Expectation of life* for US women taking oral contraceptives with reported relative risk (RR) of hepatocellular carcinoma

Age at which contraceptives taken	RR=1.0	RR=4.4	RR=20.1
20-24	77.35	77.35	77.35
30-34	77.33	77.33	77.31

*The expectation of life for women who have not taken oral contraceptives is 77.34 years.

possible risk of hepatocellular carcinoma does not substantially alter the pattern of risks and benefits already known.

To place the risk of hepatocellular carcinoma in a public health perspective, in 1979 there were 116 deaths from hepatocellular carcinoma among all US women (users and non-users of oral contraceptives) aged 15-49. These deaths should be compared with the more than 1000 deaths a year from ovarian cancer that are annually averted by current patterns of oral contraceptive use. While there are case reports of women who get hepatocellular carcinoma while taking oral contraceptives, it is not possible to document those who do not get ovarian cancer. There were 2314 deaths from lung cancer among US women aged 15-49 in 1979, almost all of these due to cigarette smoking. To put it another way, oral contraceptive use changes slightly the profile of diseases from which women die, but for women under 35 the overall benefits continue to outweigh the risks.

Finally, the findings from these two studies should not be extrapolated to the many developing countries where the incidence of hepatocellular carcinoma is 10-20 times that in the United Kingdom or United States. Higher rates of hepatocellular carcinoma in developing countries are probably due to a much stronger association with the predisposing factors of hepatitis B virus infection and cirrhosis than in developed countries. Past or current hepatitis B virus infection is found in 74-95% and cirrhosis in 60-90% of all hepatocellular carcinoma cases world wide, but these factors are much less prevalent in young women with hepatocellular carcinoma especially those who used oral contraceptives. Therefore, the percentage of cases of hepatocellular carcinoma in developing countries attributable to oral contraceptive use would be much lower than in developed countries.

JUDITH A FORTNEY
MICHELE BONHOMME
GARY S GRUBB
MALCOLM POTTS

Family Health International,
Research Triangle Park,
NC 27709 USA

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Iron and akathisia

SIR,—The authors of your recent leading articles "Happiness is iron" (12 April, p 969) and "Akathisia—or not sitting" (19 April, p 1034) may be surprised to hear that they could be wedded. The union requires combining an old observation that Ekbom's syndrome has a clear relationship with iron deficiency¹ and the opinion that akathisia bears close similarities to Ekbom's syndrome in that both consist of an irresistible urge to move and bizarre dysaesthetic symptoms in the legs.

The mechanism of akathisia and other neuroleptic-induced movement disorders is poorly understood and it is important to realise that they are not easily explained by a simple theory of dopamine receptor blockade with secondary receptor supersensitivity. For instance, the time course of the involuntary movements (and of the beneficial action of neuroleptics) is by and large at odds with what the pharmacologists tell us about the periods of maximum receptor blockade or the development of hypersensitivity.

Neuroleptics have been known for many years to have an action on ligating metal ions. We have recently confirmed and extended this interesting observation and shown clinically that serious neurological consequences can occur when phenothiazines are combined with an acute iron flux induced by giving desferrioxamine.² Thus ligation of metals may be crucial to a neuroleptic's action. There is evidence that iron may form an integral part of the dopamine (D₂) receptor,³ and certainly it is in very high concentration in the basal ganglia, where most of these side effects must be mediated. As mentioned in Dr D P Addy's perceptive article, iron deficiency alters mentation in man, and we would add motor activity (increased "restlessness" during light exposed periods) in rats.⁴ It would be interesting to know whether extrapyramidal syndromes induced by neuroleptics are commoner in iron deficient people.

D R BLAKE
A C WILLIAMS
H PALL

Medical School,
University of Birmingham,
Birmingham B15 2TJ

Department of Pharmacy,
Selly Oak Hospital,
Birmingham B29 6JD

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Akathisia—or not sitting

SIR,—We were delighted to see Dr E Szabadi's review of akathisia and the prominence given in your journal to this important area of psychiatric practice (19 April, p 1034). However, several points warrant further comment, particularly in the light of our recent work.

Dr Szabadi lists many of the symptoms and signs of akathisia induced by antipsychotic drugs and points out the difficulty and clinical importance of differentiating akathisia from other states of restlessness. However, he fails to mention the specific clinical features which may best distinguish it from these other states of restlessness.

Our investigations have delineated the subjective sense of restlessness associated with akathisia as being specifically referable to the legs, and this often includes the experience of localised parasthesiae. By contrast, we found that a more generalised sense of tension and "inner restlessness" was a common, non-specific complaint among acute psychiatric inpatients. In addition, contrary to Haskovec's original term and the title of the leading article, most patients with akathisia perceive their symptoms as being worse while standing, and this is often borne out by observation. Furthermore, we have observed in patients with akathisia characteristic stereotyped movements

which allow for more accurate identification of the condition in disturbed and psychotic patients. These include shuffling and tramping of the feet when sitting, rocking from foot to foot and "walking on the spot" when standing, and a low frequency, jerky tremor of the feet.^{1,2}

Dr Szabadi mentions that akathisia "usually responds to anticholinergic drugs, and if treatment continues it commonly subsides after two or three months." We found that the condition occurred in association with severe parkinsonism in a small proportion of patients and only in these cases responded to anticholinergic drugs.¹ Current clinical opinion does not support the use of anticholinergic agents as a generally effective treatment for akathisia.^{3,4} The clinical course of akathisia also remains uncertain as no prospective, longitudinal study of akathisia has, to our knowledge, been undertaken. Our observations on patients with chronic schizophrenia suggest, as Dr Szabadi points out, that akathisia may indeed persist in some patients continuing on treatment with antipsychotic drugs and in such cases may possibly be a forerunner of tardive dyskinesia.^{5,6} In addition, we have reported examples of akathisia developing for the first time in patients exposed to long term drug treatment but unrelated to a recent increase in drug dose. The appearance of this "tardive akathisia" may also herald the onset of tardive dyskinesia.^{5,7} These findings have led us to suggest that the presence of akathisia unrelated to recent drug dose increase should alert the clinician to the possible emergence of tardive dyskinesia.⁶

WALTER M BRAUDE

THOMAS BARNES

Cheadle Royal Hospital,
Cheadle,
Cheshire SK8 3DG

Horton Hospital,
Epsom,
Surrey KT19 8PZ

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Effects of indomethacin and sulindac on blood pressure of hypertensive patients

SIR,—Dr R V Lewis and others (5 April, p 934) provided further information about the effects of prostaglandin inhibitors on blood pressure in hypertensive patients. A sustained and substantial pressor effect occurred in subjects who had received indomethacin. Earlier reports proposed that the indomethacin induced pressor effect was related to inhibition of renal cyclo-oxygenase,^{1,2} but similar pressor responses occurred in indomethacin treated anephric subjects.³ Headache is a common side effect of indomethacin, and it has been shown in animals that indomethacin reduces cerebral blood flow.^{4,5} Indomethacin impaired coronary artery blood flow has also been reported.⁶

Vane showed that non-steroidal anti-inflammatory drugs were potent inhibitors of prostaglandin synthesis,⁷ and since then the effects on the 2

series prostaglandins which arise as metabolites of arachidonic acid have been studied intensively, while the effects on the I series have been ignored. Prostaglandin E₁ (PGE₁) appears to play an important part in determining the flow properties of blood through its effect on red cell deformability, and PGE₁ has been shown to improve red cell filterability.^{8,9} The PGE₁ induced enhancement of red cell flexibility has been confirmed by spin labelling.¹⁰ Although there is no information about the adverse effects of non-steroidal agents on PGE₁ synthesis, there are reports of PGE₁ infusions being beneficial in conditions as diverse as Raynaud's phenomenon, peripheral vascular disease, small vessel arterial ischaemia, the adult respiratory distress syndrome, and persistent leg ulcers.

Hypertension is associated with raised blood viscosity,¹¹⁻¹³ and it is possible that the increased blood pressure is needed to overcome the enhanced peripheral resistance arising from hyperviscous blood in the microcirculation. As red cells with reduced flexibility increase blood viscosity, the adverse effects on red cell deformability of an indomethacin induced reduction in PGE₁ synthesis would be additive to any pre-existing abnormality of blood viscosity. Peripheral resistance would rise commensurately and a further increment in blood pressure would be needed to maintain a normal rate of blood flow in the microcirculation.

If an indomethacin induced reduction in PGE₁ synthesis is a key factor in explaining the pressor effects of the drug, then enhanced levels of PGE₁ should be associated with a reduction in blood pressure. Oil of evening primrose, which contains the PGE₁ precursors and linoleic and gamma-linolenic acids, improved red cell filterability in cigarette smokers¹⁴ and in healthy volunteers (unpublished). When given as a dietary supplement to spontaneously hypertensive rats it inhibited the development of hypertension.¹⁵ There is compelling evidence that the ω 3 fatty acid, eicosapentaenoic acid, which occurs in fatty fish and in fish oil, can reduce blood pressure.¹⁶ Furthermore, it reduces blood viscosity and increases red cell filterability.¹⁷ The mechanisms by which the polyunsaturated fatty acids improve red cell flexibility are unknown.

In hypertensive patients the indomethacin induced rise in blood pressure is probably caused by an enhancement of a pre-existing abnormality of blood viscosity. Recognition of this cause and effect allows the well documented effects of diet in reducing blood pressure to become explicable.

L O SIMPSON

Pathology Department,
University of Otago Medical School,
Dunedin, New Zealand

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Sexual abuse of children

SIR,—I was pleased to read Dr N J Wild's account of sexual abuse work in Leeds (26 April, p 1113). The striking rise in the diagnosis of sexual abuse has been paralleled in our own experience. Since we began our sexual abuse project in 1982 referrals have doubled each year—25 cases in 1982, 52 in 1983, 104 in 1984, and 235 in 1985. It is extremely important that the consistent skilled physical examination of children should be coupled with skilled interviewing of the child. In our view each area should be designating specific doctors to carry out such physical and psychological examinations of children.

The Leeds team have shown the advantage of paediatricians taking a special interest in this subject and gaining forensic training and then linking together with the police and police surgeons. In a number of areas there are experiments in training skilled police and social work interviewers to carry out interviews with children who have been abused. To carry out interviews with children who may well be extremely anxious about revealing any information about the abuser, particularly if it is an intrafamilial abuse, requires considerable interviewing skills. There are problems for such interviews in that the laws of evidence in court hearings at all levels mean that questions which rely on leading a child may be seen as somehow influencing the child to talk about abuse and thereby accusing an adult inappropriately.

The problem in our experience is that without the use of such questions it is very hard indeed for children to give information about abuse. The use of dolls certainly helps children who find it hard to speak, particularly younger children. Again, it is not always possible to get children to be able to describe activities spontaneously because they fear punishment or retaliation from the perpetrator or a family breakdown if they reveal or talk about their experiences; even in very young children the risk of family breakdown can be used as a threat.

We know all too well how easy it is for children to retract statements already given, or give them in such a way that they will be disbelieved. There needs to be considerable sensitivity to children's ways of communicating to enable us to make a satisfactory diagnosis. This means the designation of particular people, and it is likely that a combination of skilled social workers and police investigators who have training together and share experience will be very helpful in the first line. Child psychiatric teams will also have to develop skills to be able to help with the more problematic cases to try to increase the knowledge of the likelihood of abuse. This is why it is so essential that all branches of the investigation of abused children

should be as well planned as possible, including the designation of medical people who will develop skills.

Satisfactory diagnosis is extremely important if a mandate for treatment is to be obtained for a treatment project. Our own experience is that the combination of family and group work with the families who have taken responsibility for the abuse of a child in their care can successfully lead to the rehabilitation of a child and possible help for the family. When professionals are convinced that a child has been abused but a diagnosis is extremely uncertain and a family will not take responsibility but rejects the child, then the outcome for treatment is hopeless for that particular family and very worrying for the child; his or her future may have to be with another family or may necessitate his being returned to the family where abuse occurred.

ARNON BENTOVIM

Child Sexual Abuse Team,
Hospital for Sick Children,
London WC1N 3JH

Occurrence of polymyalgia rheumatica in rheumatoid arthritis

SIR,—We agree with Dr R G Palmer and colleagues (29 March, p 867) that the diagnosis of polymyalgia rheumatica in the presence of rheumatoid arthritis is difficult. We are, however, uncertain that their paper has clarified the situation and we are particularly concerned that its message could result in many patients with a flare of rheumatoid arthritis being started on steroid therapy unnecessarily.

The symptoms and signs of rheumatoid arthritis characteristically vary in both severity and site over the course of the disease. Many patients develop symptoms in either shoulders or hip joints after the onset of the disease.¹ This flare might be associated with a raised erythrocyte sedimentation rate and could therefore be confused with polymyalgia rheumatica. Such an exacerbation of rheumatoid arthritis might be expected to respond to prednisolone.

This paper makes no mention of the initial erythrocyte sedimentation rates in two of the five patients nor is the haemoglobin or immunoglobulin status reflected in the table. There is no indication of the response of the erythrocyte sedimentation rate to steroid therapy in these patients, particularly in terms of how rapidly it came down. There is also no mention of C reactive protein values, which are said to reflect response to therapy more precisely than erythrocyte sedimentation rate in polymyalgia rheumatica.²

At present we must conclude that the evidence presented in this paper is insufficient to substantiate the claims made and that the diagnosis of polymyalgia rheumatica in the presence of rheumatoid arthritis remains difficult.

I M RICHARDS
H CAPELL

Centre for Rheumatic Diseases,
Royal Infirmary,
Glasgow G4 0SF

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SIR,—The report by Dr R G Palmer and colleagues draws attention to the difficulties posed in establishing the existence of more than one rheumatic disease in the same patient when specific diagnostic tests are lacking and there is overlap between the respective clinical features and diagnostic criteria. While this problem is often of little practical consequence, it assumes importance when different