Papers

Are short normal children at a disadvantage? The Wessex growth study

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Abstract

Objective: To examine whether short stature through childhood represents a disadvantage at around 12 years.

Design: Longitudinal non-intervention study of the physical and psychological development of children recruited from the community in 1986-7 after entry into primary school at age 5-6 years; this is the second psychometric assessment made in 1994-5 after entry into secondary school at age 11-13 years.

Setting: Southampton and Winchester health districts.

Subjects: 106 short normal children (< 3rd centile for height when recruited) and 119 controls of average stature (10th-90th centile).

Main outcome measures: Psychometric measures of cognitive development, self concept development, behaviour, and locus of control.

Results: The short children did not differ significantly from the control children on measures of self esteem (19.4 *v* 20.2), self perception (104.2 *v* 102.4), parents' perception (46.9 *v* 47.0), or behaviour (6.8 *v* 5.3). The short children achieved significantly lower scores on measures of intelligence quotient (IQ) (102.6 *v* 108.6; $P < 0.005$), reading attainment (44.3 *v* 47.9; $P < 0.002$), and basic number skills (40.2 *v* 43.5; $P < 0.003$) and displayed less internalisation of control (16.6 *v* 14.3; $P < 0.001$) and less satisfaction with their height ($P < 0.0001$). More short than control children, however, came from working class homes ($P < 0.05$). Social class was a better predictor than height of all measures except that of body satisfaction. Attainment scores were predicted by class and IQ together rather than by height. Height accounted for some of the variance in IQ and locus of control scores.

Conclusions: These results provide only limited support for the hypothesis that short children are disadvantaged, at least up until 11-13 years old. Social class seems to have more influence than height on children's psychological development.

Introduction

Early research generally portrayed short children as psychosocially disadvantaged.[1-3] More recent studies, however, have found their self concept to be normal,[4] and several studies indicate that short children's self esteem is equivalent to or higher than norms.[5-7] None the less, short children have been reported to display less social competence and more behavioural difficulties compared with normative samples[4 6] or with controls.[8] Lower levels of attainment are still reported despite average intelligence.[8-10] Most studies, however, have been conducted with referred samples and without controls[4 9] and often with mixed diagnostic groupings.[5] It is therefore difficult to generalise their findings to all short children.

The Wessex growth study is an ongoing longitudinal study, begun in 1986, comparing the physical growth and psychological development of a cohort of short "normal" children with that of a cohort of children of average stature.[11] All the children were recruited from the community at age 5-6 years, and the sample avoids the imbalances in social class and sex found in referred samples. The children have been measured for height and weight every six months, and three major psychometric assessments were planned: after entry into primary school (age 7-9 years), after entry into secondary school (age 11-13 years), and at the end of compulsory education (age 16 or over). The first was made in 1989-91, when no differences were found between short and control children in intelligence quotient (IQ), attainment, self esteem, and behaviour once allowance had been made for social class.[12] This article reports the second assessment, made in 1994-5.

Subjects and methods

Subjects

All children beginning primary school in two adjacent health districts in Wessex during 1985-6 and 1986-7 were screened for short stature.[11 13] There were 180 children below the third centile for height by Tanner-Whitehouse standards.[14] Forty children, including 32 diagnosed as having an organic cause for short stature, did not enter the study. The 140 remaining short normal children were each matched for sex, age, and school class with a control of average height (10th-90th centile[14]).

Sample attrition—Of the 140 short normal children originally recruited, 21 have subsequently received treatment as part of a growth hormone trial and therefore were not available for the present assessment. The results to date of the trial have been reported elsewhere.[15] The treated children were compared on all measures with the short children remaining in the larger study and no significant differences were found.[15] There were 106 short children and 119

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Table 1 Physical characteristics of sample at time of 1994-5 psychometric assessment

Height group	No of boys	Mean age (SD) (years)	Mean height SD score (SD)	Mean height (range) (cm)
Short (n=106)	60	12.80 (0.50)	–1.90 (0.57)	139.1 (124.7 to 154.2)
Control (n=119)	65	12.84 (0.54)	0.26 (0.80)	155.4 (142.6 to 172.9)

controls remaining at the time of the 1994-5 assessment. Of the 13 short children who left the study, six left the area and seven refused to continue. Of the 21 control children who left the study, 19 left the area, one refused, and one developed diabetes. Table 1 shows the characteristics of the remaining sample.

Current height—It should be emphasised that the two groups were recruited on the basis of their height at age 5-6 years, and there is now a degree of overlap between the heights of the short and control children. Their present height centile, however, is probably a transient feature of their entry into puberty. Those short children who develop early will temporarily increase their centile whereas late developing controls will decrease theirs. Therefore, in almost all of our analysis, the children are kept within the height group that characterised the major part of their experience and not redistributed on the basis of a passing phase. There is evidence that short normal children at age 5 years are likely to become short adults.[16] It is likely therefore that any overlap in height apparent at age 11-13 years will be considerably lessened at final height.

Current pubertal status—There were no significant differences between our short and control girls in age at menarche or in age at peak height velocity. Nearly all the boys in both groups were prepubertal in 1994-5 and had not yet begun their growth spurt. We therefore had no reason to suppose that more of the short normal children would be delayed in puberty relative to the controls.

Methods

Parents supplied information needed to update social class.[17] Cognitive development was assessed by measures of intelligence (British ability scales (BAS) short form IQ test[18]) and attainment (BAS word reading and basic number skills[18]). Locus of control was measured by Nowicki and Strickland's scale[19] and behaviour was assessed by teachers on Rutter's children's behaviour questionnaire.[20] Self esteem was measured by the culture free self esteem inventory[21] and self perception by Harter's self perception profile for children.[22] Parents' perception was measured by using an adapted Harter scale.[22] Body image was measured by a body satisfaction index, derived from Dowdney *et al*.[23] Statistical analysis was performed with SPSS. Means were compared by *t* tests or one way analyses of variance. Analysis of covariance was made on all measures, and when appropriate, multiple analysis of variance was also performed. Ordinal data were compared with the Mann-Whitney U test. Correlations were measured by Pearson's coefficient.

Table 2 Comparison of height group means for all measures

Measure	Short children		Control children		P value
	Mean (SD)	No*	Mean (SD)	No*	
Intelligence	102.6 (16.7)	106	108.6 (15.6)	119	0.005
Reading attainment	44.3 (8.8)	106	47.9 (8.5)	119	0.002
Mathematics attainment	40.2 (7.2)	106	43.5 (9.2)	119	0.003
Locus of control	16.6 (5.0)	98	14.3 (5.1)	115	0.001
Behaviour	6.8 (7.5)	84	5.3 (6.8)	93	0.16
No (%) with disorder score	29 (30.5)	95	29 (27.6)	105	0.77
Self esteem	19.4 (4.4)	106	20.2 (4.0)	119	0.16
Self perception	104.2 (16.8)	103	102.4 (15.3)	117	0.42
Parents' perception	46.9 (7.2)	98	47.0 (6.6)	112	0.92

*Varies according to numbers of incomplete or spoiled forms or non-response rates.

Results

Tables of means

Table 2 shows means (SD) for the tests comparing short normal and control children. The short children achieved significantly lower scores on IQ and both measures of attainment. They showed significantly less internalisation of control on the measure of locus of control (as indicated by higher scores).

Table 3 shows that the social class distributions of short and control children differed significantly ($P = 0.042$). Table 4 shows the means for all measures by social class. Children in classes D and E did "worst" on all measures—that is, recorded the highest scores on the measures of locus of control and behaviour and the lowest on the other measures. Children from non-manual homes, typically those in class B, did "best."

Table 3 Social class composition of sample at time of 1994-5 psychometric assessment. All figures are percentages

Social class*	National average	Short (n=103)	Control (n=117)	All children (n=220)
A	3	6.8	5.1	5.9
B	14	11.7	19.7	15.9
C_1	26	10.7	17.9	14.5
C_2	25	30.1	30.8	30.5
D	19	27.2	14.5	20.5
E	13	13.6	12.0	12.7

Mann-Whitney U test=5091.5, P=0.042.

*Based on occupational status of chief income earner in household, provided that status had existed for at least two years. Classification and national average figures are taken from the Market Research Society (1991): A, senior management and professional; B, middle management and owners of small businesses; C_1, junior management and clerical; C_2, skilled manual; D, semi skilled and unskilled manual; E, dependent on benefit. Social class was not known for three short children and two controls.

Analyses of covariance

As class is associated with some of the measures used,[19 24] it was necessary to determine and correct for its effect before we investigated the effects of height group and sex. Accordingly, analyses of covariance were performed on all measures with class as the covariate and height and sex as explanatory variables.

Social class had a significant effect on all measures (P values 0.005 for self perception; 0.001 for behaviour; and <0.001 for the remaining measures). After we controlled for class in this way, height group still had an effect on IQ ($P = 0.014$), reading attainment ($P = 0.006$), basic number skills ($P = 0.023$), and locus of control ($P = 0.008$). Table 5 shows the differences between means for these measures before and after adjustment for class. All the differences between short and control children were only slightly reduced and remained significant.

After we controlled for class, sex still had a significant effect on behaviour. As described elsewhere,[6] boys had more reported difficulties than girls (7.6 *v* 5.0; $P = 0.018$). There were no significant height-sex interactions, indicating that sex differences in the short children were parallelled in the controls.

Table 4 Means (SD) for all measures by social class

Measure	A (n=13)	B (n=35)	C_1 (n=32)	C_2 (n=67)	D (n=45)	E (n=28)
Intelligence	114.8 (14.7)	115.1 (12.0)	109.9 (15.9)	104.8 (14.6)	101.4 (16.1)	96.0 (18.7)
Reading attainment	50.9 (6.5)	51.0 (7.8)	49.5 (7.8)	46.4 (7.6)	42.2 (9.2)	41.2 (9.3)
Mathematics attainment	47.4 (7.9)	47.5 (9.4)	44.4 (8.8)	41.2 (6.8)	39.1 (6.6)	37.4 (8.2)
Locus of control	13.9 (5.3)	11.4 (5.6)	15.1 (5.4)	15.7 (5.4)	16.8 (4.3)	16.3 (5.4)
Behaviour	5.3 (7.2)	3.4 (4.8)	3.0 (3.0)	5.6 (7.9)	6.9 (7.0)	8.5 (7.7)
Self esteem	21.4 (3.3)	21.5 (4.4)	20.4 (3.7)	20.3 (4.1)	17.4 (4.4)	19.4 (3.7)
Self perception	103.2 (19.9)	108.9 (14.8)	102.7 (15.6)	106.5 (14.7)	97.0 (18.0)	98.3 (14.6)
Parents' perception	46.90 (6.8)	48.42 (5.6)	49.19 (5.0)	47.56 (7.7)	44.98 (6.4)	42.35 (6.5)

Clearly, IQ is associated with attainment. An analysis of covariance that corrected for individual IQs revealed that class continued to have a significant effect on reading ($P = 0.007$) and number skills ($P = 0.044$) whereas height did not. Thus, attainment is explained by class and IQ together rather than by height.

Multiple analyses of variance

When a measure contains subscales, an analysis of covariance cannot indicate which of these show significant differences. Multiple analyses of variance were therefore performed on these measures, again with class as a covariate. No significant height-sex interactions were found, but height had a significant effect within the subscales for IQ and self perception and sex within subscales for self perception. Univariate *F* tests revealed that the short children's lower IQ score was explained by the difference in performance on verbal reasoning (short 51.0 *v* control 54.7; $P = 0.042$) and speed of information processing (54.3 *v* 59.0; $P < 0.001$). On the self perception profile, short children scored significantly higher on appearance (16.9 *v* 15.7; $P = 0.020$). Boys and girls differed on self perceived athletic ability (boys 17.0 *v* girls 15.0; $P = 0.001$), appearance (16.9 *v* 15.5; $P = 0.016$), and behaviour (16.6 *v* 17.6; $P = 0.013$).

Multiple regression analysis

Multiple regression analysis was performed on those measures where both class and height were seen to have a direct effect. Social class was found to explain 14% of the variance in IQ scores while height explained only a further 2%. Analysis of the locus of control scores showed that social class explained 7% of the variance in scores while height explained 3%.

Body image

There was a significant difference in satisfaction with height on the measure of body image. Thirteen (12%) short children were happy with their height compared with 56 (47%) controls ($P < 0.0001$); and 92 (87%) short children wanted to be taller compared with 49 (41%) controls ($P < 0.0001$).

Discussion

The short children in the Wessex growth study have, in two separate assessments made some four years apart, shown normal psychosocial adaptation equivalent, with some exceptions, to that of the controls. While stature did affect some measures—IQ, locus of control, and body satisfaction—its influence fell far short of that of social class. As this study has avoided the (generally middle) class bias of referred samples[5 8 9] and because it includes representation from the full range of social class, it has been possible through analysis of variance to determine the independent effects of class and stature.

Cognitive measures and locus of control

Performance in cognitive tests was clearly related to social class (see table 4). Multivariate analysis supported the view that social class is a better predictor than height of measured intelligence.

None the less, height did seem to have some effect on IQ. The short children were significantly less able on two subscales, but on these the controls had scores well above established norms. There is no indication, therefore, that the short children may have had specific cognitive deficits, as suggested elsewhere.[25] It is also unlikely that the scores reflected differences in biological maturity as neither gestational age nor pubertal status differed significantly between our groups.

Alternatively, short children may be treated differently by their parents and teachers.[26] If they are perceived to be less "mature" then expectations may be lowered and reflected in the results of these tests. The locus of control measure indicates the degree to which children have internalised control or taken responsibility for their own actions, and, as may be expected, this internalisation typically increases with age. Short children in this sample displayed significantly less internalisation of control than the average stature group even after we corrected for social class. This finding may also relate to the way in which short children are perceived and treated by adults.

Behaviour and self esteem

The behaviour ratings of the children by their teachers did not distinguish between the two groups, which conflicts with reports elsewhere of behavioural disturbance in short children.[4 6 8] Our results accord with other work in finding that short children's self esteem seems to be healthy.[4-7] On two measures of this construct,[21 22] the groups displayed similar levels of self esteem equivalent to or higher than norms.[21 27] The differences between sexes in self perception and behaviour displayed by this sample are consistent with those reported in other studies[6 7] and with norms,[20 27] suggesting that the

Table 5 Difference in mean scores (95% confidence intervals) between short and control children before and after adjustment for class

Measure	Unadjusted difference	P value	Adjusted difference	P value
Intelligence	6.0 (1.8 to 10.3)	0.005	5.0 (0.9 to 9.0)	0.016
Reading attainment	3.6 (1.3 to 5.9)	0.002	3.0 (0.8 to 5.1)	0.007
Mathematics attainment	3.3 (1.1 to 5.5)	0.003	2.5 (0.5 to 4.5)	0.018
Locus of control	2.2 (0.8 to 3.6)	0.003	1.9 (0.5 to 3.3)	0.010

Key messages

- Most studies into the psychology of short stature in childhood have been of children referred to clinics, who do not necessarily come from a range of social classes
- In this study, in which referral bias was avoided, short children displayed normal psychosocial adjustment up to age 11-13 years
- Social class was shown to be a better predictor than stature of psychometric performance.

sample is not unrepresentative. These findings were supported by parental perceptions.

The parity between the short and control groups in this study on the measures of behaviour and attainment lends some support to speculations that samples referred to clinics are more likely than community samples to include short children with existing psychosocial difficulties.[6]

Body image

While the body satisfaction index showed that fewer short than control children were happy with their height, the short children recorded more satisfaction with their appearance on the self perception profile.[22] It seems that any dissatisfaction elicited when children were questioned specifically about their height did not affect other areas of their emotional wellbeing and that short stature per se is not a major source of distress. Most of the children, irrespective of their short or control status, reported that they would like to be "quite tall" or "average," indicating a desire for conformity.

Comparison on the basis of current height

We have argued that it is psychologically appropriate to keep the children in their original height groups. In support of this, we found no evidence that the children's current height is a better predictor than original height of psychological wellbeing or that the shortest children are more likely to experience significant problems. The only significant differences between the original short and control groups were in IQ, attainment, locus of control, and body image. No further differences were found when the children were divided on the basis of their height at the time of testing into very short (<2nd centile), quite short (2nd-10th), and average (>10th) groups. The average children still had significantly "better" scores in IQ, attainment, locus of control, and body image. The quite short and very short groups, however, did not differ significantly on these or any other of the measures. These results are consistent with others[5 6] that suggest that the very shortest children are not necessarily the most psychologically vulnerable.

Conclusions

These results provide only limited support for the hypothesis that short children are disadvantaged. Stature seems to have no direct effect on the measures of attainment, behaviour, self esteem, parent's perception, or self perception. Stature does, however, seem to influence IQ, locus of control, and body satisfaction. By recruiting from the full range of social class, we have shown that class has more effect than stature on children's psychological development. These findings apply up to age 11-13 years. What will happen in later adolescence and adulthood remains to be seen.

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Case-control study of leukaemia among young people near La Hague nuclear reprocessing plant: the environmental hypothesis revisited

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Abstract

Objective: To investigate the association between childhood leukaemia and established risk factors or other factors related to La Hague nuclear waste reprocessing plant.
Design: Case-control study.
Setting: Area within a 35 km radius of La Hague, Normandy, France.
Subjects: Twenty seven cases of leukaemia diagnosed during the period 1978-93 in people aged under 25 years and 192 controls matched for sex, age, place of birth, and residence at time of diagnosis.
Main outcome measures: Antenatal and postnatal exposure to *x* rays and viral infections, occupational exposure of parents (particularly ionising radiation), living conditions, lifestyle of parents and children.
Results: Increased trends were found for use of local beaches by mothers and children ($P \leq 0.01$); relative risks 2.87 (95% confidence intervals 1.05 to 8.72) and 4.49 (1.52 to 15.23) when categories were aggregated in two levels (more or less than once a month). Consumption of local fish and shellfish also showed an increased trend (P 0.01); relative risk 2.66 (0.91 to 9.51) when categories were grouped in two levels (more or less than once a week). A relative risk of 1.18 a year (1.03 to 1.42) was observed for length of residence in a granite-built house or in a granitic area. No association was shown with occupational radiation exposure in parents.
Conclusions: There is some convincing evidence in childhood leukaemia of a causal role for environmental radiation exposure from recreational activities on beaches. New methods for identifying the environmental pathways, focusing on marine ecosystems, are warranted.

Introduction

La Hague (France) is one of the three nuclear reprocessing plants operating in the world on an industrial scale (the other two are Sellafield, England, and Dounreay, Scotland). In recent years there has been considerable scientific and public interest in clusters of leukaemia in children in the vicinity of the British plants, which are still considered as being a matter of concern.[1-8] Subsequently, Gardner *et al* reported that occupational exposure to ionising radiation in fathers before conception of the child yields an eightfold increase in risk of childhood leukaemia and could explain the cluster observed around Seascale.[9] These results have been much debated, however, and more recently Doll *et al* concluded that this association is "largely or wholly a chance finding."[10] Hence, the reasons for the increased incidence of childhood leukaemia around the nuclear reprocessing plants are still largely unknown.

In this respect, La Hague, whose mode of operations and nature of discharges are more similar to those at Sellafield and Dounreay than at other nuclear plants, offers an independent opportunity to shed some light on this issue. Two preliminary studies were inconclusive, but in a recent paper we highlighted a small but increased risk of childhood leukaemia in the electoral ward in which the plant is situated.[11-13] The aim of our case-control study, which is the first to be carried out in France although heavy investment in nuclear energy has been made there, was to examine whether childhood leukaemia among young people near the La Hague reprocessing plant is associated with established risk factors or with factors related to the plant.

Subjects and methods

The La Hague facility is situated in Normandy (France) in the rural "Nord-Cotentin" area. The study was undertaken within a 35 km radius of the nuclear plant, hence including the usual places of residence of its workforce. Three other nuclear establishments are located nearby, making this study area one of the most densely nuclearised in the world: a contiguous low level radioactive waste depository; a nuclear power station, 16 km away; and the navy dockyards, 19 km away, where submarine nuclear fuel is handled.

The process for the identification of cases has been fully described elsewhere.[13] Briefly, a list of cases of leukaemia diagnosed (and histologically confirmed) from January 1978 to December 1993 among people aged under 25 years with a residential address in the study area has been retrospectively compiled from local and regional hospitals and pathology laboratories. Doctors' permission to approach the parents was obtained for all 27 cases.

To circumvent the absence of sampling lists (register of live births, National Health Service central register, family practitioner committee registration, etc) and the French tough regulation constraints (access to nominal data from the population census is strictly forbidden), we have relied on the general practitioners of the area who had delivered care to children with leukaemia. No one had computerised patient records, which could have represented a database for sampling. So general practitioners prospectively identified all adult patients who had a child fulfilling the matching criteria with the index case—that is, sex, age (within 2 years), place of birth (inside the current study area or outside), and place of residence (the same electoral ward or a contiguous one) at time of diagnosis of leukaemia of the corresponding case. If so, doctors filled in a brief descriptive form, whatever the final decision regarding the family participation in the study, and sent it immediately to the research team. To avoid a selection bias quality control procedures were applied.

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Table 1 Numbers (percentages) of cases by subtypes of leukaemia, sex, year of birth, and age at diagnosis around La Hague, France, 1978-93

Group	No (%)
Leukaemia subtypes:	
Acute lymphatic leukaemia*	20 (74.1)
Acute myeloid leukaemia	5 (18.5)
Chronic myeloid leukaemia	2 (7.4)
Sex:	
Female	11 (40.7)
Male	16 (59.3)
Year of birth:	
1956-69	7 (26.0)
1970-80	10 (37.0)
1981-90	10 (37.0)
Age at diagnosis (years):	
0-4	10 (37.0)
5-14	11 (40.7)
15-24	6 (22.3)

*One child had Down's syndrome.

Firstly, doctors were asked to check at the end of each week if they had missed some potential parents of controls among their outpatients and if so to get in touch with them. Secondly, when the identification forms were received, their accuracy was checked by the research team, which declared the control eligible or not. Finally, the research team stopped the recruitment for a given general practitioner when the 10th eligible control was included; but because of tight matching criteria and time constraints on the control identification phase (which ended in October 1995), 235 families were asked to participate in the study. Two refusals, one lost to follow up, five absences of answer despite repeated requests, and 35 ineligible controls who did not meet the matching criteria left 192 eligible controls.

Data were collected from parents by way of face to face interviews at home between November 1993 and January 1996. Parents were asked to sign an informed consent form, and those employed at nuclear establishments were also asked for signed permissions for access to their occupational records. Two trained interviewers administered a detailed structured questionnaire that included information on sociodemographic data, medical history, residential history, lifestyle (recreational activities on beaches, consumption of local fruit and vegetables, drinking of raw milk, drinking well water, exposure to electromagnetic fields), and occupational exposure of parents before the child's conception, during pregnancy, and after the birth. Specific data about antenatal exposures (*x* rays, viral infections, drug treatments during pregnancy with the index child) were collected. Regarding children, places of residence, lifestyle, viral infections, and *x* ray exposure up to the date of diagnosis were also recorded.

Radiation dosimetry data for parents ever employed in a nuclear facility were obtained from occupational medical officers who were unaware of the children's status. Radiation details were available in the form of external whole body ionising radiation dosimetry in millisieverts (mSv). We assessed lifetime levels before conception and radiation doses in the three and six months before conception, during pregnancy, and from birth to date of diagnosis of leukaemia. Because of the available data format, these period doses were estimated proportionally from the cumulative doses up to 1982, from yearly doses between 1983 and 1987, and from monthly doses later. The father of one affected child (who had been employed at La Hague only after the birth of his child) and the father of one control refused access to their dosimetries. For a further man hired by a subcontracting company, no information on ionising radiation could be retrieved.

To compare general characteristics between cases and controls, exact Mann-Whitney and χ^2 tests were performed with StatXact-3.[14] Risk factors analyses were carried out within the sets of cases and controls and findings are represented as relative risks (95% confidence intervals). The results were calculated with the exact conditional logistic regression module of the LogXact computer package.[15] Linear trends in the relative risks for ordinal variables were tested by regularly scoring the categories and using these scores as continuous variables. Only univariate analyses were

Table 2 Characteristics of parents and children by case-control group in study of leukaemia among young people around La Hague, France, 1978-93. Values are numbers (percentages) of cases and controls unless stated otherwise

Variables	Cases	Controls	P value
Mothers			
Mean (SD) age at interview (years)	44.9 (11.4)	43.9 (10.7)	0.65
Smoking habits at interview:			
Non-smoker	20 (76.9)	149 (78.4)	1.00
Smoker	6 (23.1)	41 (21.6)	
Educational level (years)*:			
≤10	19 (70.4)	141 (73.4)	0.82
≥11	8 (29.6)	51 (26.6)	
Social class*†:			
1/2/6/8/9/10	21 (77.8)	160 (83.3)	0.55
7	2 (7.4)	16 (8.3)	
3/4/5	4 (14.8)	16 (8.3)	
Mean (SD) No of children	2.8 (1.3)	2.9 (1.6)	0.66
Fathers			
Mean (SD) age at interview (years)	47.4 (11.5)	46.3 (10.6)	0.39
Smoking habits at interview:			
Non-smoker	13 (54.2)	112 (62.6)	0.28
Smoker	11 (45.8)	67 (37.4)	
Educational level (years)*:			
≤10	20 (74.1)	160 (83.3)	0.24
≥11	7 (25.9)	32 (16.7)	
Social class*†:			
1/2/6/8/9/10	5 (18.5)	42 (21.9)	0.21
7	14 (51.9)	119 (62.0)	
3/4/5	8 (29.6)	31 (16.1)	
Children			
Place of birth:			
Hospital	25 (92.6)	184 (95.8)	0.52
Home	2 (7.4)	8 (4.2)	
Admission to a special care baby unit:			
No	22 (84.6)	171 (89.1)	0.62
Yes	4 (15.4)	21 (10.9)	
Congenital abnormality:			
No	25 (96.2)	182 (94.8)	1.00
Yes	1 (3.8)	10 (5.2)	

*At time of child's birth.
†According to INSEE (French National Statistical Institute for Economical Studies) classification widely used in France for administrative and research purposes: 1/2/6/8/9/10— farmers/farm workers/non-manual employees/domestics and service workers/artists, clerical staff, army, and police/non-active people; 7—blue collar; 3/4/5—proprietors, self employed people/directors, managers, professionals, upper white collar workers/technical staff, lower white collar workers.

Table 3 Numbers of cases and controls with relative risks by mothers' lifestyle factors during pregnancy in study of leukaemia among young people around La Hague, France, 1978-93

Recreational activities on local beaches	No (%) of cases	No (%) of controls	Relative risk (95% confidence interval)	P value	No of discordant sets	No of subjects
Never	4 (17.4)	56 (30.1)	1.00	<0.01*	22	207
Holidays only	1 (4.3)	39 (21.0)	0.60 (0.01 to 8.06)			
<Once a month	2 (8.7)	19 (10.2)	2.10 (0.16 to 20.74)			
Once a month to <once a week	9 (39.1)	21 (11.3)	6.69 (1.46 to 42.44)			
Once a week to <every day	4 (17.4)	45 (24.2)	1.99 (0.29 to 16.21)			
Almost every day	3 (13.0)	6 (3.2)	11.84 (0.98 to 157.36)			

*P value for trend across six categories.

performed, the small numbers eligible for inclusion in the study precluding any powerful multivariate analysis. All the statistical tests were two sided and P values ≤ 0.05 were considered significant. For the sake of clarity among the 173 items analysed, only variables associated with a P value ≤ 0.20 are detailed except for fathers' dosimetries.

Results

A total of 27 parents of cases and 192 parents of controls were investigated, the median and modal number of controls being 9 and 10 per case, respectively. Table 1 shows the characteristics of cases by subtypes of leukaemia, sex, year of birth, and age at diagnosis. The distribution of various characteristics of parents and children (at time of birth and interview) were similar in case and control groups (table 2).

Neither parents' medical history nor characteristics of pregnancy or birth revealed significant associations ($P > 0.20$, results not shown but available on request to authors). Regarding viral infections during childhood we found a relative risk (95% confidence interval) of 17.95 (0.93 to 1060.49) for glandular fever (two cases and one control).

Table 3 presents some details about maternal lifestyle during pregnancy. The analyses were restricted to the 23 mothers who lived during their pregnancy and gave birth in the study area. Analysis by recreational activities on local beaches indicated a significant increased trend ($P < 0.01$) and a relative risk of 4.49 (1.52 to 15.23) if categories were grouped in two levels (cut off point of once a month). Analyses by eating habits, use of seaweed as fertiliser, exposure to electromagnetic fields, or characteristics of residences did not indicate any associated risk ($P > 0.20$, results not shown).

Table 4 summarises some aspects of the children's lifestyle. Results for recreational activities on local beaches showed a significant increased trend (P 0.01) and a relative risk of 2.87 (1.05 to 8.72) when categories were aggregated in two classes (cut off point once a month). Consumption of local fish and shellfish yielded similar findings with a significant increased trend (P 0.01) and a borderline significant increased

Table 4 Numbers of cases and controls with relative risks by child's lifestyle factors in study of leukaemia among young people around La Hague, France, 1978-93

Lifestyle factor	No (%) of cases	No (%) of controls	Relative risk (95% confidence interval)	P value	No of discordant sets	No of subjects
Recreational activities on local beaches:						
Never	2 (7.4)	28 (14.6)	1.00	0.01†	26	217
Holidays only	6 (22.2)	64 (33.3)	1.49 (0.20 to 18.30)			
<Once a month	2 (7.4)	18 (9.4)	1.21 (0.08 to 18.89)			
Once a month to <once a week	4 (14.8)	28 (14.6)	2.28 (0.26 to 30.76)			
Once a week to <every day	11 (40.7)	47 (24.5)	4.99 (0.84 to 56.74)			
Almost every day	2 (7.4)	7 (3.6)	6.59 (0.31 to 147.82)			
Eating local fish and shellfish:						
Never	0	24 (12.5)	1.00	0.01†	25	211
Holidays only	0	3 (1.6)	*			
<Once a month	1 (3.7)	13 (6.8)	1.41 (0.04 to ∞)			
Once a month to <once a week	4 (14.8)	26 (13.5)	5.49 (0.60 to ∞)			
Once a week to <every day	22 (81.5)	123 (64.1)	7.62 (1.16 to ∞)			
Almost every day	0	3 (1.6)	*			
Usual local vegetable or fruit consumption:						
No	13 (48.1)	54 (28.1)	1.00	0.20	22	192
Yes	14 (51.9)	138 (71.9)	0.50 (0.18 to 1.38)			
Drinking well water:						
Never	23 (85.2)	179 (93.2)	1.00	0.13	12	124
Ever	4 (14.8)	13 (6.8)	3.45 (0.71 to 13.77)			
Use of electric hair dryer:						
Never	16 (59.3)	152 (79.2)	1.00	0.13	20	161
Ever	11 (40.7)	40 (20.8)	2.28 (0.81 to 6.45)			
Length of residence (No of years):						
On ground floor			0.92 (0.83 to 1.03)	0.15	22	190
In a granite built house or granitic area			1.18 (1.03 to 1.42)	0.01	12	109

*Not calculated.
†P value for trend.

Table 5 Numbers of cases and controls with relative risks by fathers' estimated radiation doses according to time of exposure in a study of leukaemia among young people around La Hague, France, 1978-93

Fathers' exposures (mSv)*	No (%) of cases	No (%) of controls	Relative risk (95% confidence interval)	No of discordant sets	No of subjects
Before conception†:					
0	27 (100.0)	169 (89.9)	1	10	89
0.1-0.99	0	5 (2.6)	‡		
1-34.99	0	7 (3.7)	‡		
≥ 35	0	7 (3.7)	‡		
In 6 months (182 days) before conception†:					
0	27 (100.0)	172 (91.5)	1	9	86
0.1-0.49	0	5 (2.6)	‡		
0.50-2.99	0	5 (2.6)	‡		
≥ 3	0	6 (3.2)	‡		
In 3 months (91 days) before conception†:					
0	27 (100.0)	173 (92.0)	1	9	86
0.1-0.19	0	4 (2.1)	‡		
0.2-1.49	0	6 (3.2)	‡		
≥ 1.5	0	5 (2.6)	‡		
From conception† to birth:					
0	25 (92.6)	171 (90.9)	1	11	99
0.1-0.99	1 (3.7)	5 (2.6)	1.13 (0.02 to 11.09)		
1-3.99	1 (3.7)	7 (3.7)	1.19 (0.03 to 11.09)		
≥ 4	0	5 (2.6)	‡		
From birth to diagnosis§:					
0	21 (80.8)	169 (89.9)	1	12	96
0.1-1.99	4 (5.4)	5 (2.6)	2.99 (0.36 to 25.03)		
2-9.99	0	7 (3.7)	‡		
≥ 10	1 (3.8)	7 (3.7)	1.97 (0.03 to 29.21)		

*Exposure categories: no exposure and thirds among controls.
†Conception was taken to be 38 weeks before date of birth.
‡Not calculated.
§From birth to diagnosis date for cases or corresponding date for controls.

relative risk of 2.66 (0.91 to 9.51) if categories were grouped in two levels (cut off point once a week). Restriction of analyses to the 209 children born in the study area gave quite similar results with significant increased trends (P 0.04 for both factors) and relative risks of 2.34 (0.82 to 7.30) and 2.31 (0.71 to 9.89) for use of local beaches and consumption of fish and shellfish (same cut off points as above), respectively. There was no evidence of any relation with drinking local raw milk or use of seaweed as fertiliser ($P > 0.20$, results not shown). We found an increased relative risk of 1.18 (1.03 to 1.42) a year for homes made of granite materials or built on granite ground. Relative risks around unity were observed for various surrogates of exposure to electromagnetic fields or for time lived in homes with double glazing ($P > 0.20$, results not shown).

There was no evidence of any association with mothers' types of occupational exposures in any period (various chemical products, wood dust, radioactive materials, ionising radiations) ($P > 0.20$, results not shown). A few mothers claimed to have been exposed to radiation, but this led to non-significant relative risks whatever the period considered ($P > 0.20$, results not shown). Fathers' types of occupational exposures were also not related to leukaemia in any period ($P > 0.20$, results not shown). A few fathers claimed to have been exposed to radiation, but no trend seemed to be significant whatever the period considered ($P > 0.20$, results not shown).

According to employment and radiation records none of the fathers of children with leukaemia had detectable lifetime doses before the conception of the child, whereas doses for fathers of controls ranged from 0.15 mSv to 79.00 mSv for the whole period, from 0.03 mSv to 9.10 mSv during the six months before conception, and from 0.02 mSv to 4.62 mSv during the three months before conception. During the gestational period, doses ranged from 0.40 mSv to 1.97 mSv for cases and from 0.06 mSv to 13.29 mSv for controls, and during the postnatal period from 0.20 mSv to 26.10 mSv and from 0.30 mSv to 162.45 mSv, respectively. Table 5 presents corresponding relative risks. We found no significant trend whatever the period of exposure.

Discussion

Our main finding was that some lifestyle factors are associated with the development of leukaemia among young people, suggesting contamination with radiation through an environmental route.

Potential limitations of our survey, as of any case-control study, should be noted. The possibility that a selection bias in the prospective identification of controls has strongly influenced the results does not seem likely for several reasons. Firstly, a two step quality control procedure (internal and external) was used. Secondly, parents and not children were recruited when they visited their general practitioner to avoid the selection of a population having complaints and calling for medical consultations. Thirdly, the high motivation of the general practitioners resulted in a high participation rate (96%) among potential eligible families. Fourthly, cases and controls were comparable for sociodemographic characteristics and perinatal conditions. Although we chose our methods to bypass

legal constraints and to cope with restrictive matching criteria, matching controls on general practitioner's catchment area led (more or less) to matching on socioeconomic status and neighbourhood, hence potentially decreasing confounding effects.[16]

Recall bias can be ruled out, in our opinion, at least for our main findings. Firstly, in contrast with Great Britain, neither public debate nor media coverage on leukaemia clusters around nuclear facilities occurred in France before December 1995 because of previous negative results.[11 12] A cluster around La Hague was suggested at that time,[13] but marine contamination had never been considered.[13] although an aerial route was hypothesised. Secondly, the data collection from cases was completed in March 1995. Hence parents of children with leukaemia would probably not link such exposure as a possible cause of their child's disease. Thirdly, nuclear occupational results are not prone to recall bias because they are derived from dosimetry files. Fourthly, the French public does not yet seem concerned about radon exposure. As a precautionary measure, we did not use the word "radon" in our survey.

Non-significant findings are difficult to interpret because of the wide confidence intervals on many of the relative risks given in relation to the small number of cases included. By performing exact conditional statistical analyses, however, we have used the most powerful statistical tool available. When some data cells are empty, maximum likelihood estimates do not exist whereas the exact method can yield median unbiased estimates, exact confidence intervals, and exact P values. Some chance findings, however are likely because of the number of variables under study.

Marine pathway

Our main finding was that the use of local beaches by children and mothers was associated with the development of leukaemia among the children. If ionising radiations are involved, this suggests a totally different pathway to occupational exposure, putting the environmental hypothesis in the limelight again. Supporting evidence for a causal effect comes from various factors. Firstly, a dose-response effect is highlighted. Secondly, a chance finding is unlikely because of the low P value (0.01) and the fact that another significant variable (consumption of local shellfish and fish) also points to a potential marine pathway. Thirdly, confounding by geographical distribution of places of residence (residence closer to the sea could increase the likelihood of a child visiting a beach to play) is not plausible because of the matching of control on general practitioner (and then on neighbourhood). Fourthly, this result does not stand in isolation, being in agreement with the study conducted by Urquhart *et al* around Dounreay.[17] The use of local beaches before diagnosis also appeared as a significant risk factor in this area (P 0.04).

An earlier study has found an excess of childhood leukaemia in the electoral ward containing the reprocessing plant.[13] A pertinent question is to what extent this excess may be explained by the demonstrated association with use of beaches. All four children with leukaemia who lived in this ward played on the beach at least once a month compared with 13 out of the 23 similarly affected children who lived in the remaining area (exact P trend on six categories 0.14). Hence, the observed geographical excess can be explained by the association of playing on the beach with leukaemia.

At La Hague most routine releases of radionuclides have been discharged through chimneys. Liquid releases occurred by direct piping below the surface of the Channel. Besides, leaks from the contiguous low level radioactive waste depository to groundwater pathways and releases from the two other nuclear establishments of the study area (both on the coastline) may have contributed to marine radioactive exposure. Nevertheless, in a comparison of the amounts of liquid releases (15 times lower than gaseous releases) the evidence would rather lie in the environmental pathways by which radiation reaches the body rather than in the quantitive aspect of releases. Individual lifestyle (bathing and playing on the beach) can extend the contact with radionuclides in the environment and result in possible uptake of high levels of contamination.[18] Besides, larger particles of insoluble materials can settle out near the discharge point. Radionuclides in particulate form are especially subject to concentration by filter feeding organisms and then by the whole aquatic food chain. As a result, intake of radionuclides such as strontium-90, which tends to concentrate in bones, is probably higher for consumers of small fish. Finally, for radiation exposures from external sources in the environment, the absorbed dose to body organs increases with decreasing body size, as with children.[18]

Paternal exposure

Our data clearly do not support a genuine association of leukaemia with fathers' occupational exposure to radiation. Among fathers of children with leukaemia, none had accumulated any dose before conceptional, detracting from the conclusions of Gardner *et al*,[9] and no significant trend was seen during the subsequent periods. These results are in line with those from two case-control studies conducted around Dounreay and in Ontario.[17 19] Apart from the fact that Gardner's results could be due to chance alone,[11] two explanations for the discrepancy between findings from Sellafield and La Hague can be put forward. Firstly, figures for all the control fathers indicated that radiation exposure in workers was somewhat lower in La Hague. For cumulative preconceptional doses, 89.5 % (17/19) lay within the range 1-49 mSv at La Hague and only 60 % (45/75) at Sellafield. Secondly, there may be differences in the occupational exposures of fathers in the two settings (internal exposure to tritium, concomitant exposure to toxic chemicals, etc).

We found some evidence of an increased risk of leukaemia associated with a surrogate for radon exposure. We verified the presence of granite in the ground or in the building materials during the home interview, but unfortunately could not do so for the previous houses inhabited by the families. Nevertheless, the strength of the association reported (relative risk 1.18 a year, P 0.01) deserves consideration. Some studies have suggested a similar connection either with terrestrial γ radiation or radon, but a recent one has challenged this association.[20-23 25]

On the whole, some convincing evidence is found of a causal role for environmental radiation exposure operating through recreational activities on beaches or

Key messages

- The reasons for leukaemia clusters around nuclear installations remain unknown
- La Hague in France (the other two are Sellafield and Dounreay in Britain) is one of the three nuclear reprocessing plants operating in the world on an industrial scale, and offers an independent opportunity for research
- Some lifestyle risk factors (use of local beaches, consumption of fish and shellfish) were associated with the development of leukaemia among young people
- Some convincing evidence was found of a causal role for environmental radiation exposure, whereas no association was found with fathers' occupational exposure to radiation

consumption of fish and shellfish, whereas there is no confirmatory evidence of the association represented by Gardner *et al*.[9] But one explanation probably does not account for all cases, and other exposures such as to radon may play some part, maybe even a synergistic one. New methods for the identification of the environmental pathways (focusing on marine ecosystems) and their integration in the dose reconstruction process for children are clearly warranted.

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Conflict of interest: None.

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ONE HUNDRED YEARS AGO

Riotous students

There have lately been several outbreaks of riotous behaviour among students in different places abroad. At Athens the medical students rose in rebellion against the authorities, apparently with the object of getting rid of an unpopular professor. They took possession of the University buildings, shot a few harmless outsiders, and threw the city into a state of anarchy. The work of the University was suspended, and the rector resigned. After a time the students appear to have capitulated and marched out with the honours of war. They then attended the funeral of one of the victims of the riot, and fraternised with the alarmed citizens. The ringleaders among them have, however, since been arrested, to the great indignation of their fellow students, who accuse the authorities of a breach of faith. At Bordeaux the other day the ceremony of inauguration of the new University of Bordeaux was marred by disorderly manifestations on the part of the students, who thought they should have had a larger share in the proceedings. Two or three medical students have been imprisoned for resisting the police. In Rome there has been trouble in consequence of a new regulation intended to facilitate the identification of students attending the lectures. The Rector appealed to the authorities, and the University buildings have been taken possession of by the military power. At Algiers, some 200 students recently made a demonstration at the gates of the Mustapha College to protest against the appointment of a Jew to a professorship. Antisemitic zeal runs high among the ingenuous youth of the college. (*BMJ* 1897;i:484.)

Changing prognosis for babies of less than 28 weeks' gestation in the north of England between 1983 and 1994

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Abstract

Objective: To investigate the changing prognosis for babies of less than 28 weeks' gestation.
Design: A prospective, collaborative, population based survey.
Setting: The former Northern Regional Health Authority.
Subjects: All the births between 1983 and 1994 at 22 to 27 completed weeks' gestation to women normally resident in the region.
Main outcome measures: Miscarriage, stillbirth, death in the first year of life, and disability in survivors.
Results: There were 479 070 registered births in the study period. No baby of 22 weeks' gestation survived; only eight (4%) of the 197 babies of 23 weeks who were alive at the onset of labour survived for a year—a proportion that did not change during the study period. Survival among other babies of less than 28 weeks improved progressively between 1983-6 and 1991-4, but administration of artificial surfactant to babies requiring ventilation from mid-1990 was associated with further improvement in survival only in those over 25 weeks' gestation. Babies of 24 weeks required three times as much high dependency care per survivor as babies of 27 weeks (76 *v* 26 days). The rate of severe disability in the one year survivors of less than 26 weeks' gestation (30/123; 24%) was similar to that seen in the sampled survivors of 26 and 27 weeks (29/108; 27%); the proportion disabled did not change significantly during the study period. All the children born in 1983, 1987, and 1991 were later reassessed in greater detail: 10% (13/136) seemed destined for a continuing life of total dependency.
Conclusions: Gestation, if accurately assessed, can give a woman facing very preterm delivery a clear indication of the prognosis for her baby and help her judge the appropriateness of accepting obstetric intervention and sustained perinatal support.

Introduction

The prognosis for very preterm babies was substantially improved 25 years ago by effective artificial respiratory support. In the past few years there has been much debate as to whether more recent developments in perinatal care have had any further impact on the limits of viability.[1] The issue has important implications for obstetric care, for the wise use of limited neonatal resources, and for the provision of sensitive and realistic nursing support for babies born 15 or more weeks early.[2 3] We therefore looked at the immediate and long term outcome of all babies delivered either dead or alive at 22 to 27 weeks' gestation in the north of England over a 12 year period.

Subjects and methods

A voluntary, collaborative, region-wide survey of perinatal mortality has been in operation in the area served by the former Northern Regional Health Authority since July 1980.[4] This started with the collection of confidential information on the outcome of all pregnancies resulting in a registrable birth, but information was also obtained on the outcome of every pregnancy lasting at least 22 weeks in 1983,[5] even if it ended in a miscarriage or termination, and similar information was collected routinely on all mothers normally resident in the region every year after 1985. Pathology and gynaecology records were reviewed to ensure that no late miscarriages were missed. Information on gestation was obtained from the obstetric notes and calculated from the mother's menstrual history unless this was uncertain or differed by at least 14 days from the estimate obtained from at least one reliable ultrasound scan undertaken before 20 weeks' gestation. Information on every stillbirth and infant death was cross correlated with the independent registration returns made to the Office of Population Censuses and Surveys, which also provided information on the total number of registered births to mothers normally resident in the region each year.

In addition, a record was kept of the progress of all surviving babies of less than 26 weeks' gestation after 1982, and this was supplemented with a more detailed assessment of the developmental attainment of every child born before 28 weeks in 1983, 1987, and 1991, undertaken in a standardised way at 2 years by one of four clinicians. Severe disability was defined by using the criteria listed in the 1994 consensus report published by the Oxford Regional Health Authority jointly with the National Perinatal Epidemiology Unit.[6] The Griffiths's developmental quotient was assessed in each child seen at 2 years. No child was lost to follow up.

Attitudes to the registration of very immature infants who showed only transient signs of life after birth are not always consistent.[7] Neonatal mortality can be influenced by the vigour with which these babies are resuscitated after delivery, while intensive care may merely delay death.[8] Studies that include only babies admitted to the neonatal unit after delivery often quote misleadingly high rates of survival. A more informative and potentially more consistent statistic relates survival to the number of babies alive at the onset of labour. Babies in this study were so classed if a normal fetal heart rate had been documented by using Doppler or real time ultrasound, or both, after the induction or spontaneous onset of labour but the baby was not registered as live born (although there were two singleton and three twin births in which advanced maceration after delivery suggested that this observation had been in error). When it was not possible to time the onset of labour precisely death was classed as having occurred during labour if the fetus was alive when the mother

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first came under observation in the delivery area with threatened labour or a suspected abruption.

Comparative data on neonatal mortality for the period 1966-9 were abstracted from case records of the Princess Mary Maternity Hospital, where carefully validated information on gestational age for every live birth was collected for research purposes by staff from the University of Newcastle upon Tyne from mid-1965.

Results

There were 479 070 registered births to mothers normally resident in the region between 1983 and 1994 inclusive, including 39 registered live births at 19 to 21 weeks' gestation (10 with a birth weight of ≥ 500 g) all of whom died on the day of birth. The outcomes for all deliveries at 22 to 27 weeks (other than those due to a notified termination of pregnancy) are shown in table 1. Reliable ultrasound information with which to validate the menstrual information on gestation was available for 96% of these pregnancies, and in all but a small minority of cases this was a measurement of biparietal diameter at between 14 and 18 weeks. The number delivered at each week of gestation rose as pregnancy progressed (fig 1).

Figure 2 shows how neonatal survival has improved for babies of short gestation over the past 25 years. The statistic of greatest relevance to the obstetrician and to the family, however, relates survival to the number of babies alive at the onset of labour: information on non-registrable late miscarriage was not available for the years before 1983, but figure 3 shows how the prognosis for these babies rose between 1983-6 and 1991-4. No baby of 22 weeks survived to 1 year (table 1), and only 7.5% (8/121) of the live born babies of 23 weeks survived (a proportion that did not increase during the 12 year study period). Of the babies of 22-23 weeks who did not survive, 92% died within two days of delivery. The widespread availability and free use of artificial surfactant in the context of the OSIRIS trial (open study of infants at high risk or with respiratory insufficiency—the role of surfactant)[9] from March 1990 was associated with a further improvement in survival in babies of 26-27 weeks in the third period of four years, but there was no comparable improvement among babies less mature than this (table 1). Birth at 27 weeks became progressively more common between 1983 and 1994, and an increase in the number of induced labours (excluding inductions after fetal death) and caesarean deliveries before the onset of labour possibly explains at least half this rise (21% of deliveries at 27 weeks were elective at the end of the 12 year period). No such trend with time was seen in babies born earlier than this. Deaths after discharge accounted for a third of all the postneonatal deaths in the first year. Table 2 shows how the amount of high dependency care[10] received varied with gestation at birth.

Severe disability among the one year survivors of less than 26 weeks' gestation (24.4%; 95% confidence

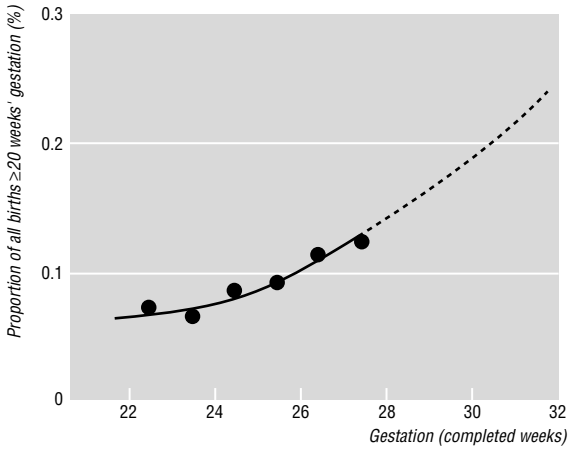

Fig 1 Relation between gestation and likelihood of delivery, 1983-94. (Recent data for babies of 28-31 weeks' gestation in this figure and figure 3 come from region's surveys of 1983 and 1991)

Table 1 Birth and survival to 1 year in babies of 22-27 weeks' gestation, 1983-94, including 74 births in which there was lethal malformation but excluding all terminations of pregnancy for any reason

Year (all registered births) and gestation (weeks)	Antepartum death	Intrapartum death	Neonatal death	Death at 28-365 days	Survival at least one year	All survivors of 22-27 weeks' gestation
1983-6 (160 411):						146
22	55*	29*	23	1	0	
23	44*	14*	37	1	1	
24	68	22	45	2	5	
25	56	16	66	2	18	
26	46	19	63	4	49	
27	37	14	47	4	73	
1987-90 (161 065):						195
22	45	44	16	0	0	
23	47	28	27	0	6	
24	45	11	60	5	13	
25	39	13	58	3	30	
26	32	14	57	10	55	
27	38	7	43	9	91	
1991-4 (157 594):						239
22	54	53	27	0	0	
23	44	34	46	2	1	
24	34	23	61	4	13	
25	27	14	59	8	36	
26	45	13	53	11	72	
27	42	10	43	7	117	
1983-94 (479 070):						580
22	154	126	66	1	0	
23	135	76	110	3	8	
24	147	56	166	11	31	
25	122	43	183	13	84	
26	123	46	173	25	176	
27	117	31	133	20	281	

*Data incomplete for 1984-5.

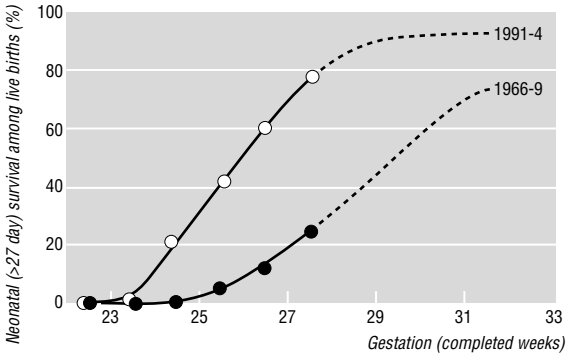

Fig 2 Neonatal survival among registered live births

Table 2 Numbers of days of high dependency care provided per child surviving to 1 year

	23 Weeks			24 Weeks			25 Weeks			26 Weeks			27 Weeks		
Detail	**1983-6**	**1987-90**	**1991-4**	**1983-6**	**1987-90**	**1991-4**	**1983-6**	**1987-90**	**1991-4**	**1983-6**	**1987-90**	**1991-4**	**1983-6**	**1987-90**	**1991-4**
Days of high dependency care	75	257	72	325	854	1183	1634	1654	2144	1342	2120	2229	1580	2556	2993
Days per long term survivor	75	43	72	65	66	91	91	55	60	27	39	31	22	28	26
Average over 12 year period		**51**			**76**			**65**			**32**			**25**	

interval 17.1% to 33.0%) was similar to that seen in the sampled survivors of 26 and 27 weeks (26.9%; 18.8% to 36.2%). The proportion with severe disability did not change during the 12 year period (table 3). The children born in 1983, 1987, and 1991 were all reassessed in greater detail when they were 2 years old. Several then had a developmental quotient of less than 50 and disabilities likely to prevent their ever developing any independent mobility or any ability to communicate intelligibly, or both. Such profound disability was not seen in any of the nine survivors of less than 25 weeks' gestation but was seen in 13 of the 136 survivors of 25-27 weeks (9.6%; 5.2% to 15.8%).

Discussion

Viability

Changes in maternity care, probably associated with the introduction of prolonged respiratory support, seem to have lowered the threshold of "viability" by two weeks during the past 28 years (see fig 2). The survival rate for 1966-9 shown here is very similar to that reported by Lubchenco *et al* from Denver, Colorado, for much the same time period.[11] There is, however, no evidence that the improving prognosis for babies of 24 or more weeks' gestation over the past 12 years has had any further impact on the lower limit of viability (see fig 3). No baby of 22 weeks' gestation survived during that time and only eight of the 197 babies of 23 weeks alive at the onset of labour. Four of these eight survivors had severe disability on subsequent follow up, but none was so disabled as to seem destined for a continuing life of total dependency—that is, unlikely to achieve independent mobility or an ability to communicated freely with others in later childhood, or both.

Other studies

The present gestation specific survival rates for live births are very similar to the only other available area based rates for the United Kingdom.[12-14] Survival has been a little higher in some of the hospital based studies published from centres in Australia,[15-18] Canada,[19-24] and the United States,[25 26] but it is widely recognised that the results achieved by a specialist institution do not always reflect those found in the population at large. Only a minority of studies report survival to 1 year rather than survival to discharge, and many exclude lethal malformation. Nevertheless, all these reports conclude that survival is never seen in babies of less than 23 weeks' gestation and is only to be expected in about 5% of all live births at 23 weeks. Other reports from Europe have found no evidence of long term survival in babies born before 24 weeks' gestation.[27-31] Only one previous study has documented death during delivery.[23] Nine of these reports included information on disability in long term survivors, but only one was a population based study,[12] and in only four was there no loss to follow up among babies of less than 28 weeks' gestation.[16 20 27 30] The failure of surfactant to have any detectable impact on survival in babies of less than 26 weeks conflicts with the interpretation placed on several other studies that have used historic controls,[32-34] but is in keeping with the only randomised, multicentre, placebo controlled trials of surfactant specifically designed to study its efficacy in babies of less than 750 g at birth.[35 36]

The findings on the limits of viability reported here stand in stark contrast with those published from the research network supported by the National Institute of Child Health and Human Development (NICHHD) in America,[37 38] which have formed the basis for the advice on viability recently issued in Canada[2] and in the United States.[3] The hospitals in this network have recently reported survival to discharge in 19% of all in-born live births of 22 and 23 weeks' gestation and a survival rate of 47% at 24 weeks' gestation.[39] These discrepancies are hard to explain, but more than 18% of the mothers in the initial NICHHD studies had received no antenatal care; there must, therefore, be some doubt about the accuracy of some of the gestational assessments. Significant errors may also creep in if such information is not abstracted directly from the obstetric record.[40] It should also be noted that nearly two thirds of the mothers in the early NICHHD studies were black and that nearly a quarter of the babies were classified as "light for dates." It is known

Table 3 Severe disability among children alive 1 year after delivery at 23-27 weeks' gestation. Figures are numbers (percentages) of children

Years	23 Weeks	24 Weeks	25 Weeks	26 Weeks*	27 Weeks*
1983-6	0/1 (0)	0/5 (0)	4/18 (22)	2/12 (17)	3/13 (23)
1987-90	4/6 (67)	3/13 (23)	6/30 (20)	3/12 (25)	9/28 (32)
1991-4	0/1 (0)	5/13 (38)	8/36 (22)	2/15 (13)	10/28 (36)

*Data for first year of each four year study period only.

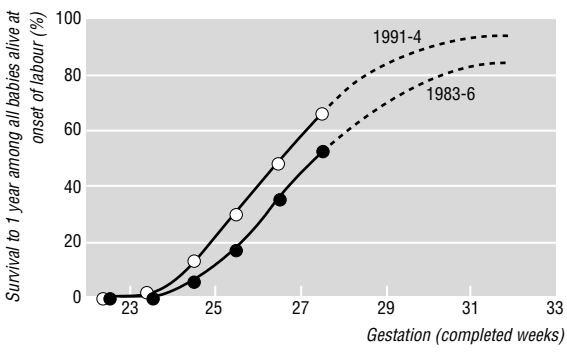

Fig 3 Survival to 1 year in babies alive at onset of labour

(from other NICHHD data) that both these factors significantly enhance rates of survival specific for birth weight.[33] These factors may well explain why NICHHD birthweight survival rates are also higher than in most other studies.

Birth weight provides an alternative yardstick for the assessment of viability and one that can be used reliably even when gestation is not known for certain. It is not, however, one that can be used to influence management before delivery. There is also evidence to suggest that gestation is a better predictor of death or disability[41 42] (and also of length of stay before discharge[5 13]) than birth weight.

Disability

The risks of severe disability in survivors born at 24-25 and at 26-27 weeks' gestation in this study were not dissimilar. Others have found a clear diminution in risk as gestation advances,[12 23] but this is far from universal.[16 19 43] At least half the very few survivors of 23 weeks' gestation, on the other hand, were severely disabled, as in every other published study.[44] While it is accepted that cognitive disability is not always recognisable in children as young as 2, the likelihood of survival and of survival without severe disability is certainly higher than many clinicians currently assume.[45 46] Boys were more likely to die, both during and after delivery, and more likely to survive with disability. Babies who were "light for dates"[47] were more likely to die (as in most other studies[33 43 48]) but no more likely to be disabled if they did survive. The proportion delivered by section rose from 12% of all live births in 1983 to 23% in 1994, but there was no significant correlation between mode of delivery and outcome after allowance was made for gestation at birth.[15 49] The disability rate in babies of less than 28 weeks' gestation was double that seen in babies of 28-29 weeks in this region (25.6 *v* 11.1%), as in another recent large community based study.[50]

Conclusions

These findings point to the importance of establishing gestation reliably to assess the viability of the very preterm baby and the risk of disability in survivors. They suggest that current recommendations,[2 3] based on NICHHD data from a predominantly black population,[37 38] cannot be used without modification to guide practice in a largely white community. They also suggest that improvements in mortality in the United Kingdom in the past 12 years associated with the arrival of surfactant therapy have not been associated with any change in the threshold of viability or in the chance of severe disability in survivors. These data should not be used to establish an arbitrary "threshold" below which resuscitation should never be offered at birth. They can be used, however, to influence the vigour with which further respiratory support is pursued in consultation with the family and in the knowledge that in the United Kingdom most babies of less than 25 weeks' gestation who do not survive currently die within two days of delivery (fig 4).

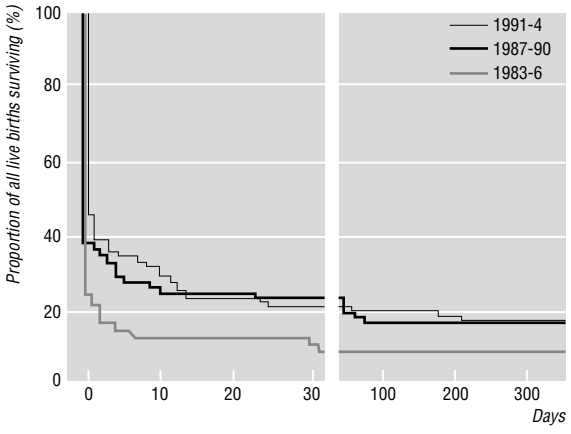

Fig 4 Survival to 1 year in live born babies of 24 weeks' gestation. Mean age of death in non-survivors rose from 2.0 to 9.5 days between 1983-6 and 1991-4

Key messages

- Survival in babies of 24-27 completed weeks of gestation has improved in the past 12 years
- The proportion of survivors with severe disability (25%) has not changed
- The survival (viability) of babies born before 24 weeks' gestation (about 4%) has not changed, and most survivors are severely disabled
- One in 10 of all survivors has a disability so profound that he or she is never likely to become independently mobile or to communicate effectively with others
- Gestation, if accurately assessed, can help women facing very preterm delivery (and their attendants) to assess the likely prognosis for the baby at the onset of labour

We are grateful to the Office of Population Censuses and Surveys (now the Office for National Statistics) and the coordinating group responsible for the region's maternity survey for access to mortality data, and to our medical, midwifery, and nursing colleagues in the Neonatal Network for the other information on which this report is based. We are particularly grateful to Drs Donald Bell and Monica Placzek for providing information on children born in South Cumbria, many of whom received their early neonatal care in Lancaster, Leeds, or Manchester. Neonatal survival data for Newcastle for the years 1966-9, analysed by gestation, was provided by the late Professor JM Parkin. Drs John Beesley, Vona Ellis, and Sue Thomas provided information from their unpublished follow up study of all the children born in 1987. An expanded version of table 1, showing the data for each calendar year separately, is available on request.

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A MEMORABLE INTERVIEW

None of his business

At the outbreak of the second world war a plastic and jaw unit was established by Sir Harold Gillies at Rooksdown House, Basingstoke. In 1954 I applied for a post in plastic surgery.

The subsequent interview was held at the hospital, a strange looking building which had been the private block of Park Prewett Hospital. On inquiry at the porter's office, I was directed by an elderly gentleman to wait in the main hall along with the other candidates. Being last in line for interview I was left in glorious isolation until joined by the porter who proceeded to make conversation. His opening gambit was to inquire how much fishing I had done in Ireland, to which I replied in the negative. As to other sporting activities, I admitted there were none at that particular time. There followed a few desultory questions about my surgical activities, which I thought were none of his business. Returning to the question of sport, he expressed further curiosity regarding my sporting interests in the past. Feeling slightly irritated and intimidated by the old man's persistence I announced that I had been a member of the Irish Olympic rowing team which competed at Henley in 1948. He was most interested in this information and casually mentioned that he had rowed for Cambridge in the Boat Race. It emerged that he had also played golf for England and that painting and fishing were his main interests apart, of course, from plastic surgery.

Shortly afterwards I was called in to see the medical superintendent who, after a few perfunctory remarks, told me that Sir Harold Gillies had interviewed me in the hall and that my application was satisfactory. During the ensuing three years at Rooksdown House Sir Harold made no reference to our unconventional interview.

Denis Sugrue *is a retired consultant in Stoke on Trent*

Dietary lipids and blood cholesterol: quantitative meta-analysis of metabolic ward studies

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Abstract

Objective: To determine the quantitative importance of dietary fatty acids and dietary cholesterol to blood concentrations of total, low density lipoprotein, and high density lipoprotein cholesterol.

Design: Meta-analysis of metabolic ward studies of solid food diets in healthy volunteers.

Subjects: 395 dietary experiments (median duration 1 month) among 129 groups of individuals.

Results: Isocaloric replacement of saturated fats by complex carbohydrates for 10% of dietary calories resulted in blood total cholesterol falling by 0.52 (SE 0.03) mmol/l and low density lipoprotein cholesterol falling by 0.36 (0.05) mmol/l. Isocaloric replacement of complex carbohydrates by polyunsaturated fats for 5% of dietary calories resulted in total cholesterol falling by a further 0.13 (0.02) mmol/l and low density lipoprotein cholesterol falling by 0.11 (0.02) mmol/l. Similar replacement of carbohydrates by monounsaturated fats produced no significant effect on total or low density lipoprotein cholesterol. Avoiding 200 mg/day dietary cholesterol further decreased blood total cholesterol by 0.13 (0.02) mmol/l and low density lipoprotein cholesterol by 0.10 (0.02) mmol/l.

Conclusions: In typical British diets replacing 60% of saturated fats by other fats and avoiding 60% of dietary cholesterol would reduce blood total cholesterol by about 0.8 mmol/l (that is, by 10-15%), with four fifths of this reduction being in low density lipoprotein cholesterol.

Introduction

The quantitative importance of diet to blood total cholesterol and, more importantly, to its fractions (low density lipoprotein and high density lipoprotein cholesterol), remains uncertain.[1-5] This is partly because metabolic mechanisms are not clear, partly because non-experimental dietary studies in community subjects are unreliable,[6-11] and partly because previous experimental (that is, "metabolic ward") studies have been too small to be reliable. Hence, selective emphasis on particular studies can lead to conflicting conclusions about important issues[12]—for example, whether isocalorically replacing complex carbohydrates by monounsaturated fats affects blood total cholesterol or its fractions.[13-16] The aim of this meta-analysis of metabolic ward studies is to provide reliable quantitative estimates of the relevance of dietary intake of fatty acids and dietary cholesterol to blood concentrations of total cholesterol and cholesterol fractions.

Methods

Studies included

Published reports of dietary intervention studies conducted under controlled conditions that ensured compliance (metabolic ward studies) with diets persisting at least two weeks were systematically sought by Medline searches, scanning relevant reference lists, and handsearching nutrition journals. We excluded studies if they were of subjects selected for some disorder (such as diabetes or dyslipidaemia), if the dietary changes were deliberately confounded by other interventions (such as weight reduction or exercise), or if there were no data available about dietary fatty acids or dietary cholesterol. The search strategy (details of which are available on request) did not, however, require the availability of data on changes in body weight. Because the dietary changes were to be isocaloric and most experimental periods lasted only a few weeks, substantial weight changes were not expected. Hence, many relevant publications did not include data on body weight after the experimental periods (and, of those that did, many found no material differences[17 18]).

Among the 81 eligible reports identified (see appendix), we excluded one long term multicentre study for poor compliance. Solid food diets were assessed in 72 of these reports among 129 groups of subjects in 395 experiments with various designs (109 randomised crossover, 57 randomised or matched parallel, 77 non-randomised Latin square, and 152 non-randomised sequential). Details of the major individual fatty acids in the diets were available for 134 experiments, and blood concentrations of high density lipoprotein and low density lipoprotein fractions of cholesterol were available for 227. Liquid formula diets, which were assessed in 32 experiments in eight reports, were examined separately because the effects of such diets may differ from those of solid food diets.[19]

Information collected

From each publication, we sought information about mean age and weight, the experimental diets (caloric intake; intake of dietary cholesterol; and percentage of calories as total, saturated, polyunsaturated, and monounsaturated fat), and blood cholesterol concentrations (total, low density lipoprotein, and high density lipoprotein) in plasma or serum at the end of the experiments. For some experiments, the mean weight, age, or dietary cholesterol had to be estimated from median or mid-range values. Fatty acids were classified by carbon chain lengths (with C18, for example, indicating 18 carbons) and by the number of carbon-carbon double bonds (such as C18:1). Saturated fatty acids have no such double bonds, monounsaturates have one, and polyunsaturates have more than one. Double bonds are *cis* if the two hydrogen atoms at each end are on the same side of the double bond and *trans* if otherwise.

Statistical methods

We used "Multilevel" regression analyses (MLN-software, London University Education Institute) that included age, weight, and dietary intake of nutrients as

well as one term per study to ensure that people within any one study were compared directly only with each other. Such analyses assessed different sources of variability: (*a*) within group, between experiments; (*b*) within study, between matched groups; (*c*) within study, between unmatched groups; and (*d*) between studies.

Results

Univariate and multivariate analyses for total cholesterol

Figure 1 plots the mean dietary saturated fat in each experiment against the mean blood total cholesterol concentration at its end, with separate plots for different types of experimental design with solid food diets and for liquid formula diets, but without adjustment for factors other than intake of saturated fat. Crude correlations might misrepresent the real relations as some experimental periods were part of the same study, but the multilevel regression analyses that are plotted take appropriate account of such differences. The four regression slopes for the different types of solid food experiments were similar, and so the results of these 395 experiments were combined. The overall effects of saturated fat were less in the liquid formula experiments, and so these are considered separately. Univariate regressions for the solid food experiments indicated that dietary intakes of saturated fat, cholesterol, and total fat were each associated with highly significant increases in blood total cholesterol, while intake of polyunsaturated fat was associated with a highly significant decrease and intake of monounsaturated fat produced no significant effect on blood total cholesterol (table 1).

Such univariate analyses might be misleading, however, because isocaloric increases in one type of fat in many of the experiments were accompanied by decreases in other dietary fats or in dietary cholesterol.

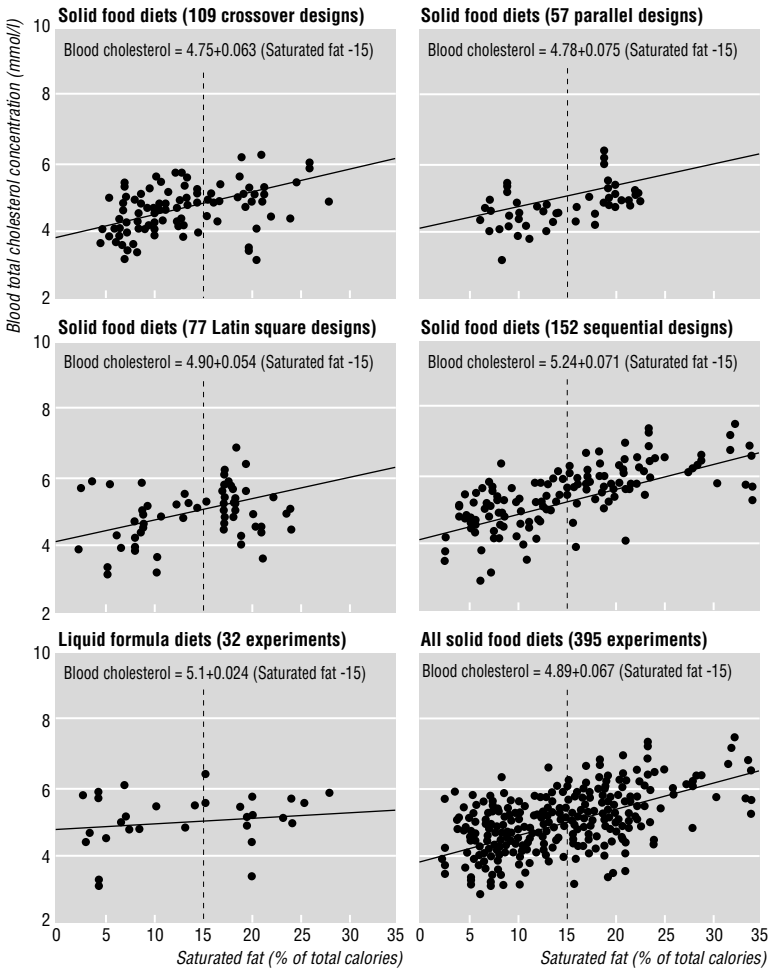

Fig 1 Univariate multilevel regression slopes of blood total cholesterol *v* dietary saturated fat in metabolic ward experiments, by different experimental design. (The equations take account of which experiments were part of the same study; dotted lines represent a typical intake of saturated fat (15% of dietary calories), and this is used as an intercept for the regression equations; no adjustments are made for total energy intake or any other aspects of experimental diets)

Table 1 Regression coefficients (SE) for effects of dietary fats on total blood cholesterol concentration (from 395 solid food experiments) and on low density lipoprotein and high density lipoprotein cholesterol concentrations (from 227 solid food experiments)

		Multivariate analysis*		
Dietary fat	Univariate analysis for total cholesterol	Total cholesterol†	Low density lipoprotein cholesterol	High density lipoprotein cholesterol
Saturated fat (% of total calories)	0.067 (0.003)	0.052 (0.003)	0.036 (0.005)	0.013 (0.002)
Polyunsaturated fat (% of total calories)	–0.063 (0.004)	–0.026 (0.004)	–0.022 (0.005)	0.005 (0.002)
Monounsaturated fat (% of total calories)	0.005 (0.006)	0.005 (0.003)	–0.008 (0.005)	0.006 (0.002)
Dietary cholesterol (mg/day)	0.0013 (0.0002)	0.0007 (0.0001)	0.0005 (0.0001)	0.0001 (0.0001)
Total fat (% of total calories)	0.027 (0.005)	0.020 (0.005)	0.012 (0.006)	0.010 (0.002)

*Change in blood cholesterol per unit of (isocaloric) change in dietary factor, adjusted for age, weight, and all other dietary factors.
†Multivariate regression coefficients for blood total cholesterol in the 227 experiments with data on low density lipoprotein and high density lipoprotein cholesterol were similar for saturated, polyunsaturated, and monounsaturated fat and for dietary cholesterol: 0.051 (0.005), –0.019 (0.006), 0.006 (0.005), and 0.0006 (0.0001) respectively.

Multivariate analyses were therefore also performed, which assessed isocaloric replacement of complex carbohydrates by particular lipids after simultaneous adjustment for other dietary factors (and, less importantly, for age and initial body weight). Thus, for example, in the multivariate analyses "effects of saturated fat" would actually mean "effects of replacing carbohydrate isocalorically by saturated fat." These produced smaller regression coefficients for blood total cholesterol than did the univariate analyses (table 1). Different types of experimental design with solid foods produced similar multivariate coefficients for the effects of specific fats on blood total cholesterol (fig 2), with smaller effects for the liquid formula diets. (Similar multivariate associations of blood total cholesterol with intake of various types of fat were observed in men and women; over or under age 35; over or under 70 kg body weight; over or under 2800 daily dietary calories; over or under 300 mg daily dietary cholesterol; and in studies of 2-4, 4-6, and over 6 weeks' duration (data not shown).) If, to ensure that attention is restricted only to randomised evidence, all results from studies of Latin square or sequential designs are ignored, then the overall findings for solid food diets would not be materially altered (fig 2).

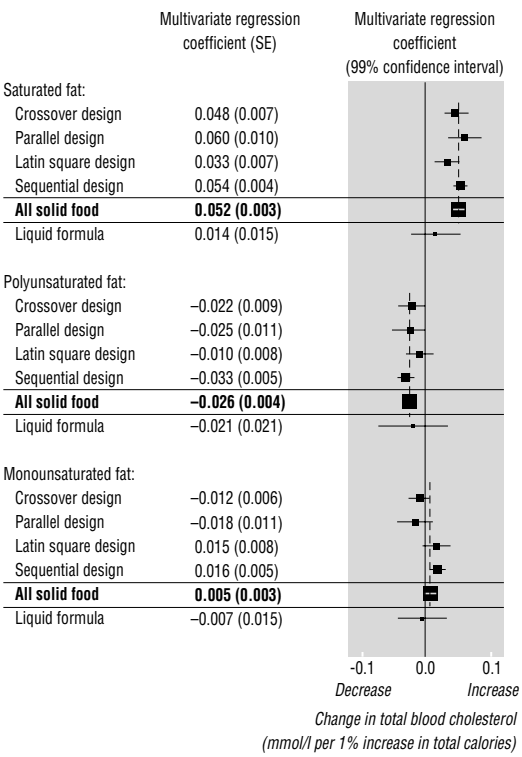

Fig 2 Multivariate regression coefficients of effects of dietary saturated, polyunsaturated, and monounsaturated fats on blood total cholesterol concentration in metabolic ward studies. (Studies with crossover or parallel design were randomised or matched, but those with Latin square or sequential design were not; the area of the squares is proportional to amount of statistical information; dotted lines represent overall coefficients for all experiments with solid foods)

Multivariate analyses for low density lipoprotein and high density lipoprotein cholesterol

A subset of 227 of the solid food experiments also reported blood low density lipoprotein and high density lipoprotein cholesterol. Multivariate analyses indicated that isocaloric increases in saturated fat intake were associated with highly significant increases in low density lipoprotein cholesterol and smaller increases in high density lipoprotein cholesterol, as were increases in dietary cholesterol (table 1). Conversely, increases in polyunsaturated fat intake significantly decreased low density lipoprotein cholesterol and increased high density lipoprotein cholesterol, while monounsaturated fat had no significant effect on low density lipoprotein cholesterol but did increase high density lipoprotein cholesterol.

Effects of realistic dietary changes

The multivariate analyses indicated that isocaloric replacement of saturated fats equivalent to 10% of dietary calories by complex carbohydrates would typically be associated with a reduction in blood total cholesterol of 0.52 (SE 0.03) mmol/l (table 2). Isocaloric replacement by polyunsaturated fat of carbohydrates equivalent to 5% of dietary calories would be expected to reduce blood cholesterol by a further 0.13 (0.02) mmol/l, whereas changes in intake of monounsaturated fat seemed to have little effect. Isocaloric replacement of saturated fats by unsaturated fats produced about three times the reduction in blood cholesterol produced by replacement of total fat by complex carbohydrates (table 2). A reduction of 200 mg/day in dietary cholesterol would be associated with a further reduction in blood cholesterol of 0.13 (0.02) mmol/l. Together, the estimated effect of these isocaloric dietary changes would be to reduce blood total cholesterol by 0.76 mmol/l (SE 0.03, 99% confidence interval 0.67 to 0.85) (fig 3), consisting of a reduction in low density lipoprotein cholesterol of 0.62 (0.04) mmol/l and in high density lipoprotein cholesterol of 0.10 (0.02) mmol/l (table 2).

Individual saturated fats

Altogether, 134 of the solid food experiments provided information on dietary intake of the major individual saturated fatty acids: laurate (C12:0), myristate (C14:0), palmitate (C16:0), and stearate (C18:0). Intake of the first three was positively related with blood cholesterol concentration, such that halving intake of each isocalorically would be expected to reduce blood total cholesterol by 0.32 (0.04) mmol/l (table 3). Stearic acid, however, which accounts for about a quarter of dietary saturated fats, did not seem to be significantly related to blood cholesterol concentration.

Forty of the solid food experiments provided information on the dietary intake of *trans* monounsaturated fats (mainly *trans* C18:1; elaidate). Multivariate regression coefficients for blood total cholesterol concentration (adjusted for other dietary fats,

Table 2 Mean daily intake of dietary fats in 395 solid food experiments compared with average diet for British men and estimated changes in blood total cholesterol (from all 395 solid food experiments) and in low density lipoprotein and high density lipoprotein cholesterol (from 227 solid food experiments) associated with particular changes in intake of fats

	Mean daily intake			Mean (SE) change in blood cholesterol concentration (mmol/l)		
Dietary fat	Experimental diets	British diet	Dietary change	Total	Low density lipoprotein	High density lipoprotein
Saturated fats (% of total calories)	14.3	16.5	Replacement of saturated fat by complex carbohydrate (10% of calories)	–0.52(0.03)	–0.36(0.05)	–0.13(0.02)
Polyunsaturated fat (% of total calories)	7.1	6.2	Replacement of complex carbohydrate by polyunsaturated fat (5% of calories)	–0.13(0.02)	–0.11(0.03)	0.03(0.01)
Monounsaturated fat (% of total calories)	12.8	12.4	Replacement of complex carbohydrate by monounsaturated fat (5% of calories)	0.02(0.03)	–0.04(0.02)	0.03(0.01)
Dietary cholesterol (mg/day)	361	390	Reduction in dietary cholesterol by 200 mg/day	–0.13(0.02)	–0.10(0.02)	–0.02(0.01)
All of above			Sum of the above changes	–0.76(0.03)	–0.62(0.04)	–0.10(0.02)
Total fat (% of total calories)	35.0	40.4*	Replacement of total fat by complex carbohydrate (10% of calories)	–0.20(0.05)	–0.12(0.06)	–0.10(0.02)

*Total fat intake in British diet includes *trans* fatty acids and glycerol derivatives as well as sum of the fats listed in table.[20]

Table 3 Estimated changes in blood total cholesterol (from 134 solid food experiments) associated with halving the intake of individual saturated fatty acids, adjusted for other saturates, polyunsaturates, monounsaturates, dietary cholesterol, age, and weight

Saturated fatty acid	Mean % of calories in these experiments	Multivariate regression coefficient (SE)	Mean (SE) change in total cholesterol (mmol/l)*
Lauric acid (C12:0)	3.7	0.045 (0.008)	–0.08 (0.01)
Myristic acid (C14:0)	1.9	0.071 (0.011)	–0.07 (0.01)
Palmitic acid (C16:0)	6.9	0.053 (0.009)	–0.18 (0.03)
C12:0-C16:0	12.5	0.052 (0.007)	–0.32 (0.04)
Stearic acid (C18:0)	3.6	0.015 (0.011)	–0.03 (0.02)

*Change from replacing half the intake of particular fatty acid by complex carbohydrate.
Heterogeneity between the regression coefficients: for all four types of saturated fatty acid, χ^2_3=18.2 (P<0.001); for C12:0-C16:0 saturates *v* stearic acid, χ^2_1=13.8 (P<0.001); for differences between lauric, myristic, and palmitic acid, χ^2_2=4.5 (P>0.05).

cholesterol intake, age, and weight) were 0.038 (SE 0.10) for *trans* monounsaturated fat, which is similar to 0.047 (0.008) for saturated fat in the same analyses. But, *trans* fatty acids account for only 2% of calories in the British diet,[20] so replacing half isocalorically by carbohydrates would be expected to reduce blood total cholesterol by only 0.05 (0.01) mmol/l.

Discussion

Because of the opposing effects on vascular disease of reductions in low density lipoprotein and high density lipoprotein, it is not sufficient to consider the effects of diet only on total blood cholesterol. Overall, because their effect on blood cholesterol is strong and the Western dietary intake is substantial, the key dietary factor in these studies was the intake of saturated fats. The present results indicate that isocaloric replacement of 60% of saturated fat by complex carbohydrates in the British diet would reduce blood total cholesterol by 0.5 mmol/l and low density lipoprotein cholesterol by 0.4 mmol/l, irrespective of sex, age, and body weight. Intake of polyunsaturated fat is also important, with effects that are about half as strong—in the opposite direction—as those of saturated fats. Intake of monounsaturated fat had no significant effect on total or low density lipoprotein cholesterol despite raising high density lipoprotein cholesterol by about as much as polyunsaturates. The combined effect of changing the type, but not the amount, of dietary fat by replacement of 10% of dietary calories from saturates by monounsaturates (5%) and by polyunsaturates (5%), together with consuming 200 mg less dietary cholesterol, would be a reduction in blood cholesterol of about 0.8 mmol/l, with the reduction chiefly in low density lipoprotein cholesterol (fig 3).

Isocaloric dietary changes such as these, which affect only the type but not the amount of dietary fat, are relevant to the control of plasma low density lipoprotein cholesterol but not to the control of obesity. Caloric restriction should eventually lead to weight loss, but this review has studied only isocaloric change. Table 2 indicates that if total dietary fat is reduced isocalorically by replacement with complex carbohydrates rather than with unsaturated fats, then the unwanted reduction in high density lipoprotein cholesterol could be so great that the ratio of low density lipoprotein to high density lipoprotein cholesterol would not be much affected.

Saturated fats with different chain lengths may have different effects, but, although intake of C18:0 fatty acids seemed less relevant than C12:0-C16:0, the evidence was limited and further direct comparisons are needed. The evidence on *cis* and *trans* unsaturated fats is also limited: *trans* unsaturated fats may be similar in effect to saturates, but intake of them is generally low in most people, and so their relevance to blood lipid concentrations is probably small. This review has not, however, tested the hypothesis[21] that *trans* unsaturates from hydrogenated vegetable oil differ in their effects from natural *trans* unsaturates.

Conclusion

The reduction in blood cholesterol concentration shown by this review with isocaloric replacement of saturated by unsaturated fats appears within just a few weeks and is greater than is sometimes appreciated.[5] Previous reviews of the effects of dietary fatty acids have yielded slightly different results from ours. An analysis of 27 studies involving 65 experiments also concluded that replacement of saturates by unsaturates produced substantial changes in the blood lipoprotein profile,[3] but the size of changes suggested by our overview are greater. Another review of 248 metabolic ward experiments yielded similar conclusions for the effects of fatty acids on blood total cholesterol but was unable to reach any conclusions for lipoprotein fractions.[4] Discrepant results from earlier reviews or individual studies[3 4 15 16 22] reinforce the need for periodically updated meta-analyses[12] of all available evidence from metabolic ward studies. (We restricted our attention to such studies because the weaker results from non-experimental dietary studies in community subjects may chiefly reflect poor compliance[5-11].)

Although dietary change is difficult, these findings are relevant to countries such as Britain, where saturated fats provide 15-17% of dietary calories (chiefly in dairy produce, meat, oils, spreads, eggs, and confectionery) and where the daily cholesterol intake is 280-390 mg (chiefly in meat and eggs).[20 23] Table 2 and figure 3 show that changes in dietary fats and cholesterol that many should find practicable would

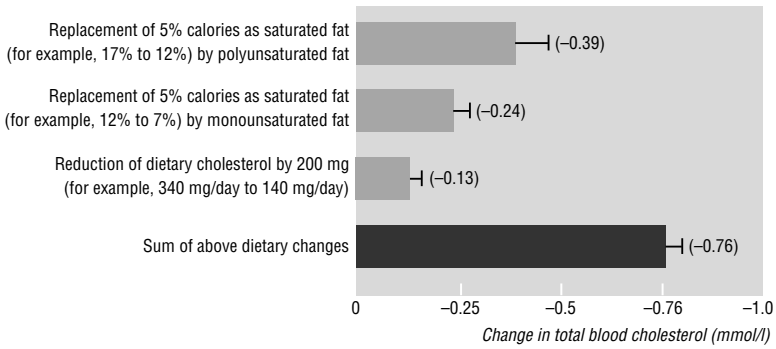

Fig 3 Mean (SE) changes in blood total cholesterol concentration associated with replacing dietary saturated fat by polyunsaturated and monounsaturated fats and with reducing dietary cholesterol

Key messages

- The quantitative importance of diet to blood cholesterol remains uncertain because non-experimental dietary studies in community subjects are unreliable and experimental ("metabolic ward") studies have been too small to be separately reliable
- We conducted a meta-analysis of 395 published, metabolic ward experiments of the effects of various dietary lipids on blood cholesterol
- Isocaloric increases in saturated fat intake were associated with increases in total and low density lipoprotein cholesterol and smaller increases in high density lipoprotein cholesterol; increased polyunsaturated fat intake decreased total and low density lipoprotein cholesterol and increased high density lipoprotein cholesterol; monounsaturated fat had no significant effect on total and low density lipoprotein cholesterol but increased high density lipoprotein cholesterol
- In the average British diet replacement of 60% of the saturated fat by other dietary fats and avoidance of 60% of dietary cholesterol would reduce blood cholesterol by about 0.8 mmol/l (that is, by 10-15%), with four fifths of this reduction being in low density lipoprotein cholesterol
- The effect on vascular disease of a prolonged difference of 0.8 mmol/l in blood cholesterol concentration depends on the relative importance at different ages of the benefits of reducing low density lipoprotein cholesterol and the hazards of reducing high density lipoprotein cholesterol, which require further study

typically reduce blood cholesterol by about 0.8 mmol/l (equivalent to a 10-15% reduction), with large beneficial decreases low density lipoprotein cholesterol concentration and only small adverse decreases in high density lipoprotein cholesterol. The effect on vascular disease of a prolonged difference of 0.8 mmol/l in blood cholesterol concentration depends on the relative importance at different ages of the benefits of reducing low density lipoprotein and the hazards of reducing high density lipoprotein cholesterol, which require further study.

Alison Mills and Joyce Hughes, MAFF Nutrition Branch of the Ministry of Agriculture, Fisheries and Foods, provided British dietary data. Vivien Reid, Anthony Keech, and Jane Armitage provided helpful comments, as did the anonymous referees.

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Conflict of interest: None.

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Table AI Metabolic ward studies included in the meta-analysis

First author and reference	No of: Groups	Experiments	People per experiment
Solid food: crossover design			
Nestel, *N Engl J Med* 1973;288:379-82	1	2	5
Harris, *Metabolism* 1983;32:179-84	1	2	12
Masarei, *Am J Clin Nutr* 1984;40:468-79	2	4	16
Kohlmeier, *Am J Clin Nutr* 1985;42:1201-5	1	2	12
Grundy, *JAMA* 1986;256:2351-5	1	3	9
Judd, *J Am Coll Nutr* 1988;7:223-34	2	8	23
Denke, *J Lipid Res* 1988;29:963-9	1	3	14
Weintraub, *J Clin Invest* 1988;82:1884-93	1	2	8
Grundy, *Am J Clin Nutr* 1988;47:965-9	1	3	10
Wardlaw, *Am J Clin Nutr* 1990;51:815-21	1	3	20
Mensink, *N Engl J Med* 1990;323:439-45*	2	4	30
Berry, *Am J Clin Nutr* 1991;53:899-907	1	4	12
Iacano, *Am J Clin Nutr* 1991;53:660-4	1	2	11
Ng, *J Am Coll Nutr* 1992;11:383-90	2	6	16
Mata, *Am J Clin Nutr* 1992;55:846-50	2	4	39
Wahrburg, *Am J Clin Nutr* 1992;56:678-83	1	3	38
Berry, *Am J Clin Nutr* 1992;56:394-403	1	4	9
Zock, *J Lipid Res* 1992;33:399-410*	2	6	28
Valsta, *Arterioscler Thromb* 1992;12:50-7	2	6	30
Lichtenstein, *Arterioscler Thromb* 1993;13:1533-42	1	4	15
Sabate, *N Engl J Med* 1993;328:603-7	1	2	18
Tholstrup, *Am J Clin Nutr* 1994;59:371-7	1	3	15
Insull, *Am J Clin Nutr* 1994;60:195-202	2	6	30
Sundram, *Am J Clin Nutr* 1994;59:841-6*	1	2	17
Marckmann, *Am J Clin Nutr* 1994;59:935-9	1	2	21
Kris, *Am J Clin Nutr* 1994;60:1037-42S	1	2	42
Tholstrup, *Am J Clin Nutr* 1994;60:919-25	1	2	12
Zock, *Arterioscler Thromb* 1994;14:567-75*	2	6	30
Lopez-Miranda, *Lancet* 1994;343:1246-9	2	4	20
Ginsberg, *Arterioscler Thromb* 1995;15:169-78	1	3	13
Almendingen, *J Lipid Res* 1995;30:1370-84*			
Zock, *Am J Clin Nutr* 1995;61:48-55*	2	4	30
Solid food: parallel design			
Dayton, *N Engl J Med* 1962;266:1017-23	4	8	49
Brussaard, *Atherosclerosis* 1980;36:515-27	4	4	15
Flaim, *Am J Clin Nutr* 1981;34:1103-8	2	2	12
Brussaard, *Atherosclerosis* 1982;42:205-19	2	2	18
Mensink, *Lancet* 1987;i:122-5	2	8	12
Jones, *Am J Clin Nutr* 1987;45:1451-6	2	4	16
Mensink, *N Engl J Med* 1989;321:436-41	2	8	15
Ginsberg, *N Engl J Med* 1990;322:574-9	3	3	12
Ng, *Am J Clin Nutr* 1991;53:1015-20S	3	9	27
Wardlaw, *Am J Clin Nutr* 1991;54:104-10	1	2	16
Barr, *Am J Clin Nutr* 1992;55:675-81	1	3	16
Fielding, *J Clin Invest* 1995;95:611-8	4	4	21
Frantz, *Arteriosclerosis* 1989;9:129-35†		2	4528
Solid food: Latin square design			
Moore, *J Clin Invest* 1968;47:1517-31	2	4	5
Grande, *Am J Clin Nutr* 1970;23:1184-93	4	16	8
Grande, *Am J Clin Nutr* 1972;25:53-60	1	5	38
Anderson, *Am J Clin Nutr* 1976;29:1184-9	1	4	12
Lewis, *Lancet* 1981;ii:1310-3	1	4	12
Chenoweth, *J Nutr* 1981;3:2069-80‡	4	12	8
Laine, *Am J Clin Nutr* 1982;35:683-90‡	4	10	6
Brinton, *J Clin Invest* 1990;85:144-51			
Wood, *J Lipid Res* 1993;34:1-11*	1	5	38
Kris, *Metabolism* 1993;42:121-9	2	8	16
Judd, *Am J Clin Nutr* 1994;59:861-8*	1	3	58

First author and reference	No of: Groups	Experiments	People per experiment
Kris, *Am J Clin Nutr* 1994;60:1029-36S	1	2	42
Solid food: sequential design			
McGandy, *Am J Clin Nutr* 1970;23:1288-98‡	2	30	10
Beynen, *Atherosclerosis* 1985;57:19-31‡	4	8	17
Hegsted, *Am J Clin Nutr* 1965;17:281-95‡	2	36	10
Keys, *Lancet* 1957;ii:959-66‡	13	43	12
McMurry, *Am J Clin Nutr* 1982;35:741-4	1	2	8
Weisweiler, *Atherosclerosis* 1983;49:325-32	1	2	15
Lasserre, *Lipids* 1985;20:227-33	1	4	22
Weisweiler, *Metabolism* 1985;34:83-7	1	3	22
Katan, *J Lipid Res* 1988;29:883-92‡	2	4	24
Baggio, *Am J Clin Nutr* 1988;47:960-4	1	2	11
Brown, *J Lipid Res* 1991;32:1281-9	1	4	14
Masana, *Am J Clin Nutr* 1991;53:886-9	1	4	11
Savolainen, *Atherosclerosis* 1991;86:145-52	1	3	22
McMurry, *N Engl J Med* 1991;325:1704-8	1	2	12
Lichtenstein, *Arterioscler Thromb* 1993;13:154-61	1	3	14
Cheung, *Am J Clin Nutr* 1994;60:911-8	1	2	8
Total solid food diets	129	395	
Liquid formula diets			
Erickson, *J Clin Invest* 1964;11:2017-25	1	7	5
Connor, *J Clin Invest* 1969;48:1363-75	1	3	6
Becker, *Am J Clin Nutr* 1983;37:355-60	1	3	12
Grundy, *N Engl J Med* 1986;314:745-8	2	6	5
Bonanome, *N Engl J Med* 1988;318:1244-8	1	3	11
Wolf, *J Nutr* 1983;113:1521-8	1	3	10
Denke, *Am J Clin Nutr* 1991;54:1036-40	1	4	10
Denke, *Am J Clin Nutr* 1992;56:895-8	1	3	14
Total liquid formula diets	9	32	

*Eight studies had complete data on intake of *trans* fatty acids, but the study by Almendingen *et al* was only used in our analysis of *trans* fatty acids.
†Excluded from our analysis because of poor compliance.
‡These seven studies had multiple groups, but in all other studies assignment of patients was either random or matched for some baseline characteristic such as age, sex, or blood cholesterol concentration.

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Serious disease saves life

My first contact with medicine was in the 1930s, watching my father perform tonsillectomies in his consulting room. The patient, usually a child, would be strapped to the pedestal and arms of a revolving chair, small children sitting on their mother's knee. A few drops of ether on the Schimmelbusch mask induced unconsciousness—more or less—and postoperative haemostasis was assisted by consuming an icecream which, at a given signal, I hurried out to buy. Until my father could afford his own premises, he had shared his father's consulting room, which was divided by a curtain. My grandfather, a general practitioner, would suggest to a patient that perhaps all was not well in the upper respiratory tract, but that, fortunately, a specialist was close at hand.

My father had developed pernicious anaemia in the late 1920s and was extremely unwell when I was born, expressing no interest in the safe arrival of his first child. He had become bedridden, when a colleague told him of the discovery, in the United States, by Minot and Murphy of the benefit of raw liver. After some weeks of eating half a pound of that delicacy daily and in spite of great improvement in his condition, he was heard to say that he would rather die than continue with that diet. Soon powdered, desiccated hog's stomach replaced the liver. Liver extract and then B12 injections followed years later and apart from irreversible neurological sequelae he remained well.

The moderate handicap resulting from his disease had advantages too. When he was taken from home for transportation to a concentration camp in the summer of 1938 he pointed out the weakness in his legs to one of the guards and explained that this would prevent him from participating in the so called "liberating" labour. So he was told to step aside and later sent home. Again, because of problems with walking he was spared internment after he came to London in 1939.

From the moment he arrived, my father loved England, admired British medicine, and would often comment on the superiority of anaesthetic techniques in his field compared with continental practice. Because of a shortage of doctors during the war he found work quite quickly and greatly enjoyed the outpatient sessions at the Royal National Ear, Nose and Throat Hospital in Grays Inn Road. One day a Royal visitor addressed a few words to my father. On receiving no reply, owing to his inadequate command of the language, she inquired of the accompanying dignitary whether the doctor was deaf as well as the patient.

My father died in his early 50s of a malignant complication of his disease, but not before he knew that I had gained a place at medical school. On the way to a restaurant in the Strand for a celebratory meal with my mother, he approached the college porter and told him that his daughter was to be a student there. I have never ceased to be grateful that I was not present at *that* interview.

G Boss *is a retired chest physician in London*

We welcome filler articles of up to 600 words on topics such as *A memorable patient, A paer that changed my practice, My most unfortunate mistake,* or any other piece conveying instruction, pathos, or humour. If possible the article should be supplied on a disk.

Thermographic changes in keyboard operators with chronic forearm pain

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Chronic incapacitating forearm pain and disability in the context of repetitive action has caused much debate. Lack of objective measurements in a condition with diverse symptoms, few physical signs, and uncertain pathology is a major problem.[1 2] Clinical observations have suggested the presence of vasomotor changes in repetitive strain injury, so we used computer assisted thermography to assess this.

Patients, methods, and results

Ten consecutive keyboard operators (six women) with chronic forearm pain exacerbated by keyboard work presenting for rheumatological assessment and 21 (12 women) asymptomatic controls matched for sex and typing speed (30-50 words/min) were recruited from rheumatology outpatient clinics. All the patients had had diffuse forearm pain for at least three months. We excluded patients with Raynaud's syndrome, neurological causes, compartment syndromes, inflammatory conditions, epicondylitis, algodystrophy, trauma, and diabetes mellitus.

We used a Talytherm infrared camera unit with thermal emission measurement software (Rank Taylor Hobson UK Ltd). Ambient temperature was controlled at 22-24° C. Baseline images were taken after acclimatisation for five minutes; the subjects then typed at their usual speed from a standard text for five minutes, and another thermogram was taken immediately afterwards. Thermograms were taken over 200-350 pixels on the 2nd, 3rd, and 4th proximal phalanges of both hands, avoiding large muscle masses which might interfere with the readings. Mean readings were recorded. All the patients were asked to return after a mean of nine months to assess reproducibility, though one refused further evaluation because of pain, two had moved away, and two did not respond. Differences between means in patients before and after typing were assessed with Student's paired *t* test and the unpaired test for intergroup means.

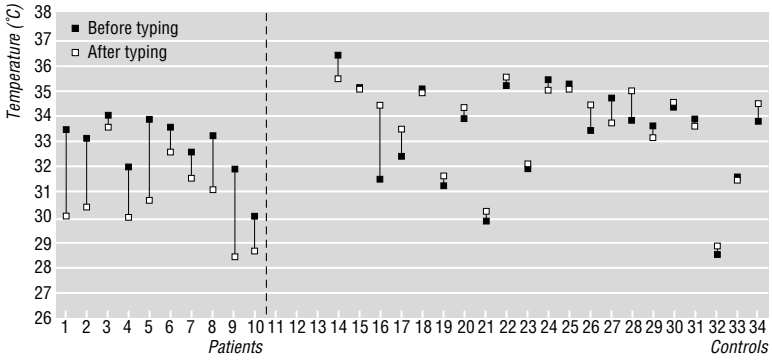

Fig 1 Temperature changes in 10 patients with repetitive strain injury and 21 controls before and after typing

After typing all the patients had symptoms. In each patient the mean temperature readings after typing were significantly reduced (fig 1) (mean 2.11°C, range 0.45-3.44°C, 95% confidence interval 1.35 to 2.26°C; $P < 0.001$). Means before typing in the two groups were similar ($P > 0.05$), though significantly different afterwards ($P < 0.001$). Only four controls showed cooling (mean 0.55°C, range 0.35-1); the 95% confidence interval of the differences between the means before and after typing in the two groups was 0.93 to 2.59°C. Of the five patients who were reassessed, four again showed cooling, while the fifth, who had clinically recovered, did not.

Comment

The changes we have described are reproducible and the method is non-invasive. It was notable that the temperature readings in the one patient who became asymptomatic changed significantly at his reassessment. Cooling in symptomatic patients may be secondary to sympathetic overactivity as a result of nociceptor and mechanoreceptor stimulation leading to a reflex neuropathic state; however, cooling after challenge suggests that it is a result rather than a cause.

Many attempts have been made to explain the relation between pain and sympathetic overactivity, mostly in algodystrophy. These suggest a central sensitisation of wide dynamic neurones within the spinal cord.[3-5] This sensitisation is thought to arise via afferents arising in peripheral nociceptors, resulting in increased sympathetic efferent activity leading to painful response rates to subsequent afferents. This results in further sensitisation, setting up a vicious circle of sympathetically maintained pain. This is unlikely to be the sole explanation, however, as sympathetic blockade has not been successful in repetitive strain injury.[1]

We conclude that thermography needs further evaluation as a diagnostic tool in evaluating repetitive strain injury. It may prove more useful in follow up, particularly in measuring response to treatment, some of which has been prescribed at enormous cost and with little evidence of benefit.

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Conflict of interest: None.

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Validation of a rapid whole blood test for diagnosing *Helicobacter pylori* infection

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Screening young dyspeptic patients for *Helicobacter pylori* and avoiding endoscopy in seronegative patients can reduce endoscopy workload by 30% without missing significant disease.[1] Serological testing is commonly used to screen for *H pylori* but requires analysis in a central laboratory, which delays results. Cortecs Diagnostics has introduced the Helisal rapid whole blood test that claims to diagnose *H pylori* status within 10 minutes. This is the first near patient test to be available in the United Kingdom but its accuracy has not been independently evaluated. Our aims were to assess the accuracy of the rapid blood test against a "gold standard" and determine its effectiveness in screening young dyspeptic patients.

Subjects, methods, and results

One hundred and seventy seven patients undergoing routine endoscopy were invited to participate. Twenty patients taking antibiotics, bismuth salts, or non-steroidal anti-inflammatory drugs within a month or proton pump inhibitors within two weeks of endoscopy were excluded, as were three patients who had received *H pylori* eradication therapy. The remaining 154 patients had a median age of 49 (range 20-85 years). At endoscopy 85 had normal findings, 18 peptic ulcer, 21 duodenitis, 21 oesophagitis, and nine other diagnoses.

H pylori status was assessed using histology (modified Geimsa stain on two antral and two corpus biopsies), microbiology (one antral biopsy cultured on selective and non-selective media), rapid urease test (on one antral biopsy), and ^{13}C urea breath test. Patients were defined as positive for *H pylori* (the gold standard) if two or more tests gave positive results (83 patients), negative if all tests gave negative results (69), and of indeterminate status if only one gave a positive result (two patients).

The rapid blood test was performed according to the manufacturers' protocol and had an 88% sensitivity (95% confidence interval 79 to 94%) and 91% specificity (82 to 97%) with a positive predictive value of 92% and a negative predictive value of 86% (table 1). Patients with an incorrect result on the rapid blood test were significantly older than those with a correct result (56.0 (SD13.8) *v* 47.7(15.8); $P < 0.05$, Student's *t* test).

Serum from 109 patients was analysed using a commercial *H pylori* serology kit (Helico G, Porton, Cambridge) with a 10 IU/l cut off (not all patients had the test performed as initially we had difficulty in obtaining funding for kits). Serology had 93% sensitivity (82 to 98%) and 87% specificity (75 to 95%), with one patient of indeterminate *H pylori* status (table 1).

Screening patients with the rapid blood test and investigating only those with a positive result would have avoided endoscopy in 41/62 (66%, 95% confidence interval 53-78%) patients aged under 45 and would have detected all seven with peptic ulcers. In older patients the test would have saved only 34/92 endoscopies (37%, 27 to 48%) and missed 2/11 peptic ulcers.

Table 1 Accuracy of rapid blood test and standard serology in diagnosing *H pylori* infection

Gold standard	Rapid blood test			Serology		
	Positive	Negative	Total	Positive	Negative	Total
Positive	73	10	83	50	4	54
Negative	6	63	69	7	47	54
Total	79	73	152	57	51	108

Comment

The rapid blood test is as accurate as a laboratory based commercial serology kit when compared with the gold standard battery of tests. It is more expensive than other serology kits, but results are available in 10 minutes, making it useful in primary care and outpatient clinics. The test must be independently evaluated in the area it is to be used because the accuracy of serology kits varies among different populations,[2 3] and the predictive value of the test relates only to patients referred for endoscopy and may not be true in the general population.

In patients under 45 years not taking non-steroidal anti-inflammatory drugs screening with the rapid blood test would have reduced endoscopy workload by 66% while detecting all peptic ulcers. This has been reported previously for serological testing[1] but has not been described for a near patient test. The rapid blood test missed two peptic ulcers in patients aged over 44, and endoscopy remains the investigation of choice in this age group.

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