resistance quite apart from obesity.[3 6 7] (3) Without specifically examining the responses in those who are glucose intolerant it is difficult to draw conclusions regarding pathophysiology, as not all first degree relatives are equally at risk.[2] (4) It is extremely difficult to interpret insulin values during oral glucose tolerance tests, and it is even possible that an initially impaired response during the first half hour may induce hyperglycaemia and subsequent hyperinsulinaemia—a pattern which has been shown since the first immunoassay.[8] Because of the poor repeatability of the oral glucose tolerance test, and the difficulty of interpreting the insulin responses, we prefer to study the response to a continuous infusion of glucose for epidemiological and pathophysiological studies.[9]

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AUTHORS' REPLY,—Dr O'Rahilly and his colleagues were, like us, surprised at the increased insulin responses to oral glucose in the children of non-insulin dependent diabetics. Similar hyperinsulinaemia has recently been reported in Mexican Americans at risk of diabetes[1] and was fundamental to the concept of heterogeneity within non-insulin dependent diabetes proposed by Fajans and cited by Dr O'Rahilly and colleagues. It remains possible that the increased insulin concentrations are secondary to hyperglycaemia. We are studying whether the children are insensitive to insulin.

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Rest pain

SIR,—The paper by Dr M Walzman and others (27 September, p 804) concludes with an exhortation to surgeons to make an accurate diagnosis in cases of intractable leg ulceration, yet the title itself contains an inaccuracy. The term "rest pain" is normally used to indicate pain felt in the leg as a result of critical arterial ischaemia and clearly should not have been used to describe this patient's symptom.

Rest pain is felt in the foot and the onset is classically associated with elevation of the leg to the horizontal—for example, when the patient gets into bed. The authors do not state whether this mode of onset was complained of nor do they indicate the degree of arterial ischaemia present in this patient by quoting the Doppler ankle-brachial pressure index. However, the fact that the pain did not resolve after revascularisation but did resolve after treatment with antibiotics suggests that the pain was indeed not due to arterial ischaemia.

The history is an important element in deciding on the need for arterial reconstruction in cases of arterial ischaemia, supported by non-invasive Doppler ultrasound pressure measurement. I fully concur with the need for accurate diagnosis in cases of leg ulceration but suggest that in this case such accuracy was not achieved because the cause of the pain was prejudged by the use of the inappropriate label "rest pain."

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AUTHORS' REPLY—The point we were making in our article is that rest pain should be regarded as a symptom rather than as a diagnosis. Mr Jones is correct in pointing out that the pain of critical arterial ischaemia classically starts in the foot, although in more advanced ischaemia, such as that which might be associated with extensive ulceration, pain may also be felt in the calf. An important similarity is that syphilitic bone pain, like ischaemic pain, is classically worse at night.[1]

We are satisfied that ischaemic pain was diagnosed on good grounds in this patient: it was supported by a Doppler ratio of 0·58 in the affected leg and the superficial femoral arterial block seen on arteriography. We therefore urge clinicians to consider syphilis in patients with persistent and unresponsive leg pain which sounds ischaemic even if there is supporting evidence of arterial insufficiency.

We agree with Mr Jones that terms such as rest pain may lead to prejudgment, and, just as every patient with rest pain may not have critical ischaemia, not every patient with a hard mass has a carcinoma and not every patient with sciatica has radicular pain.

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Use of the general health questionnaire in clinical work

SIR,—Professor David Goldberg's leading article (8 November, p 1188) has prompted me to write of my clinical experience with the general health questionnaire in general practice. My aims were to estimate (*a*) how common psychiatric illness is in my general practice, (*b*) how much I "miss," and (*c*) whether the general health questionnaire could help me miss less. I administered the questionnaire to a 10% random sample of adult patients (17-64 years) attending my surgery over five months. Patients completed the questionnaire while waiting to see me, and I assessed the nature and degree of any psychiatric illness blind to the score on the general health questionnaire.

No patient refused to complete the questionnaire and 97% of 234 questionnaires were suitable for analysis. A threshold score of 8/9 (rather than 4/5) seemed to give the best trade off between sensitivity and specificity as the lower threshold identified too many people whose symptoms were clearly so mild that no clinical action was called for. My results were:

	Men	Women
GP diagnosed psychiatric disorder (%)	22	31
Questionnaire scores over 8/9 (%)	25	29

When the assessments differed the diagnosis was reviewed retrospectively. The questionnaire did not identify patients (particularly men) with severe chronic psychiatric illness, for which purpose it was not designed. More important clinically were the 11 men and 10 women with high scores on the general health questionnaire whom I had missed. In retrospect I can accept most of these as "cases" and most had serious chronic illness well known to me. I reflect that the GP's continuing contact with his patients, normally invaluable in clinical management, can blind him to coexisting (and treatable) depressive illness in patients he is used to seeing with major physical disease.

Using the psychiatric interview as the ultimate criterion of "caseness," Skuse and Williams point out that the general health questionnaire overidentifies and the GP underidentifies psychiatric cases.[1] The GP who is seeing eight patients an hour may prefer to base his prognosis more on personality, social functioning, and knowledge of previous illness behaviour than on precise diagnosis and psychiatric symptoms.[2] Outcome may be the best criterion and I have followed up my sample for a year in terms of a second general health questionnaire, prescribing of psychotropics, and frequency of attendance over the index year and for five years previously. Eighty five per cent have completed a second general health questionnaire but analysis of the data will have to await more leisurely time over the Christmas holidays.

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Typing of Staphylococcus aureus resistant to methicillin

SIR,—The new method described by Dr J R Stephenson and colleagues for typing methicillin resistant *Staphylococcus aureus* (6 September, p 581) uses the analysis of sulphur-35 methionine labelled proteins, which is time consuming and technically complex. Methicillin resistant *S aureus* is usually multiply resistant and usually contains one or several plasmids. The analysis of staphylococcal low molecular weight plasmids by agarose gel electrophoresis is simple, rapid, and well established, and many workers have found plasmid profiling a useful method of epidemiological typing during hospital outbreaks of methicillin resistant *S aureus*.[1-3]

In Hong Kong methicillin resistant *S aureus* is now a common cause of hospital infection, and we have studied the epidemiology of these organisms in our new 1400 bedded teaching hospital since its opening in May 1984. Despite attempts at control, there were more than 200 non-duplicate patient isolates of methicillin resistant *S aureus* during the first 24 months of operation. There was great heterogenicity

of our isolates when analysed by plasmid type, sensitivity pattern, or phage type (kindly performed by the Central Public Health Laboratory, Colindale), but all the strains analysed contained at least one and up to five plasmids, and we could group the isolates relatively easily into 18 different plasmid types. These types showed significant correlations with phage type, sensitivity pattern, and epidemiological distribution.

Infections with methicillin resistant *S aureus* have been particularly prevalent in the neonatal unit, with epidemiological evidence of probable cross infection to the paediatric wards, and in the burns unit, with cross infection from the orthopaedic wards. The neonatal isolates were mainly of our plasmid type 1, which contains a low molecular weight plasmid of 2·14 megadaltons, usually reacts with phages 29 and 77, and is usually resistant to gentamicin, erythromycin, and tetracyline. Most of the burns isolates were our plasmid type 4, which contains three low molecular weight plasmids of 1·43, 1·37, and 1·21 megadaltons, is usually not typable by phage, and is usually resistant to gentamicin, erythromycin, tetracycline, and chloramphenicol. The remaining 16 plasmid types occurred sporadically on many wards. The multiplicity of types, some occurring as single isolations only, may be the result of organisms being transferred with patients and staff from other affected hospitals.

Our experience (which will be presented in more detail elsewhere) corresponds with that of other workers,[1 2] who find plasmid typing of methicillin resistant *S aureus* more stable and more informative than phage typing, biotyping, or typing by antibiogram. This typing method requires that the isolates contain plasmids, but this is usually the case with methicillin resistant *S aureus*. Plasmids may be analysed further by endonuclease digestion. The possibility of plasmid gain or loss is not necessarily a disadvantage, since this may correlate with and explain phenotypic changes in epidemic strains.[3]

Most Western reports of hospital outbreaks of methicillin resistant *S aureus* are with single epidemic strains. In Hong Kong, where methicillin resistant *S aureus* infection is endemic and affects a wide variety of organisms, plasmid analysis is a simple, rapid, and effective method of typing. The technique may also be applied to many other organisms of hospital infection[4] and is thus a particularly useful epidemiological tool in non-specialist hospital laboratories.

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Hypnotic benzodiazepines

SIR,—May I say how much I agreed with what Professor Malcolm Lader wrote (25 October, p 1048), except that he directed a roguish dart at me with his final reference to my leading article (15 March, p 715). I had not made a "plea" to make benzodiazepines more freely available. They are easily available already. However, there are illogicalities in the present situation.

In Australia the state of Victoria decided that from late 1983 temazepam and nitrazepam could be sold in quantities enough for five nights on the decision of the pharmacist and without medical prescription. Various expressions of horror preceded the legislation, but time has not borne out the fears,[1] so confirming Michael O'Donnell's prediction.[2] An over the counter hypnotic has been available now for 18 months in the UK. It has not been advertised to the public, it is expensive per dose, but with only eight doses per purchase it is cheaper than the NHS prescription charge.

The WHO wants all benzodiazepines to be medically prescribed. It is a body that receives advice from cautious medical committee members. But are they overcautious? Doctors used to make a living as experts on purgation but no longer have exclusive rights. They do not prescribe alcohol, which any adult can buy and which causes far more trouble than do benzodiazepines. In the light of the Victorian experience we may wonder whether doctors cling too tightly to their exclusive mysteries and whether their expensive intervention is essential for the purchase of small quantities of hypnotics, half of which may sit in a family medicine chest for a year before they are used without medical supervision.

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Humoral response to wheat protein in patients with coeliac disease and enteropathy associated T cell lymphoma

SIR,—Dr Cliona O'Farrelly and colleagues (11 October, p 908) explore relations between circulating α gliadin antibodies in patients with presumptive coeliac disease and T cell lymphomas. Their results highlight the difficulties in diagnosing gluten sensitivity in this uncommon, yet important, clinical area in which α gliadin antibodies do not appear to offer a confident guarantee of success. Thus the fundamental problem remains: how to distinguish coeliac associated from non-coeliac associated small intestinal lymphoma.

Despite much burning of midnight oil, neither of us could discern the precise state of 16 cases of presumed non-coeliac lymphoma. The diagnosis in many of these cases is by no means clear, despite the lack of α gliadin antibodies, since the patients in cases 2, 4, 8, and 14, who were all DR3 positive women who had had symptoms for 30-60 years, could have had coeliac disease. In another 6 of 12 patients the meaning of "transient clinical response" is vague, while another individual who "responded" must presumably have been another patient with coeliac disease. There is too much uncertainty about the diagnostic state of many of these patients to believe that α gliadin antibodies distinguish one from the other.

In much of our recent work we have attempted to define positive histological criteria in patients with coeliac disease compared with controls with other diseases, with or without flat mucosas. Although computerised image analysis has been used in many of these studies, most of the criteria can be obtained with simpler techniques applied to routine histological material. Such criteria include the presence of large immunoblastoid epithelial lymphocytes both within surface,[1 2] and crypt,[3] epithelium, a greatly increased population of epithelial lymphocytes within coeliac crypts,[3] and a raised (>0·2%) mitotic index among surface epithelial lymphocytes.[4 5] Indeed, in addressing the same question as that posed by Dr O'Farrelly and colleagues we found a low mitotic index among epithelial lymphocytes in non-coeliac induced flat lesions with lymphoma, in contrast to the high mitotic indices characteristic of untreated patients with coeliac disease.[1 5] Indeed, a mitotic index might well have helped to clarify the final diagnostic groups in their paper by indicating how many of the 14 non-responders with α gliadin antibodies, the 7 non-responders without antibodies, and the 16 individuals with supposed T cell lymphoma had coeliac disease.

There is still a pressing need for a more stringent "test" of gluten sensitivity. Clearly, serum concentrations of α gliadin antibody do not meet this requirement entirely so that these authors have not succeeded in presenting a very convincing case.

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Use and misuse of digoxin assay service

SIR,—An audit of two geographically distant laboratories (Scotland and south west England) shows a similar picture to that drawn by Mr I Gibb and colleagues (13 September, p 678).

In a laboratory 597 digoxin samples were analysed over six months; 75% came from patients over the age of 70 and 34% had creatinine concentrations greater than 125 μmol/l (1·4 mg/100 ml). The dose-sample interval was unknown in 23% and less than six hours in 10%. The other laboratory assayed 1050 specimens over 15 months; 28% had creatinine concentrations greater than 125 μmol/l and in 8% the potassium concentration was less than 3·5 mmol(mEq)/l. In 35% of cases the dose-sample interval was unknown and in 12% it was less than six hours. Clinicians must ensure that digoxin requests, like other laboratory investigations, are clinically justified and taken at an appropriate time. Administering digoxin as an evening dose should alleviate many problems, and following discussion with local cardiologists this is being instituted in their patients. Possibly laboratories should refuse to analyse inappropriate samples from both patient safety and financial viewpoints.

One increasingly pertinent problem in analysing and interpreting digoxin specimens is that of digoxin like immunoreactive substances.[1] The digoxin method used by the Newcastle group, Serono MIAI radioimmunoassay, has been tested in premature and full term infants[2] but not, to my knowledge, in adults with renal and hepatic disease. To investigate this we analysed serum