deal of historical analysis can be undertaken while the introduction of the new NHS patient numbering system, which will solve the problem, is awaited.

The software to achieve this is fairly straightforward, and I will provide a copy of it to anyone who is interested.

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1 Radical Statistics Health Group. NHS "indicators of success": what do they tell us? *BMJ* 1995;310:1045-50. (22 April.)

Incidence of gastrointestinal bleeding in Italy is similar to that in Britain

EDITOR,—I was interested in the paper on the audit of acute upper gastrointestinal haemorrhage in the United Kingdom.¹ As current knowledge of the epidemiology of acute upper gastrointestinal haemorrhage comes from English speaking countries, I wish to draw attention to the results of a prospective, population based survey conducted in the Treviso area (north east Italy) a decade ago.² Treviso hospital is a general hospital with 1264 beds serving a population of about 270 000 inhabitants (232 000 aged over 15). During 27 months, from 1 October 1983 to 31 December 1985, 526 emergency admissions for acute upper gastrointestinal haemorrhage were recorded, while bleeding occurred in 61 patients already in hospital.

The table compares some of the findings of our unselected study with those of T A Rockall and colleagues. There are impressive similarities in the

Comparison between two studies on acute upper gastrointestinal haemorrhage. Figures are numbers (percentage) of patients

	Rockall and colleagues ¹	Loperfido et al ²
Year	1993	1983-5
Adult population	12 500 000	232 000
No of cases	4185	587
Mean age (years)	66	61
Haemorrhage in inpatients	584 (14)	61 (10)
Peptic ulcer	1448/4137 (35)	347/587 (59)
Varices	180/4137 (4)	81/587 (14)
Negative diagnosis	1014/4137 (25)	28/587 (5)
Overall incidence (No/100 000/year)	103	112
Mortality in emergency admissions	365/3473 (11)	68/526 (13)
Mortality in inpatients	191/578 (33)	23/61 (38)

overall incidence of acute upper gastrointestinal haemorrhage, proportion of cases of bleeding occurring in inpatients, and mortality. On the other hand, the distribution of sources of bleeding differs between the two populations investigated, the main difference concerning the high proportion of cases of bleeding in which the cause was undetermined in the English series (25% v 5% in our study). Since digestive endoscopy for acute upper gastrointestinal haemorrhage seems to have become routine, the finding that a quarter of the sources of bleeding were undiagnosed in the English series is surprising, even when we take into account that cases of bleeding of undetermined cause carried a high mortality (20%) and included similar proportions of emergency admissions and cases of haemorrhage in inpatients. The design of the large English study, involving 74 hospitals, and the advanced age of most of the patients may help to explain this peculiarity. Nevertheless, data on the performance of emergency endoscopy and on variability among areas might be an important clue.

Overall mortality in patients admitted after the onset of acute upper gastrointestinal haemor-

rhage outside hospital fell in our area from 12.9% (68/526) in 1983-5 to 3.8% (10/262) in 1993, and, specifically, mortality from bleeding oesophagogastric varices fell from 43% (35/81) to 11% (4/38) and mortality from bleeding peptic ulcer from 7.3% (23/313) to 1.3% (2/158). On the other hand, our experience agrees with the common one that the prognosis of upper gastrointestinal haemorrhage in inpatients, a very high risk group, is still poor.³

One question arising from the findings of the English series is how to transfer the advances in terms of improved outcome that have been achieved (at least for emergency admissions) at specialised centres into general hospital practice, even if the proportion of elderly patients continues to increase everywhere.

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1 Rockall TA, Logan RFA, Devlin HB, Northfield TC, on behalf of the steering committee and members of the national audit of acute upper gastrointestinal haemorrhage. Incidence of and mortality from acute upper gastrointestinal haemorrhage in the United Kingdom. *BMJ* 1995;311:222-6. (22 July.)

2 Loperfido S, Monica F, Vallenari A, Demattè P, Fabi F, Di Falco G, et al. Epidemiologia dell'emorragia del tratto digestivo superiore in una provincia italiana. *Giornale Italiano di Endoscopia Digestiva* 1988;11:45-56.

3 Loperfido S, Monica F, Maifreni L, Paccagnella A, Famà R, Dal Pos R, et al. Bleeding peptic ulcer occurring in hospitalized patients: analysis of predictive and risk factors and comparison with out-of-hospital onset of hemorrhage. *Dig Dis Sci* 1994;39: 698-705.

Vitamin D receptor genotype and bone mineral density

Evidence conflicts on link

EDITOR,—Two linkage studies of vitamin D receptor genotype and bone mineral density have reported different results. In Australian twins the vitamin D receptor gene was in strong linkage with bone mineral density.¹ In contrast, in American twins we found no evidence of linkage of the vitamin D receptor gene with bone mineral density.² We were therefore interested in the study in British twins to see if it sheds light on these contrasting findings.³ Unfortunately, it does not.

Hip bone mineral density (n=20 pairs) and spinal bone mineral density (n=23 pairs), measured by dual energy x ray absorptiometry, in relation to TaqI polymorphism (T=presence of restriction site) in discordant adult female dizygotic twins. Twin pairs are connected by a line. Mean absolute differences between pairs and their significance, tested by analysis of variance, are also shown

Despite the fact that there were no significant ($P < 0.05$) differences between dizygotic intraclass correlations in twins concordant and discordant for the vitamin D receptor gene at any of five skeletal sites, the authors conclude that bone mineral density is linked to the gene. The dizygotic intraclass correlation for bone mineral density of the spine, the site with strongest linkage in Australian twins, was 0.36 (SE 0.12) in concordant and 0.33 (0.14) in discordant British dizygotic twins. Furthermore, the direction of the difference between discordant dizygotic twins is not shown, and thus it is uncertain which allele associates with low or high bone mineral density. In dizygotic twins as individuals, the genotype tt has significantly lower adjusted bone mineral density than Tt or TT. However, 45% of these dizygotic twins had used oestrogen for a median of 24 months, and subjects of genotype tt (that is, those with the lowest bone mineral density) had lowest use (32%) and shortest median duration of use (12 months) of oestrogen, which in postmenopausal women leads to lower bone mineral density. Bone mineral density was corrected for use and duration of use of oestrogen, but it is not clear how this was, or indeed if it can be, done. It would be important to see an analysis without twins who had used oestrogen and to explain how data were corrected for use and duration of use of oestrogen.

The authors argue that their results contrast with ours because the number of discordant dizygotic twins in our study was small. Since our publication on 39 dizygotic pairs, 14 of whom were discordant for TaqI,² we have studied more dizygotic premenopausal twins not taking oestrogen, bringing our total number of dizygotic pairs to 53, 23 of whom are discordant for the vitamin D receptor gene. The larger sample supports our original conclusion of no linkage between the gene and bone mineral density. The dizygotic intraclass correlations for bone mineral density are higher, but not significantly, in discordant dizygotic pairs (dizygotic intraclass correlation: spine=0.59, hip=0.53) than in concordant dizygotic pairs (spine=0.44, hip=0.42). Moreover, the direction of differences in bone mineral density within twin pairs is random in relation to the vitamin D receptor gene (figure).

In summary, the British twin study shows no evidence of significant linkage between the vitamin D receptor gene and bone mineral density and corroborates both our original and our updated

studies. Of the three linkage studies, only the Australian study¹ shows evidence of significant linkage between the gene and bone mineral density.

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Authors' reply

EDITOR,—Munro Peacock and colleagues' discussion of the three published sets of data on twins apparently ignores the increasing number of studies that have confirmed the association between vitamin D receptor genotype and bone mineral density.¹⁻³

Although the intraclass correlation in dizygotic twin pairs concordant for vitamin D receptor genotype was consistently higher than that observed in the dizygotic twin pairs that were discordant for the genotype, none of these differences reached significance. Intraclass correlation, however, is a measure of similarity, not of magnitude or direction of effect. Our conclusion of association (not linkage) between vitamin D receptor genotypes and bone mineral density was based not on the analysis of differences between intraclass correlations but on the analysis of covariance of all dizygotic twins irrespective of zygosity. In this model we adjusted bone mineral density for potential confounders (that is, use and duration of use of hormone replacement therapy, age, weight, years since menopause, etc) before the analysis of the genotypic effect by using a multiple linear regression model as described in the paper in considerable detail. In this analysis we found a significant effect of the vitamin D receptor genotype on bone mineral density at all skeletal sites except the distal radius. Another method of analysis of the association between the vitamin D receptor gene locus and bone mineral density is obtained by performing a modification of the Haseman-Elston sib pair analysis.⁴ In this method we regressed the squared difference in bone mineral density of each dizygotic pair against the proportion of vitamin D receptor alleles shared. The results of this analysis confirmed the vitamin D receptor genotypic effect obtained from the analysis of covariance.

In both zygosityes there was no difference between genotypes with respect to the proportion of women who had ever used hormone replacement therapy (that is, TT 42.7%, Tt 42.0%, and

tt 36.2%; $\chi^2=0.89$, $P=0.64$). In dizygotic twins there were no significant differences in the proportion of women currently using hormone replacement therapy ($\chi^2=3.33$, $P=0.19$) or in the duration of use ($P=0.41$). Also, we detected no interaction effect between use of hormone replacement therapy and genotypes, suggesting that the effect of hormone replacement therapy was equal among genotypes and that the analysis of covariance model was justified. Thus it is unlikely that use or duration of use of hormone replacement therapy was a confounder in the study. Indeed, when the analysis was confined to those women who had not taken hormone replacement therapy the effect of the vitamin D receptor genotype ($P<0.05$) was observed at the femoral neck, Ward's triangle, and whole body but not at the lumbar spine or distal radius. This analysis, however, obviously had lower power since the number of subjects was reduced by 44%.

Interestingly, the data in Peacock and colleagues' figure include two twin pairs whose bone mineral density differs by more than 3.5 SD. This difference suggests appreciable unrecognised environmental or other genetic factors that may be affecting bone mineral density in their population and confounding the analysis.

In summary, we disagree with Peacock and colleagues and believe that our data, on the largest group of twins studied, have shown a significant association between vitamin D receptor genotypes and bone mineral density independent of hormone replacement therapy, age, weight, and years since the menopause. Discrepancies between populations may be better addressed by examination of specific gene and environmental interactions that may influence the phenotypic expression of the effect of the vitamin D receptor gene on bone mineral density. In addition, the candidacy of the vitamin D receptor gene must be critically addressed since a role for flanking polymorphic genes which might explain the discrepancies between populations has yet to be evaluated.

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Psychosis is also common in users of "normal" cannabis

EDITOR,—A S Wylie and colleagues report that three of eight patients on a methadone programme experienced psychotic symptoms after using modest amounts of "skunk" cannabis.¹ The tetrahydrocannabinol content of cannabis resin seized in 1984-9 varied widely among batches, years, and

countries of origin,² the average content being between 5.78% (in 1987) and 11.3% (in 1984). The tetrahydrocannabinol content in samples of Moroccan cannabis—the most commonly available variety in south Wales—varied between 6.8-8.9% (in 1988) and 11.7-26% (in 1984). These figures do not support Wylie and colleagues' suggestion that "normal" cannabis contains less than 5% tetrahydrocannabinol.

There are few published data on the prevalence of psychotic symptoms related to use of cannabis. Cannabis users attending alcohol and drug clinics in south Wales smoke large amounts of cannabis (10.5 g a week), 60% being daily users.⁴ In a self report study of 100 people attending a clinic in south Wales 43% reported having suffered acute toxic confusional states after using cannabis and 18% reported psychotic symptoms in clear consciousness.³ Fluctuations in the tetrahydrocannabinol content of all varieties of cannabis may contribute to these high rates in high dose users. In a study of 199 users of cannabis in New Zealand, identified through an electoral register survey, 15% reported psychotic symptoms after smoking cannabis (H Thomas, unpublished findings). These studies suggest that psychotic symptoms related to use of cannabis are common, particularly in clinic populations, and are not confined to users of skunk.

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Allocating census data to general practice populations

Survey data have their problems too

EDITOR,—Glen Scrivener and David C E F Lloyd conclude that the linkage of general practice data and census data is too inaccurate to use.¹ But this conclusion is not warranted by their findings. Whether such linkage is too inaccurate depends on the use in question and is a personal judgment; it cannot be determined by the correlation coefficient. Furthermore, by using correlation the authors fail to display the limits of the agreement and gain maximum benefit from their work.

Correlation measures the degree of linear association and not agreement.² The agreement of the two proportions of people aged over 64 is better shown by the difference between the two proportions plotted against the mean of those proportions. The 95% confidence interval for this can be calculated and gives a useful view of the accuracy of the agreement. In this study it is not surprising that the correlation was not 1.0. One proportion was derived from a source known to be inaccurate: general practice lists that contain ghosts. The other proportion was estimated indirectly. The accuracy of the general practice lists will probably vary from practice to practice. The limits of agreement are not as well shown by the authors in table II, which gives the actual and predicted percentages of patients aged over 64, as by the method proposed by Bland and Altman.³

The authors suggest that the best way to know