nervousness, or anaemia he runs a risk of being diagnosed as "lead poisoning." So it must always be remembered in such cases that epidemiologically acceptable evidence of a causal association between the symptoms and the level of lead absorption is not available.—I am, etc.,

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¹ Lane, R. E. *et al.*, *British Medical Journal*, 1968, 4, 501.

Yellow Fever Vaccination

SIR,—Much inconvenience and irritation is caused at this yellow fever vaccination centre to patients who have to be refused vaccination because they have been vaccinated against smallpox by their practitioners a few days before.

Burroughs Wellcome, who make the yellow fever vaccine, state: "Smallpox and yellow fever may be given simultaneously in an emergency but if smallpox vaccination is carried out first, and it 'takes,' 21 days must elapse before yellow fever vaccine may be given."

The Department of Health and Social Service gives similar advice in its "Notice to Travellers," except that it specifies "primary" vaccination rather than vaccination which has taken. All authorities agree that yellow fever vaccine should be given first, and it would greatly help if practitioners would advise their patients needing yellow fever vaccination to have it first and refrain from vaccinating them against smallpox until this has been done.—I am, etc.,

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Rhesus Isoimmunization and Twins

SIR,—We read with interest the paper by Dr. I. M. Ellis and others (7 March 1970, p. 609) on rhesus isoimmunization in association with multiple pregnancy, and would like to report our recent experience of such a case. Intrauterine transfusion of twins has been recorded by three other groups.¹⁻³ Some of the difficulties in identifying each sac, using radio-opaque media or various dyes, together with the difficulties in interpreting liquor analysis and attempting intrauterine transfusion have been described by these authors. To make accurate prediction for each child it is necessary to sample each sac separately.

Our patient was pregnant for the fourth time. She was aged 30, with blood group O rhesus negative, probable genotype cde/cde. The father was group A rhesus positive, probable genotype CDe/CDe.

In 1964 and 1966 she had had spontaneous vertex deliveries at home and there is no record of the presence of antibodies. In 1970 she had a spontaneous vertex delivery at term of a live infant. The infant was jaundiced at birth, but did not require exchange transfusion. Antibodies were recorded at 28 weeks' gestation—anti-D 1/2 enzyme, 1/2 I.A.G.T., and anti-C 1/4 enzyme. At term the readings were anti-D 1/32, 1/2 I.A.G.T., anti-C 1/8 enzyme.

In the present pregnancy a diagnosis of twins was made at her first visit in the 29th week and antibodies were found. The patient was admitted to hospital and serial amniocentesis performed (Table I). Routine check on antibody titre was kept and total oestriol levels on the urine estimated regularly (Table II).

TABLE II—Serial Oestriol Estimations on 24-hour Collection of Urine

Date	Gestational Age in Weeks	Total Oestrogens in mg/24 hours
29 November	33+	14
2 December	34	11
6 December	34+	11
9 December	35	12
13 December	35+	18

An elective lower uterine segment caesarean section was performed at the end of the 36th gestational week. Two premature, uniovular, male children, weighing 1.65 kg

and 1.6 kg were delivered. Immediate replacement transfusions were carried out, and a further four replacement transfusions for twin I and a further three replacement transfusions for twin II were required (Table III).

The position of the placenta, anterior and to the left (located by sonar) and the position of the sacs, one lying almost directly anteriorly to the other (located at caesarean section) precluded accurate prediction for each child and precluded also intrauterine transfusion, though it was indicated.—We are, etc.,

ANDREW AULD
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Glasgow

- ¹ Bowes, W. A., and Droegemueller, W., *California Medicine*, 1968, 108, 380.
² Crosby, W. M., and Gheen, D. L., *Obstetrics and Gynecology*, 1967, 29, 674.
³ Raphael, M. J., Gordon, H., and Schiff, D., *British Journal of Radiology*, 1967, 40, 520.

TABLE I—Amniocentesis

Date	Gestational Age in Weeks	Optical Density Difference at 450 mμ	Bilirubin Content in mg/100m			Position on Liley's Prediction Graph
			Total	Direct	Indirect	
18 November	32	0.100	0.210	0.100	0.110	Upper Zone 2
25 November	33	0.090	0.200	0.050	0.150	Upper Zone 2
1 December	34	0.085	0.143	0.061	0.082	Upper Zone 2
16 December	36 (at caesarean section)	Sac 1 0.185 Sac 2 0.150	0.386 0.296	0.230 0.190	0.156 0.106	Lower Zone 3 Lower Zone 3

TABLE III

Date	Serum Bilirubin in mg/100 ml											
	Twin 1						Twin 2					
	Before Transfusion			After Transfusion			Before Transfusion			After Transfusion		
	T.	D.	I.	T.	D.	I.	T.	D.	I.	T.	D.	I.
16.12.71	7.6	1.1	6.5				5.9	0.8	5.1			
(Cord blood)												
16.12.71	9.2	1.0	9.2	6	1.2	4.8	10.4	1.2	9.2	8.0	1.4	6.6
17.12.71												
84 Hours	16.0	1.4	14.6				12.0	1.2	10.8			
14 Hours	17.0	1.3	15.7	9.4	1.6	7.8	14.8	1.5	13.3			
							19.2	1.6	17.6			
24 Hours	12.6	1.3	11.3				20.8	2.1	18.7	12.6	1.6	11.0
30 Hours	17.6	0.6	17.0				21.9	1.6	20.3			
18.12.71	20.8	0.8	20.0				23.2	1.2	22.0	14.4	1.0	13.4
"	22.2	0.6	21.6	7.2	1.1	6.1	20.8	1.2	19.6			
"	22.4	1.2	21.2									
"	27.6	1.0	26.6	17.2	1.2	16.0						
19.12.71	14.4	1.3	13.1				17.2	2.2	15.0	10.8	1.4	9.4
"				10.4	1.0	9.4						
"	18.4	1.4	17.0				10.8	1.1	9.7			
"	14.0	2.2	11.8				14.4	1.8	12.6			
20.12.71	11.8	0.6	11.2				9.0	0.8	8.2			
17. 1.72												

Date	Haemoglobin (mg/100 ml), P.C.V., and M.C.H.C.											
	Twin 1						Twin 2					
	Before Transfusion			After Transfusion			Before Transfusion			After Transfusion		
	Hb	P.C.V.	M.C.H.C.	Hb	P.C.V.	M.C.H.C.	Hb	P.C.V.	M.C.H.C.	Hb	P.C.V.	M.C.H.C.
16.12.71	6.8	20	34				7.1	20	38			
(Cord blood)												
16.12.71	9.0	27	33	11.8	35	34						
17.12.71												
84 Hours	10.6	34	31	17.2	50	34	9.9	30	33	13.4	41	33
18.12.71	13.8	42	33				14.8	46	32	19.8	60	32
19.12.71	13.7	42	33	20.0	60	33	12.6	38	33	16.6	50	33
17. 1.72	7.9			9.6			8.4			9.2		

T = Total
D = Direct
I = Indirect

Hb = Haemoglobin
P.C.V. = Packed cell volume
M.C.H.C. = Mean corpuscular haemoglobin concentration

Treatment of Early Breast Cancer

SIR,—We must apologize for requesting the courtesy of your columns once more to discuss the paper on the treatment of early breast cancer by Sir Hedley Atkins and others (20 May, p. 423) and the accompanying leading article (p. 417). But it appears from the letter by Sir Hedley (24 June, p. 765) that the criticisms in our letter (17

June p. 423) have been incompletely understood. Sir Hedley accuses us of misreading the description of his life-table analyses. The original article merely states that life-table analyses were carried out, and displays graphs to show the outcomes of these analyses. As no details of the analyses are given it is difficult to see how we could have misread them. From the criteria suggested by Lionel and Herxheimer¹ for assessing the reports of therapeutic trials we must conclude that the report of the trial by Sir Hedley and his colleagues is unsatisfactory, as the statistical tests are not described nor are important results of the analyses given.

Sir Hedley Atkins also glosses over our criticism of the small numbers on which he and his colleagues based their conclusions. It is well known that the effective sample size in a life-table analysis is greater than the number of patients actually followed up for the maximum length of time,² but obviously cannot be greater than the total number of patients studied. We clearly pointed out how unsatisfactory the numbers studied by Sir Hedley and colleagues are even if all the 370 patients had been followed up for the full 10 years.

Now, Sir Hedley very correctly points out that it may be "mischievous" to delay analysis beyond the time when a valid conclusion can be made. Unfortunately, he does not explain how the decision to analyse was made. Was it decided to analyse at the ten-year point or when 370 patients were admitted to the trial, and when was this decision made? Mention is made of monitoring the deaths and recurrences in the trial by means of pegs on extensible threads, but the dangers of an informal sequential analysis as a form of "data snooping" should be well known to Sir Hedley and his colleagues. Surely, a valid sequential analysis, by the sign method³ would have provided a statistical basis for the decision to continue or stop the trial.

Liquor Bilirubin Levels in Rhesus Haemolytic Disease

SIR,—In the interesting paper by Dr. B. R. Pridmore and others (15 July, p. 136) the authors state that "samples contaminated with blood should be discarded and not sent for analysis." However, in our experience valuable information may be obtained from

Finally, Sir Hedley seems to have missed both the points in the penultimate paragraph of our earlier letter. Firstly, we pointed out that both the operation and the radiotherapy differed in the two treatment regimens, producing confounding of main effects in the trial. Any difference found could be due to the difference in surgery, or in radiotherapy, or to the interaction of the surgery and radiotherapy. The trial carried out by Sir Hedley and his colleagues cannot distinguish among these alternatives, and yet these authors attribute the differences seen to the difference in surgery. The second point we made in this paragraph concerned the immunological effects of radiotherapy. The fact that the radiotherapy may have been sub-optimal for tumour destruction does not, as Sir Hedley mistakenly implies, mean that the radiation will have no effect on the immune response. Indeed, a suboptimal dose of radiation may well be the most harmful in that it may damage the immune response more than it damages the tumour.

Now, it would be churlish to suggest that the trial by Sir Hedley and colleagues is of no value, but we remain fully convinced that the accolade awarded to this paper in your leading article was, to say the least, undeserved. The unfortunate effects of this high praise on practising surgeons who choose not to read the full trial report can hardly be overemphasized, and it is hoped that a retrogressive drift back to radical mastectomy will not take place.—We are, etc.,

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¹ Lionel, N. D. W., and Herxheimer, A., *British Medical Journal*, 1970, 3, 637.

² Cutler, S. J., and Ederer, F., *Journal of Chronic Diseases*, 1958, 8, 699.

³ Armitage, P., *Sequential Medical Trials*. Oxford, Blackwell, 1960.

The details of two pregnancies in which this examination has proved valuable are given in the Table. At delivery neither infant was affected by haemolytic disease of the newborn. We consider therefore that it is very important to study some blood-stained

Age	Parity	Maturity	Obstetric History	Antibody Titre		D-group of Fetus		Probable Genotype Father
				Sal.	Alb.	Amniocentesis	Post Delivery	
29	5+2	36 weeks	Last baby exchange transfusion and neonatal death	2	32	Neg.	Neg.	R ₁ /r(CDe/cde)
30	1	36 weeks	First baby unaffected	1	1	Neg.	Neg.	R ₁ /r(CDe/cde)

the examination of red cells contaminating amniotic fluid. Where the husband is heterozygous for the D-antigen it is important to carry out the Kleihauer-Betke method of staining on these red cells. If significant numbers of fetal cells are present these should then be grouped. The demonstration of a D-negative fetus may prevent further unnecessary investigations, including a repeat of the amniocentesis.

liquors, in particular when the father is heterozygous for the D-antigen.—We are, etc.,

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Was it a Drug?

SIR,—I have for some years now and with scant success been trying to follow Ministerial reasoning as expressed by his appointed referees in cases of "Was it a drug?" as reported in the *B.M.J.* The latest of these concerned Allergilac prescribed for an infant apparently sensitive to ordinary cow's milk, but not to this preparation (*Supplement*, 29 July, p. 108).

I can remember the days when the general position in such matters was fairly clear. If, outside a hospital, a patient's condition required some special diet or food, however vital, this ranked with warmth, clothing, and housing as something that could not be prescribed on an E.C.10. Then along came *Proplis*, whose notions had a profound effect and apparently still linger on in the minds of the referees. This publication therefore needs close retrospective examination.

It was edited by a distinguished committee, the Joint Standing Committee on the Classification of Proprietary Preparations, and, without any logic that I or anyone I have spoken to can expound, it decided to suggest an increasing number of exceptions that might be made in the case of substances that otherwise would be considered foods. The only basis I could postulate for these exceptions lay in whether the substance was supplied from the kitchens or the dispensary when ordered in hospital. *Proplis* made the extraordinary recommendation that Casilan might be considered a drug in cases of biochemically proved hypoproteinaemia. One would have thought that the learned joint standing committee would have been the first to recognize that such a requirement was nonsense. Hypoproteinaemia, broadly speaking, occurs in two conditions. Firstly, when there is excessive loss, as in nephrotic syndrome or carcinoma, and, secondly, when there is deficient manufacture, as in liver disease. It does not occur in ordinary starvation. Whatever the cause of hypoproteinaemia no amount of protein feeding by mouth can raise it unless the cause can be remedied. It follows that any suggestion that Casilan is given only to raise the blood proteins and is not really a food is absurd.

Proplis and, I had hoped, this kind of reasoning has now very rightly been withdrawn. Local medical committees are once more required to make a decision in each case on what seems to them logical and reasonable grounds—above all, one hopes, on principles that are consistent and will give the prescribing practitioner an idea of what to expect. This particular case of Allergilac was only briefly reported by you. Neither the reasoning of the local medical committee nor of the referees was given. Since, however, the local medical committee decided it was a food one must assume that it decided that its effect was to provide nutrition, and even if it was a specially modified and vitally necessary food it was still a food.

I now challenge the referees to state their lines of reasoning. If, as I expect, they fail to do so then we have the right to ask whether they intend to continue making invidious distinctions, as did *Proplis*, or whether they will allow salt-free butter and bread for patients on a low salt diet, fat-free or fat-substituted milk powder for those on low cholesterol diets, and starch-free and sugar-free foods for diabetics.