ing the emphasis of the medical course away from the technically minded, curatively oriented Western style towards the preventive approach based on simple techniques in which the rural worker is regarded as being at the top of the pyramid of care rather than at the bottom.

The disparaging remarks which Dr. Senewiratne makes about medical auxiliaries do not accord well with experience in China[1] and Africa, where it is being found that a simply trained medical worker in close contact with the people and under the direction of doctors can improve basic health more effectively and much more cheaply than under a conventional Western-type system —as well as making the doctor's work, in organizing a team approach, more rewarding.

It is inevitable that medical training in a developing country patterned on Western methods will encourage migration, as will postgraduate courses in Europe and America. As Dr. Senewiratne points out, much insidious harm is done by such courses, which could be avoided if the teachers were instead seconded to the country concerned for a period. This would also have the valuable effect of widening the participant's viewpoint immeasurably.—I am, etc.,

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1 *Health Care in China.* Geneva, Christian Medical Commission, 1974.

Complications of Laparoscopy

SIR,—Though a straightforward laparoscopic sterilization is probably a shorter procedure than a tubal ligation after laparotomy, the advantage is marginal and if there is an increased incidence of complications laparoscopy would be unjustifiable. However, the shorter time taken for laparoscopic sterilization is not the chief justification for its use and Mr. E. E. Rawlings and Mr. B. Balgobin (29 March, p. 727), by keeping such patients in hospital for three to four days, nullify the main advantage.

Several consultants in this unit consider this procedure to be suitable for day cases, though the patients always have the option to choose to be kept in overnight or to change their mind after recovering from the anaesthetic. The table shows the number of patients admitted for laparoscopic sterilization as day cases and the number who were transferred for overnight recovery during the past year, since the day area in this hospital opened. The dramatic change in August reflected the increasing confidence of the sister in charge of the unit, who was not previously experienced in looking after such cases.

	Day Cases	Overnight Stay
1974		
March/April	16	10*
May	27	10
June	19	6
July	18	9†
Total	80	35
August	23	1†
September	11	0
October	5	1†
November	6	2
December	8	1
1975		
January	10	2
February	9	—
March	11	1
Total	83	8

*Laparotomy and sterilization carried out in two cases.
†Laparotomy and sterilization carried out in one case.

Since August 1974 83 patients have been operated on in this way and, excluding the two laparotomies, have required 89 bed days. The same number of patients treated by Mr. Rawlings and Mr. Balgobin would have required 283 bed days. The saving is even greater since the day area is staffed by nurses working only between 8 a.m. and 5 p.m. No complications of any consequence have occurred in this small number of cases. The calibre of anaesthesia is obviously of great importance. Most of the patients have been given follow-up appointments and there is no doubt that this approach is popular with patients, who so often have young children.—I am, etc.,

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Injudicious First-aid

SIR,—We are deeply concerned by the implications of your leading article (5 April, p. 5). We wonder if the State-registered nurse who gave external cardiac massage to a shopper who had collapsed was criticized unjustly after the pathologist found internal laceration but "no underlying disease . . . which would have caused her collapse."

Every experienced pathologist is well aware that no definite cause of death can be found in a proportion of patients who die suddenly. If widespread coronary atheroma is present this may reasonably be presumed to be the cause of death; a very recent infarct will not be evident unless special stains are used, and many patients die of ventricular fibrillation in the absence of any fresh ischaemic event. Units providing resuscitation facilities outside hospital can testify to the frequency of primary ventricular fibrillation without apparent cause. The data from Seattle[1] are of special interest. Of 143 patients who survived out-of-hospital fibrillation, 48 had no previous history of cardiovascular disease and no fewer than 97 had no evidence of infarction on serial electrocardiograms. Moreover, we know of many conditions that can cause ventricular fibrillation, such as Wolff-Parkinson-White syndrome complicated by atrial fibrillation and the syndromes of prolonged Q-T interval, which would show no abnormality at necropsy. Thus it would be wrong to assume that the collapse of the patient mentioned in your leading article could not have been due to cardiac arrest simply because the pathologist found no evidence of underlying disease.

We believe that tissues which have become engorged and relatively stiff after circulatory arrest are more susceptible to damage by trauma. We wonder if the injuries described by the pathologist could have occurred because the patient was already dead when the massage was given, rather than the patient having died because of the injuries.

External cardiac massage is not free from risks even in experienced hands. We strongly support the notion that only skilled first-aid workers should be instructed in its use. However, the risks are small compared with the successes that can be achieved. We might mention that 16 patients survived in our area in 1974 after resuscitation outside hospital by paramedical personnel. We very much hope that nurses, ambulancemen, and other first-aid workers are not exposing themselves to risk of censure by attempting resuscitation, for if they were to be discouraged in this way many lives might be lost unnecessarily.—We are, etc.,

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1 Baum, R. S., Alvarez, H., and Cobb, L. A., *Circulation*, 1974, **50**, 1231.

SIR,—Death due to injudicious first-aid, as described in your leading article (5 April, p. 5), must be a rare event. I am not sure that injury due to first-aid is uncommon. I have certainly seen in the past two years two patients to whom this happened. The first was a man who was on holiday in East Anglia with his wife. He is a man subject to attacks of hypoglycaemia and on this occasion he left his hotel before breakfast to post a letter. He felt faint while waiting to cross the road. A passer-by was a nurse from an intensive care unit. She assumed cardiac arrest and immediately applied heart compression, as a result of which the patient was in hospital with a fractured sternum and several fractured ribs for several weeks. Recently a patient of mine, subject to faints, had an attack in church. On this occasion artificial respiration fractured several ribs. The warnings in your article should be heeded by all.—I am, etc.,

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Hormonal Pregnancy Tests and Congenital Malformations

SIR,—Your leading article (30 November, p. 485) reviewed the evidence for and against a teratogenic effect of hormones administered to women during early pregnancy and concluded that the findings of associations between sex steroids and congenital anomalies "require confirmation or refutation from elsewhere."

The Committee on Safety of Medicines has received through its spontaneous reporting scheme only a small number of reports alleging a possible causal association between the use of drugs during pregnancy and the subsequent delivery of a malformed child. However, in order to detect possible associations the committee has collaborated with the medical division of the Office of Population Censuses and Surveys (O.P.C.S.) in an investigation of pregnancies which resulted in the birth of a malformed child in England and Wales during 1971 and 1972. This investigation has been based on notifications to the O.P.C.S. of babies born with a malformation. General practitioners who had cared for the mothers during pregnancy were identified with the help of family practitioner committees. Details of the maternal "drug histories" were obtained from the general practitioners' records during interviews with doctors employed by the Committee on Safety of Medicines. Each case history was paired with that of a normal

Drugs Taken during First Trimester of Pregnancy	Mothers of Babies with Malformations	Mothers of Control Babies
Hormonal pregnancy test used:		
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
Hormonal pregnancy test not used:		
Fe and/or folic acid (no other drugs)	40	53
Fe and/or folic acid and one or more other drugs	39	42
One o: 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 made[1] 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 Pattrick, 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 readmitted 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.

Congenital heart disease and prenatal exposure to exogenous sex hormones

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British Medical Journal, 1977, **1**, 1058-1060

Summary

One-hundred and four infants with congenital heart disease were identified from their birth certificates and matched with normal controls. Their gestational histories were examined to see whether they had been exposed to exogenous sex hormones. Exposure was 8·5 times more common among the infants with malformations than among controls. A history of hormone exposure was more common among those patients with multiple malformations, and the exposed infants were also more likely to have died (and to have died earlier) than those who had not been exposed, which suggests that hormone exposure causes severe types of malformations. The commonest type of exposure was to hormone pregnancy tests, which was needless exposure. Only two of the mothers of malformed infants had inadvertently used oral contraceptives in the first trimester.

Introduction

In 1973 Levy *et al*[1] reported that transposition of the great vessels was significantly associated with the maternal use of oestrogen-progestogen preparations during pregnancy. Almost simultaneously, Nora and Nora[2] presented similar data showing that the VACTEL syndrome of malformations (vertebral, anal, cardiac, tracheal, oesophageal, and limb) was also associated with maternal use of oestrogen-progestogen preparations during pregnancy. Subsequently three other reports[3-5] showed that the use of these preparations during pregnancy is associated with other types of birth defects. Nora and Nora,[6] presenting further details, noted the importance of multiple malformations and the particular vulnerability of the cardiovascular system in the association with sex hormones. About 20% of infants with congenital heart disease also have developmental abnormalities of other systems.[7] We have conducted a series of retrospective matched case-control studies on several types of birth defects. The data reported here are from a controlled study designed to determine whether exogenous sex hormones during pregnancy are associated with CHD, either by itself or in combination with other types of malformations.

Methods

Infants were selected for study on the basis of the nominal description of the malformation recorded on the child's birth certificate. Only live born infants whose condition was serious enough to be recognised at birth were included. Our selection procedure excluded stillbirths but included malformed infants born alive who died soon afterwards. The infants studied were all born during 1971-4. Any birth certificate mentioning CHD was eligible for study irrespective of whether the child had single or multiple defects.

Contacting and interviewing procedures were identical for patients and controls, and these procedures were the same as those used in our other studies.[3 8] Once we had located the mother of one of the infants with CHD we contacted the doctor who had signed the birth certificate for approval to interview the mother. Whenever approval was obtained we selected a control from the adjacent birth records, which are permanently bound in chronological order within the county. Births from New York counties outside New York city were eligible, and our matching procedure controlled for date of birth (±2 months) and county of residence. Each control was matched to its patient by mother's age (±2 years) and race. (Our final study group was 98% White.) The doctor who had signed the birth certificate of the control infant was then contacted, and from that point the cases and controls were handled identically. In each case we conducted a blind telephone interview with the mother. The interviewer was not aware of the mother's status until the end of the interview. We studied 104 infants who, according to their birth certificates, had CHD and their controls.

Through contacting doctors and mothers, we gained additional diagnostic information in some cases. We also searched for the death certificate of each infant with CHD and obtained the cause of death in those who had died. Although these infants had been included in the study solely on the basis of information recorded on the birth certificate, we eventually used the additional information to classify cases according to type of malformation. This classification was performed by one of us without knowledge of the data on drug use. Patients were subdivided in a generally stepwise fashion. Patients with definite CHD were subdivided from those with probable CHD but for whom we had insufficient information to identify specific defects. We also determined that five infants whom we had included definitely did not have CHD. Although these five infants did have other types of congenital malformations, CHD was ruled out by the additional diagnostic information.

The results of this subclassification are shown in table 1. Seventy of the 104 infants had definite CHD (group 1), and 44 of these had died (63%). Twenty-nine had probable CHD (group 2), and nine of these had died (31%). The remaining five, none of whom had died, did not have CHD (group 3). Class 1 infants were subdivided according to the presence or absence of multiple malformations within the cardiovascular system, and groups 1 and 2 were further subclassified according to the presence of additional malformations outside the cardiovascular system.

Results

We compared the infants with CHD and controls in respect to maternal age, maternal education level, previous stillbirths, previous miscarriages, and previous live births. No noteworthy differences

TABLE I—*Classification of cases of CHD according to specific defect and systems affected*

Category	Cardiovascular system only	Multiple systems	Total
Group 1 (cardiac defect specified)	52	18	70
Single cardiac defect	22	6	28
Multiple cardiac defect	25	12	37
Unknown*	5		5
Group 2 (probable CHD, cardiac defect not specified)	21	8	29
Dead at interview	2	7	9
Alive at interview	19	1	20
Group 3 (No CHD)			5
Total	73	26	104

*Single cardiac defect was definitely present and there may have been others.

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were observed except in the category of previous live births. The mothers of the 104 infants with malformations had had a total of 151 previous live births, while the mothers of the controls had had only 125 previous live births. Since the patients and controls were successfully matched by maternal age, we saw no obvious explanation for this moderate increase in the number of previous live births among the cases. An increase in previous miscarriages or stillbirths among the mothers of the infants with malformations might have influenced the likelihood that supportive hormones would have been prescribed during the index pregnancy, but that was not the case since the observed parity increase was limited to live births.

Our primary concern was to discover whether the use of any type of sex hormone during pregnancy increased the risk of CHD in the offspring. We used the paired study design for analysing data. Hormone pregnancy tests, supportive hormone treatment, and inadvertent oral contraceptive use were grouped as hormone exposures. Among the mothers of the infants with malformations there were 18 exposures: 10 had had hormone pregnancy tests; six supportive hormone treatment; and two inadvertent oral contraceptive use. Among the mothers of controls there were three exposures: two had had hormone pregnancy tests and one supportive hormone treatment. Seventeen of the 18 exposures among the mothers of malformed infants were started in the first trimester, and all three hormone exposures among the control mothers were started during the first trimester.

Table II shows the results of paired comparisons of hormone exposure among the entire group of 104 study pairs and among specified subgroups. The McNemar test was used to test for significance, and paired observations were used to calculate relative risks of exposure. The greater incidence of exposure among the patients was highly significant in the total group ($P < 0{\cdot}001$) and the relative risk of hormone exposure was 8·5. The same analysis, limited to the 70 patients in group 1, showed that hormone exposure remained significant among the patients ($P < 0{\cdot}01$), and the relative risk was 6·5. CHD tends to be familial, and we analysed the exposure rate after removing the six infants who had a sibling with CHD. The results remained significant ($P < 0{\cdot}01$). Finally we looked at exposure rates among the 51 patients who were still alive at the time of the interview (table II). Among this group the relative risk was only 3·0 and the association was not significant.

TABLE II—*Hormone exposure among patient and control pairs in whole group and subgroups*

Group (No of pairs)	Patients exposed, controls unexposed	Patients unexposed, controls exposed	Patients and controls exposed	Patients and controls unexposed	Relative risk	P* value
Total study group (104)	17	2	1	84	8·5	<0·001
Group 1 patients only (70)	13	2	0	55	6·5	<0·01
Familial cases removed (98)	15	2	1	80	7·5	<0·01
Patients surviving to interview (51) ..	6	2	1	42	3·0	NS

*McNemar or paired χ^2 test. NS = Not significant.

We also examined the use of other types of treatment during pregnancy from the information provided by the mother. Altogether 91% of the mothers of infants with malformations (95/104) and 80% of the mothers of controls (83/104) used prescribed medication (including all treatment prescribed by a doctor that was used at any time during pregnancy). In the first trimester, eliminating those who used hormones and those who used only vitamins or iron, or both, 15 mothers of patients and 21 mothers of controls reported using some form of prescribed medication. We therefore found no evidence that the use of other medications during the first trimester weakened the strong association between CHD and hormones. We also examined the data on infections during pregnancy. No one had a history of exposure to rubella or any other known teratogenic infectious agents. In 10 patients and six controls there was a history of some type of infection during pregnancy, but this difference might easily have arisen by chance ($P > 0{\cdot}3$), and a history of infection did not influence the association between congenital heart disease and hormone use during pregnancy.

We examined the frequency of hormone exposure in relation to infant survival in group 1. Forty-four of these 70 infants had died. For the entire group the association with hormone exposure was significant ($P < 0{\cdot}01$) and the relative risk was 6·5. In the 26 survivors the relative risk was only 3·0, but among those who had died the relative risk was 10·0. The average age at death in those not exposed to hormones was 3·0 months; in the exposed group it was 1·3 months. Therefore hormone exposure was most strongly associated with the severe types of CHD, which tend to cause early death.

We also examined the frequency of hormone exposure in relation to multiple malformations in group 1. Table III subdivides the 70 group 1 patients according to whether they had single or multiple malformations of the heart and coexistent malformations outside the cardiovascular system. In five cases there was insufficient evidence to classify the CHD as a single or multiple malformation. Exposures were more common among infants with coexistent malformations, irrespective of whether the malformation occurred inside or outside the cardiovascular system. Even when all five of the uncertain cases were assigned to either the single or multiple cardiac malformation category this pattern persisted. In the small group of 12 infants with multiple cardiac malformations plus malformations outside the cardiovascular system six were exposed to exogenous hormones during gestation.

TABLE III—*Percentage of group 1 patients with a positive history of hormone exposure according to presence of single or multiple malformations*

Category	Single cardiac	Multiple cardiac	Cardiac status uncertain	Total
Cardiac defect only ..	9·1 (2/22)	16·0 (4/25)	20·0 (1/5)	13·5 (7/52)
Cardiac defect plus other affected systems ..	0·0 (0/6)	50·0 (6/12)	0·0 (0/0)	33·3 (6/18)
Total ..	7·1 (2/28)	27·0 (10/37)	20·0 (1/5)	18·6 (13/70)

Discussion

Our results support the hypothesis that hormone exposure during pregnancy may cause CHD. Furthermore, our data strongly suggest that exogenous hormones during pregnancy are more strongly associated with multiple malformations than with single heart lesions. In future studies it will be important to determine whether this observation is also true for other types of combinations of multiple malformations. The actual number of cases caused by these agents cannot be directly estimated from a paired case-control study. Birth certificates tend to identify only the more severe and relatively uncommon types of CHD. By using the point estimate of relative risk (8·5) from our data, and assuming that the frequency of the type of CHD that we studied is no more than one live born case among 2000 births, we can predict that no more than 19 additional cases of CHD would be produced by a similar level of hormone use during pregnancy among a population of 100 000 births. If hormone-related cases of CHD tend to be more severe, and so the infant dies early, the actual burden of hormone-caused CHD among surviving infants is probably small, although not negligible.

Several studies on CHD and sex hormones have produced negative findings.[9-11] Mulvihill *et al*[9] used a precise retrospective study design to investigate a group of cases selected from a CHD treatment unit, and their results were clearly negative. If, however, hormone-related CHD tends to be severe and have poor prognosis, it would be difficult to detect a hormone association among children with CHD who are brought for treatment of their lesion. MacMahon *et al*[12] have shown that the life expectancy among children with CHD is short: nearly a quarter die in the first day, and about a half are dead by 3 months of age. Therefore negative findings in controlled series collected from cardiac treatment units might not reflect the true relation between these hormones and CHD.

The interpretation of the results of retrospective studies should be tempered by recognising the limitations of the data. Maternal recall may be an important source of bias and we have made considerable efforts to develop a standardised procedure for obtaining a uniform quality of data on both

patients and controls. We have used these same study procedures for matched case-control studies of other birth defects (anencephaly (66 pairs); spina bifida (135 pairs); Down's syndrome (103 pairs); hypospadias (99 pairs)). Neither in the total group of 403 pairs, nor in any of the subgroups, did we find a significant or substantial increase in the number of patients exposed to hormones. This suggests that our study procedures do not produce results that are biased toward detecting hormone exposures among patients. Our study is not large in terms of number of cases, so that the results should be interpreted cautiously because the confidence limits on the relative risks tend to be wide. Our point estimate on relative risk of exposure is 8·5 and it is statistically significant, but it would be prudent to await the results of other studies before finally judging the actual relative risk value. Finally, our results suggest that other studies that include a greater proportion of less severe cases of CHD should find lower relative risk estimates than we have found. But this difference should not affect the attributable risk estimates for severe CHD among live births.

Inadvertent exposure to oral contraceptives during pregnancy represented the smallest proportion of exposures in the group we studied (2 out of 18). Both of these infants were boys and both died within the first week of life. In judging the risk-benefit of each of the three types of hormone exposure the small risk associated with inadvertent exposure through oral contraceptives seems negligible in comparison with the large-scale benefits from effective contraception. Hormone pregnancy tests were the most common type of exposure (10 out of 18). These represent needless exposures and their continued use is not justified because other types of pregnancy tests are available. The risk benefit of supportive hormone treatment cannot be evaluated from any existing data. If the weight of clinical judgement still favours a possible benefit from supportive hormone treatment during pregnancy then a controlled clinical trial should certainly be conducted to determine whether the benefit outweighs the risk.

We thank Dr Margaret Hoff and the staff of the Office of Biostatistics, New York State Department of Health, for their help in analysing the data. This research was supported by Contract NO 2 HD 52802, National Institute of Child Health and Human Development.

References

1 Levy, E P, Cohen, A, and Frazer, F C, *Lancet*, 1973, **1**, 611.
2 Nora, J J, and Nora, A H, *Lancet*, 1973, **1**, 941.
3 Janerich, D T, Piper, J M, and Glebatis, D M, *New England Journal of Medicine*, 1974, **291**, 697.
4 Harlap, S, Prywes, R, and Davies, A M, *Lancet*, 1975, **1**, 682.
5 Greenberg, G, *et al*, *British Medical Journal*, 1975, **2**, 191.
6 Nora, A H, and Nora, J J, *Archives of Environmental Health*, 1975, **30**, 17.
7 *Lancet*, 1975, **2**, 692.
8 Janerich, D T, Flink, E M, and Keogh, M, *British Journal of Obstetrics and Gynaecology*, 1976, **83**, 617.
9 Mulvihill, J J, Mulvihill, C G, and Neill, C A, *Teratology*, 1974, **9**, A30.
10 Hook, E B, *et al*, *Teratology*, 1974, **9**, A21.
11 Yasuda, M, and Miller, J R, *Teratology*, 1975, **12**, 239.
12 MacMahon, B, McKeown, T, and Record, R G, *British Heart Journal*, 1953, **15**, 121.

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Nicotine chewing gum as a substitute for smoking

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Summary

The capacity of nicotine-containing chewing gum to produce plasma nicotine levels comparable to heavy cigarette smoking was tested in 21 subjects. On a fixed schedule of one piece of gum (4 mg nicotine) per hour, the average peak plasma nicotine concentration was 175·7 nmol/l (28·5 ng/ml) compared to 189·3 nmol/l (30·7 ng/ml) obtained from normal ad libitum smoking. Unpleasant side effects were common and in some cases plasma nicotine concentrations were two and even three times as high as with smoking. The chewing gum provided some satisfaction to all but four subjects, but its degree was not related to the concentration of plasma nicotine it produced, neither was there an inverse relation between the plasma nicotine concentration while taking the gum and the subjective sense of missing cigarettes. This suggests that the capacity of the gum to act as a substitute for smoking is not necessarily related to its capacity to provide nicotine. Flexible dosage dictated by individual needs would probably lower the incidence of side effects and might secure closer approximation to smoking concentrations of plasma nicotine.

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Introduction

The development of nicotine chewing gum as an aid to cigarette withdrawal[1-5] is based on two assumptions. Firstly, that nicotine intake is an important component of dependence on smoking, and secondly that absorption of nicotine from chewing gum is sufficient to reproduce whatever positive pharmacological effects the smoker seeks to obtain, or to prevent whatever negative nicotine withdrawal effects he smokes to relieve or avoid. Neither assumption is yet unequivocally established, though much circumstantial evidence points to the importance of nicotine for most smokers.[6]

In assessing the potential clinical usefulness of nicotine chewing gum it would seem essential firstly to show that it can produce plasma nicotine concentrations comparable to those obtained from cigarette smoking. It has been available in two strengths, with 2 mg or 4 mg nicotine in each piece of gum. Owing to its local irritancy and lack of palatability we found that

Vomiting of either bile or food occurred, but except for one patient after PGVP, was not severe. Postprandial fullness after PGV has been noticed by others,[7 8 22] the incidence in these reports being similar to our figure of 23%. Other symptoms such as nausea, flatulence, epigastric pain, and heartburn caused few problems. One patient reported serious degrees of all four symptoms after PGV but no physical cause could be found. Dysphagia has also been reported to be troublesome after PGV. With the exception of the patient mentioned above, in which it occurred two years after operation, it posed no great problem and was only recorded in one patient to a mild degree after PGV.

When considering the overall result by means of the Visick grading, it is perhaps disappointing to find that only 39 (78%) and 36 (77%) patients had a grade I or II result after PGV and PGVP respectively. A further seven (14%) and two (4%) patients respectively had symptoms sufficient to remove them to grade III, but still with a satisfactory result. Beyond this, the grade IV results are due to recurrence after PGV and dumping or recurrence after PGVP. The single patient with a grade III unsatisfactory result after PGV was the same man who had severe symptoms without demonstrable physical cause; after PGVP such a result was due to dumping.

PGV itself can cure duodenal ulcers without imposing serious side effects such as diarrhoea, dumping, or vomiting. When combined with pyloroplasty the number of patients with dumping increases dramatically, and since there is no other advantage to the addition of gastric drainage it should not be combined with PGV. The problem of recurrent or persistent ulcers remains. Whatever the circumstances, some recurrent ulcers probably will occur, and the number may well be equal to or slightly above those occurring after either truncal or selective vagotomy and gastric drainage. Recurrent ulcers may be treated both medically and surgically, however, whereas dumping, diarrhoea, and vomiting usually cannot, and this is the most cogent argument in favour of PGV.

We should like to thank all those who have referred patients to us; Mrs J A G Goodwin for performing the statistical analyses; and Mrs A Johnston for typing the script. All the insulin and pentagastrin tests were performed by the late J I MacNaughton.

References

1 Wastell, C, *et al*, *British Medical Journal*, 1972, **1**, 28.
2 Goligher, J L, *British Journal of Surgery*, 1974, **61**, 337.
3 Wastell, C, Wilson, T, and Pigott, H, *Proceedings of the Royal Society of Medicine*, 1974, **67**, 1183.
4 Wastell, C, *Annals of the Royal College of Surgeons*, 1969, **45**, 193.
5 Grassi, G, *et al*, *Surgery, Gynecology and Obstetrics*, 1973, **136**, 726.
6 Liedberg, G, and Oscarson, J, *Scandinavian Journal of Gastroenterology*, 1973, **8** (suppl 20), 12.
7 Amdrup, E, *et al*, *Annals of Surgery*, 1974, **180**, 279.
8 Kronborg, O, and Madsen, P, *Gut*, 1975, **16**, 268.
9 Jordan, P, *Archives of Surgery*, 1976, **111**, 370.
10 Grassi, G, in *Surgery of the Stomach and Duodenum*, 3rd edn. Boston, Little, Brown, (in press).
11 Lyndon, P J, Johnston, D, and Greenall, M J, *Gut*, 1975, **16**, 829.
12 Hallenbeck, G A, *et al*, *Annals of Surgery*, 1976, **184**, 435.
13 Joergensen, P M, Holst-Christensen, J, and Kronborg, O, *British Journal of Surgery*, 1977, **64**, 44.
14 Holst-Christensen, J, *et al*, *British Journal of Surgery*, 1977, **64**, 42.
15 Hood, J M, Spencer, E F A, and Macrae, K D, *British Journal of Surgery*, 1975, **62**, 665.
16 Robbs, J V, Bank, S, and Marks, I N, *British Journal of Surgery*, 1973, **60**, 601.
17 Kronborg, O, *Gut*, 1974, **15**, 714.
18 Kronborg, O, and Madsen, R, *Scandinavian Journal of Gastroenterology*, 1976, **11**, 465.
19 Cox, A G, Spencer, J, and Tinker, J, in *After Vagotomy*. London, Butterworths, 1969.
20 O'Leary, J P, *et al*, *Annals of Surgery*, 1976, **183**, 613.
21 Nelson, P G, *Medical Journal of Australia*, 1968, **2**, 522.
22 Kennedy, T, *et al*, *British Medical Journal*, 1975, **2**, 301.
23 Holle, F, *et al*, *Langenbecks Archiv für klinische Chirugie, vereinigt mit Deutsche Zeitschrift für Chirurgie*, 1972, **330**, 197.

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Maternal drug histories and congenital abnormalities

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Summary

We obtained drug histories for the first trimester of pregnancy for 836 mothers of congenitally malformed babies and for an equal number of control mothers of normal babies from the same doctors' practices. There was an association between the use of a hormonal pregnancy test and the subsequent birth of a malformed baby. There was also a greater use of barbiturates by mothers of affected children compared with mothers of control babies, mainly accounted for by treatment of epileptic mothers with phenobarbitone. For all other drugs usage was similar in both sets of mothers.

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Introduction

When in 1964 a Register of Adverse Reactions was established by the Committee on Safety of Drugs, based on the voluntary reporting of suspected adverse drug reactions, particular importance was attached to identification of possible teratogens. Although about 13 000 babies with visible malformations are born each year in England and Wales, only about 50 reports linking abnormalities with maternal use of drugs have been sent annually to the Committee on Safety of Medicines (CSM). Since so few reports were received it seemed likely that teratogenic effects would be missed, and a new method of surveillance was planned. The Office of Population Censuses and Surveys (OPCS) co-operated in a pilot study carried out in 1969, which showed the feasibility of a case-control survey. The major survey began in 1972.

In April 1975 we reported a possible association between congenital malformations and the use of hormonal pregnancy tests seen in the first 149 case-control pairs in our series.[1] We now report on data obtained in the larger series, which support this association.

Patients and methods

The doctor, midwife, or health visitor attending the birth of an abnormal baby may report the abnormality to the area health authority. This information is then passed to the OPCS. Though voluntary, we believe that notification of visible and severe malformations is reasonably complete.

When the study was planned we hoped to investigate all cases of oral cleft (hare lip or cleft palate) and a 5% random sample of babies with other abnormalities. We did not, however, achieve this target, so we had to reduce the number of cases of oral cleft studied and eliminate all minor malformations included in the original 5% sample. The distribution of types of abnormality in our study groups does not therefore resemble that in the total population of abnormal births.

Medical officers of health or community physicians were asked to identify the baby and provide the name and address of the general practitioner, who was then (if willing to participate) interviewed by one of the Committee's medical field workers. Details were obtained about the antenatal, personal, and family history and drugs prescribed during the first trimester.

Similar information was obtained at the same interview about the mother of a "control" baby, defined as a normal baby born in the same practice within three months of the date of birth of the abnormal baby. This selection procedure for controls ensured that any change in the doctor's prescribing habit resulting from the birth of an abnormal baby in his practice was unlikely to have influenced his choice of treatment for the mother of the control child. Information provided from memory was recorded separately from that obtained from written notes, and was not used in this analysis. Interviews could not be conducted without participants knowing whether they were discussing a case or control: instructions were given to field workers to begin alternate interviews with the discussion of a control baby to reduce the tendency to concentrate the attention on case children.

The OPCS sent 2867 notifications of abnormal births to the CSM. Of these 1462 were not followed up: preliminary enquiries showed that 77 were normal babies; 292 had minor abnormalities; in 145 cases no field worker was available; and 948 cases of oral cleft were not followed up because resources were limited. This left 1405 cases for which investigation was attempted. Of these attempts, 479 were unsuccessful: in 120 the control was incorrectly selected; in 130 the doctor could not be traced; in 46 the doctor had no record; in 53 he could not co-operate; and the remaining 130 failed for various reasons such as difficulty in identifying the child from the records.

There remained 926 pairs successfully followed up. Ninety of these were subsequently excluded because the abnormality proved to be minor, leaving a total of 836 pairs on which this paper is based. Seven hundred and forty-five study babies were born in 1972 and 1973; 89 study babies (11%) were born in 1969 and investigated during the pilot survey (table I).

TABLE I—*Birth dates of study babies*

Year	Cases		Controls	
	No	%	No	%
1969	89	11	88	11
1970	1	<1	2	<1
1971			16	2
1972	470	56	449	54
1973	275	33	273	33
1974	1	<1	8	<1
Total	836	100	836	100

Results

AGE AND PARITY OF MOTHERS

The mean age of mothers of malformed children was 26·5 years (range 16-51) and of control mothers 26·6 years (range 16-43). One hundred and eleven mothers of abnormal babies (13%) and 97 control mothers (12%) had a past history of miscarriage. One hundred and twenty-one case families (14%) and 23 control families (3%) had a history of congenital malformations occurring in either siblings of the study baby or in other close relatives (grandparents, parents, uncles, aunts, and first cousins). The total number of births to mothers of affected babies was 1823 and to control mothers 1804 (average 2·18 and 2·16, respectively). The average number of previous pregnancies was 1·17 for mothers of affected babies and 1·15 for control mothers. Eight of the former and six of the latter had had previous twin pregnancies. Eleven of the children with abnormalities were members of twin pairs. Eight of their co-twins were normal and three were abnormal. Of the three pairs of abnormal twins, an anencephalic twin to one case baby and a twin with hypospadias to another case baby were not included in this study because they were not the baby described in the notification form. One pair of conjoined twins was included as a single case, each member of the pair having a hare lip. Each abnormal twin was matched with a single control. Table II shows some of these data and summarises characteristics of mothers of case babies exposed to certain groups of drugs during the first trimester.

TYPE OF ABNORMALITY

Distribution of malformations is shown in table III. Each baby appears only once in this table, in the first appropriate category reading from above—for example, if a child had spina bifida and a cleft palate it appears only in the category of neural tube defects. Only these three categories (neural tube defects, oral clefts, and limb malformations), which included 50 or more babies, were analysed in detail.

DRUGS PRESCRIBED DURING FIRST TRIMESTER

The number of prescriptions for mothers of case babies during the first trimester was similar to that for control mothers (2094 and 2025, respectively). Medicines containing 331 different active ingredients had been prescribed. For four groups of drugs—hormonal pregnancy tests (HPT), benzodiazepines, antibiotics, and barbiturates—there was a notable difference between case and control usage (table IV). Significantly more mothers of malformed babies had used HPT. Considering only discordant pairs, the ratio of case to control exposure

TABLE II—*Characteristics of mothers of case and control babies, including details of drugs used by case mothers in first trimester and numbers (%) of mothers with past history of miscarriage or personal or family history of congenitally abnormal births*

Characteristic	Drugs used				All cases	All controls
	HPT	Benzodiazepines	Antibiotics	Barbiturates		
Age range (years)	16–41	17–51	17–38	16–39	16–51	16–43
Average age (years)	25·4	29·7	24·6	27·8	26·5	26·6
Past history (%):						
Miscarriage	11 (12)	5 (14)	7 (11)	7 (25)	111 (13)	97 (12)
Congenital abnormality	9 (10)	7 (19)	6 (10)	3 (11)	121 (14)	23 (3)
Total births*	237	83	130	81	1823	1804
Average No of births	2·55	2·31	2·09	2·89	2·18	2·16
No of mothers in group	93	36	62	28	836	836

*Differs from total No of pregnancies because of some twin births.
HPT = Hormonal pregnancy test.

was 2·09 ($P < 0·01$). Fewer case and control babies had been exposed to benzodiazepines (ratio for discordant pairs 1·57) and barbiturates (ratio for discordant pairs 2·25).

TABLE III—*Distribution of types of malformation among case babies. Categories are mutually exclusive*

Malformations	Affected babies	
	No	%
Neural tube defects	189	23
Oral clefts	412	49
Limb malformations	59	7
Other abnormalities	176	21
Total	836	100

TABLE IV—*Drug usage among mothers of case and control babies in first trimester*

Class of drug	Case and control	Case only	Control only	Neither	Total	Ratio case:control (discordant pairs)
Hormonal pregnancy test	20	73	35	708	836	2·09**
Benzodiazepines	3	33	21	779	836	1·57 NS
Antibiotics	2	60	42	732	836	1·43 NS
Barbiturates	1	27	12	796	836	2·25*

**$P < 0·01$; $\chi^2 = 5·03$.
*$P < 0·05$; $\chi^2 = 12·68$.
NS = Not significant.

Table V shows drug usage among mothers of case and control babies after all case-control pairs who had a family history of congenital malformation in either or both families of the pair had been excluded to remove this possible confounding influence. The ratio for discordant pairs falls for each drug; the excess use of HPT by case mothers remains statistically significant ($P < 0·01$) but the excess use of barbiturates does not.

TABLE V—*Drug usage in first trimester, excluding any family with a history of congenital malformation*

Class of drug	Case and control	Case only	Control only	Neither	Total	Ratio case:control use (discordant pairs)
HPT	17	67	35	708	827	1·91**
Benzodiazepines	3	26	21	779	829	1·24 NS
Antibiotics	2	54	39	732	827	1·38 NS
Barbiturates	1	24	12	796	833	2·00 NS

**$P < 0·01$; $\chi^2 = 9·42$.
NS = Not significant.

Fifteen mothers of abnormal babies and three control mothers were epileptic (table VI). One epileptic mother had received no anticonvulsants during pregnancy. Eleven of the 14 treated mothers of abnormal children and one of the three control mothers had received phenobarbitone alone or in combination with one or more anticonvulsant.

No other drug or groups of drugs showed an appreciable difference in usage between cases and controls (table VII). More control mothers than mothers of affected babies had used iron, with or without folic acid, but the difference was not significant. An antiemetic had been prescribed for 178 control mothers and 157 mothers of affected babies; this difference was not significant. There was a moderate though not significant excess of prescriptions for progestogen used to maintain pregnancy in mothers of affected babies (19 compared with 12 controls), and 11 mothers of abnormal babies and ten control mothers became pregnant while taking oral contraceptives. Thirty case and 32 control mothers had used oral contraceptives during the three months before conception.

The distribution of malformations in babies born to users of the four main drug groups is shown in table VIII. The number of babies

TABLE VI—*Usage of anticonvulsants among epileptic mothers of case and control children*

Drug	Case mothers	Control mothers
Phenobarbitone	11	1
Phenytoin	6	2
Primidone	2	1
Sulthiame	3	
Total*	22	4

*Totals exceed the numbers of epileptic mothers on anticonvulsants because seven case mothers and one control mother were taking more than one anticonvulsant simultaneously.

TABLE VII—*Other principal drugs prescribed for mothers of case and control babies in first trimester*

Drug or drug group	Case and control	Case only	Control only	Neither	Total
Iron without folic acid	48	83	97	608	836
Iron with folic acid	161	190	242	243	836
Oral contraceptive		11	10	815	836
Hormonal support of pregnancy	2	17	10	807	836
Doxylamine	13	63	75	685	836
Promethazine	4	41	37	754	836
Meclozine	6	28	35	767	836
Phenothiazine tranquillisers	2	21	17	796	836
Monoamine oxidase inhibitors		12	11	813	836
Tricyclic antidepressants		10	6	820	836
Anti-obesity agents		8	8	820	836

with each type of abnormality does not correspond to that shown in table III because some mothers used more than one drug. Each baby appears under one category only. For example, column five shows 14 babies with oral cleft exposed to barbiturates. In fact 17 babies so exposed had oral cleft but three of these also had neural tube defects and are therefore shown only under this category. The distribution of malformations was remarkably consistent within the drug groups, suggesting that any possible teratogenic effect was probably nonspecific.

Discussion

Ideally the mothers of abnormal babies and of control babies should have been matched in all respects, so that, age, parity, obstetric and family history, and date of birth of the babies would be identical. Birth date of babies was selected as the most important matching factor because of the possibility that the birth of an abnormal baby might affect the doctor's prescribing practice; it was therefore essential to ensure that every control mother had completed the first trimester of her pregnancy before the abnormal birth had occurred. This was achieved by accepting as controls only babies born within three months of the case baby. This matching having been achieved, we could not match for other factors such as maternal age and parity because the number of potential controls in a single practice was usually too small. Field workers were instructed that once a suitable control baby had been selected it should on no account be rejected if, for example, the mother had suffered from some condition such as rubella or came from a family with a history of congenital abnormalities.

Cases and controls were matched closely for all factors except history of previous children with abnormalities in the study families (see table II). Furthermore, the proportion of mothers of case babies with such a history is uniformly higher in the individual treatment groups shown in table II, as well as in the group of "all cases," than in the controls. Clearly this could be an important confounding factor. A separate analysis, excluding mothers with a personal or family history of abnormality, shows that this cannot account for the effect associated with HPT, but could account for differences associated with other drug groups (table V). Nine of the 93 mothers of abnormal babies who had

TABLE VIII—*Number (%) of malformed babies born to mothers who had used specific drugs during first trimester, according to type of malformation. Categories are mutually exclusive**

Malformation	Hormonal pregnancy test	Benzodiazepines	Antibiotics	Barbiturates
Neural tube defects	25 (27)	9 (25)	16 (26)	8 (29)
Oral clefts	47 (51)	18 (50)	28 (45)	14 (50)
Limb malformations	6 (6)	2 (6)	4 (6)	2 (7)
Other	15 (16)	7 (19)	14 (23)	4 (14)
Total	93 (100)	36 (100)	62 (100)	28 (100)

*Babies born with more than one type of malformation appear in one category only.

used HPT had a personal or family history of congenital malformations. None of the 55 control mothers had such a history. The difference between case and control use of HPT remains significant when these nine mothers of affected babies are excluded (χ^2 9·42; P <0·01; McNemar's test[2]).

Several studies have shown a possible association between the use of female sex hormones and congenital abnormalities. Gal *et al*[3] were the first to report a possible association between neural tube defects and HPT. Although our results are consistent with a general teratogenic effect of HPT, they do not suggest any specific effect on the development of the neural tubes. Gal's study, however, was restricted to children with this type of abnormality. Laurence *et al*[4] found no significant association between the use of oestrogens and progestogens as pregnancy tests and the birth of children with neural tube malformations. Multiple congenital malformations were described by Nora and Nora[5] in babies exposed to oestrogen-progestogen mixtures or to progestogen alone. Levy *et al*[6] described congenital heart disease associated with maternal use of hormones during pregnancy, while Janerich *et al*[7] showed an association between exposure to exogenous sex hormones during gestation and congenital limb reduction deformities. Heinonen *et al*[8] found associations between exposure to progestational agents and oestrogens and cardiovascular abnormalities; Janerich *et al*[9] also showed an association between congenital heart disease and exposure to exogenous sex hormones.

Milkovich and van den Berg,[10] Saxén,[11] and Safra and Oakley[12] suggested a possible link between benzodiazepines and congenital abnormalities. Hartz *et al*[13] did not confirm this. Heinonen *et al*[8] found no statistically significant evidence that benzodiazepines were teratogenic. In the present study the number of patients exposed to these drugs was small, with no significant difference between case and control usage.

The relation between congenital abnormalities and barbiturates used in the treatment of epilepsy has been extensively documented. Since a high proportion of patients with epilepsy received anticonvulsant treatment the effect of the disease cannot be distinguished from that of the drugs used in its control. Table IV shows a significant excess of barbiturate use among cases, mainly accounted for by the use of phenobarbitone by epileptic mothers of affected babies (see table VI). Shapiro *et al*[14] suggested that the rates of malformations in children of parents with epilepsy are not materially affected by the choice of maternal anticonvulsant treatment.

The excess use of HPT by case mothers found by us was not great and the association with malformations nonspecific; alternative risk-free methods of pregnancy diagnosis are, however, available and the use of HPTs is unnecessary.

Except for the risks associated with HPT we found no evidence that any of the drugs studied is a teratogen. Nevertheless, the benefits of drug treatment in the first trimester should continue to be carefully weighed against the existence of possible but hitherto undetected hazards. Weak teratogenic activity of a drug not commonly used would not have been detected by this study. We intend to undertake further studies, with increased numbers, so that small risks may be detected and newly marketed or rarely used drugs may be monitored for teratogenic effects.

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References

1 Greenberg, G, *et al*, *British Medical Journal*, 1975, **2,** 191.
2 McNemar, Q, *Psychometrika*, 1947, **12,** 153.
3 Gal, I, Kirman, B, and Stern, J, *Nature*, 1967, **216,** 83.
4 Laurence, M, *et al*, *Nature*, 1971, **233,** 495.
5 Nora, J J, and Nora, A H, *Lancet*, 1973, **1,** 941.
6 Levy, E P, Cohen, A, and Fraser, F C, *Lancet*, 1973, **1,** 611.
7 Janerich, D T, Piper, J M, and Glebatis, D M, *New England Journal of Medicine*, 1974, **291,** 697.
8 Heinonen, O P, Slone, D, and Shapiro, S, *Birth Defects and Drugs in Pregnancy*. Littleton, Massachusetts, Publishing Sciences Group, Inc, 1977.
9 Janerich, D T, *et al*, *British Medical Journal*, 1977, **1,** 1058.
10 Milkovich, L, and van den Berg, B J, *New England Journal of Medicine*, 1974, **291,** 1268.
11 Saxén, I, *International Journal of Epidemiology*, 1975, **4,** 37.
12 Safra, M J, and Oakley, G P, *Lancet*, 1975, **2,** 478.
13 Hartz, S C, *et al*, *New England Journal of Medicine*, 1975, **292,** 726.
14 Shapiro, S, *et al*, *Lancet*, 1976, **1,** 272.

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CORRESPONDENCE

Correspondents are urged to write briefly so that readers may be offered as wide a selection of letters as possible. So many are being received that the omission of some is inevitable. Letters must be signed personally by all their authors.

Continued use of hormonal pregnancy tests

SIR,—Hormonal pregnancy tests (HPTs) were very widely used until the mid-1960s, when a general post-thalidomide reluctance to give drugs during pregnancy coupled with the development of simple immunological tests led to their gradual abandonment. In 1975 this trend was given official approval when the Committee on Safety of Medicines (CSM) issued a warning based on a preliminary report of an association between HPTs and subsequent congenital abnormalities.[1] The committee said then that HPTs should not be used.

Following a further report which confirmed the association,[2] the CSM issued a second warning in November 1977 and stated again that "hormonal tests for pregnancy should not be used. Alternative methods are available which are free from this risk." This warning received considerable publicity in the lay as well as the medical press and questions were asked in Parliament, where the Secretary of State declined to ban the proprietary drug concerned.[3]

Informal inquiries among colleagues indicated that HPTs were still being prescribed and I conducted a small survey to discover the extent of their use. During December 1977 and January 1978—that is, shortly after the latest CSM warning—600 consecutive patients requesting abortion were asked whether they had been given HPTs since the discovery of their latest pregnancy. Twelve patients (2%) had received such tests. Six separate branches of the British Pregnancy Advisory Service took part in this survey and all reported at least one HPT per 100 patients, so that this finding is unlikely to reflect either chance or the presence of a particularly recalcitrant general practitioner in just one area.

The figure of 2% is almost certainly an underestimate of the actual use, because only a minority of the women had consulted a GP before coming to BPAS, so that most of them were not at risk. Although in some cases the GPs may have prescribed HPT in the belief that the pregnancy would be terminated and that teratological risks could therefore be ignored, some of the HPTs were prescribed by GPs who subsequently refused to refer the woman for abortion. In any case, a significant proportion of women change their minds about abortion and decide to go to term. No doubt some women ask for "something to bring on a period," but oestrogens are effective as abortifacients only within a day or two of conception and GPs are deluding themselves as well as their patients if they believe otherwise.

This study has revealed an area of persistent malpractice which represents an easily avoidable hazard. If banning the drug in question —Primodos—is thought an unacceptable infringement of professional freedom, perhaps the Department of Health and Social Security will consider making it a controlled drug with a requirement that before prescribing it the doctor must satisfy himself by an immunological test that the recipient is not pregnant.

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[1] Greenberg, G, *et al*, *British Medical Journal*, 1975, **2**, 191.
[2] Greenberg, G, *et al*, *British Medical Journal*, 1977, **2**, 853.
[3] *Hansard*, House of Commons, 21 November 1977, cols 465-467.

Teratogenic effects of waste anaesthetic gases

SIR,—Knill-Jones *et al*[1] found no evidence of an excess of major congenital malformations among the 5175 offspring of British male anaesthetists. It would therefore be wise to interpret with caution Dr P J Tomlin's (14 January, p 108) finding of four children with congenital abnormalities and one with an ependymoma among 135 offspring of 75 Birmingham anaesthetists. If we assume that major congenital defects occur in about 1% of all births,[1] the probability of observing by chance four malformed children in a sample of 135 is about 0·05. This is not a rare occurrence. If, for example, we were to divide Britain up into areas each containing about 75 anaesthetists we would expect, by chance alone, a situation as extreme as or more extreme than that observed by Dr Tomlin to exist in 5% of them. Furthermore, studies of small series in which no odd effects are seen are neither likely to be submitted to journals nor published if submitted, so that the conventional method of assigning a P value to