toms, and the possible psychoactive properties of oestrogen. However, even if hormone replacement therapy increases wellbeing or improves mood, this would not necessarily mean that depression is caused by low levels of oestrogen.

Taken together the above findings suggest that to attribute depression in a middle aged woman automatically to the menopause is overly simplistic and usually unjustified. The menopause has a psychological, social, and cultural, as well as a biological importance. On the biological level there is more evidence in support of prolonged or severe vasomotor symptoms causing distress than hormone levels. Nor should we forget that for most women the menopause is not a major crisis and that many feel relieved to be free from menstrual periods and the possibility of pregnancy.

When a middle aged woman seeks help for depression several possible causes need to be considered. For example, any stresses or conflicts in her life, bereavements, lack of social support, ill health, as well as severe or prolonged vasomotor symptoms that can lead to sleeplessness. She may feel uncertain about the effect of the menopause, have concerns about the physical and social consequences of aging, or her self esteem may be affected by a culture that values youth and reproductive capacity. In my experience a group setting can provide a useful place for women to discuss these issues, to reappraise past events and achievements, and to look to the future. Finally, to attribute depression to the menopause implies a hormonal cause, ignores psychosocial factors, and may indirectly promote the negative beliefs that have been found in epidemiological studies to predict depressed mood in middle aged women.

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Pet birds and lung cancer

Now no evidence of a link

See pp 1233, 1236

The question of whether keeping pet birds increases the risk of lung cancer was first raised by Holst.[1 2] Having noted a higher occurrence of lung cancer among bird owners in a Dutch general practice population, he and colleagues carried out a case control study comparing hospital patients with community matched controls and showed a 6.7-fold increase in risk.[3] Two subsequent studies produced further evidence in support of this observation: one reported a twofold increase in risk of lung cancer in relation to exposure to pet birds in a German population,[4] while the other, from Scotland, showed no significant association with exposure to pet birds in general but a 3.5-fold increase in risk of lung cancer in those who kept pigeons.[5]

At the time, we argued that, although of great importance if valid, these observations might have arisen from residual confounding by cigarette smoking.[6] All of the case-control studies had controlled for smoking in their analysis but categorised cases and controls as smokers or non-smokers; the degree of smoking was not analysed quantitatively. In the ensuing correspondence, the authors of the two more recent reports argued that residual confounding was unlikely to have been a major influence because smoking histories seemed to have been similar in cases and controls.[7 8] Others pointed out further methodological and confounding factors that might also have contributed to false positive results.[9 10] In the end it was probably fair to conclude that the relation between bird keeping and lung cancer needed to be assessed further, in studies with sufficient power and appropriate measures of confounding variables to separate out the independent effects involved.

Two such studies, one from Missouri and the other from Sweden, are published in this issue of the *BMJ* (pp 1233, 1236).[11 12] Like their predecessors, both are case-control studies, but their strengths are that, with 652 and 380 cases respectively, they are considerably more powerful; they have ascertained incident cases only and thus avoided potential survival bias in relation to bird keeping in prevalent cases; they have measured smoking quantitatively and used this quantitative information in their analysis; and they have controlled for confounding by diet and socioeconomic status. They found no evidence whatever of an increase in risk of lung cancer in relation to any measure of bird keeping or exposure. Indeed, in some of the subgroups of exposure to pet or farm birds the risk of lung cancer was significantly reduced. The Missouri study is limited to women only,[11] but the Swedish study includes both sexes and shows no evidence of a gender difference in effect.[12] While there are inevitable potential criticisms of both studies, which the authors acknowledge, in our view none of these is likely to have resulted in odds ratios so close to unity in both reports. We therefore accept the authors' conclusion that keeping domestic birds does not seem to be associated with any excess risk of lung cancer.

So what is the explanation for the discrepancy between these new findings and the previous evidence? We argue, as before, that residual confounding by smoking is highly likely to have distorted the risk estimates in previous studies. In the new Swedish study the estimated odds ratios for lung cancer in current smokers of 20 cigarettes a day were about 32 and 43 respectively for men and women, ratios which far exceed the estimated effect of keeping pet birds in all earlier investigations. In the presence of effects so strong, the potential for bias in estimating the influence of other exposures even loosely related to smoking is substantial. An alternative explanation advanced by the authors is that exposure to pet birds in the populations they have studied is somehow different in intensity or in terms of associated exposures such

as infections, infestations, or other factors related to bird keeping in different countries.

Another potential explanation for the discrepancy is that neither of the two new studies has looked specifically at pigeon keeping, which was the only significant association with lung cancer in the study from Scotland.[5] In Britain at least there is likely to be a substantial difference in the number of birds kept, and consequent degree of exposure, between those keeping pigeons for racing and those who keep one or two birds as indoor domestic pets. It is perhaps still possible that the previously reported associations relate to an underlying effect that is specific to pigeon keeping.

To resolve these uncertainties it would be necessary to repeat these studies yet again in the populations that gave rise to the original observations of an association, taking particular care to deal with confounding effects. However, these two new studies seem to be conclusive in two respects. First, they provide further evidence that, irrespective of any perceived misconception,[13] cigarette smoking remains by far the single strongest and most commonly encountered avoidable cause of lung cancer. Secondly, and importantly for vast numbers of people, they show that keeping domestic pet birds such as budgerigars, canaries, and parrots does not seem to be associated with an increased risk of lung cancer. The question of whether heavier exposure to pigeons carries an increased risk remains unresolved.

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Non-compliance with oral chemotherapy in childhood leukaemia

An overlooked and costly cause of late relapse

In childhood acute lymphoblastic leukaemia, complete remission is usually followed by relapse unless patients receive prolonged outpatient "maintenance" treatment based on daily oral 6-mercaptopurine and weekly methotrexate.[1] When patients relapse unexpectedly some months or years after completing their planned schedule of treatment (as still occurs in 20-30% of patients in Britain), the maintenance component of treatment has probably failed for some reason.

One contributory factor used to be insufficient doses of antimetabolites. Before 1980, four year disease free survival in Britain was less than 50%. Then a more rigid and detailed national protocol was introduced, where maintenance was more aggressively applied and attenuation of the drug dose was not left up to the individual physician. The result was an increase in toxicity accompanied by a 15-20% improvement in long term survival.[2] This experience has persuaded paediatric oncologists in Britain to prescribe the maximum tolerated dose of antimetabolites and to avoid interruptions to treatment wherever possible.

So far, so good. But the story does not end there. It is now becoming increasingly apparent that some children simply do not take the drugs they are prescribed. Based on experience with asthma,[3] tuberculosis,[4] cystic fibrosis,[5] diabetes,[6] and penicillin prophylaxis for sickle cell disease,[7] we know that children often fail to follow important diets or treatment schedules. It is therefore illogical to assume that, just because they have a life threatening disease, young patients with leukaemia will all reliably take pills every day without fail for two years when they (mostly) are in normal health. But despite warnings[8] that is precisely what has been assumed until recently.

The best data on non-compliance come from studies where drug or drug metabolite concentrations have been measured. Several years ago an American study looking at urinary excretion of 17-ketogenic steroid in children supposedly taking prednisone for leukaemia showed that their excretion increased when they were supervised as inpatients.[9] More recently, a study in South Africa measuring urinary excretion of 6-mercaptopurine the morning after a supposed evening dose showed that some patients had no trace of the drug.[10] In Britain we have noted wide variations in the levels of slowly cycling intracellular metabolites of 6-mercaptopurine in some children who are supposedly taking a constant dose.[11] These and other reports[12 13] suggest that 10-30% children fail to take a substantial amount of their prescribed chemotherapy.

It would seem that non-compliance forms a continuum from the occasional lapse to total refusal. The patients most likely to fail are adolescents,[9 11 12] though the problem is by no means confined to this age group. Other risk factors seem to be family size (the smaller the better) and time on treatment (compliance can drift over time).[12] Educational, cultural, and socioeconomic factors are also important.[13]

The evidence that poor compliance matters in terms of disease free survival is circumstantial but persuasive. Firstly, there are widely different outcomes of similar treatment for acute lymphoblastic leukaemia in different countries and communities. Even allowing for possible variations in the incidence of disease subtypes or risk groups, there is a substantial shortfall in the proportion of children achieving long term disease free survival where there is poverty, malnutrition, poor communication between parents and doctors, or low standards of parental education.[14 15] Remission rates may be broadly comparable, but relapse rates are much higher. Many patients default on outpatient care. Persuading some ethnic groups that maintenance treatment is important when the child appears to be "cured" is difficult, and in some countries, 25 to 45% of families fail to attend clinic at all during this phase of treatment.[14]

Then there is other more subtle evidence, even where children are regular clinic attenders and solicitously collect their drugs. Unexpected relapses arise more often in children who tolerate full doses of oral antimetabolites than in those who