AUTHOR'S REPLY.—My article made clear that single enzyme measurements are rarely diagnostic in the first 12 hours. Serial measurements are more useful, but in the real world of a busy hospital and an understaffed biochemistry laboratory this is unlikely to find much favour, particularly when the method requires four hourly blood sampling and construction of a "log creatine kinase slope." Even if the method were practicable it would not permit diagnosis until 12 hours or more after admission (perhaps 16 hours after infarction), when the benefits of thrombolytic treatment are considerably diminished and when electrocardiography often shows unequivocal changes.

Practical considerations aside, I am less enthusiastic than Dr Mullen about the validity of this method. The main differential diagnosis in patients with cardiac chest pain is between unstable angina and acute infarction. Difficulties arise only if the electrocardiogram taken on admission to hospital is non-diagnostic, and an additional test may be required. Collinson *et al* gave no information about admission electrocardiograms, and in the 1989 study only one patient had unstable angina compared with 34 with acute infarction—which makes it difficult to assess the test's discriminatory value. Indeed, they seem to acknowledge this difficulty by diagnosing five patients as "ischaemia ? infarction," a conundrum that was not resolved by measuring creatine kinase activity. Dr Mullen asserts that accurate diagnosis can be obtained from a time-activity slope based on only two data points. This is hard to accept, and I would point out that only four of his patients had non-diagnostic electrocardiograms on admission and there was no proper control group of patients with unstable angina. It would be interesting to know how many of the electrocardiograms remained non-diagnostic 16 hours after infarction when Dr Mullen was still gathering blood samples for log creatine kinase analysis.

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SIR,—Though we agree with Dr Adam D Timmis's assertion that "electrocardiography is still best," he has neglected to mention the importance of interpreting the electrocardiogram in its clinical context.¹ He is correct that the electrocardiogram taken on admission to hospital is abnormal in about four fifths of patients, but it does not always show the regional ST elevation and Q wave changes we would regard as diagnostic. For example, he quoted the study by Lee *et al* in which only 47% of patients' electrocardiograms had such changes at presentation.²

Clinical and electrocardiographic data have been combined statistically to produce algorithms that are readily usable and can increase diagnostic accuracy.^{3,4} We have tested an algorithm produced by linear discriminant analysis of such data—with over 200 patients tested prospectively, the sensitivity and specificity of diagnosis both approached 90%. The optimal use of clinical and electrocardiographic data should be the standard against which new diagnostic tests are judged. Pushing biochemical tests for myoglobin or cardiac specific isoenzymes to their limits is unlikely to help with individual difficult patients, even if such tests were available on a 24 hour basis. Complex imaging techniques are subject to financial and other constraints and may never be available to most patients. Many of these techniques, in any case, need time for the infarct to mature and visualise only tissue that is already necrotic and could not, therefore, be salvaged by thrombolysis. Recent evidence suggests that only a modest reduction of time delay in administering thrombolysis during the early hours after symptoms begin may benefit the patient haemodynamically.⁵

In following the current recommendations that only patients with diagnostic electrocardiographic

changes be treated with thrombolytic drugs we are certainly treating those with larger infarcts and a higher chance of serious complications.⁶ But are we treating those most likely to benefit from thrombolysis? The major trials showing benefit from these drugs did not use electrocardiographic changes as entry criteria. Thrombus formation is also important in unstable angina and non-Q wave infarction and efforts to reduce thrombus may also reduce morbidity and mortality.⁷

Thrombolytic treatment is fairly safe in practice but is often misused or underused.⁸ The only practical way of optimising its use is for us to make better use of routine clinical information. We will not be able to make a perfect diagnosis in every case, but we should be able to stratify patients into groups according to their risk of life threatening events and to balance such considerations against any potential disadvantage of treatment. There is a case for widening the usage of thrombolytic treatment and it could certainly be disadvantageous to adopt a wait and see policy for the many patients presenting with suspected acute myocardial infarction who lack diagnostic electrocardiographic changes at presentation.

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SIR,—Dr Adam D Timmis's editorial¹ agrees with our local experience that history and electrocardiography are the bases for rapid identification of patients for thrombolytic treatment. None of the blood tests currently used can give reliable answers soon enough.

We used a new cardiospecific immunoassay of creatine kinase (CK-MB, Novo-Nordisk Diagnostic) to assess whether this could improve results. Sixty seven unselected patients in the coronary care unit who had chest pain were given the usual three serial daily electrocardiographic examinations and routine serial estimation of serum aspartate aminotransferase and hydroxybutyrate dehydrogenase and total creatine kinase activities on admission, the next morning, and the morning after that.

The results of all these tests were available to the doctor in charge, who made the final diagnosis. In addition, on admission and the morning after a serum sample was taken for the immunoassay of creatine kinase; these results were not known to the doctor in charge.

Twenty eight patients had definitely had a recent myocardial infarction, 36 had definitely not, and in three the diagnosis was doubtful. Cut off points for diagnosis of myocardial infarction were aspartate aminotransferase activity greater than 50 IU/l,

hydroxybutyrate dehydrogenase activity greater than 200 IU/l, total creatine kinase activity greater than 195 IU/l in men and greater than 170 IU/l in women, and creatine kinase concentration greater than 30 µg/l. Among the 28 patients with a definite myocardial infarction the first value was abnormal for the creatine kinase immunoassay in nine, for total creatine kinase in 13, aspartate aminotransferase in six, and hydroxybutyrate dehydrogenase in four.

Thus none of these enzyme tests would have been useful in making a decision on thrombolytic treatment. Overall aspartate aminotransferase activity compared quite well with creatine kinase concentration as an indicator, but the specific immunoassay for creatine kinase is much more expensive than are all other tests together and does not lend itself to automation.

We thank Novo-Nordisk Diagnostics for the kind gift of reagents for the CK-MB assay.

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- 1 Timmis AD. Early diagnosis of acute myocardial infarction. *BMJ* 1990;301:941-2. (27 October.)

Selling the pathology service

SIR,—Dr W R Timperley suggests that like the pathologists, radiologists were probably not consulted about the production or contents of the *Pathology Guide* booklet.¹ We are able to confirm that this was indeed the case. This injudicious and flawed document often refers to radiological services, something the reader could not divine from its title.

Perhaps even more often than in pathology a radiology department offers a clinically directed service with a consultative role. The *Pathology Guide* seems to identify only the end product. Although in one section it does have a footnote to the effect that a request to an imaging department is a request for a clinical opinion, elsewhere it suggests the possible provision of uninterpreted radiographs.

There can be few departments of clinical radiology in NHS hospitals that have spare capacity in terms of standard radiography. When more technological services such as magnetic resonance imaging are considered the case is in some respects very different: few of these machines have been financed, even in part, by NHS funds, and thus some magnetic resonance imaging services in NHS hospitals have been established to be at least partially dependent on private patients. Those managing these services have therefore already fully identified their market, without which they could not exist. Related considerations often necessitate using such equipment beyond the working hours of the rest of the department.

Radiotherapy is referred to only very briefly in the booklet and in a manner that indicates that its role is imperfectly understood by the authors. The statement that "30% of private hospitals have X-Ray treatment facilities" is of course nonsense; only a few radiotherapy machines exist in the United Kingdom outside the NHS. For this and other reasons the document's application to clinical oncology is extremely limited.

It is true that in the United Kingdom as a whole capital equipment is less well used than it would be, say, in the United States. But introducing an extended shift system for the general department must produce sufficient financial return to balance the increased costs of salaries and consumables. Extended use must therefore be a local decision formulated between management and the individual department.

It is to be hoped that NHS managers will not give any credence to this type of ill researched and

meretricious publication, which overemphasises throughput and gives scant consideration to quality (the priority needed for NHS patients) and the wider clinical obligations of radiologists, oncologists, and their departments.

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1 Timperley WR. Selling the pathology service. *BMJ* 1990;301:828. (13 October.)

Hirsutism

SIR,—Dr Gerard S Conway and Professor Howard S Jacobs emphasise the use of cyproterone acetate in combination with oestrogen for treating hirsutism.¹ In our experience Dianette, which contains 35 µg of ethinylloestradiol and only 2 mg of cyproterone acetate, is relatively ineffective, and it is in any case not licensed for long term maintenance therapy. Marvelon, a licensed oral contraceptive containing 30 µg ethinylloestradiol and 150 µg desogestrel is at least as effective a treatment for hirsutism as Dianette.²

Higher dose combinations of cyproterone acetate, which are more effective than Dianette and probably than Marvelon, are not licensed for use in hirsutism. The major disadvantage of cyproterone acetate is its long half life (two to five days in the deep compartment).³ This means that to produce regular menstruation it must be given in a regimen of 10 days out of 28, with ethinylloestradiol for 21 days.⁴ This so called reverse sequential regimen leads to wide fluctuations in both circulating concentrations of the antiandrogen and gonadotrophin suppression. Cyproterone acetate is also a weak glucocorticoid and leads to adrenocortical suppression at high doses.⁵ The rather complicated regimen leads to poor compliance. Furthermore, cyproterone acetate has been shown to cause liver tumours in rats, and a warning to this effect is given in the Dianette data sheet.

Spironolactone is presently the only serious alternative antiandrogen for severe hirsutism. Its efficacy in a dose of 50 to 200 mg daily has been shown in several studies.^{6,7} Because it has no progestational activity it can be given continuously in combination with an oral contraceptive such as Marvelon, with a likely additive effect as Marvelon probably acts principally by suppressing endogenous ovarian androgen production.

Dr Conway and Professor Jacobs dismissed spironolactone on the basis of a circular letter from the Committee on Safety of Medicines, which limited licensed indications notably for hypertension.⁸ Doubt over the long term safety of spironolactone was raised because of the development of mammary tumours, liver tumours, and myelocytic leukaemia in rats given potassium canrenoate, an aldosterone antagonist to which spironolactone is chemically related and with which it shares a common metabolite (canrenone). In long term animal studies there was no evidence of a tumourigenic or carcinogenic effect in rats given spironolactone.⁹

Unfortunately, unless unlicensed drugs are used there is no effective treatment for women with severe and often disabling hirsutism. The drug companies are unlikely to seek to extend the licences for drugs long out of patent. Meanwhile those of us concerned with treating such women will continue to use these drugs, while conducting the much needed long term efficacy and safety studies and fully discussing the safety issues with our patients.

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SIR,—We agree with Dr Gerard S Conway and Professor Howard S Jacobs that current treatments for hirsutism are associated with considerable complications or theoretical risks.¹ Weight loss is not an option for normal weight women with the polycystic ovary syndrome, and though cosmetic measures are of value in some women, they are expensive for prolonged treatment and their provision by the NHS is inconsistent and of low priority.

The authors suggest that Dianette may not be sufficient for reversing excess hair growth. We have recently assessed Dianette as a first line treatment of hirsute women with the polycystic ovary syndrome. Full results will be reported elsewhere. Briefly, 28 oligomenorrhoeic hirsute women with polycystic ovaries, as shown by ultrasonography, and with a median score on the Ferriman-Gallwey index of 13 (range 5-32) were treated for up to one year with Dianette.

We found significant improvements in facial and chest hirsutism by 24 weeks' treatment and in abdominal and leg hirsutism by 36 weeks, with a corresponding decrease in the median Ferriman-Gallwey index.² Two women withdrew from the study prematurely because of lack of response (initial Ferriman-Gallwey scores 15 and 22), and four others showed no overall improvement. There were no changes in glucose tolerance or mean insulin concentrations in response to an oral glucose load after six months' treatment with Dianette despite an appreciable decrease in the mean concentration of free testosterone. Dianette was well tolerated overall.

The disassociation between rapid improvement of biochemical hyperandrogenism and slower clinical response to antiandrogen treatment is well recognised and does not seem to be influenced by the drug used. Dianette is of value in the initial treatment for hirsutism in women with the polycystic ovary syndrome, particularly for those women with lesser degrees of hirsutism, in whom avoidance of higher dose cyproterone acetate may lessen side effects.

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AUTHORS' REPLY,—Dr O'Driscoll and Professor Anderson seem to have misunderstood our reference to drug licensing. Our aim was to note that although several preparations are used to treat hirsutism, only Dianette is licensed. We did not intend to suggest that other drugs ought not to

be used merely because they were not licensed for the indication. This is in fact a common misunderstanding of the role of the Committee on Safety of Medicines, which is to advise the Licensing Authority on the Safety of Medicines, not to determine the practice of medicine.

To our knowledge, there have been no randomised trials comparing the effectiveness of spironolactone with that of combined antiandrogen drugs. We have found spironolactone less effective than cyproterone acetate, and we cannot help noticing that most of the published reports proposing its use originate from countries where cyproterone acetate is not yet available.

In terms of efficacy we consider the reversed sequential regimen of cyproterone acetate and ethinylloestradiol the appropriate first line treatment for moderate to severe hirsutism. As Dr Golland and Professor Elstein show, patients with milder disease may benefit from milder treatment. Whether, in terms of safety, this approach is optimal remains to be established, but newer drugs (such as flutamide) and newer strategies (such as treatment with inhibitors of 5 α -reductase) may eventually offer safer treatment.

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SIR,—Although Dr Gerard S Conway and Professor Howard S Jacobs allude to defects in adrenal steroid synthesis as a cause of hirsutism,¹ perhaps more emphasis should have been given to the non-classic forms of congenital adrenal hyperplasia, which are present in an important subgroup of young women presenting with hirsutism and other clinical manifestations of hyperandrogenism.

Five enzymes are necessary for the conversion of cholesterol to cortisol, and partial deficiencies of three of these (21-hydroxylase, 3 β -hydroxysteroid dehydrogenase, 11 β -hydroxylase) are well recognised.² Partial 21-hydroxylase deficiency is the most widely studied and may be the commonest, occurring in approximately 0.3% of the general caucasian population; there is considerable ethnic variation such that about 3% of east European Jews are affected.³

The condition most commonly presents after the menarche with symptoms of hyperandrogenism with and without menstrual disturbance,^{4,5} and may be responsible for up to 6% of unselected hyperandrogenic women presenting to hospital clinics.⁶ It is clinically indistinguishable from the polycystic ovary syndrome^{6,7} and, indeed, the appearances of polycystic ovaries on ultrasonography are often seen in non-classic 21-hydroxylase deficiency.^{8,9} Standard measurements of serum concentrations of androgens such as testosterone, androstenedione, and dihydroepiandrosterone sulphate cannot discriminate between the two conditions,^{6,9} but non-classic 21-hydroxylase deficiency can be readily distinguished by an exaggerated serum 17-hydroxyprogesterone response (measured at 60 minutes) to 0.25 mg soluble tetracosactrin administered intravenously.¹⁰ Unstimulated morning measurements of serum 17-hydroxyprogesterone concentrations may also be diagnostic, but values in the normal range cannot be used to exclude the condition.¹¹

The importance of diagnosing non-classic 21-hydroxylase deficiency lies in the excellent prognosis on glucocorticoid replacement therapy. A small dose of dexamethasone (0.25-0.5 mg) taken at bedtime leads to suppression of adrenal androgens, resolution of clinical signs of hyperandrogenism, and resumption of normal menses and fertility.^{10,12} At present, the incidence of non-classic 21-hydroxylase deficiency among women presenting with symptoms of hyperandrogenism to endocrine and gynaecology clinics in the United Kingdom is unknown. The cost effectiveness of screening such patients for the condition