tinue to use cephaloridine as a local application in the prophylaxis of potentially contaminated wounds. We are indebted to Glaxo Research Ltd. for the supply of cephaloridine (Ceporin) and Aspro-Nicholas Ltd. for the gentamicin (Genticin).—We are, etc.,

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Referees and Rejects

SIR,—Dr. Samuel Johnson was only once worsted in debate, and even then by a woman. "Money," he declaimed, "there is no happiness that money lets in." "Very true," replied Mrs. Thrale, "but how much unhappiness does it keep out?" Mutatis mutandis, Mrs. Thrale—a very sensible person—would have said the same about medical referees.

I am greatly surprised to learn that nowadays authors argue with referees. My most earth-shaking papers were always returned, but no editor ever gave his reasons. In fact the last one you sent back to me did not even report your personal regret. In my declining years as a referee it never for an instant struck me that I should explain myself. In both cases Martial's all-sufficient reason was self-evident—"I do not love thee, Dr. Fell. . . ." Remember the Lord Chief Justice's advice to the young judge; "Give your verdict; it will probably be correct. Never give your reasons; they will usually be wrong."

Is it possible that we have been watching too much professional soccer, where referee baiting is half the fun? For your own sake, dear Editor, watch your step. All too soon we may see you carrying your leader writers shoulder high in a lap of honour round Tavistock Square and successful authors will be kissed on at least two cheeks.

Virgin authors should not be put off. There is no paper so brilliant that it will never be accepted by anyone; and none so poor that some good Samaritan will not give it room. Indeed some journals never publish anything else. And remember they all sell reprints, and the least-regarded journals of uncontrolled experiments and plagiarized clinical reports have usually the glossiest covers.—I am, etc.,

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Epidemic Neuromyasthenia

SIR,—We would like to thank Drs. G. G. Wallis and F. S. Perry (23 March, pp. 574 and 575) and Dr. R. A. Thompson (6 April, p. 60) for their interest in our paper on epidemic neuromyasthenia (23 February, p. 301).

In answer to Dr. Wallis the considerations which forced us to limit investigations, by the same token prevented us from involving psychiatrists in the evaluation of these

patients. However, we did not feel there was sufficient psychiatric symptomatology to justify psychiatric referral. Of those affected, 50% had been nursing for less than 18 months. Morale was good and there was no "belle indifférence." We feel that disturbed consciousness is not a necessary feature of infective illness. Imipramine and amitriptyline were used in doses of up to 150 mg/day for up to four weeks.

Dr. Perry draws attention to the fact that the hospital patients were not affected and seeks an explanation. We felt that symptomatic illness may be age-related as the hospital patients were children. Since there are reports of children affected^{1,2} Parish³ suggested that the limited physical activity of hospital patients may protect them. We agree that nurses were predominantly involved, possibly due to their close proximity in the nurses' home. We also agree that we did not find an infective agent, but there was suggestive indirect evidence of an infective process. Toxic agents have been sought unsuccessfully in previous epidemics.^{1,2,4,5} In fact one of us (A.J.S.) previously investigated a similar outbreak⁶ for possible toxins with negative results. We felt that though this was not a good reason for not looking again, in our outbreak the evidence for a poison was slim and we were endeavouring to limit investigations.

We agree with Dr. Thompson that we overstated the relationship between anti-complementary activity and immune complexes in serum. We would add that sera from our patients were not bacterially contaminated, were tested within days or weeks of collection, and were consistently anti-complementary with higher titres in the acute stage of the illness.

One purpose of our paper, having taken investigations to a certain point, was the hope that others may have a platform from which to embark on further attempts to discover the cause of this odd disease.—We are, etc.,

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- 1 Sigurdsson, B., et al., *American Journal of Hygiene*, 1950, 52, 222.
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Primary Responses to Transplantation Antigens

SIR,—The techniques of unidirectional mixed lymphocyte culture (M.L.C.) and cell mediated lympholysis (C.M.L.) have recently allowed the in-vitro study of the induction and effector phases of primary responses to transplantation antigens in man. In reciprocal M.L.C. the cells of mothers and newborns had given poor proliferative responses.¹

We studied 13 families and unrelated controls using lymphoid cells (adult and cord blood) in the M.L.C. and C.M.L. technique

previously described.² Results³ showed again¹ that the newborns' cells underwent more cellular proliferation than controls when stimulated by the unrelated cells ($110.7 \pm SE 16.9$ v $89.6 \pm 15.6 \times 10^3$ c.p.m. ³H-thymidine incorporation). However, in the same cultures fewer cytotoxic lymphocytes were generated than in the control cultures, as judged by the percentages of ⁵¹Cr-release in target specific C.M.L. ($28.4 \pm SE 5.3\%$ v $39.4 \pm 6.0\%$). This suggests that at least two different subsets of lymphoid cells respond to an allogeneic stimulus by cellular proliferation with and without the development of cytotoxicity. The proliferative non-cytotoxic subset would make a higher proportion of the newborns' cells than of the adults' cells, thus suggesting an earlier function during ontogeny and phylogeny. The newborns responded to their mothers by low cellular proliferation ($48.5 \pm 13.4 \times 10^3$ c.p.m.; newborns v fathers $72.3 \pm 14.1 \times 10^3$ c.p.m.) and extremely low cytotoxicity ($9.8 \pm 3.0\%$; newborns v fathers $20.6 \pm 5.9\%$). These M.L.C. were across one major histocompatibility difference only).

The mothers were either primiparae or secundiparae, which did not seem to affect the results. The mothers' cells at delivery had practically a normal ability to develop cytotoxicity towards allogeneic cells (of unrelated $34.6 \pm 9.1\%$; of father $36.2 \pm 7.8\%$) and also developed cytotoxic lymphocytes towards cells of the newborns ($23.5 \pm 9.3\%$, as compared to $31.4 \pm 9.3\%$ in the fathers v newborns' reactions. These C.M.L. tests were across one major histocompatibility difference only). Low cellular proliferative and high cytotoxic responses were particularly found in the mothers v newborns reactions. Further study is needed to see whether this pattern could be due to in-vivo acquired immunity to paternal alloantigens. The overall results of C.M.L. alone did not reveal transplantation immunity in the mothers at delivery. On the other hand they clearly indicated that tolerance is not the mechanism which explains the successful allograft of pregnancy.

This work was supported by grant No. 3.695.71 of the Swiss Foundation for Scientific Research. G.D.B. is currently at the Cellular and Tumor Immunology Section, Laboratory of Cell Biology, National Cancer Institute, Bethesda, U.S.A.—We are, etc.,

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- 1 Ceppellini, R., et al., *Transplantation Proceedings*, 1971, 3, 58.
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Sudden Death in Infancy

SIR,—We would support the view expressed by Dr. R. H. Anderson and others (20 April, p. 135) that further study is needed of the conducting tissues of the heart in the sudden infant death syndrome. There are, however, several aspects of their paper which we feel require comment.

They compared 15 "cot death" cases with 15 "controls." The ages of the cot death patients ranged from 11 days to 2 years, though most workers in this field agree that the sudden infant death syndrome probably does not occur before 4 weeks of age and is rare after 9 months.¹ Seven of the 15 control cases died within four days of birth, and since they may have been subject to postnatal respiratory problems they cannot be considered comparable with a series of cot deaths. It was stressed that no evidence of degeneration was found in the atrio-ventricular bundle. However, remoulding of the junction between the atrioventricular node and the bundle of His where it penetrates the central fibrous body, an area we term the isthmus, does occur.^{2,3} Furthermore, such remoulding is not present at birth but is apparent within 2-3 weeks.⁴ Perhaps this reshaping of the atrioventricular conducting tissue is not apparent by the method of sectioning the heart described by Dr. Anderson and his colleagues, but it is easily seen if the complete heart is processed intact and serially sectioned by the technique of Ferris and MacLennan.⁵ The atrio-ventricular node receives its blood supply from the right coronary artery or the circumflex branch of the left and the His bundle from the anterior descending branch of the left coronary artery. It is interesting to note that this remoulding occurs at the junction of these separate blood supplies.

Haemorrhages were reported in both the cot death and control series. However, no cause of death was given in the control series, and since we contend that petechial haemorrhages in the heart occur in death associated with terminal hypoxia and a rapid change in intrathoracic tension it is important that any terminal hypoxic episode should be recorded. There is much evidence⁶ in favour of an acute respiratory death associated with virus infection in some cot deaths. In a partly completed study of 38 cot deaths and 30 control cases we have found petechial haemorrhages in the hearts of 18 of the cot death cases and in only two of the controls (see table). One of the two control cases with cardiac haemorrhage died from massive inhalation of vomit and the other from acute myocarditis. In a series reported by Ferris⁷ haemorrhages were found within the atrial wall, and while the histological identification of internodal tracts is disputed there is considerable physiological evidence for the existence of such tracts.⁸ Haemorrhages close to these tracts may be an important factor in the failure to survive in cases of what might otherwise be acute recoverable hypoxia.

In one of the cases illustrated by Dr. Anderson and others (their fig. 2) there was a history of cardiac arrest followed by cardiac massage. The illustration of the atrioventricular node shows abnormal vascularity and an unusual pattern of nodal tissue similar to that seen in hypertrophic

cardiomyopathy.⁹ In this case the nodal haemorrhage may be due either to hypoxia associated with cardiac arrest or to direct trauma. We think that the presence of cardiac petechial haemorrhages in the sudden infant death syndrome supports the view that these infants die during an acute hypoxic episode and that haemorrhages in the conducting tissue structures probably prevent survival.—We are, etc.,

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Skin Reactions to Practolol

SIR,—I have read with interest the letter from Drs. R. H. Felix and F. A. Ive (11 May, p. 333) since I am at present preparing for publication the details of a group of patients who have presented with skin reactions and eye signs following treatment with practolol.

The skin eruptions have tended to be of psoriasiform type and the eye symptoms and signs have either developed with the skin eruption or have followed it. The usual finding has been a shrinkage of the conjunctiva with some xerosis. The shrinkage has atypical features and is unlike the conjunctival scarring seen in association with either erythema multiforme or benign mucous membrane pemphigoid. It seems probable that patients on long-term medication with practolol who develop skin eruptions should also have a careful ophthalmic examination.—I am, etc.,

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Vitamin A, Pregnancy, and Oral Contraceptives

SIR,—Mrs. Jennifer Wild and her colleagues (12 January, p. 57) have joined Briggs *et al.*¹ in confirming our original findings that the serum vitamin A levels are raised in women taking oral contraceptives.^{2,3} Finding an "accurate" method for vitamin A estimation is a recurrent problem in vitamin A research,⁴ and it is therefore important that these studies, using different techniques

(fluorometric, ultraviolet irradiation, and colorimetric), revealed similar trends. Some of the methods and conclusions of Mrs. Wild and her colleagues could, however, be considered open to criticism.

In Great Britain the present pattern of serum vitamin A levels in pregnancy is different from that observed 30 years ago in the United States.⁵⁻⁷ During normal pregnancy the maternal serum vitamin A concentration decreases until about the end of the first 12 weeks, then increases gradually until term (pattern consistent between individuals).⁷ Because of this changing pattern Mrs. Wild and her colleagues' method of comparing their first trimester values with the second and third trimester values of studies conducted many years ago does not seem appropriate.

It may also be misleading to draw conclusions from studies of pregnant patients when they are grouped according to the time interval between stopping oral contraception and conception, unless the stage of pregnancy is stated. With these methods it would be difficult to establish whether or not the serum vitamin A is raised in early pregnancy following oral contraception, as our figures have shown that women in their fourth month of pregnancy have levels similar to those of women on oral contraceptives.^{2,7} In the non-pregnant state at least three months is required for the serum vitamin A level to revert to normal after oral contraception.³ By investigating patients four months after such therapy Mrs. Wild and her colleagues probably missed this stage, which may explain why their index and control groups showed no differences. According to my observations, if pregnancy occurs during this time the vitamin A concentration is higher than average in both maternal and fetal tissues.⁸

The authors' study gives no reassurance regarding the teratological significance of the raised vitamin A levels since their observations were made on women past the crucial early stages of pregnancy. Their data concerning the outcome of pregnancies may also not be altogether reassuring. While the first group's figures (women becoming pregnant not more than 20 weeks after oral contraception) corresponds to the normal expectation, the second group (women with blood vitamin A levels above 94 µg/100 ml) could show differences. Excluding cases with unknown outcome of pregnancy and counting only in the second group one baby which appeared in both groups, the proportions of all abnormal pregnancies would be estimated as 6.7% and 14.8% respectively in the first and second groups, and if abortions are excluded the figures are 2.4% and 7.8%. The relatively high incidence of urogenital anomalies in male infants (2.4% and 11.8% in the two groups) deserves attention because an influence of maternal progestogen therapy (from oral contraceptives) cannot be ruled out. Since the sex distribution of the infants was not given I was obliged to base the calculations above on a rough estimate of 50% for each of the sexes.

Vitamin A and synthetic sex hormones are teratogens in experimental animals and the teratological safety of these substances has never been proved in humans. It is well known that drugs can on occasion be powerful teratogens without giving symptoms of

	Total Cases	Distribution of Petechial Haemorrhages				
		Intrathoracic	Cardiac			
			Atrial Wall	A-V Node	Isthmus	His Bundle
Cot deaths (8 wks-9 months)	38	35	15	—	1	3
Controls (3 days-30 months)	30	3	—	—	—	2