patients with HIV infection. In our previous evaluation three years ago in 86 patients with HIV infection we found a rate of discrimination of 40%.² In Italy legislation protects people with HIV infection, but seemingly health care workers are often discriminatory.

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Acanthamoeba keratitis

EDITOR,—Having read D V Seal's editorial on acanthamoeba keratitis,¹ we would like to report a case of *Acanthamoeba culbertsoni* keratitis in a 28 year old man who wore soft contact lenses and cleaned them daily with kitchen water. This patient was referred to our institute from Kerala, south India, for a corneal ulcer of the left eye that was refractory to all antibacterial and antifungal agents. The ulcer was paracentral and ring shaped with raised margins and a severe inflammatory response. Diagnoses of tubercular, fungal, and herpes virus aetiologies were considered, but no bacterial or fungal agent was found or cultured. Instead the wet mounts of corneal scrapings and button showed numerous acanthamoeba cysts measuring 17-19 µm with wrinkled endocysts. Cysts had six or seven ostiols with moderate scallops. The patient did not respond to any medical treatment, and vision could be restored only by keratoplasty followed by local iatracanazole and neomycin.

The acanthamoeba culture (figure) grew luxuriantly and has been maintained for the past three years on non-nutrient agar plates seeded with enteric bacteria. The parasite was identified as *A. culbertsoni* on the basis of morphology and growth at 40°C,^{2,3} which was later confirmed at the National Institutes of Health, Bethesda, USA, by immunological and animal pathogenicity experiments.⁴ As a follow up to this case, we isolated *Acanthamoeba* spp from chlorinated drinking water of a residential campus.

Acanthamoeba is being recognised as a major aetiological agent of keratitis in the United States and elsewhere,^{1,2,4} including India.⁵ This, however, is the first case of *A. culbertsoni* causing keratitis in a contact lens wearer from India. All nine cases reported previously occurred in people who did not wear contact lenses, secondary to physical trauma.^{1,5} Our finding of acanthamoeba in chlorinated water emphasises the resistance of this

organism to chlorination¹; this poses a health threat to contact lens wearers who cannot afford commercial cleaning solutions and use drinking water.

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Limitations of methods of describing populations

Inaccuracies in data must not be forgotten

EDITOR,—F Azeem Majeed and colleagues use standard techniques to transpose descriptions of populations defined one way (as census data by ward) to those of populations defined in another way (practice list by ward).¹ In their discussion they recognise some of the limitations of both the data and the technique. Their observation that they "were not able to validate any of the other census variables for the practices and so do not know how accurately they were measured" by this method deserves emphasis. The only variable apparently accessed by both methods was the percentage of the population aged under 5. The concordance of the two measures of what is in theory the same thing (if the method works) was tested by correlation—a rather odd test, surely—and described as "significant but weak."

The shortage of accurate practice data, and the planners' need to know, is driving many authorities to perform these transformations. Unfortunately, published measures of their accuracy at practice level are scarce, for the same reason. I am concerned that the intensity of our wish to know results may tempt us to make a passing acknowledgment of the unmeasured error and then to take the results as accurate.

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- 1 Majeed FA, Cook DG, Anderson HR, Hilton S, Bunn S, Stones C. Using patient and general practice characteristics to explain variations in cervical smear uptake rates. *BMJ* 1994;308:1272-6. (14 May.)

Authors' reply

EDITOR,—Our paper had two main objectives: firstly, to show how routine data could be used to produce a range of patient and practice variables for each general practice in one family health services authority and, secondly, to show how these variables could be used to explain variations in one aspect of a practice's performance (cervical cytology). Although these methods may lead to more flexible ways of planning general practice services and of measuring practices' performance, we agree with Peter Fitton that further research is required to validate them. This is especially important as modern information technology puts such methods within the reach of most family health services authorities and may lead to their

widespread use by people who are not fully familiar with their limitations.

We discussed the limitations of our methods in our paper and suggested some ways in which they might be overcome (for example, by use of census data for enumeration districts). Detailed validation of our methods requires substantial additional research and was beyond the scope of our paper. We compared the estimated percentage of each practice's population under the age of 5 obtained from census data with the percentage obtained from the family health service authority's age-sex register. Because family health services authorities may be more interested in the relative rankings of practices than in the absolute values of any of the patient variables we used correlation to compare the two measures as this allows the linear agreement between the two measurements to be examined. If the absolute agreement is to be compared, however, a more appropriate method would be to use the limits of agreement approach described by Bland and Altman.¹ We aim to address some of the issues raised in this letter in our subsequent work.

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Low serum cholesterol and depression

EDITOR,—S Lori Brown and colleagues conclude that "after several factors relating to health had been controlled for, no significant association between low cholesterol concentration and severe depressive symptoms was found."¹ We remain sceptical about this finding.

Firstly, brain serotonin-1A and serotonin-2A receptors and their functional interactions have been implicated in the pathogenesis of depression.² Preclinical evidence suggests that extreme lowering of plasma cholesterol concentration with fairly high doses of cholesterol lowering agents such as gemfibrozil and cholestyramine alters the functional state of these receptors and their interactions. Another factor that may need to be considered is the duration of the low cholesterol state.

Secondly, in our continuing pilot study in schizophrenic patients we have found considerably lower plasma total cholesterol and low density lipoprotein concentrations in non-responders (patients receiving clozapine) than in responders (patients responding to typical antipsychotic drugs). However, although total cholesterol concentrations were in the range seen in normal controls, low density lipoprotein concentrations were still considerably higher than those in normal controls. These results suggest that the abnormalities of cholesterol metabolism may play a part in generating a refractory state with regard to serotonin receptors in schizophrenia.³ This implies that simultaneous determinations of both high density and low density lipoproteins should also be performed, which was not done in Brown and colleagues' study.

Thirdly, the relation between peripheral and central cholesterol concentrations needs to be addressed. The study's findings seem to support the opinion that peripheral concentrations do not directly indicate central concentrations, although the authors do not discuss this. As all body cholesterol, including that in the brain, is in continual metabolic flux, however, there seems no logical reason why peripheral cholesterol

"Acanthamoeba culbertsoni" grown from cornea of a wearer of soft contact lenses who developed keratitis

concentration should not reflect similar brain concentrations. Considerable indirect evidence supports this view, though we are not aware of any study that has looked at this issue directly or which, if any, brain regions and receptors are deemed the most sensitive to the lowering of peripheral cholesterol concentration.

In conclusion, we believe that the degree of the low cholesterol state combined with its duration might be a risk factor for the development of an abnormal mental state. Further research is required to investigate the role of both high density and low density lipoproteins in addition to total cholesterol. Magnetic resonance imaging techniques that visualise brain cholesterol in relation to serum concentrations should be used in future investigations.

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"Place of publication" bias?

EDITOR,—As keen followers of the developing hypotheses on the possible influences of early life on the risk of adult disease, we wish to report an observation regarding publications on this topic. The phenomenon of publication bias, whereby research with positive results is more likely to be published than research with negative results, is well recognised.¹ A further variant of this phenomenon—"place of publication" bias—may also exist. Articles supporting a hypothesis may be more likely to be placed in one journal than another because of the authors' preference or editorial policy. The *BMJ* and *Lancet* are widely read and respected journals. Initial publications from the Southampton group that advocates that early development has an important role in determining the risk of adult disease appeared in both journals.^{2,3} Recent (1990-3) empirical work, however, has been published in the *BMJ* (11 papers) rather than the *Lancet* (no papers), whereas in the preceding four years the situation was more balanced (1986-9: *BMJ* four papers, *Lancet* three papers; Fisher's exact test between time periods, $P=0.04$).

One possible explanation for this difference is that a journal can become associated with a hypothesis and therefore articles both for and against the hypothesis will be sent there. For example, articles relating to the debate over childhood leukaemia and nuclear power stations are predominantly published in the *BMJ*. To examine this possibility we examined all original papers and reviews and editorials by researchers other than the

Southampton group that relate to the "programming hypothesis." These articles were generated by a computerised search for papers that cite articles written by the Southampton group published since 1986. Articles were classified as supportive, ambiguous, or unsupportive in relation to the hypothesis. Letters were excluded from the classification. The *BMJ* had indeed published more articles than the *Lancet*, although the difference was not great (19 v 11). The articles in the *BMJ*, however, were more likely to be in favour of the hypothesis (table; references are available from us).

Our contention is illustrated by the simultaneous publication, on 29 January this year, of two studies of twins. The publication in the *BMJ* reported an association between birth weight and blood pressure, in support of the "programming" hypothesis.⁴ The paper in the *Lancet* found no increased risk of coronary heart disease among twins, who have lower average birth weight than singleton births—a finding at variance with the predictions of the programming model.⁵

A final example is a (presumably unplanned) $n=1$ "crossover" trial. An initial publication from the Kuopio ischaemic heart disease risk factor study, published in the *BMJ*, suggested that socioeconomic conditions in childhood are particularly important in determining the risk of coronary heart disease in adulthood.⁶ The inadequacy of the statistical methods used in this report was noted, it being suggested that a "more sophisticated analysis is required to separate the effects of childhood socioeconomic conditions from the whole lifecourse of differential exposures with which they will be associated."⁷ A subsequent analysis, from the same study, has attempted to disentangle the effects of childhood and adult environments. It indicates that, within a given socioeconomic stratum in adulthood, low socioeconomic status in childhood has little or no effect.⁸ The authors now support the suggestion⁹ that understanding the risk of death may depend on taking a "lifecourse approach."⁸ This further publication of results from Kuopio, perhaps unsurprisingly, appeared in the *Lancet*. Could this place of publication bias be expected systematically to alter the perceptions of journal readers, so that those reading the *BMJ* have a more enthusiastic view of the influence of factors in early life than those reading the *Lancet*?

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GPs' awareness of surgical techniques

Better communication with consultants is needed

EDITOR,—The assumption that the quality of care will suffer if general practitioners do not understand the advantages and disadvantages of various clinical procedures highlights a naïveté of the purchasing process shown by many hospital clinicians. T Potamitis and colleagues suggest that care will suffer either because a fundholder insists on purchasing procedures that are suboptimal or because some consultants are offering a suboptimal service and fundholders are not in a position to realise this.¹ For both of these possibilities the solution lies with consultants and their professional bodies. For a consultant to continue to use a procedure that has been clearly shown to be less efficacious than an equivalent procedure is surely unethical under any circumstances.

General practitioners are generalists by definition and will never be up to date with every aspect of every specialty. As the commissioning body a fundholding general practitioner will enter into a contract with a provider to deliver specific services. If this seems to be inappropriate to the hospital consultant surely that consultant should convince the fundholder that he or she is not purchasing the most appropriate service by supplying the necessary information and education.

For purchasing to work well purchasers and providers must work together to ensure that the resultant health care is the best possible. The contracting process should not be seen as lasting for only the few days each year during which the contract is finalised. Bilateral discussions about these issues should take place all year. This requires improved communication and willingness to share and discuss ideas rather than the adversarial position still favoured by far too many consultants and general practitioners.

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Keeping up with all advances is difficult

EDITOR,—T Potamitis and colleagues' paper on general practitioners' awareness of different techniques of cataract surgery highlights one of the main problems with commissioning on a small scale by general practice fundholders.¹ It is increasingly difficult for general practitioners to keep up with the latest advances and changing practices across a wide range of specialties, most of which are changing at least as fast as ophthalmology. Clearly we cannot be expected to maintain the specialist technical knowledge sufficient to make meaningful comparisons between different emerging surgical practices. Indeed, it would not be in our patients' best interests for us to spend our time gathering and analysing such large amounts of information. Unfortunately, as this paper shows, such know-

Numbers of articles relating to "early life hypothesis" published in *BMJ* and *Lancet*, excluding work by Southampton group

	<i>BMJ</i>			<i>Lancet</i>		
	Supportive	Ambiguous	Non-supportive	Supportive	Ambiguous	Non-supportive
Original papers	10	3	2	3	0	4
Reviews and editorials	2	2	0	1	2	1
Total	12	5	2	4	2	5

Trend test comparing total No of publications in *BMJ* and *Lancet*: $\chi^2=3.79$, $P=0.05$.