Drugs Taken during First Trimester of Pregnancy	Mothers of Babies with Malformations	Mothers of Control Babies
<i>Hormonal pregnancy test used:</i>		
Fe and/or folic acid (no other drugs)	10	1
Fe and/or folic acid and one or more other drugs	4	1
One or more other drugs (no Fe or folic acid)	6	3
No other drugs	3	3
Total (hormonal pregnancy test)	23	8
<i>Hormonal pregnancy test not used:</i>		
Fe and/or folic acid (no other drugs)	40	53
Fe and/or folic acid and one or more other drugs	39	42
One or more other drugs (no Fe or folic acid)	20	18
No drugs	27	28
Total (no hormonal pregnancy test)	126	141
All mothers	149	149

baby (without congenital malformation) born to a mother in the same practice within three months of the abnormal birth.

Currently two groups of malformations are being studied. The first consists exclusively of babies with clefts of lip or palate; the second includes babies with a wide variety of other serious malformations selected on a random basis from notifications received by the O.P.C.S. The present report relates to the second group, which consists of 149 abnormal babies (70 with malformations of the central nervous system, nine with reduction deformities of the limbs, 13 with congenital disease, 11 with Down's syndrome, and 46 with other malformations) together with 149 practice-matched controls. Detailed analysis of these cases and of the series of babies with clefts will be reported in a paper in preparation. At present we can make only a preliminary report of our findings in relation to maternal exposure to withdrawal-type hormonal pregnancy tests consisting of a short course of treatment with a mixture of a progestogen and an oestrogen. Pregnancy is usually confirmed if bleeding does not occur after the test.

The findings are shown in the table. A total of 23 mothers of abnormal babies had been exposed during the first trimester of pregnancy to drugs containing hormones compared with only eight of the control mothers. One of the 23 had also taken an oral contraceptive and tablets of norethisterone. The use of iron and folic acid and of other drugs in the first three months of pregnancy was approximately the same in the case and control groups.

This evidence supports the recommendation given in your article that "there is little justification for the continued use of withdrawal-type pregnancy tests when alternative methods are available.—We are, etc.,

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Viruses and the Heart

SIR,—Your recent leading article on viral myocarditis (15 March, p. 589) was most interesting, but I think that you overstress the difficulties of a presumptive clinical diagnosis. In my experience the chief

differential diagnosis is myocardial infarction because the presenting symptom is chest pain or faintness, often accompanied by palpitations. The pain may often be presumed to arise from diaphragmatic pericarditis or pleurisy; its severity may justify the old name "Devil's grip."

The following features could alert one to the diagnosis of viral carditis, for almost certainly the three layers of the heart will be involved to some extent as in rheumatic heart disease: severe chest pain which is not quite central and which occurs in a patient somewhat young for ischaemic heart disease; upper respiratory symptoms at the time of chest pain or shortly afterwards and a history of household contacts having similar respiratory upset; low-grade fever lasting more than 48 hours; diminished total white cell count and/or lymphocytosis; normal erythrocyte sedimentation rate. The E.C.G. in viral carditis frequently shows a P-R interval in excess of 0.20 seconds, sinus bradycardia, ST elevation suggestive of pericarditis, with (of course) upright T waves, and conduction blocks of various types at atrioventricular or bundle-branch level.

Quite often the clinical diagnosis will be clinched by the finding of herpangina or generalized muscle tenderness. One must remember that the carditis may be part of a wider illness such as Bornholm disease or, in fact, a non-viral illness such as Q fever or brucellosis. Finally, fairly acute cardiac upset may arise from the direct spread of a bronchial carcinoma into the myocardium.—I am, etc.,

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Diagnosis of "Reflux Oesophagitis"

SIR,—Dr. G. W. Stevenson (15 February, p. 395) draws attention to the use of the "acid barium swallow" in the diagnosis of reflux oesophagitis. He maintains that this test is preferable to the acid perfusion test and suggests a direct comparison between these two techniques. Such a comparative study has been made¹ and showed that acid perfusion was positive in 100% of patients with "reflux symptoms," whereas acid barium swallow yielded a positive result in only 60%. This is easily understandable when one recalls that the acid perfusion test detects oesophageal pain^{2,3}—the important symptom of reflux oesophagitis—whereas a positive response to an acid barium swallow

depends on abnormal motility of the oesophagus, which is not always associated with gastro-oesophageal reflux.⁴

The principles underlying an individual test are important. The best way to measure the acid refluxing into the oesophagus is to monitor the intra-oesophageal pH by continuous recording.^{5,7} Acid perfusion tests detect oesophageal pain; acid swallows demonstrate an oesophagus which responds to acid stimulation with a motor response, but this tells one neither that it causes symptoms nor that the patient suffers from gastro-oesophageal reflux.—We are, etc.,

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- 1 Benz, L. J., *et al.*, *Gastroenterology*, 1972, 1, 62.
- 2 Bennett, J. R., and Atkinson, M., *Lancet*, 1966, 2, 1150.
- 3 Sladen, G. E., Riddell, R. H., and Willoughby, J. M. T., *British Medical Journal*, 1975, 1, 71.
- 4 Atkinson, M., and Bennett, J. R., *American Journal of Digestive Diseases*, 1968, 13, 346.
- 5 Stanciu, C., and Bennett, J. R., *Lancet*, 1974, 1, 109.
- 6 Spencer, J., *British Journal of Surgery*, 1969, 56, 912.
- 7 Patrick, F. G., *Gut*, 1970, 11, 659.

Essential Fatty Acid Deficiency Due to Artificial Diet in Cystic Fibrosis

SIR,—We wish to draw the attention of your readers to a possible hazard of feeding infants with an elemental diet.

A baby girl was born to unrelated parents after a normal pregnancy. She developed intestinal obstruction and was referred to the University Hospital of Wales, Cardiff, on the third day of life. Radiological investigation and laparotomy confirmed a diagnosis of meconium ileus. Analysis of meconium showed an increased albumin content, and an albumin: α -antitrypsin ratio of 6.9. Subsequently a sweat chloride level of 110 mmol/l was obtained. Because of postoperative chest infection, diarrhoea, and failure to thrive she was treated with a standard artificial dietary regimen. The basic constituents of the diet are Albumaid, a beef serum hydrolysate, Caloreen, a glucose polymer, and medium-chain triglyceride oil, and the amounts used were calculated according to body weight as described by Allan *et al.*¹ Weight gain was satisfactory and she was discharged from hospital at the age of 14 weeks, to continue on the diet with added iron, vitamins, and cloxacillin. Though a daily intake of margarine or an egg yolk was also prescribed, no particular emphasis was given to this feature and it later transpired that these supplementary foods were not given at home.

She continued to thrive until she was nearly 5 months old, when she developed intermittent vomiting, anorexia, and diarrhoea. When re-admitted to hospital she was pale and dehydrated, with an extensive red, scaly rash on her trunk and legs. There was severe perianal excoriation which spread on to the buttocks, and she passed frequent watery, dark green stools. There were widespread crepitations in her chest, and x-ray showed right upper lobe and lingular consolidation. Her serum protein level was low (35 g/l) with a low albumin level (18 g/l), but the blood sugar and plasma amino-acids were normal. Plasma fatty acids on the third hospital day showed a marked deficiency of linoleic and arachidonic acids (see table).

After initial rehydration milk feeds were given, and during the first two days she rapidly improved, with cessation of the diarrhoea. The rash cleared within four days. This clinical improvement occurred even though the essential fatty acid (E.F.A.) level remained low (see table), but the diarrhoea recurred after one week on resumption of the artificial diet. Intravenous feeding, including a fat preparation (Intralipid) was therefore given for three weeks and oral feeds gradually reintroduced thereafter. She is now maintained on a normal diet with pancreatic supplements and is in excellent health at the age of 18 months.

Fatty Acid	Day 3	Day 7	Four Months Later	Normal Adults (9) (mean $\pm$ S.E.M.)
14:0 Myristic ..	1.3%	*	1.9%	1.5 $\pm$ 0.1%
16:0 Palmitic ..	27.9%	30.0%	26.6%	23.5 $\pm$ 0.5%
16:1 Palmitoleic ..	9.7%	11.5%	3.5%	5.3 $\pm$ 0.2%
18:0 Stearic ..	7.5%	8.4%	7.0%	9.5 $\pm$ 0.3%
18:1 Oleic ..	44.0%	38.7%	25.6%	29.3 $\pm$ 0.5%
18:2 Linoleic ..	2.5%	2.0%	19.5%	27.0 $\pm$ 0.9%
20:4 Arachidonic ..	1.7%	*	6.5%	Others 3.9 $\pm$ 0.4%
Total	3158 mg/l	3262 mg/l	3570 mg/l	Approx. 3000-4500 mg/l

*Insufficient to estimate.

Deficiency symptoms have previously been reported in experimental conditions in human infants fed on a milk formula containing only traces of linoleic acid. The features which occurred included dry, scaly, thickened skin which became red and desquamated; perianal irritation; loose, dark green, watery stools; weight loss; and increased susceptibility to chest infections. Prompt recovery occurred when E.F.A. were restored to the diet. The authors of that paper found average blood values of dienoic acids to be about 5.6% of total fatty acids in deficient infants, and stated that 12.9% $\pm$ 2.6% was the minimum level found in infants fed on formulae with acceptable linoleic acid content. They noted that the skin changes were the most characteristic deficiency symptom.²

Dermatological features suggestive of E.F.A. deficiency were seen in a girl of 4½ years treated with a low-fat diet for chylous ascites.³ Apart from the infants used in the dietary experiments referred to above, no other instances of E.F.A. deficiency induced by artificial diet seem to have been recorded in man. However, the condition has been well documented in patients maintained on prolonged intravenous nutrition and deprived of fat, both infants⁴ and adults,⁶ and recently it was reported in three adult patients with malabsorption secondary to intestinal resection.⁷

Considerable interest is currently being shown in the use of the artificial diet in cystic fibrosis. It may be used as a supplement to ordinary food or to supply all the nutritional needs of the child.¹ In the latter event we believe that it is particularly important to emphasize to the parents the need for an additional source of dietary fat. Clinical evidence and animal experiments suggest that infants, because of their rapid growth rate, are particularly at risk and that in the absence of dietary E.F.A. they will develop deficiency symptoms in about two months.²

A recent paper speculates that E.F.A. deficiency may be responsible for some of the clinical features in cystic fibrosis,⁸ but the above case suggests that when it does occur it produces a characteristic acute illness which should be easily recognized.

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—We are, etc.,

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1 Allan, J. D., Mason, A., and Moss, A. D., *American Journal of Diseases of Children*, 1973, 126, 22.

2 Hansen, A. E., et al., *Pediatrics*, 1963, 31, 171.

3 Warwick, W. J., et al., *American Journal of Diseases of Children*, 1959, 98, 317.

4 Paulsrud, J. R., et al., *American Journal of Clinical Nutrition*, 1972, 25, 897.

5 Caldwell, M. D., Jonsson, H. T., and Othersen, H. B., *Journal of Pediatrics*, 1972, 81, 894.

6 Collins, F. D., et al., *Nutrition and Metabolism*, 1971, 13, 150.

7 Press, M., et al., *British Medical Journal*, 1974, 2, 247.

8 Elliott, R. B., and Robinson, P. G., *Archives of Disease in Childhood*, 1975, 50, 76.

9 Love, W. C., et al., *Biochemical Society Transactions*, 1973, 1, 141.

Beta-blockade and Myocardial Infarction

SIR,—In reply to the letter from Dr. I. M. Graham and his colleagues (15 March, p. 627) we should like to make the following comments.

(1) They suggest that our study (18 January, p. 117) could not be accurately described as "prospective." We stated in our introduction that the study was prospective with respect to our previous retrospective observations on the behaviour of patients who had previously entered our coronary care unit. A prospective study of the type they suggest—that is, that "patient matching and follow-up should have started before the initiation of beta-blockade"—though desirable, would not in our opinion be either ethical or practical, since the beneficial effects of beta-blockade for stable and unstable angina are now well proved and such a study would mean withholding this form of therapy from half the patients. Furthermore, it would require a large number of patients and would predictably take a long time to complete within one cardiac department.

(2) They question the comparability of our control and beta-blocker groups. In our protocol we stated that both groups had a similar "cardiac history." They were, in fact, comparable in terms of previous angina, myocardial infarction, and incidence of hypertension. We did not record smoking habits. To the best of our knowledge there is no evidence that smoking influences hospital mortality after acute myocardial infarction in coronary care units.

(3) They question the term "myocardial necrosis without infarction" and consider coronary insufficiency as "too 'soft' an end-point" to be acceptable in the study. In our criteria for selection it was stated that all patients had a three months' history of

symptoms of coronary artery disease and were admitted with a prolonged attack of ischaemic pain. The mean duration of chest pain for the two groups was similar (4.75 and 4.5 hours); likewise the mean duration of chest pain of those patients diagnosed as having coronary insufficiency (4.5 hours) was not significantly different from those with myocardial infarction (4.75 hours). It cannot be accepted therefore that coronary insufficiency was "too 'soft' an end point." While we agree that the diagnostic term "acute coronary insufficiency" is frequently used, the definition of this syndrome varies throughout the literature. The term "myocardial necrosis" was used in preference to subendocardial infarction since the E.C.G. criteria for this diagnosis are often uncertain and inaccurate; furthermore, it is possible for patchy microscopic myocardial necrosis to promote elevated myocardial enzyme levels without a characteristic accompanying E.C.G. pattern.

(4) They suggest that our consecutive selection of controls had prejudiced the results of our study. We do not concede this since there were only 122 out of the 251 remaining patients who could have been selected as matching controls. Subsequent analysis of the 32 other possible matching control patients reveals that they behaved in a similar manner to the published control group (see table).

(5) Our statistician has rechecked our results and we apologize for the error pointed out with regard to late cardiac failure. He also discovered that the total incidence of ventricular arrhythmias was not statistically greater in the control group as we had stated. Since we drew no conclusions from these figures they do not influence our final comments. The statistician has confirmed that all other statistical values are correct. The superficially impressive difference in mortality between the control and beta-blockade groups of patients following acute myocardial infarction (presented by Dr. Graham and his colleagues) is not supported statistically ($P > 0.2$). The finding that four of the patients in the beta-blockade group and six of the controls who died had sustained previous myocardial infarcts and that the mean peak SGOT levels of the patients who died were similar and exceedingly high in both groups (423 $\pm$ 118 IU for the beta-blocker group and 438 $\pm$ 109 IU for the control group) is in accordance with our suggestion "that a myocardial infarction sufficiently extensive to be fatal was not prevented by beta blockade."

We do not, on the basis of our observations alone, advise the routine use of prophylactic beta-blockers but believe that our data warrant us to report that "established

Incidence of Myocardial Infarction, Myocardial Necrosis without Infarction, and Coronary Insufficiency in the 251 Patients not on Beta-blockers Admitted with Prolonged Ischaemic Myocardial Pain. Results are Numbers of Patients

Group	Myocardial Infarction	Myocardial Necrosis without Infarction	Coronary Insufficiency	Total
Published controls	62	14	14	90
Patients without past history of three months' coronary artery disease	94	15	20	129
Outstanding possible controls with suitable past cardiac history	20	7	5	32
Total	176	36	39	251