SIR,—I can understand and have some sympathy with the irritated comments of Dr. P. M. S. Gillam (11 March, p. 685) on the two trials of clofibrate in the treatment of ischaemic heart disease. One finds that not only patients but also some doctors (who cannot have read the two papers) are expecting that the symptom of angina will improve as soon as the drug is consumed. There is no evidence and has been no claim for this whatever.

But I must answer his criticism of the Newcastle trial, for which I bear much responsibility. Regarding "the most important criticism"—namely, that non-cardiac deaths have not been reported—the facts are that I have records of seven patients who withdrew because of illness and later died—four of them in the clofibrate group (three dying of cancer) and three in the placebo (one dying of cancer). If these figures, which are I suspect incomplete, are added to the Scottish ones, which are believed to be complete, then we have 12 known deaths in the clofibrate group (six from cancer and four from cerebrovascular accidents) and 13 in the placebo (six from cancer and two from cerebrovascular accidents).

Doubtless some patients in both trials who withdrew for reasons other than illness died later of non-cardiac causes before the 5½ years of the trials were completed, the most frequent causes being, as in the above list, cancer and cerebrovascular accidents. One can only say that there is no evidence at all that clofibrate either prevents or precipitates these maladies.

The wisdom of admitting patients to the trial on the basis of history alone can indeed be questioned, but less than a quarter of the patients had normal E.C.G.s, and it is hard to believe that when all of them were personally selected by experienced consultant physicians as suitable for a trial more than a tiny fraction would be wrongly diagnosed.

Regarding status on entry, some of the parameters were so obviously similar in the treated and controlled groups as not to need statistical analysis. In the remainder, including for example smoking habits on entry, statistical tests were applied, and in no instances were differences significant at the 5% level discovered.

Regarding the subsequent fate of the clofibrate patients who withdrew from the trial, it is difficult to see how this can have much bearing on the conclusions. The great majority of them certainly discontinued the drug. If they fared better than the placebo group it would strengthen the trial results in which Dr. Gillam does not believe. If they fared worse it could, as with anticoagulant therapy, be attributed to a rebound ill effect from stopping treatment. It seemed to us best just to disregard them.

Finally Dr. M. F. Oliver and I were well aware of the dubiety of combining the results of two trials whose criteria of entry differed. We did not therefore combine the figures, except in one instance—the non-fatal infarcts. We simply set them close together for easy comparison, and for the same reason preceded them with a full exposition of those differing criteria.

Dr. W. H. S. St. John-Brooks's strictures (18 March, p. 750) cover some of the same points, but he also refers to others of some importance. He states that in the relatively few females in the trial and in those patients on anticoagulants the causative factors and the course of their ischaemic heart disease

might well differ significantly from what they would be in the uncoagulated males. This is very true, and it is one of our regrets that in the design of the trial females were included. It was our hope that patients on anticoagulants would not be included but the trial was mounted at a time when there was more confidence in their value than there is today, and several physicians did not care for that treatment to be discontinued on entry, and some patients were put on it during the course of the trial when they were doing badly. Because of this, as Dr. St. John-Brooks noted, the mortality of those on anticoagulants was greater than that of the remainder. It was also, he may note, equal in the clofibrate and the placebo groups. Because this anticoagulant group comprised so many with a poor prognosis it seemed to us wisest in the analysis to include them. For the same reason we included against Dr. St. John-Brooks's objections, those who withdrew from the trial up to the time of that withdrawal. If clofibrate had made the patients so much worse from repeated infarcts and/or angina that they had insisted on withdrawing, would Dr. St. John-Brooks have wished them still to be excluded? One cannot have it both ways.

Finally his composite statement of some of the Newcastle results is founded on the selection of those where the advantage to clofibrate attained statistical significance. There were several others where owing to lack of numbers the advantage, though clear and consistent, did not attain this level.

In the same way, though it is true that some of the advantageous results could have been thrown up by chance, it is unlikely that this would have happened to the same results in both the Newcastle and Scottish trials, and it is for this reason that we think that the protection, especially against sudden death, afforded to patients with angina is probably genuine. Like Dr. Oliver I would be delighted if a new trial of male patients with angina only could be mounted to confirm this point.—I am, etc.,

H. A. DEWAR

Newcastle upon Tyne

Termination of Pregnancy

SIR,—Professor Stallworthy and others¹ indication that there is an element of serious risk attached to some operations for pregnancy termination gives cause for very real concern. The report from Mr. S. V. Sood (30 October 1971, p. 270) is likewise rather disturbing, and Beric and Kupresanin,² Dr. S. Lewis and colleagues (4 December, p. 606), and Dr. K. C. Loung and others (20 November, p. 477) have mentioned an appreciable incidence of complication with abortion procedures.

It may therefore be appropriate to report a personal series of 1,000 consecutive pregnancy terminations by curettage in which there was no case of cervical trauma, uterine perforation, or excessive blood loss, and in which no transfusions or laparotomies were required.

These cases were all operated upon for the Birmingham Pregnancy Advisory Service between 1 August 1970 and 31 December 1971 at four private nursing homes. There were no significant complications at operation or during the 24-hour admission period, and no patient needed to be detained. The

only readmissions reported were one patient accommodated overnight for transient pelvic pain and another having a repeat curettage at a National Health Service hospital without retained products being found. Most of the patients came from the Midlands and over 70% gave permission for their general practitioner to be informed. Follow-up information is being sought from these doctors.

Analysis of data submitted for publication shows the largest age group to be 20-24 years with 12 patients aged only 14 or 15 years. Sixty-three per cent. of the patients were single, divorced, separated, or widowed. Housewives comprised 22.5% and office workers 21.8%, while there were 19 school-girls. There were 561 nulliparae and 439 multiparae in the series, with 1,049 existing children. Recommendations for legal abortions were made under Section 2 for 76.4% of the patients and under Sections 2 and 3 jointly for the remainder—general practitioners referring 53.5% of cases and half of them signing Certificate A. Most of the pregnancies were terminated between 9 and 12 weeks of gestation, but there were 139 cases of 13 or 14 weeks and 11 cases of 15 or 16 weeks. Seventy-two per cent. of the patients had not previously practised reliable contraception (16 October, p. 156).

It is accepted that there may well have been pyrexia or other complications following discharge from the clinics, and of course long-term effects may occur as a result of the surgical intervention. Such facts are extremely difficult to obtain from patients who have had a legal abortion, but in view of reports from European countries³ some attempt must be made. To this end it would be helpful if the Lane Committee, in its report, recommended compulsory notification of pregnancy and certain other related conditions occurring at any time following legal abortion. This would have to be done without disclosing the names of patients.

If the Royal College of General Practitioners would co-operate in obtaining reliable clinical data the possible incidence of infertility, recurrent abortion, chronic pelvic sepsis, cervical incompetence, dystocia and other complications in childbirth, as well as any emotional effects on patients, could be more accurately assessed.

The above findings support the view that with scrupulous attention to technique it should be possible for individual surgeons to carry out 1,000 consecutive terminations by curettage without any immediate complication. Once this particular fact is recognized, the potential physical and emotional sequelae of the abortion procedure need to be evaluated scientifically in order to resolve current controversies.—I am, etc.,

DESMOND BLUETT

London W.1

¹ Stallworthy, J. A., Moolgaoker, A. S., and Walsh, J. J., *Lancet*, 1971, 2, 1245.

² Beric, B. M., and Kupresanin, M., *Lancet*, 1971, 2, 619.

³ Kotasek, A., *International Journal of Gynaecology and Obstetrics*, 1971, 9, 118.

Acute Renal Failure and Open Heart Surgery

SIR,—Mr. E. D. Yeboah and colleagues (12 February, p. 415) have had a difficult task to analyse the Hammersmith Hospital open heart surgery cases retrospectively and have produced interesting and not unexpectedly

high incidence of renal complications following this surgery.

In a review of 250 cases operated upon at Southampton our incidence of severe renal failure was more than 12%.¹ In the light of our experimental and clinical work on the subject for the last seven years, we think the following points from our experience are relevant.

Mr. Yeboah and others give a definition of severe and minor renal failure (to which we fully ascribe). They then state "some degree of renal impairment was observed in 130 (30%) of cases," without however mentioning what is meant by renal impairment. We think that in response to cardiopulmonary bypass there is alteration of kidney function judged by one or other renal function tests. At one end of the scale is normal, at the other extreme several renal failure, and in between renal dysfunction of variable degrees. We take the view that a temporary (one to two day) rise in blood urea in itself should not be considered as a "minor" renal failure or renal impairment. This is so constantly and frequently observed, particularly during the early postoperative phase, as to be regarded as one type of temporary dysfunction response after cardiopulmonary bypass. Only raised blood urea accompanied by a low urine urea observed over period of a few days, and a tendency to remain so, should be considered as renal impairment or minor renal failure. Taking this into account the apparently high incidence of renal failure (severe and minor) and renal impairment becomes truly lower and less alarming than Mr. Yeboah presents.

Unlike Mr. Yeboah and his colleagues we did not find any correlation between a higher pre-operative blood urea and post-operative renal failure.

We found no relation between the age of patients and renal complications, but there was a definite relationship between the type of cardiac lesion and postoperative renal failure. There was definitely a high incidence in patients with acquired valvular disease.

Analysis of our cases showed that the most important contributory factor for development of renal failure was the length of perfusion. The incidence of renal failure in those patients with under two hours perfusion was less than 5% in contrast to those having two to four hours, which was above 25%. We were later able to show experimentally the changes which took place in renal blood flow and renal functions during and following perfusion of short (up to two hours) and long (above two and up to four hours). This experimental work confirmed a definite deterioration in renal function during and after the long period of bypass.²

Mr. Yeboah claims no beneficial effects from diuretics in renal failure cases. We would agree that this is so in established and extreme cases. But in those cases of renal dysfunction (as mentioned above) diuretics play an important beneficial role, and indeed it is through the good management and careful handling of diuretics and fluid balance that these cases may and do come to a successful result. We found mannitol useful at least in three circumstances: (i) During the operation when urinary output is low (below 40 ml/hour); (ii) when there is haemoglobinuria during and after a long period of perfusion; and (iii) when one has to decide whether the

postoperative oliguria is renal or pre-renal (that is, mannitol challenge).

So far as the treatment is concerned, our results agree with the authors, in spite of early dialysis. Here it is relevant to note that observation and review of a large series indicates two types of renal failure chronologically speaking—that is, an early post-operative renal failure (second and third day) and a later (four to five days) one. In the early renal failure cases the treatment appears to be particularly difficult, and in our experience, unsuccessful, whereas in the later renal failure cases there appears to be a good chance of success.—We are, etc.,

K. MOGHISSI

Cardiothoracic Surgery Unit,
Castle Hill Hospital,
Cottingham, Yorks

I. K. R. McMILLAN

Cardiothoracic Surgery Unit,
Southampton Chest Hospital

¹ Moghissi, K., Paper presented to the annual meeting of the Society of Cardiovascular and Thoracic Surgeons, Oxford, 1968.

² Moghissi, K., Machell, E. S., and Munday, K. A., *Cardiovascular Research*, 1969, 3, 37.

Genetic Counselling

SIR,—I wonder if I might comment on some of the statements in your leading article on genetic counselling (19 February, p. 458). This is an emotional field in which hopes readily dominate facts, and the number of similar annotations vaguely implying the need to concentrate resources into selecting the unborn by exhortation or advice seems to be increasing. In such fields it is perhaps wise to consider what would be achieved, given sound diagnosis, informed prognosis, and prospective parents obedient to the dictates of what was regarded as reasonable by those advising them. If, even then, the prospects of appreciable effects are remote, then the diversion of resources, either fiscal or emotional, is difficult to justify.

The first statement "Parents make sensible use of information on the chances of a particular genetic (or part-genetic) disorder in the family recurring in future children" in fact means that they respond to information in the way the donor of this information thinks they should. In practice "information" easily becomes degraded into advice.

The next sentence welcomes the increasing demand for advice. While I welcome the increasing demand for information, and the extension of those services, especially paediatrics and pathology, on which sound information must be based, advice implies more than information, and I personally do not welcome this increasing demand, if, indeed, it exists. I agree that people who cannot interpret information are not usually ideal ancestors for our descendants, but to advise patients on their reproduction as opposed to giving the information they seek about the disorder with which they, or their children, present, is another matter.

The sentence continues "we may hope gradually to reduce the number of children born with genetically determined disorders." This implies a truly cosmic idea of gradual. If counselling is extended to include selective abortion, then some disorders can be eliminated within present technology by ensuring that death precedes birth. These include familial mongolism, and in some racial groups systematic screening for heterozy-

gotes may be effective in weeding out some homozygotes in utero. However, this is hardly counselling.

The next paragraph I also find difficult. Why should a history of near relatives be taken in an accurately diagnosed recessive? Does the class of poorly understood disorders of low recurrence rate constitute a group of known mode of inheritance? Is "polygenic" or "multifactorial" a euphemism for ignorance or a known variety of inheritance?

Should cases needing information obtain it from general practitioners, or through referral to established specialists, or by providing new categories of specialist? As most cases of clearcut severe genetic disease are already seen by specialists, the question reduces to whether, for example, neurologists are competent to advise on muscular dystrophies, or paediatricians on fibrocystic disease and mongolism, or haematologists on haemophilia. If they are, the problem is solved. If they are not, should resources be diverted to improving their education, their selection, their facilities, or their numbers, or should a supplementary service be established?—I am, etc.,

J. H. EDWARDS

Department of Human Genetics,
Infant Development Unit,
Birmingham Maternity Hospital,
Birmingham

Plasma Amino-acids of Infants

SIR,—Though plasma amino-acid levels do vary with time of day, as pointed out by Dr. D. P. Davies (19 February, p. 512), we do not believe that the variations that have been shown to occur¹ would affect the significance of our results (25 December 1971, p. 789) in any way.

The blood amino-acid concentrations in the neonate have been shown to be relatively constant between 8 a.m. and 8 p.m., but to fall to a significantly lower level at 4 a.m.² The infants we studied were in fact all bled at about the same time (9 a.m.), but this information was not included in our report as changes in plasma amino-acid levels are related to the sleep/wakefulness cycle and not to the time of day, making the significance of the sampling time difficult to assess in small infants.² Further, by direct comparison between groups of infants on different protein intakes but sampled and analysed under the same conditions, the effect of such factors is included in the means and ranges of the results obtained.—We are, etc.,

H. B. VALMAN
R. J. K. BROWN
T. PALMER
V. G. OBERHOLZER
B. LEVIN

Queen Elizabeth Hospital for Children,
London E.2

¹ Feigin, R. D., Beisel, W. R., and Wannemacher, R. W., Jun., *American Journal of Clinical Nutrition*, 1971, 24, 329.

² Feigin, R. D., and Haymond, M. W., *Pediatrics*, 1970, 45, 782.

Resistance to β -adrenoceptor Stimulants

SIR,—We still have no direct evidence of the mechanism whereby pressurized aerosols may be involved in deaths from asthma, and the work of Conolly *et al.*¹ obviously needs to be pursued.

Most of us, however, have a very strong clinical impression that the problem is one