Serum Neutralizing Antibody Tests in Tissue Culture

Coxsackie virus type	Sera with Titres of 1/4 or Greater		Significance of χ^2 test)
	Diabetics	Controls	
B1	35/102 (34%)	54/201 (27%)	Not significant
B2	47/102 (46%)	90/201 (45%)	"
B3	56/102 (55%)	107/201 (53%)	"
B4	77/102 (75%)	120/201 (59%)	$P < 0.01$
B5	46/102 (45%)	73/201 (36%)	$P < 0.05$

give a significant answer and, in view of the difficulty of obtaining a suitable control group, we doubt whether fewer than 100 patients would suffice.

It may be of interest that in our second survey 102 acute-onset diabetics have so far been compared with 201 controls by testing for the presence of serum neutralizing antibody to Coxsackie B virus at a dilution of 1/4 and a significantly greater proporion of diabetics have been found to have antibodies to Coxsackie B4 virus than controls. The provisional results are shown in table above.

In conclusion we would like to stress that, despite our further positive findings, it is still premature to draw further conclusions about their possible clinical significance. We are, however, particularly anxious that further work on the relationship between virus infection and the aetiology of diabetes should not be impeded. Both laboratory and epidemiological investigation of this problem is proceeding rapidly in the United States and large-scale studies ought similarly to be carried out in Western Europe.—We are, etc.,

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Anaesthesia in Sickle-cell States

SIR,—The plea by Drs. K. A. Oduro and J. F. Searle (9 December, p. 596) for simplicity in anaesthesia in sickle-cell states seems over-sanguine to me. Admittedly, for the trait states one would expect no more than competent anaesthesia with adequate oxygenation, maintenance of good circulation, etc., as is required for all patients. However, among the 42 patients without haemoglobin A one death associated with sickle-cell crisis occurred. It happened to one of the 21 SC patients—the group most at risk among the sickle-cell states because of their relatively high haematocrit. Surely an anaesthetic death rate of 2·5% is not that found in non-sicklers and cannot be considered acceptable?

It is known that simple procedures—5% glucose infusion, bicarbonate treatment—counteract sickling. Three reports on alkalinization are quoted, two claiming that it prevents sickle-cell crisis and one contradicting this. The latter, however, records only a failure to find acidosis in patients admitted in sickle-cell crisis—that is, after the intravascular block has become established. It cannot be claimed to have disproved that prior treatment with alkali might have prevented the crisis.

In recent years the pragmatic advice of the past has become understood on a theoretical basis. "Isotonic" glucose causes haemodilution and thereby lowers the haematocrit. It is also physiologically hypotonic, and because of the Donnan equilibrium will cause red cells to sphere and thereby lower their intracellular haemoglobin concentration. Acidosis lowers the oxygen affinity—that is, favours sickling—and the higher the pH (well within the normal range) the more does the alkaline Bohr effect raise the affinity of the haemoglobin for oxygen. Thus there is every reason why 5% glucose and alkalinization should counteract the sickling of red cells, though one would not expect that they would necessarily reverse the precipitation of deoxyhaemoglobin S in an established infarct. A failure to obtain a reversal does not permit the conclusion that these measures are useless in prevention. They are hardly so complex that they can be classed with urea treatment and exchange transfusion as unnecessary in a plea for simplicity.—I am, etc.,

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Rh Immunization in Ruptured Tubal Pregnancy

SIR,—We were interested to read the letter of Dr. R. D. Barr (4 November, p. 295), who queried the data in our paper (16 September, p. 667), and this has prompted a formal reply. We think the criticisms fall into three categories, which we will endeavour to answer.

(1) Dr. Barr quotes work done on sickle-cell disease and other haemoglobinopathies in West Africa, stating the high incidence recorded. We are aware of these findings but wish to point out that a very different state of affairs exists among South African Negroes. In our haemoglobinopathy unit no patient with an abnormal haemoglobin has been found in the indigenous populations, and haemoglobin surveys carried out in Cape Town[1] and many parts of South Africa[2] have shown that polymorphic haemoglobin variants are extremely rare. Thus we do not see high Hb F values resulting from these diseases.

(2) Dr. Barr queries the apparent excessive number of fetal cells found in the intraperitoneal cavity (44 per 150,000 maternal cells) and the maternal circulation (14 per 150,000 maternal cells) after a tubal rupture. As we did not quantitate the amount of maternal blood in the peritoneal cavity we have no way of knowing the total amount of fetal blood present. However, in the maternal circulation the maximum number of fetal cells was 14 per 150,000 maternal cells. When intraperitoneal tubal rupture occurs the total blood volume of the fetus will be present in the maternal peritoneal cavity and the blood will be absorbed until such time as laparotomy is performed and the intraperitoneal blood removed. Recently Van Iddekinge,[3] in a review of ectopic pregnancies in the South African Negro, reported that 30% have a greater than eight-week gestation period. In our study we have found that a significant fetomaternal haemorrhage (five or more fetal cells per 150,000 maternal cells in the mother's circulation) occurs in 24% of ruptured tubal pregnancies, and we believe that the higher fetal cell scores resulted from the rupture of a greater than eight-week tubal pregnancy. An 8-10-week fetus[4] has an erythrocyte count of $0{\cdot}3\text{-}0{\cdot}5 \times 10^6$/mm.^{3} In order to score 14 fetal cells per 150,000 maternal cells the total amount of fetal blood in the maternal circulation would be approximately 1·5-2·0 ml. A score of five fetal cells per 150,000 is equivalent to about 0·5 ml of fetal blood. Blood volume studies have not been performed on human embryos. However, an 8-10-week fetus is 3-8 cm in length, and weighs 1 g at eight weeks and 14 g at 12 weeks; therefore 0·5-1·5 ml of fetal blood that we found in eight of the 38 patients who were studied is not excessive. Previous studies[5 6] have shown that a score of 5-10 Rh-positive erythrocytes (0·2-0·5 ml) will result in primary immunization, and this amount was found in 24% of our patients with ruptured tubal pregnancies.

It appears that Dr. Barr is unaware that the Rh antigen has been detected in a 38-day-old fetus,[7] and therefore these cells must be considered antigenic.

(3) All the South African negro patients who were studied were Rh-positive. Rh antibody studies were therefore not performed, but this was not the point of the paper, as our intention was to demonstrate that tubal rupture results in fetomaternal haemorrhage. We are well aware of the low incidence of Rh-negativity in the South African negro,[8] and this was another reason not to look at Rh immunization in the group we studied.

I hope that these comments will answer some of the queries raised by Dr. Barr.—We are, etc.,

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Diet and Congenital Defects

SIR,—The most striking feature of the incidence of anencephaly in England and Wales over the period 1962-70 is the uniformly steady decline in the rate, with no significant variation on either side of the regression line of incidence on calendar year (−0·045 for anencephalic stillbirths). This is shown in the table below. The one relatively high rate is

Year	1962	1963	1964	1965	1966	1967	1968	1969	1970
Anencephaly rate	1·82	1·78	1·73	1·66	1·65	1·56	1·47	1·50	1·51

for 1970, and this followed a low potato blight year, 1969.

Dr. J. H. Renwick's table of the figures for 1962-9 (20 January, p. 172) (taken from mid-February to mid-February and including live-born anencephalics), which are already corrected for regression of −0·06, show this same constancy. His diagram, which shows no zero, magnifies the small annual variations in the incidence of anencephaly in comparison with those for blight.

In view of this uniform rate of decline in anencephaly it is unlikely that the marked annual variation in the percentage of blighted potatoes, or indeed any other agent which shows marked annual variation, could be making a substantial contribution to the incidence of anencephaly. If there were one main environmental agent responsible for anencephaly it must be something that has been steadily declining in strength over the decade.—I am, etc.,

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SIR,—Scottish statistics on anencephaly have been extensively quoted in epidemiological studies in recent years, most recently by Dr. J. H. Renwick,[1] who correlated the stillbirth rate from anencephaly in Scotland with the presumed teratogenic insult from blight in the susceptible areas in the west of Scotland. He estimated that the incidence of blight was moderately severe in 1950 and 1953 and found that the stillbirth rate from anencephaly was higher in 1951 and 1954 than in other years. The table below gives the stillbirth rate from anencephaly in Scotland from 1947 to 1956 arranged according to the parity of the mother. It shows that the overall rate per 1,000 total births increased from 2·4 in 1950 to 2·7 in 1951. It was higher in 1st and 5th+ pregnancies but lower in 2nd, 3rd, and 4th pregnancies. In 1954, while the overall rate was higher than in 1953, the rise occurred in 2nd and 3rd pregnancies and a slight fall occurred in 1st and 5th+ pregnancies. These trends were repeated inside each social class. Analysis of the same data by the age of the mother, using the technique of the five-years moving average, shows that the rate rose in the 15-19 age group from 1947 onwards, in the 20-24 age group from 1952, and in the 25-29 age group from 1958.

In his more recent letter (20 January, p. 172) Dr. Renwick makes a similar comparison for England and Wales in the years 1961-8 and draws similar conclusions although the rates are lower and the variations much smaller. If a teratogen acting during pregnancy, such as potato blight, is so important as to be responsible for 95% of the deaths from anencephaly, one would expect that it would act on women of all ages and parities alike in the years in which its concentration had reached dangerous levels. The fact that the stillbirth rate from anencephaly was rising from 1950 onwards in Scotland even in the years when blight in the previous year was negligible also raises doubt as to the probability of a causal relationship.—I am, etc.,

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1 Renwick, J. H., *British Journal of Preventive and Social Medicine*, 1972, **26**, 67.

Pregnancy	Stillbirth Rate from Anencephaly per 1,000 total births (Scotland)									
	1947	1948	1949	1950	1951	1952	1953	1954	1955	1956
1st	2·1	2·7	2·2	1·8	3·1	3·7	3·6	3·3	2·6	3·1
2nd	1·4	1·6	1·5	2·2	1·8	1·6	1·7	2·8	2·1	2·3
3rd	2·2	2·1	2·6	2·8	1·8	1·9	2·4	2·8	2·9	2·9
4th	2·5	3·3	2·3	3·4	2·6	3·6	3·1	3·1	3·5	3·2
5th	4·2	4·1	2·3	3·8	4·4	3·5	2·8	2·6	4·5	3·3
All	2·2	2·5	1·1	2·4	2·7	2·9	2·8	3·0	2·9	2·9

Gastric Ulcer after Highly Selective Vagotomy

SIR,—Mr. A. Hall's report (30 December, p. 789) on gastric ulcer after highly selective vagotomy is important, and a reminder of the unknown outcome of this operation despite the encouraging early reports from Leeds and Copenhagen. I have no reason to doubt the rationale of this procedure and no cause for complaint in observing the progress of almost 100 patients treated in my unit. Nevertheless I do not think this operation should be generally adopted at this stage.

Mr. Hall reports postoperative secretion studies, which are of interest but would have been even more valuable if compared with preoperative tests. A proper assessment of the operation demands good facilities for measuring gastric function as well as a reliable follow-up. Unless this can be done we are in danger of discarding operations with known results in favour of a fashionable technique whose true value may be missed by inadequate appraisal. Not long ago a distinguished Continental surgeon described our gastric surgeons as "individualists, each of whom had his own branch of the vagus which he divided or preserved according to his ideas." We could improve our image by exercising some patience until the way is clear.—I am, etc.,

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SIR,—I was interested to read Mr. R. Hall's letter (30 December, p. 789) regarding a case of benign lesser curve gastric ulcer following proximal gastric vagotomy (highly selective vagotomy) without drainage done apparently for basal duodenal and pyloric channel disease.

Three years ago I began using proximal gastric vagotomy for duodenal ulceration, preserving the prepyloric vagal supply to 5-6 cm. One patient developed later a benign lesser curve gastric ulcer, and gastric retention was shown using the food/barium meal. A gastroenterostomy was done later to drain the antrum and to cure the ulcer. Amdrup (personal communication) had a similar case, also with retention.

Preservation of the vagal supply to 5-6 cm from the pylorus invites gastric retention and benign lesser curve gastric ulcer. I think that Amdrup in Denmark and Hedenstedt in Sweden, as well as Johnston and myself in this country, are retaining much more innervated stomach and all choosing the same point of preservation. This is in fact the point that Holle in Munich has used for many years. It is easily chosen above the point where the main anterior nerve of Latarjet crosses the lesser gastric curve. About 8-9 cm of stomach remains innervated and food/barium studies show that there is no retention postoperatively in the absence of organic stenosis in the pyloric canal or in the duodenum.

Damage to the nerves of Latarjet may too, of course, cause gastric retention and benign lesser curve gastric ulcer, and great care is needed at operation to protect these nerves.—I am, etc.,

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Radiography of Potentially Pregnant Females

SIR,—It is to be hoped that a full discussion of this subject will be prompted by the letter from Drs. G. M. Ardran and F. H. Kemp (18 November, p. 422). Ultimate agreement on the responsibilities of clinician, patient, and radiologist within an accepted scheme for avoiding this hazard would be an ideal conclusion.

The code of practice issued by the Department of Health[1] states that radiological examinations involving the lower abdomen should, if practicable, be carried out within the first 10 days following the first day of the menstrual period. The practical difficulties of a strict application of a "10-day rule" are considerable. The clinical staff of the Aberdeen hospitals discussed this matter with the radiologists in 1967. While accepting their responsibility for ensuring that patients who might be pregnant were not referred for *x*-ray unless absolutely necessary, the clinicians could not give a guarantee to include invariably the date of the last menstrual period on the request form. The radiologists undertook to ascertain the date of the last menstrual period in cases of booked appointments occurring some time after the original request; they felt that a rigid application of a "10-day rule" for outpatients was virtually impracticable. The system which has been in force for the past five years is, in effect, a "28-day rule." It applies to outpatient appointments for barium examinations, intravenous pyelography, and micturating cystography previously booked on all female patients (married or unmarried) aged between 15 and 50 years. This simply means that the date of the last menstrual period is obtained by a nurse and/or radiographer and transmitted to the radiologist when the patient arrives at the *x*-ray department.