Gall stones induced by octreotide

EDITOR,—The beneficial effects of treatment with octreotide are accompanied by an increased risk of gall stones. Grant W Bigg-Wither and colleagues found that in 22 patients (13 of whom had acromegaly) octreotide increased the fasting gall bladder volume; they propose that this may predispose to the formation of gall stones.¹ We believe, however, that this is unlikely to be the main factor in the pathogenesis of gall stones induced by octreotide. We have measured fasting gall bladder volumes in nine acromegalic patients before and after octreotide and found no significant increase during treatment.² Furthermore, although the fasting gall bladder volume in 31 untreated acromegalic patients was 30% larger than that in normal subjects, we found only a minor increase in the prevalence of gall stones.³

Octreotide impairs contraction of the gall bladder in response to a fatty meal and increases the residual volume of the gall bladder. This might be expected to promote the formation of stones because of relative stasis of the gall bladder. The residual volume of the gall bladder in untreated acromegalic patients, however, is three times that of normal subjects and yet the increase in gall stone prevalence in these individuals is small.

Our data suggest that although a reduction in gall bladder emptying may well play a role in the formation of stones, an increased fasting gall bladder volume is not a major factor in their pathogenesis. Native somatostatin increases the cholesterol saturation in bile,⁴ and we have found similar changes in acromegalic patients with gall stones associated with octreotide.⁵ These observations suggest that changes in bile chemistry may be at least as important as motor dysfunction of the gall bladder in the pathogenesis of gall stones induced by octreotide.

SUSAN M CATNACH JOHN A H WASS
JOHN V ANDERSON MICHAEL BESSER
PETER D FAIRCLOUGH

Departments of Gastroenterology and Endocrinology,
St Bartholomew's Hospital,
London EC1A 7BE

HYDER HUSSAINI
HERMON DOWLING

Gastroenterology Unit,
Guy's Hospital,
London SE1 9RT

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Renal transplantation in tuberous sclerosis

EDITOR,—In their editorial on new insights in tuberous sclerosis David W Webb and John P Osborne rightly emphasise that the outlook for many adult patients with the disease is not as poor as previously thought.¹ They point out that renal disease was the leading cause of death in a recently reported series of patients² but do not mention that renal transplantation can now substantially prolong survival of patients who develop end stage renal disease. Colleagues and I have reported the outcome of three patients with tuberous sclerosis

given transplants at our centre and have reviewed an additional six previously reported cases. I summarise here the main findings of this study.³

Survival is excellent. Our patients (three women aged 27-46 at the time of transplantation) were fully rehabilitated, with the graft functioning 65 to 132 months after transplantation. In the four other reported cases for which follow up data are available the course was equally satisfactory, only one patient dying, from an infection unrelated to tuberous sclerosis.³

No manifestations of neurological disease were observed in any of the seven patients after renal transplantation. Neurological disease before transplantation was mild: six patients had suffered a minor form of epilepsy, and none was mentally retarded. Probably patients with mild neurological disease survive longer, allowing renal failure to develop. Interestingly, all the patients given transplants were female, a finding in keeping with the reported higher early mortality—usually from neurological complications—in male patients.⁴ Renal cell carcinoma was found in one kidney removed before transplantation,⁵ and nuclear abnormalities of cystic epithelial cells suggestive of malignant transformation were observed in a kidney removed at transplantation from another patient. The overall prevalence of renal cell carcinoma in tuberous sclerosis is 4%, which is higher than that in a control population.⁶

In conclusion, patients with tuberous sclerosis with end stage renal failure are good candidates for renal transplantation. Neurological disorders did not progress after transplantation in the reported cases. The probable small risk of neoplastic transformation of native kidneys, which might be potentiated by immunosuppressant drugs, warrants bilateral nephrectomy before or at the time of renal transplantation.

Y PIRSON

Department of Nephrology,
University of Louvain Medical School,
B-1200 Brussels, Belgium

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Assessing observer variability

EDITOR,—In their review of methods for assessing observer variability in clinical measures Paul Brennan and Alan Silman recommend using the κ statistic and the limits of agreement when studying categorical and continuous variables, respectively.¹ I do not think that using the limits of agreement is the best method. Indeed, Bland and Altman described its use for method comparison studies—that is, experiments aimed at assessing the reproducibility of two well defined methods, say A and B.² The purpose of studies of observer variability is generally not to assess the reproducibility of the performance of two well defined observers, except perhaps in internal audit, but to evaluate the concordance of two among many potential observers—that is, to quantify the observer variability in general.

In the language of analysis of variance, both methods A and B are a fixed factor while both observers are a random factor. Moreover, the signs of the differences have to be considered in the comparison of both methods but are irrelevant in a

study of variability between two, among possibly other, observers. For instance, if the difference between measurements obtained with methods A and B is x for one subject and $-x$ for another one the resulting mean difference to be considered for these patients should be zero in a method comparison study and $|x|$ in an assessment of observer variability. The method of limits of agreement, which takes the signs of the differences into account, is thus well suited to comparing two methods but not two observers, at least in the general case.

I think that a better way of assessing observer variability is to use the intraclass correlation coefficient, originally described by Bartko,³ which is the proportion of the total variability accounted for by the variability among subjects. If it is high not much of the variability is due to variability in measurements of different observers; thus the reproducibility is high. The intraclass correlation coefficient may be estimated from the components of a two way analysis of variance, taking into account variability between subjects and variability between observers. In the particular case of only two observers, however, it may be directly computed by the formula

$$\frac{s^2(x)+s^2(y)-s^2(d)}{s^2(x)+s^2(y)+d^2-(s^2(d)/n)}$$

where n is the number of subjects, $s^2(x)$ and $s^2(y)$ are the variances of measures for observers X and Y, and d and $s^2(d)$ are the mean variance of the differences between measures of both observers, respectively.⁴

Finally, the intraclass correlation coefficient is mathematically equivalent to the κ statistic used for categorical measurements,⁵ which is the method that Brennan and Silman recommend for assessing observer variability in this situation.

JACQUES JAMART

Biostatistical Consultation,
Mont-Godinne Academic Hospital,
B 5530 Yvoir,
Belgium

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AUTHORS' REPLY,—We broadly agree with Jacques Jamart's comments about the value of the intraclass correlation coefficient and had made similar points in an earlier version of our paper. During the revision process we removed this to make the article clearer for a non-statistical readership. We differ with Jamart, however, on the appropriate use of this measure. Though he is correct in stating that the intraclass correlation coefficient is conceptually and mathematically equivalent to the κ statistic, it also suffers from the same disadvantage of interpretation. Specifically, as the intraclass correlation coefficient may be considered to be the proportion of variation due to the observers it depends on the absolute variability due to the subjects. The suggested method of calculating the limits of agreement does not suffer from such a dependence and therefore results in more meaningful measures.

The variability between observers may also be calculated from an analysis of variance approach with the observers being considered as random effects, and this is indeed appropriate when there are more than two observers. Using the limits of agreement, however, does not provide meaningful results for methods of measurement in which

different scales are used. In such a case the intraclass correlation coefficient computed for each method will indicate which is the more reliable, provided each method of measurement uses the same population, as in a dataset we recently examined.¹ In summary, we agree with Chinn when she says that "the intraclass correlation coefficient should be used only for comparative purposes. The within-subject standard deviation or 95 per cent range for change should be calculated as the absolute measure of repeatability."²

PAUL BRENNAN
ALAN SILMAN

Arthritis and Rheumatism Council Epidemiology Unit,
Manchester University Medical School,
Manchester M13 9PT

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Toxic dilatation and infective diarrhoea

EDITOR,—In their article on non-specific inflammatory bowel disease in the ABC of colorectal diseases S Pettit and M H Irving state: "Toxic dilatation is a life threatening condition which has to be treated by urgent colectomy . . . regardless of underlying aetiology."¹ Over the past decade the regional infectious diseases unit in Sheffield has seen 20 cases of toxic dilatation of the colon complicating acute diarrhoea (of less than three weeks' duration) of largely infective aetiology (unpublished data). Intensive medical management consisting of intravenous steroids, antibiotics, and supplementary nutrition similar to the Truelove regimen² resulted in resolution in 17 patients. Three patients required subtotal colectomy and ileostomy for actual (two) or incipient (one) perforation of the transverse colon, but none developed a severe peritonitis and all subsequently recovered with eventual reversal of the ileostomy.

Like others,³ we believe that in toxic dilatation with a likely infective aetiology initial aggressive medical treatment offers a good chance of recovery with preservation of the colon. Naturally, the risk of perforation must be minimised and any complication identified early. Our policy is to involve a surgical team in case medical management fails and operative intervention is necessary.

J A SNOWDEN
M W MCKENDRICK

Regional Infectious Diseases Unit,
Lodge Moor Hospital,
Sheffield S10 4LH

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Medical audit in general practice

EDITOR,—The North of England Study of Standards and Performance in General Practice claims to have shown that medical audit and standard setting can change doctors' behaviour and improve the care of patients.¹ A problem is that the study seems neither to have completed any medical audit nor set standards in the usually accepted sense.

In *Medical Audit Tools* the authors write: "An explicit standard is a declared, usually written,

statement. For medical audit it will describe a desired state of affairs and state a recommended level of performance."² I agree—as do most authors.^{3,6} On the other hand, in a report of this study they write: "A clinical standard is an explicit statement of what a doctor's performance should be. . . . The most common form is the structured essay. . . . We set out only to describe standards, not to make judgement of their quality."⁷ Such clinical standards are usually referred to as guidelines, which are usually much too diffuse and comprehensive to be used as a measure against which performance can be compared.⁸ It is this form of standard that the study used.¹

Again, the authors write that their objective was "to estimate the effect of medical audit, particularly setting standards, on clinical behaviour."¹ But setting standards—or, as I have suggested, developing guidelines—seems to be the only part of the audit cycle undertaken. No targets were set; although data were collected for research purposes, they were not fed back as part of an audit process—indeed, the paper states that after the end of the study data were well received by trainers; and no resolutions for change were made by comparing targets with performance.

So what did happen? Apparently, groups of trainers studied certain conditions and drew up guidelines for management. After that their behaviour changed to accord more closely with the guidelines they had developed themselves, but not in response to guidelines drawn up by others. That seems a believable and likely result of an educational exercise, but it is not standard setting in the usually accepted sense of the word and it is not audit. Such confusing use of terminology can only delay a generally agreed understanding of medical audit and setting standards.

MARTIN LAWRENCE

Department of Public Health and Primary Care,
Oxford University,
Radcliffe Infirmary,
Oxford OX2 6HE

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Agenda for health in Europe

EDITOR,—Surely in setting the agenda for health in Europe it must be relevant to include the public health problems of other parts of the world, particularly the Third World, otherwise the North-South divide will increase.¹ Any action undertaken in the developed world must not have a "dumping" effect on the developing world; this was the main theme of the earth summit in Rio de Janeiro.² It is not just environmental issues that are of global importance but also matters related to health.

Take, for example, the harmful effects of cigarette smoking. If the Western world is successful in reducing tobacco consumption and at the same time does not discourage the manufacturers from continuing to produce cigarettes these companies will inevitably sell their product in countries whose market can be exploited. These tend to be

the poorer nations of the world. The net result will be to shift the problem from a well organised society to an impoverished state. Several other examples of this exist, including the sale of discarded brands of drugs and the encouragement of artificial breast feeding.

What is needed, therefore, is a strategy that improves the health status of people in Europe without prejudicing the lives of people in other parts of the world. The global need for health must influence the European strategy.

IAN HOLTBY
SAM RAMAIAH

South Tees Health Authority,
Poole Hospital,
Nunthorpe,
Middlesbrough,
Cleveland TS7 0NJ

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Black dog of depression

EDITOR,—The author of a recent personal view gives an eloquent and moving account of his 40 year struggle with depression; it is admirably free of the "tendency towards self pity and wallowing in gloom" that he fears may antagonise those who surround him.¹ How sad it is, therefore, to read that he is too embarrassed to reveal his identity and does not want the people he mixes with to know of his illness. Presumably if he had been reporting a lifetime as a doctor coping with blindness or some disabling neurological disorder he would have thought this a worthwhile struggle and one of which he need not feel ashamed.

Mental illness still, it seems, carries enormous stigma, and I am not suggesting that sufferers should be unwillingly "outed" in medical journals. Perhaps we should ask ourselves why a senior doctor, writing in a column that will principally be read by his professional colleagues, is unwilling to be identified as someone who has achieved success in both the personal and professional spheres of his life despite having a chronic incurable disability. I hope that psychiatrists are not alone in entreating patients and their families and colleagues to regard psychiatric illnesses as what they are: just illnesses. Mental illness is as deserving of attention and treatment as any other, and those who have overcome it equally deserve our admiration.

ROBERT HOWARD

Institute of Psychiatry,
London SE5 8AF

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Poland: collaboration or advice?

EDITOR,—Karin Chopin's article on aid to Poland¹ was published the day we left with five other clinical biochemists from Glasgow and Dublin to serve as lecturers on a postgraduate course on strategies in clinical biochemistry held in Professor S Angielski's department of clinical biochemistry in Gdansk, Poland. This was one of the activities of the joint European project "clinical biochemistry education in Poland" supported by the European Community's TEMPUS programme. It is a collaborative project between the departments of clinical biochemistry at the Western Infirmary and university in Glasgow, St James's Hospital and Trinity College in Dublin, and the Medical Academy in Gdansk.

The project's overall aim is to update undergraduate and postgraduate teaching in clinical biochemistry in Gdansk and to strengthen education on preventing cardiovascular disease. The