that heterosexual transmission of HIV is understood and that manifestations of AIDS and HIV infection that are particular to women are recognised—notably, disease of the female genital tract. But the overwhelming evidence shows that most manifestations of HIV infection are gender non-specific in type and incidence.

Ford is unfair and, indeed, incorrect in citing the recent clinical teaching text by my colleagues Parkin and Peters.² Their case oriented book, based on actual patients, uses a problem solving approach to help clinicians learn about AIDS. Most cases of AIDS in the developed world have been in men, and so real patients are described as man/he/him; it would be offensive to those men gratuitously to change their gender. Sadly, as heterosexual spread of HIV and ignorance and denial of it continue more cases will be seen among women, but the delay between infection and disease means that this spread will not be apparent as clinical disease for some years.

Current cumulative figures on AIDS in the United Kingdom show 5215 cases in men and 341 in women. In the vast majority of case histories, radiographs, and histological material, and most clinical slides, however, gender would be indistinguishable. Furthermore, Ford says that only two of 153 presentations in this book are of women, but, in fact, of 138 cases, 10 are in women and for 27 the gender is not specified; of 63 clinical photographs, six are of women and one shows a family.

Parkin was a coauthor of a report on one of the first women in the United Kingdom (a monogamous English housewife) to acquire AIDS through heterosexual transmission.¹ Parkin and other members of my team have repeatedly emphasised the importance of heterosexual spread over many years and have learnt much from patients; we have endeavoured to pass this on to our colleagues and the public in many forums. Ford's attack on young and enthusiastic colleagues is unwarranted.

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EDITOR,—We agree with Chris Ford that services for diagnosing, treating, and preventing HIV infection in women have lagged behind those targeted at people whose major risk behaviour is male homosexual contact.¹ The pattern of risk behaviour has changed in recent years; of the 263 HIV seropositive heterosexuals who attended St Stephen's Clinic to the end of 1991, 110 were female and 49 of these presented after January 1990. In response to this change a clinic for women only was initiated in April 1991 to attract women with a range of risk behaviours who were not using existing facilities. This clinic is staffed exclusively by women for women and has proved to be popular.² Similarly, a clinic providing genitourinary medicine services for lesbians has been instituted in the district as the sexual health of this group is underresearched and lesbians have had difficulty in gaining access to appropriate medical services.

Ford also cites a short article by one of us as an example in which "information about the disease is still male dominated."³ This article was intentionally written without specific references to either the sex or orientation of the infected subjects and to apply equally to all with HIV infection or AIDS. We hope that HIV infection will be regarded as a multi-system disorder that may affect people from any walk of life but is amenable to risk reduction—

the adoption of measures such as safer sex and not sharing drug using equipment.

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Tachycardia during cisapride treatment

EDITOR,—Sten Olsson and I Ralph Edwards report seven cases of tachycardia or palpitations associated with treatment with cisapride.¹ These presumably represent all or most of these events reported spontaneously to four national centres over three years.

We have studied cisapride in 13 233 patients and have compared the rates of palpitations, tachycardia, and extrasystoles with data collected under substantially identical conditions from 240 381 patients in 23 recent prescription event monitoring studies. This database, which comprises about 40% of our records, includes 1960 records of tachycardia, palpitations, or extrasystoles, 595 of which were noted to have occurred during the first month of observation (table).

Number of cases of palpitations, tachycardia, and extrasystoles recorded during first month* in 23 prescription event monitoring studies: rates per thousand in descending order

Drug	No	Rate/1000
Nicardipine	160	14.6
Lisinopril	99	8.0
Xamoterol	35	6.5
Enalapril	72	4.7
Fluvoxamine	44	4.0
Buspirone	43	3.9
Diltiazem	25	2.5
Fluoxetine	29	2.3
Betaxolol	2	1.3
Ormeprazole	20	1.2
Terodiline	14	1.1
Cisapride	11	0.8
Nedocromil	10	0.6
Flunitrazepam	6	0.8
Misoprostol	9	0.7
Tenoxicam	4	0.4
Etofolac	3	0.3
Famotidine	3	0.3
Nizatidine	2	0.3
Nabumetone	2	0.2
Acrivastine	1	0.1
Cetirizine	1	0.1
Loratadine	0	0
All studies	595	2.5

*Includes patients who had stopped treatment with relevant drug.

The rate of these events during the first month was 0.8/1000 for cisapride compared with a mean rate of 2.5/1000 in all the studies. Even allowing for the fact that several studies were of drugs used to treat cardiovascular conditions in which tachycardia would be expected to be common, our results provided no epidemiological support for Olsson and Edwards's hypothesis. We therefore examined all relevant records in our study of cisapride individually. There were 104 such records—67 of palpitations, 23 of tachycardia, five of extrasystoles, and nine of heart block. Fifty five of the events occurred during the follow up period, up to a year after the patient had stopped using cisapride. Only eight patients using cisapride experienced one of these events during the first

month of treatment. We consider that all these events were coincidental and almost certainly unrelated to cisapride. For all 104 patients, no doctor stopped treatment with cisapride because of these events or attributed them to the drug.

The few reports to the World Health Organisation's programme suggest an extremely low risk, even if there has been considerable underreporting. We believe that these reports represent only a small fraction of the events of this type that would be expected with or without treatment with cisapride. Palpitations and tachycardia are common and have occurred coincidentally in all of the groups we have studied. Spontaneous reporting systems were designed to detect previously unsuspected reactions that were too infrequent to be identified during premarketing clinical trials. When events are reported that commonly occur in the absence of any recognisable association with treatment it is inappropriate to draw conclusions from them, especially if alternative causes have not been eliminated.

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- 1 Olsson S, Edwards IR. Tachycardia during cisapride treatment. *BMJ* 1992;305:748-9. (26 September.)

EDITOR,—Sten Olsson and I Ralph Edwards report that treatment with cisapride may induce tachycardia.¹ They conclude that the mechanism of this action is not obvious but may be a procainamide-like effect. A tachycardic response to cisapride has, however, been reported previously,² and we suggest that activation of serotonin-4 receptors is a more likely explanation for this effect.

The existence of serotonin-4 receptors has only recently been established.¹ These receptors are positively coupled to adenylyl cyclase¹ and are present on pig heart,⁵ where they mediate a chronotropic response. Experiments have also shown the presence of serotonin-4 receptors on human right atrium, where they mediate an inotropic response.⁶ In this atrial tissue the response to serotonin was associated with raised levels of cyclic AMP⁷; thus, although the rate response was not measured, it is likely that, as in pig heart, stimulation of serotonin-4 receptors mediates a chronotropic as well as an inotropic response. Furthermore, it is well documented that cisapride is an agonist at serotonin-4 receptors,¹ and, in particular, exhibits partial agonist activity at the serotonin-4 receptor found in human right atrium.⁸

We conclude that the tachycardic response to cisapride in humans may be due to activation of atrial serotonin-4 receptors. Possibly this occurs infrequently in clinical practice because cisapride is a particularly weak partial agonist at serotonin-4 receptors in the human heart.⁹

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Thoracoscopic pericardiectomy

EDITOR,—In their editorial on the management of malignant pericardial effusions David Keane and Graham Jackson quote a 30 day mortality of up to 60% for open surgery in cases of malignant pericardial disease.¹ They then present the case for percutaneous balloon pericardiectomy as a non-surgical alternative. There is, however, an important alternative surgical option—namely, thoracoscopic pericardial window. Minimal access thoracic surgery done with videothoracoscopy and endoscopic instruments allows thoracic surgical procedures to be performed without the morbidity and mortality associated with thoracotomy.²

The patient is positioned as for a standard thoracotomy in the lateral position. Under general anaesthesia one 1 cm and two 0.5 cm incisions are made in the left sixth intercostal space. A thoracoscope with attached video camera is introduced through one of these, and endoshears and forceps are passed through the others. Under one lung anaesthesia the lung collapses and falls posteriorly to give an excellent view of the mediastinum. To relieve tamponade a pericardial window of suitable size and shape is cut, avoiding the phrenic nerve. Pericardial fluid is aspirated from the thorax, and an intercostal drain is inserted through the larger incision.

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Measuring glycated haemoglobin

EDITOR,—Douglas A Robertson and colleagues report three cases in which haemoglobin F resulted in certain assays giving falsely high haemoglobin A₁ concentrations.¹ We recently changed from using affinity chromatography to using an in house high pressure liquid chromatography method, with an ion exchange packing material, because results from the affinity chromatography method had become unreliable. With high pressure liquid chromatography various types of haemoglobin are seen as separate peaks in a chromatogram; this technique allows haemoglobin F and other variants to be identified and measured easily.

We have analysed more than 5000 samples in nine months and have found 16 patients with haemoglobin variants. All have been heterozygous and none had been suspected to be. Two had haemoglobin F, both in much higher concentrations (26% and 22%) than those reported by Robertson and colleagues. One had haemoglobin E. Seven had haemoglobin D, a common Punjabi variant, which reflects Coventry's large Punjabi population. We believe that the five with sickle cell trait were of West Indian origin. Intriguingly, haemoglobin J was found in an Irishman; this is a rare Spanish variant.

Conventional charge dependent methods of measuring haemoglobin A₁, in which haemoglobin fractions are eluted from a column and measured colorimetrically, do not separate haemoglobin F from haemoglobin A₁ and thus overestimate it.² Conversely, falsely low values for haemoglobin A₁

are obtained when abnormal haemoglobins such as S, C, D, G, and E are present.¹ These variants are not separated from haemoglobin A by these methods, which therefore underestimate the haemoglobin A₁:haemoglobin A ratio, although Torke *et al* suggested that a correction can be made if the percentage of the variant haemoglobin is known.¹

Having changed to high pressure liquid chromatography we can now detect haemoglobin variants easily and report the haemoglobin A₁ concentration without the previous errors. We are now finding cases of sickle cell trait during routine management of diabetic patients, which could necessitate genetic counselling.

We note, incidentally, that in case 2 Robertson and colleagues do not mention the haemoglobin F concentration. We wonder whether it was measured in this case and, if so, whether the value was comparable with that in the other cases.

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- 1 Robertson DA, Tunbridge FKE, John WG, Home PD, Alberti KGMM. Diagnostic confusion in diabetes with persistence of fetal haemoglobin. *BMJ* 1992;305:635-7. (12 September.)
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EDITOR,—D A Robertson and colleagues point out that some widely used methods of measuring glycated haemoglobin that are charge dependent give erroneously high values for glycated haemoglobin because they include haemoglobin F.¹ But some instruments based on charge dependent separation using high pressure liquid chromatography give haemoglobin A₁ or haemoglobin A_{1c} results with minimal interference from haemoglobin F.² Moreover, one such analyser, the Diamat (Bio-Rad Laboratories, Hemel Hempstead), is suitable for measurement of haemoglobin F.¹

The authors mention the increased prevalence of slightly raised haemoglobin F concentrations in diabetic children.¹ Our observations made with a Diamat analyser confirm that these raised concentrations also occur with increased frequency in adolescent and young adult diabetic patients. Of 561 consecutive specimens from patients aged 11-25, 210 (37.4%) had haemoglobin F concentrations above the often quoted upper limit of normal of 0.5%, and 46 of these concentrations were above 1.0%. This frequency was significantly greater (χ^2 test, $p < 0.001$) than that observed in 44 control specimens taken from the non-diabetic hospital population and blood donors in the same age range, of which four (9%) had values above 0.5%, the highest being 0.8%. The increase was seen in both sexes but occurred significantly more commonly in female than male diabetic patients (χ^2 test, $p < 0.01$). In the 280 specimens from female patients the 26 values above 1.0% were from 18 patients, in 14 of whom pregnancy was excluded as a cause.

Misinterpretation may also occur during long term monitoring of high risk groups such as patients with cystic fibrosis. Where the method includes haemoglobin F its proportion is not known and the extent to which it may change over the years cannot be predicted. These estimations are frequently performed on very young children. In a series of eight children aged 3 years or under

with cystic fibrosis five had haemoglobin F concentrations in the range 1.0-2.9%.

For these reasons and those described by Robertson and colleagues we would discourage people from using methods of measuring glycated haemoglobin that include haemoglobin F. Of the non-charge dependent methods that the authors suggest, however, thiobarbituric acid and affinity chromatography methods are not readily suited to large numbers of samples and enzyme immunoassay can grossly underestimate glycated haemoglobin in patients with structural haemoglobin variants.²

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Early analgesia for acute abdominal pain

EDITOR,—Zachary Cope's warning of the dangers of giving morphine before making a diagnosis was justifiable in 1921, when a dose of 30 mg was not unusual, but it has been heeded for too long, and the trial of Alex R Attard and colleagues (using a maximum dose of 12.5 mg morphine) is very welcome.¹

It is interesting that no inappropriate operations were performed among the 50 patients receiving papaveretum but six were performed among the 50 who received saline. It seems that some patients when first seen by the registrar, one hour after injection, were doubtful and were observed, because 10 in the papaveretum group and six in the saline group left hospital with a diagnosis of non-specific abdominal pain and had not been subjected to operation. However, six patients in the saline group must have seemed on first examination to have disease requiring surgery because a laparotomy was needed to eliminate this possibility.

Experience with the acute abdomen in infancy may be helpful here. In a frightened, uncomfortable 2 year old it can be impossible to elicit reliable abdominal signs because of struggling and crying; it is then necessary to sedate the child, most readily with rectal diazepam.² After an hour the child is usually asleep and if a warm hand is slipped under the bedclothes a good examination of the abdomen can be made without awakening the infant. Here one is seeking the objective signs of muscle guarding, a mass, or, if the appendix is far from the anterior parietal peritoneum, deep tenderness which causes the child to stir. These signs do not rely on the subjective sensations of the patient.

Most patients with non-specific abdominal pain show tenderness in the right iliac fossa, but guarding is unusual.³ One of the hidden advantages of early analgesia may be that it enables the patient to relax; it is then easier to recognise that, though there is local tenderness, there is a significant absence of guarding. It is then logical to await developments, make recordings every half hour, and re-examine the patient in two to three hours rather than proceed immediately to operation.

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