was used after 1963. In particular, the incidence of convulsions recorded for 1965 was more than double the 1963 figure. I find difficulty in grasping how such evidence indicates an association between removal of adjuvant and disappearance of serious reactions. Even Dr Tiru, whom he cites, seems far from sure.

Department of Bacteriology and Virology,
University of Manchester,
Manchester M13 9PT NOEL W. PRESTON

SIR,—The merits of whooping-cough vaccination will never be settled by a series of letters in *The Lancet*, but I feel nevertheless that I must correct two of the statements made by Dr Bassili and Professor Stewart in their letter of May 15 (p. 1074). In the first place, Sako did publish clinical observations on vaccinated and control subjects, taking careful note of exposure: 30 cases in 159 exposed vaccinated *vs.* 137 cases (with 13 deaths) in 149 exposed unvaccinated infants or young children. This is detailed in the reference cited, and further details can be found in a later paper.[1] But others did far more carefully designed studies than Sako, and obtained similar answers; the work of Silverthorne, Miller, Kendrick, Singer-Brooks, Coppolino, Bell, and others is liberally cited in the literature and I will not take up space by detailed references here. One cannot, however, overlook the masterful studies by the British Medical Research Council,[2] and the fact is that, with three exceptions, every properly controlled study on whooping-cough vaccine has shown it to be moderately to highly effective. It is, of course, possible to prepare a poor vaccine and, conceivably, a good vaccine that is irrelevant because of differences in serotype. But these problems have been corrected in the U.K., and Dr Fraser's analysis (May 1, p. 969) suggests that, with a little more attention to the younger infants, whooping-cough vaccine in Glasgow might prove satisfactory to all.

My second point concerns alum. In the first place its use has not "long been discontinued" as a component of vaccines; at least four U.S. manufacturers still use it and it is included in one of the most widely used forms of diphtheria-tetanus-pertussis vaccines. However, its use is diminishing since it is thought to be less effective as an adjuvant than the other salts of aluminium. Yet this very fact renders Sako's results more, rather than less, impressive.

5 Ellerdale Road,
London NW3 GEOFFREY EDSALL

GENETIC RISKS OF VINYL CHLORIDE

SIR,—Dr Paddle (May 15, p. 1079) asks us to specify the method of data collection used in our study (April 13, p. 734) and to show a tabulation of the data before age adjustment.

As mentioned several times, the data were obtained by interview with the workers. The range for response-rates, which were similar for the study and control groups, were also included. As we stated, the questions about pregnancy outcome were contained in a much larger interview questionnaire which was the initial item of a cross-sectional health survey that included a physical examination, X-rays, and laboratory tests. The results of the survey demonstrated very few significant differences, and no consistent bias toward a higher prevalence for the indices measured in either the study or control group. The interview protocols were administered by six interviewers (two successive teams of three interviewers) from the Center for Disease Control, each with experience in field health surveys. Each interview took 15–30 min, and was carried out in a mobile van interview booth. The interviewers had participated in a formal review of the questionnaire before the study. In addition, a physician member of the survey team reviewed positive responses immediately after the interview and, where appropriate, sought further elaboration from the interviewee.

1. Sako, W. *J. Pediat.* 1947, **30**, 29.
2. Medical Research Council *Br. med. J.* 1959, i, 994.

PATERNAL AGE DISTRIBUTION FOR FETAL DEATHS ACCORDING TO HUSBAND'S V.C. EXPOSURE

Paternal age (yr)	"Controls"		Primary exposure	
	Pregnancies	Fetal deaths	Pregnancies	Fetal deaths
Before exposure:				
<20	31	2 *(6·5%)*	7	0
20–24	80	4 *(5·0%)*	44	2 *(4·5%)*
25–29	38	4 *(10·5%)*	56	7 *(12·5%)*
30–34	6	1	27	5 *(18·5%)*
>35	4	0	14	1
All ages, crude rate	159	11 *(6·9%)*	148	15 *(10·1%)*
Mean paternal age at conception	*23·0 yr.*	. .	*26·4 yr.*	. .
Age-adjusted rate*	. .	. . *(6·9%)*		*(6·1%)*
After exposure:				
<20	1	0	0	. .
20–24	43	4 *(9·3%)*	22	3 *(13·6%)*
25–29	87	3 *(3·4%)*	48	11 *(22·9%)*
30–34	87	7 *(8·0%)*	36	3 *(8·3%)*
>35	55	10 *(18·2%)*	33	6 *(18·2%)*
All ages, crude rate	273	24 *(8·8%)*	139	23 *(16·5%)*
Mean paternal age at conception	*30·4 yr.*	. .	*30·2 yr.*	. .
Age-adjusted rate*	. .	. . *(8·8%)*	. .	. . *(15·8%)*

* Fetal mortality-rates for primary V.C. exposure group are direct age adjusted to the paternal age distribution of the pregnancies in the control group.

The table shows data for age-specific fetal mortality-rates before age adjustment, for both time periods (i.e., before and after the husband's exposure).

Before the husband's exposure, the crude fetal mortality-rates are 10·1% for the study group and 6·9% for the control group. However, after direct age adjustment the study-group rate became 6·1%. This is the result of a younger paternal age for pregnancies in the control group. For example, pregnancies to wives of men less than 30 years of age made up 93·7% (149/159) of the control-group pregnancies as compared to 72·3% (107/184) of the study-group pregnancies. Our paper indicated this difference in age between the groups for before exposure comparisons. Table I in that paper showed that the mean paternal ages were 23·0 years for the control group and 26·4 years for the study group.

As shown here in the table, subsequent to husband's exposure, the crude fetal mortality-rates were 8·8% and 16·5% for the control and study groups, respectively. With direct age adjustment the 16·5% was reduced to 15·8%. Age adjustment for the subsequent to exposure comparisons resulted in little change in the rates because the age distributions for pregnancies in both the study and control groups after exposure were similar. For example, pregnancies to wives of men younger than 30 years of age made up 48·0% (131/273) of the control-group pregnancies and 50·4% (70/139) of the study-group pregnancies.

We hope this explanation of the age-adjustment procedure is now clear. It is the fact that the two standard age distributions derive from the control group's populations of pregnancies, rather than of persons (whether fathers or not) that probably accounts for the numerical behaviour that Dr Paddle finds "misleading".

In the subsequent to husband's exposure comparisons, the significant difference in fetal mortality-rates was a result of pregnancy outcome associated with husbands younger than 30 years of age. This difference was significant at $P<0·001$ ($\chi^2=10·52$, D.F.=1). If vinyl chloride (V.C.) is indeed related to this observed difference, the excessive fetal mortality at these ages could, in theory, be a reflection of placing newly hired personnel, with little or no seniority, in exposure categories that had relatively worse environmental exposures.

In our paper of April 3 we cited eight references which have demonstrated that V.C. had elicited a positive response in microbial test systems and had been associated with significant excesses of chromosomal aberrations in lymphocytes of workers occupationally exposed to it. Three additional studies which also have demonstrated a positive mutagenic response to

v.c., have been drawn to our attention recently; in two of these studies, the microbial test system was used,[1 2] while in the third, *Tradescantia* was used.[3] Therefore, we do not agree with Dr Paddle's statement that this is an "isolated" question.

Division of Surveillance, Hazard Evaluations and Field Studies, National Institute for Occupational Safety and Health, Cincinnati, Ohio 45226, U.S.A. and Bureau of Epidemiology, Center for Disease Control and School of Public Health, University of North Carolina

PETER F. INFANTE
JOSEPH K. WAGONER
ANTHONY J. MCMICHAEL
RICHARD J. WAXWEILER
HENRY FALK

PLASMA-GLUCAGON AFTER PANCREATECTOMY

SIR,—Dr Barnes and Dr Bloom (Jan. 31, p. 129) reported no circulating immunoreactive glucagon (I.R.G.) in both the basal state and after arginine stimulation in five pancreatectomised patients. Dr Gerich and his colleagues (April 17, p. 855) have made similar observations in another patient. We have evaluated I.R.G. dynamics in a totally pancreatectomised patient, with results quite different from those cited above. Because of the heterogeneity of I.R.G. species measured by antiserum 30K, we assay before and after acetone extraction. The post-extraction assay measures predominantly I.R.G. of <9000 daltons (S-I.R.G.), and subtracting S-I.R.G. from total plasma-I.R.G. (unextracted) allows quantification of the larger molecular weight I.R.G. species (L-I.R.G.).

A 30-year-old male, member of a multiple endocrine adenoma type I family, underwent a total pancreatectomy, hemigastrectomy, and duodenectomy in 1967 for removal of an insulinoma. He has remained free of disease subsequently. Further evidence of total pancreatectomy was afforded by essentially unmeasurable basal levels of C peptide with failure to rise during an arginine infusion (by A. Rubenstein, University of Chicago). His basal, fasting concentrations of S-I.R.G. and L-I.R.G., before an arginine infusion, 24 h after receiving his standard insulin dose (21 units lente and 10 units semilente) were 35 pg/ml and 104 pg/ml, respectively. These values are within normal limits for our laboratory. The accompanying table depicts the plasma levels of small and large molecular weight I.R.G., glucose, and C peptide during the administration of arginine (500 mg/kg/30 min). The arginine infusion produced a small but definite rise in S-I.R.G. with no change in L-I.R.G. In addition, a 50 mg/dl increase in plasma-glucose concentration occurred concurrently with the increase in S-I.R.G.

Several factors may be involved in the difference between our observations and those of Dr Barnes and Dr Bloom. Unger et al., using antiserum 30K, failed to demonstrate I.R.G. in the plasma of pancreatectomised dogs;[4] subsequently several investigators[5–8] have observed circulating I.R.G. (30K) in pancreatectomised dogs (and other species) when they are deprived of insulin for several days, demonstrating the sensitivity of extrapancreatic alpha cells to inhibition by insulin. Because of ethical considerations achieving this degree of insulin deficiency may not be appropriate in man, but our patient may have been more insulin deficient than those previously reported. Although alpha cells indistinguishable from pancreatic alpha cells have been reported in the stomach of man,[9] earlier work by Muller et al.[10] failed to demonstrate a rise in I.R.G. (30K) with arginine infusion in two pancreatectomised patients. However, these patients did have significant plasma-I.R.G. levels in the basal state. Plasma contains several different molecular weight species that are measured as I.R.G. (30K).[11 12] Therefore, it is possible that the antiserum used by Dr Barnes and Dr Bloom does not react with all the I.R.G. plasma components measured in assays using antiserum 30K. In addition, the partial gastrectomy and duodenectomy that is usually done in conjunction with a total pancreatectomy in man may result in at least partial removal of the source of extrapancreatic glucagon and may vary in different patients depending upon the extent of the surgery.

GLUCOSE, I.R.G., AND C PEPTIDE CONCENTRATIONS DURING ARGININE INFUSION

Time (min)	Glucose (mg/dl)	S-I.R.G. (pg/ml)	L-I.R.G. (pg/ml)	C-peptide (ng/ml)
Control	224	35	104	0·7
10	238	57	103	..
20	242	74	101	..
25	..	..	..	0·7
30	253	91	99	0·7
35	..	..	..	0·7
45	265	77	98	..
60	272	68	92	..
90	274	51	99	..

While our patient is potentially unique in being a member of a family with multiple endocrine neoplasia, we feel that on the basis of his results we can only conclude that: (1) in this pancreatectomised man, I.R.G. (30K) of both large and small molecular weight(s) circulates in the basal state, and that at least the small-molecular-weight fraction shows a rise with arginine; (2) the increase in plasma-glucose that accompanied the S-I.R.G. rise suggest that this S-I.R.G. is biologically active; and (3) the existence of an extrapancreatic source of biologically active glucagon in man has not been excluded.

Department of Medicine, Diabetes Center, University of Washington, Seattle, Washington 98144, U.S.A.

JERRY P. PALMER
PHILLIP L. WERNER
JAMES W. BENSON
JOHN W. ENSINCK

SIR,—We read with interest the article by Dr Bloom and Dr Barnes (Jan. 31, p. 219) on the absence of pancreatic glucagon-like immunoreactivity (I.R.G.) in the plasma of pancreatectomised man. The data generated diametrically opposed views on the diabetogenic role of pancreatic glucagon by Dr Gerich and his colleagues on the one hand (April 17, p. 855) and Dr Donowitz and Dr Felig on the other (April 17, p. 855). We wish to add information which may help to resolve these contradictory views.

In contrast to the findings of Bloom and Barnes, we[13] found high levels of "pancreatic" I.R.G. in the plasma of a pancreatectomised patient, as did Muller et al.[14] in two other patients. Although 50% of the pancreatic I.R.G. could be accounted for by factors in plasma which interfere with the assay[15] the rest appeared immunometrically as pancreatic I.R.G. and presumably derived from an extrapancreatic source. In contrast to I.R.G. in porcine duodenal extracts,[16] which closely resembles true pancreatic I.R.G., the I.R.G. in pancreatectomised human plasma is dissimilar in physicochemical properties (gel electrophoresis), is not stimulated by arginine, insulin hypoglycæmia, or tolbutamide, or suppressed by glucose, and has no apparent role in blood-glucose regulation.[13] We have previously[17] referred to the various forms of gastrointestinal pancreatic I.R.G. found

1. Garro, A. J., Guttenplan, J. B., Milvy, P. *Mutation Res.* 1976, **38**, 81.
2. Andrews, A. W., Zawistowski, E. S., Valentine, C. R. *ibid.* (in the press).
3. Sparrow, A. Personal communication.
4. Unger, R. H., Ohneda, A., Aguilar-Parada, E., Eisentraut, A. *J. clin. Invest.* 1969, **48**, 810.
5. Vranic, M., Pek, S., Kawamori, R. *Diabetes*, 1974, **23**, 905.
6. Matsuyama, T., Foa, P. *Proc. Soc. exp. Biol. Med.* 1974, **147**, 97.
7. Mashiter, K., Harding, P., Chou, M., Mashiter, G., Stout, J., Diamond, D., Field. J. *Endocrinology*, 1975, **96**, 678.
8. Dobbs, R., Sakurai, H., Faloona, G., Valverde, I., Baetens, D., Orci, L., Unger, R. *Science*, 1975, **187**, 544.
9. Unger, R. *Lancet*, 1975, i, 1036.
10. Muller, W., Brennan, M., Tan, M., Aoki, T. *Diabetes*, 1974, **23**, 512.
11. Valverde, I., Dobbs, R., Unger, R. *Metabolism*, 1975, **24**, 1021.
12. Valverde, I., Villanueva, M., Lozano, I., Marco, J. *J. clin. Endocr. Metab.* 1974, **39**, 1090.
13. Botha, J. L., Vinik, A. I., Child, P., Jackson, W. P. U. Unpublished.
14. Muller, W. A., Brennan, M. F., Tan, M. H., Aoki, T. T. *Diabetes*, 1974, **23**, 512.
15. Weir, G. C., Tuiner, R. C., Martin, D. B. *Horm. met. Res.* 1973, **5**, 241.
16. Sasaki, H., Rubalcava, B., Baetens, D., Blasquez, E., Srikant, C. B., Orci, L., Unger, R. H. *J. clin. Invest.* 1975, **56**, 135.
17. Vinik, A. I., Jackson, W. P. U. *Lancet*, 1975, i, 694.