Cartensen H. *J Steroid Biochem* 1974;**5**:257-60.

⁵ Studd J. *Br Med J* 1979;**ii**:410.

⁶ Taylor RW. *Curr Med Res Opin* 1977;**4**, suppl 4: 35-40.

⁷ Strecker JR. *Fortsch Med* 1980;**98**:145-7.

⁸ Romanini C, Liverani A, Arduini D, Lafuente G, Manfredi L. *Ann Oset Ginecol Med Perinat* 1979; **100**:250-65.

⁹ Taylor RW, James CE. *Curr Med Res Opin* 1979;**6**, suppl 5:46-51.

¹⁰ Day JB. *Curr Med Res Opin* 1979;**6**, suppl 5:40-5.

*We sent this letter to the authors, and Mr O'Brien's reply is printed below.—ED, *BMJ*.

SIR,—Our recent article appears to have aroused a mixture of predictable reactions, many of which contradict each other. Although the study shows subjects which have a measurable increase in the classical symptoms of the syndrome, specifically during the premenstrual phase, Dr Katharina Dalton suggests that they are not adequately defined. In her definition (5 July, p 61) she states that in premenstrual syndrome "symptoms should recur regularly at the same phase of each

menstrual cycle, followed by a symptom-free phase in each cycle"—a definition which does not even require that symptoms occur premenstrually. In her previous writings¹ she has included women whose symptoms occur during ovulation and menstruation and even implied that those who are postmenopausal may suffer.

While Drs Martin and Downey (above) recognise that I have defined the subjects using the premenstrual mood index (PMI) this is not to their satisfaction. The "symptomatic" group were initially self-referred for treatment and subsequently volunteered for the study. The PMI² was used as a scientific method for defining the groups and excluding women without significant premenstrual syndrome—that is, those with so-called "menstrual distress." Even so, the serum progesterone values for the same subjects when self-defined differ only marginally from those reported in the paper (that is, defined by the PMI). In symptomatic subjects (n=20) the mean ($\pm$ SE) serum progesterone was 22.3 ± 3.9 nmol/l (69.7 ± 12.2 ng/ml) whereas in control subjects (n=8) it was 8.9 ± 2.7 nmol/l (27.8 ± 8.4 ng/ml). This was again statistically significant ($p < 0.025$).

Although Drs Martin and Downey point out quite rightly that blood samples in each phase of the cycle cannot be related to ovulation, this has been overcome by retrospectively redating the values from the onset of the next menstrual cycle. These were represented graphically and again the difference in progesterone values was shown. We were, however, careful to point out that daily samples for each patient would be necessary to confirm the finding. Not surprisingly, the inclusion of menstrual cycles of normal duration meant that the majority of day 18 samples fell in the important days of the study.

Dr Martin's argument is inconsistent. He questions the validity of the findings because of the small unequal groups and the omission of the Moos menstrual distress questionnaire for symptom measurement. At the same time he attempts to support his argument by citing several studies with unequal groups of smaller size,³ which did not use the Moos menstrual distress questionnaire and even failed to define the syndrome. These studies concluded that symptoms correlated more closely with oestrogen than with oestrogen:progesterone ratio or progesterone deficiency. Moreover they looked only at the premenstrual six days and therefore the changes follow the onset of symptoms in the majority of patients.

The most surprising fact is that these letters quote results of studies^{4,5} which were not double blind and in some cases not even controlled by placebo therapy—a major omission since there is a well-established placebo effect in this syndrome, frequently reported to be greater than 40%.⁶

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¹ Dalton K. *The premenstrual syndrome and progesterone therapy*. London: Heinemann Medical Books, 1977:61.

² O'Brien PMS. *Endocrine changes in the premenstrual syndrome*. MD thesis: 1979.

³ Bäckström T, Cartensen H. *J Steroid Biochem* 1974;**5**:257-60.

⁴ Taylor RW. *Curr Med Res Opin* 1977; **4**, suppl 4: 35-40.

⁵ Greene R, Dalton K. *Br Med J* 1953;**ii**:1007-14.

⁶ Day JC. *Curr Med Res Opin* 1979;**6**, suppl 5: 40-5.

Symptoms in middle life and the menopause

SIR,—While one admires the techniques employed by Dr G T Bungay and others and reported in their recent article (19 July, p 181) it is impossible not to be disappointed by their neglect of basic features of their subject matter. In this they are unfortunately not alone, for most studies of menopausal symptoms repeat the same mistakes.

Symptoms are by definition the complaints of the patient. They are means of communication by which she secures the attention of her doctor, asks for his help, and explains her plight to him. They are not data. They are not a scientific report on unpleasant sensations caused by physical factors. In acute conditions such sensations are likely to overshadow everything else: the patient's complaints may then be clinically very informative. Not so in subacute or chronic illness. The patient then often utilises bodily sensations only to communicate her discomfort or illustrate her malaise. Moreover she always does so with a changing emphasis, which depends on her emotional state, her social position, and her culture. Studies which investigate symptoms of this type as if they were data are sure to produce distorted results.¹

Symptoms vary with the situational factors obtaining at the meeting between patient and doctor.^{2,3} They depend on the relationship between them, different symptoms being presented by the same patient, in the same illness, to different doctors. Symptoms always have, moreover, an important non-verbal aspect. This may, in fact, often be much more significant than their verbal component. Medical practitioners have always known it; they have always recognised that what the patient does not verbally say, is even not completely conscious of, may be of greater importance than what she says. Questionnaires can obviously never probe this aspect of semeiology, or be utilised to study the totality of the patient's symptoms.

The position in the related field of evaluation of the reactions to complex stimuli may therefore be of interest. USA advertising firms are, for instance, now increasingly turning away from questionnaires as a tool of market research. Instead they investigate the impact of their advertisements by examining the encephalograms of people who watch television advertising under conditions similar to those obtaining in their homes. No verbal comment is sought. Researchers in medicine, however, still place the same reliance on symptoms as they did when Cullen devised his nosology.⁴ Compounding misunderstanding, they pluck them out of context, in the medical interview, in repeated attempts at analysis by impersonal questionnaires, treating them as if they were census data.

What do these studies prove? At most they show that women and men in Oxford, or among similar populations, have a cultural pool of verbal symptoms which they utilise in middle life—that Western women in the climacteric pay special attention to vasomotor sensations and utilise them, when disturbed, to express their dissatisfaction. It may even be justifiable to conclude that this pool of verbal symptoms and their non-verbal counterparts provides the material from which a "folkloric expression of the menopause" is formed. This may then be presented as a syndrome by women who are unable to cope with social stress at this time.⁵ Had the study been carried in another country the results would have been very different. Not only do social stresses vary in different societies, but modes of communication are different in different cultures. So are symptoms and illnesses.⁶

As the authors remark, their study provides no "evidence concerning the effectiveness of hormone treatment." Evaluation of improvement in symptoms, in the context of the medical interview, by the same therapist, is, however, as amply proved by generations of doctors, a reliable method of assessing the treatment of illness. This, needless to say, can never be unifactorial. It should always include both pharmacological agents aimed at

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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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 ($p < 0.018$, 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 Zacharias¹ 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

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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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 itself²—for example, to thrombosis and lysis³ 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 study⁶ 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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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 trial¹ 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