SIR,—It is regrettable that your leading article on angina pectoris (19 April, p. 134) again fails to stress the importance of a search for and correction of anaemia in the management of this condition.

I have recently seen two patients, (one with iron deficiency and one with vitamin B₁₂ deficiency) presenting with classical effort angina. In both cases the angina was totally relieved by appropriate treatment of the anaemia.—I am, etc.,

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Anencephalus and Spina Bifida

SIR,—With reference to your leading article on anencephalus and spina bifida (12 April, p. 67), it would indeed be surprising if monozygotic co-twins of index patients with anencephalus or spina bifida were very rarely affected. In the largest consecutive series available (unfortunately not widely known), based on the records of a 10-year series of births in New York,¹ the pair concordance figures were:

	Like Sex	Unlike Sex
Anencephalus	4/24	1/15
Spina bifida	3/24	1/14

Further, one like sex pair had anencephalus and spina bifida respectively.

Since about half of like sex pairs are likely to be monozygotic, and the members of the concordant pairs will have usually both been index patients, these findings are certainly compatible with, say, 20% of monozygotic co-twins and 6% of dizygotic co-twins also affected. These proportions would be compatible with the heritability suggested by the sib data.

There is a need for further twin series in which the type of twinning is established—for example, from cord blood.—We are, etc.,

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REFERENCE

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Complications with I.U.D.s

SIR,—The commonest way in which the average practising gynaecologist in Britain comes into contact with intrauterine contraception is when a patient appears in his clinic with a complication. Often this consists of vaginal discharge, menstrual disturbance, or pelvic pain, which is solved by simple removal of the device. Sometimes the problem is abortion, or continuing pregnancy with the device in situ. Really serious flare-ups of pelvic inflammatory disease are not so common and perforations of the uterus and their consequences relatively rare. In general, the gynaecologist has been able to console him-

self with the thought that innumerable statistically controlled trials have been conducted and that massive international I.U.D. programmes with computer monitoring appear to be proceeding quite happily. It seems to be just a few of the failures that have come his way.

In these circumstances it is a matter of some concern that a year or two ago the association of ectopic gestation with intra-uterine devices came to light in the form of a clinical report¹ before statistical verification was provided from large-scale controlled studies.²

Taking a second look at the numerous and comprehensive reports on I.U.D.s, one is struck by two components. The first of these is the almost naive and zealous optimism of the workers in this field, who record incidences of 3% to 30% of expulsions, 1% to 9% of pregnancies, up to 8% of pelvic inflammatory disease, and 2% to 78% of menstrual disorders³ and then tend to conclude that this is a safe, effective, and acceptable contraceptive method. The second component is a small item appearing in one form or another in most of the major statistical studies which boils down to "patients lost to follow-up," and amounts to between 5 and 20% of cases. This is a much more serious factor, which invalidates the major numerical findings of these programmes. It is unfortunate that when an I.U.D. catastrophe occurs the patient does not in general return to the clinic where the device was fitted but has recourse to a hospital with an acute gynaecological unit and resists contact for follow-up purposes. This is not just a matter of resentment—gynaecological patients are loyal creatures, and do not like to upset the kind doctors who fitted the device by recounting a failure. In terms of cold hard fact, it means that when the *Eighth Progress Report of the Co-operative Statistical Programme for the Evaluation of Intra-Uterine Devices*⁴ reports a pregnancy rate of 2.6% in the first year of use, the real pregnancy rate may be anything between 2.6% and 16.1%. When Tietze⁵ reports 43 uterine perforations in 22,403 women, this may mean a perforation rate of anything between 0.2% and 9.8%.

The recent survey of critical illnesses and deaths associated with intrauterine devices⁶ conducted among the Fellows of the American College of Obstetricians and Gynaecologists is also open to objections on statistical grounds. On the other hand, it does present the other side of the picture—the side seen by the practising specialist gynaecologist. Of the ten deaths reported four were due to septic or inflammatory complications of the insertion of the device, and three to infection occurring with the device in situ. In the other three deaths the relation of the I.U.D. to the outcome is by no means clear. The remainder of the report details 369 cases of critical illness due to inflammatory complications and 207 due to perforation of the uterus, 12 of these with consequent intestinal obstruction.

The survey leads one to recall the review of the dangers of intrauterine contraceptive devices published by the American Medical Association Committee on Contraceptive Practices in 1937.⁷ A report on Gräfenberg rings telling of 17 deaths from general peritonitis or septicaemia, 176 major septic conditions where the patient survived, seven perforations of the uterus, and four ectopic gestations is included, and comparable reports on other I.U.D.s are mentioned. The report ends with the committee indicating its complete disapproval of these methods of contraception.

No rational practitioner will deny that many women use I.U.D.s successfully, or that the I.U.D. appears to be the only practical form of contraception for a proportion of patients. In the context of world population problems there is clearly a need for study programmes concerned with the development of safe and effective methods of contraception. Current justifications for the use of I.U.D.s are expediency and experiment. Care should be taken not to give the impression that at the present time there is evidence that the I.U.D.s are the best method of contraception available. We must not blind ourselves to the occurrence of failures and the undoubted existence of hazards to health and possibly even to life which their use involves.—I am, etc.,

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"Cold Cures" and Monoamine-oxidase Inhibitors

SIR,—We were interested to see the experiments reported by Dr. M. F. Cuthbert and others (15 February, p. 404) concerning the interaction of phenylpropanolamine and the monoamine-oxidase inhibitor tranlycypromine. Their advice concerning communication of the risks involved to physicians and patients is well intended but should be made more explicit.

In 1965 we conducted a survey among the outpatients taking these drugs at the Maudsley Hospital, where these interactions were first discovered and where the dangers were well known and publicized.¹ Even so, 7 out of 50 patients who completed a questionnaire had used cough medicine in the previous month, and less than half the patients knew the identity of the monoamine-oxidase inhibitor they were taking. Some continued to eat potentially dangerous foodstuffs despite warnings, while others were unaware of the risks. In this regard it is worth reiterating several points:

Not all drugs which inhibit monoamine-oxidase are used exclusively in psychiatry. For instance, the hypotensive agent pargyline and the antibacterial drug furazolidone both belong in this category. The former has been shown to cause interactions with dopamine and several foodstuffs²⁻⁴ and the latter with tyramine and amphetamine.⁵

The foodstuffs which contain tyramine or allied amines are unpredictable. The list continues to lengthen and becomes increasingly improbable. We recently encountered a West Indian who experienced a hypertensive

crisis after eating green bananas stewed with the skins on.

Vague admonitions to avoid certain foods or medicines are valueless. The worst the patient expects is indigestion; this is more so since many have already eaten the substances with impunity and so imagine they are immune. We have previously listed the many variables which interact to determine whether or not foodstuffs ingested on a particular occasion cause hypertension.⁶ These include the type, duration, and dosage of inhibitor. In our experiments with the yeast extract Marmite we showed how the same amount of this substance could be harmless on one occasion but produced dangerous hypertension on another, depending on treatment variables.

Patients prescribed monoamine-oxidase inhibitor drugs should be categorically warned that consumption of the known foodstuffs and medicines could possibly induce a fatal episode of high blood pressure, and that the uneventful consumption of these items on one occasion is not a licence for their safety at all times. If the patient is not ill enough to justify such a drastic admonition, another drug should be prescribed.—We are, etc.,

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Disodium Cromoglycate and Induced Asthma

SIR,—The comparison by Dr. H. Herxheimer and Miss Helga Bewersdorff (26 April, p. 220) of their studies with our own¹ on the effects of disodium cromoglycate in induced asthma requires detailed critical examination.

They quote the summary of our report as claiming that "all were fully protected by the inhalation of 20 mg. of cromoglycate powder," and question this by quoting our text as saying that "one of the mite asthma patients was only partially protected." Our summary in fact reads: "inhalation of disodium cromoglycate inhibited all the allergic reactions produced by inhalation of the appropriate allergens." If the inhibition had been complete we would have said so. Indeed, in the one exception this was virtually the case, since the disodium cromoglycate reduced the fall in F.E.V.₁ produced by the allergen challenge to 8%, in comparison with falls in the initial test of 29% and in the final placebo plus allergen test of 24%. A fall of 8% in the F.E.V.₁ is within the limits of variation of the method. It is to be expected, however, that disodium cromoglycate would be less effective in inhibiting more vigorous reactions to challenge than the already appreciable ones on which our study was based;

reactions which were of a comparable order to those listed by Dr. Herxheimer and Miss Bewersdorff.

In their experiments with the aerosol of disodium cromoglycate they report on full protection in two subjects, partial in another, and possible, but not definite, protection in two others. Examination of their figures shows that two of the 13 patients, F and G, should not have been included in their study because their falls in vital capacity and peak flow after challenge were 5% and 20% in one patient and 8% and 10% in the other, and were too small for satisfactory study. These values were, in any case, far lower than the reactions they claim to have established in their patients beforehand—namely a fall in vital capacity of 10% to 20% and in peak flow of 30% to 40%. In the remaining 11 patients there was protection by the disodium cromoglycate in A, B, C, D, and E, and evidence of protection in I and L judged only by the vital capacity, and in J judged only by the peak flow, thus bringing their numbers with evidence of protection up to 8 out of the 11.

They also cast doubts upon our methods, stating that the F.E.V.₁ measurement is not suitable for this purpose because "it impairs lung function," presumably ventilatory function. There must be few reputable pulmonary physiologists who would not accept the F.E.V.₁ measurement as one of the better methods of ventilatory measurement in the present context. The vital capacity measurement used by Dr. Herxheimer and Miss Bewersdorff may be little altered in patients with marked decrease in the F.E.V.₁ and with obvious airways obstruction. The peak flow rate, which they also used, useful though it is, is subject to greater variability than other single breath tests. But overriding all these considerations is the fact that in the patients we studied the F.E.V.₁ gave consistent and reproducible readings in repeated measurements. In the control inhalation tests with carbol-saline, performed before the allergen challenge in order to exclude patients with excessive variability, the F.E.V.₁ and F.V.C. showed little or no change in any of the patients at repeated tests and at any time during the day. Further factual evidence of the overall consistency of the F.E.V.₁ test in our studies is shown by the reproducible reactions produced by the initial allergen test and the final placebo plus allergen test. The falls in F.E.V.₁ measurements in pairs for these two tests were as follows in each patient: -33% and -30%; -27% and -23%; -29% and -24%; -30% and -18%; -45% and -41%; -18% and -13%; -54% and -43%; -23% and -39%; -33% and -24%; and -18% and 0%.

The mode of administration of allergen is also questioned by Dr. Herxheimer and Miss Bewersdorff, who maintain that their closed-circuit method has the advantage of making it possible to estimate the amount of allergen retained. Once again the reproducibility of the reactions we produced shows that our method was eminently satisfactory for the purpose. Indeed, our results were more consistent in all respects than those of Dr. Herxheimer and Miss Bewersdorff. Their use of the closed-circuit method and the termination of reactions by isoprenaline inhalation, usually within 10 minutes, may be part of the explanation for their failure to reproduce our results. It is quite possible that this early termination of the reactions may have masked their true severity, against which the disodium cromoglycate may have been less effective.

An important part of the argument of these workers arises from the assumption that, because of the size of the coarse particles in the powder, it "could therefore not be expected to reach the finer bronchioli" and would therefore be ineffective in this form. They conclude that "we do not believe that the coarse particles can have more than a fraction of the effect of the fine aerosol, such as we used," and that the results obtained by us with the powdered preparation

"must be seriously questioned." We ourselves have no particular brief for the disodium cromoglycate as a powder, but the facts speak for themselves. Used as a powder in the tests as performed, we showed unequivocally that it had a potent inhibitory effect.

Dr. Herxheimer and Miss Bewersdorff have the temerity to comment on the clinical efficacy of disodium cromoglycate on the basis of single inhalations of the aerosol in five asthmatic patients. This part of their work is quite inadequately documented, and it is not clear when it was they made their measurements showing only trivial changes in lung function. Presumably, by analogy, if a single even large dose of corticosteroid did not improve ventilatory function, these workers would accept this as evidence that corticosteroids would not work in asthma.

They suggest that the patients on disodium cromoglycate reported by other workers in whom corticosteroid drugs were stopped or reduced had only very slight mild asthma. In our letter (15 February, p. 443) on steroid-pseudorheumatism in patients under treatment with disodium cromoglycate and in whom the corticosteroids were reduced or stopped, it can be seen that there were three patients on 10 mg. prednisone, one on 7.5 and one on 2.5 mg./day in whom corticosteroids were stopped; one on 12.5 and another on 7.5 mg./day in whom it was reduced to 2.5 mg./day; and two on 10 mg./day in whom it was reduced to 1 mg./day. These patients had been on corticosteroid treatment for at least several years in most cases, and repeated attempts had been made to stop it. They could not be regarded as patients with very mild asthma. We do not know how long such impressive progress will last, but these findings are like those of some of the other workers. The major problem at present is to see why there are wide divergences in opinion about disodium cromoglycate. Close comparison of clinical criteria and methods of assessment may help to explain the differences and to show which patients are most likely to benefit.

The grudging concession by Dr. Herxheimer and Miss Bewersdorff that disodium cromoglycate may protect from induced asthma, and that it seems to help a small minority of patients, would have met more respectful consideration if they had put their "beliefs" to the test and followed the same procedures as we, and others, have employed.—We are, etc.,

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REFERENCE

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Torsion of Testis

SIR,—I was interested to read Mr. K. Mohay-ud-Din's letter (15 February, p. 445) and the subsequent correspondence (15 March, p. 715) on this subject in your columns. I am surprised that no one has mentioned manipulation of the torsed testis and the instant relief of pain that this brings. Since qualifying two years ago I have seen eleven cases of torsion of the testis and in every case have been able to untwist the torsion by rotation of the testis away from the