Further investigation of our patient revealed information which, in our opinion, could be very importnat.

1. Our patient's parents were first-cousins.

2. The patient's mother had 13 pregnancies. When the fetus was female, the pregnancy was normal in every case. But when the fetus was male, it usually died in the 2nd–3rd month, and the course of pregnancy was full of complications. Only one male was delivered at full term, after a difficult pregnancy; this child died, however, on the day of circumcision. The cause of death was hæmorrhage from the wound—a most rare complication.

3. We examined, in vitro and in vivo, the ethambutol-binding capacity in the blood of the mother and one of the sisters of our patient, and here, too, we discovered that the drug was not bound in the blood.

We cannot explain the strange pharmacological behaviour of ethambutol in our patient, her family, and the other patients. For some reason, perhaps genetic, the drug does not bind with a blood component, and is therefore quickly excreted in the urine, so that therapeutic levels are not achieved.

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HEPATITIS-ASSOCIATED ANTIGEN IN CHRONIC LIVER DISEASE

SIR,—Professor Sherlock and her colleagues [1] suggest that acute viral hepatitis with positive hepatitis-associated (H.A.) (Australia) antigen may be followed by chronic liver disease and cirrhosis, and that this can proceed to liver-cell cancer. Such an unfavourable course is supported by our findings on H.A. antigen in chronic liver disease in Greece.[2,3] Thus, in earlier work, H.A. antigen was detected in 6 (40%) of 15 patients with active chronic hepatitis, 5 (21%) of 24 with active cryptogenic cirrhosis, and 4 (31%) of 13 with primary liver-cell carcinoma superimposed on active cirrhosis.[2] These initial observations were largely confirmed in a recent investigation,[3] the overall findings of which are apparently in complete agreement with those reported by Professor Sherlock. In this investigation, H.A. antigen was detected by immunodiffusion [4] in a total of 23 Greek patients with chronic liver disease: 1 had persistent hepatitis, 8 had chronic aggressive hepatitis, 8 had active cirrhosis, and 6 had primary liver-cell carcinoma. 22 of these patients were male, and their mean age was 55 years. Again in agreement with Professor Sherlock's observations,[1,5] chronic aggressive hepatitis was seen in the absence of the classic clinical syndrome of active chronic (lupoid) hepatitis. Furthermore, in most of these patients the clinical and biochemical changes of chronic liver disease and of activity were either mild or even absent.

The above observations support the view that chronic aggressive hepatitis of viral ætiology may proceed to cirrhosis and possibly to liver-cell carcinoma, and may do so even in the absence of jaundice or the classic syndrome of active chronic hepatitis. The high incidence of H.A. antigen in our series,[2,3] and the prevalence of Greek patients in the H.A.-antigen-positive series at the Royal Free Hospital, further indicate that chronic liver disease of viral ætiology may be much commoner in Greece than in some other countries.[5–8] Whether this is related to geographical variations in the incidence of viral hepatitis and H.A. antigen or to ethnic variations in individual susceptibility remains to be determined.

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CHILDREN OF MOTHERS WHO TOOK L.S.D. IN PREGNANCY

SIR,—Whether lysergic-acid diethylamide (L.S.D.) is a teratogen and whether it produces persisting chromosomal damage during prenatal life are questions which have received considerable attention lately.[1–5] To help answer them, it is important to accumulate prospective data on offspring of mothers known to have taken L.S.D. during pregnancy. We wish to report the results of a study of such a group of infants.

CHROMOSOME RESULTS IN BABIES WITH PRENATAL L.S.D. EXPOSURE VERSUS CONTROLS

Maternal L.S.D. history			Percentage of cells having: major chromosomal abnormality including isochromatid breaks		questionable chromosomal abnormality—chromatid gaps	
Subject	Timing of L.S.D. dose (weeks' gestation)	No of doses	Subject	Control	Subject	Control
1	2	1	0	2*	0	0
2	2–21	7?	0	0	2	0
3	2–38	15?	0	0	0	0
4	3?–32	30?	0	0	0	0
5	3–4	2	0	0	6	0
6	3–8	3	0	0	0	0
7	4–32	12?	0	0	4	0
8	8	1	0	0	0	0
9	Unknown	Unknown	0	0	0	0
10	Unknown	Unknown	4†	0	2	0

* Ring chromosome (1 cell). † Tetraploidy (2 cells).

During a 12-month period, 10 pregnant women were ascertained as having ingested L.S.D. in amounts sufficient to produce hallucinatory phenomena. These women were subsequently delivered of 10 living children, all girls. Each child was examined by the first author within 48 hours of birth, and no major or minor congenital anomaly was discovered in any baby. 3 were premature as judged by weight, physical features, and estimated gestational timing of 32, 35, and 36 weeks.

Blood-specimens were obtained from each subject baby and from a control baby in the same nursery, matched for sex and approximate birth-weight. Leucocytes were cultured for 72 hours, and prepared for chromosome study by standard methods, and 50 metaphase spreads were examined for each subject and each control. The chromosome preparations were examined "blind" and checked by a second observer. The accompanying table shows the results of this study.

We detected neither evidence of teratogenic effect nor chromosomal damage which we would interpret as meaningful in any of these 10 babies considered to have been

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exposed to L.S.D. in utero. It is not possible to determine from this limited study whether the 3 instances of prematurity were in any way related to L.S.D. Actually, the most unusual feature of this series was that all 10 children were girls.

Obviously, further prospective studies are needed before a rational judgment can be made concerning the dangers of L.S.D. to the early developing human being.

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DOCTORS' PAY

SIR,—The Council of the B.M.A. recommended acceptance of the ninth Review Body report under protest.[1] This policy was endorsed by the Special Representative Meeting held in June, 1968.[2] I would remind Dr. Connor [3] that the B.M.A. subsequently negotiated a substantial pay increase for medical assistants.

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ROSETTE TESTS IN AUTOIMMUNE HÆMOLYTIC ANÆMIAS

SIR,—The paper by Dr. Elson and Dr. Bradley (April 18, p. 798) prompts me to report our own findings in patients with autoimmune hæmolytic anæmia.

The immunocytoadherence technique was performed as described by Biozzi et al.,[4] modified by Bach and Antoine.[5] Serial studies were carried out: 5 patients had Coombs-positive hæmolytic anæmia; and there were 33 controls of whom 12 were healthy blood-donors or members of our medical staff and 21 were having hospital treatment for blood diseases without hæmolysis. We determined the number of rosette-forming cells with sheep red blood-cells and with autologous red blood-cells. The number of rosette-forming cells present in 1000 mononucleate cells was counted.

RESULTS OF ROSETTE TESTS IN FIVE PATIENTS WITH COOMBS-POSITIVE HÆMOLYTIC ANÆMIAS

Patient	Date of test	Treatment	Sheep-red-blood-cell rosettes per 1000 mononuclears	Autologous-red-blood-cell rosettes per 1000 mononuclears
1	Jan. 7, 1970	Azathioprine	0	2
	Jan. 14, 1970		24	0
	Feb. 24, 1970		60	22
	March 6, 1970		65	20
2	Dec. 16, 1969	Prednisolone	5	4
	March 12, 1970		0	4
3	Jan. 19, 1970	..	16	20
	Jan. 21, 1970		20	2
4	Jan. 23, 1970	Prednisolone	24	3
	Jan. 29, 1970		30	6
5	Feb. 19, 1970	..	37	4

Sheep-red-blood-cell rosettes were found in all controls and patients; the average was 38 ± 11 rosette-forming cells per 1000 mononucleate cells. Among the controls, autologous-red-blood-cell rosettes were never found (no background). Among the 5 patients with Coombs-positive hæmolytic anæmias, rosette-forming cells were invariably present (see accompanying table).

Our preliminary results with the rosette technique correlate well with the Coombs technique in autoimmune hæmolytic anæmias. The number of rosette-forming cells varies from patient to patient, and in individual patients. In one patient, one out of four tests was negative. The test remains positive during treatment (like the Coombs test) despite clinical evidence of improvement in hæmolysis.

Further experiments on the rosette technique to determine the type of immunoglobulin involved in the immune reaction and its specificity are in progress.

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UNIMPAIRED MUCOCILIARY CLEARANCE IN THE LUNG OF A CENTENARIAN SMOKER

SIR,—The ciliary mechanism appeared early in evolution, is morphologically closely similar in molluscs and humans, and some believe its absence is incompatible with life. We assess mucociliary efficiency by inhalation, under standard conditions,[1] of monodisperse 5μ particles labelled with a small quantity of a short-lived isotope [2] (^{99m}Tc, 6-hour half-life, γ radiation only). Their removal is monitored by a scintillation counter placed centrally over the chest. (This procedure has been approved by the Medical Research Council's isotope panel, the ethical subcommittee of this school, and the Atomic Energy Research Establishment, Harwell.[3])

In excised mucous membrane, exposure to small concentrations of many noxious substances, or physical change such as drying, will slow or stop the cilia. In the intact human being however, they are much more hardy; we have found no measurable effect after inhalation of 10 vital-capacity breaths containing up to 80 p.p.m. of sulphur dioxide, and no permanent impairment as a result of cigarette smoking.[4]

The accompanying figure shows the clearance curve in a centenarian (born Feb. 27, 1870). Also shown for comparison are the mean curves of groups of 10 male cigarette smokers and 6 male non-smokers. The standard deviation (S.D.) of the mean for the smoking group is shown. The S.D. for the non-smokers was similar. The mean ages and ranges of the smokers and non-smokers were 69·7 (43–87) and 71·8 (48–92). None of the 17 subjects showed functional evidence of restrictive or obstructive

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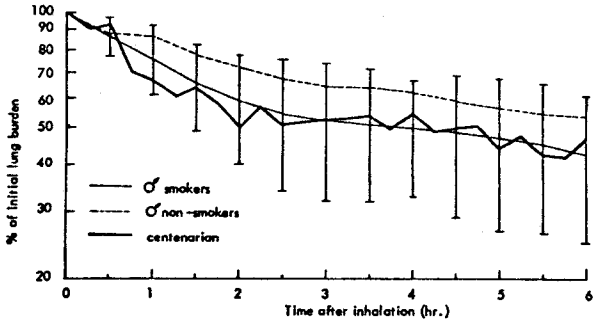

Mucociliary clearances in a centenarian smoker, 10 male smokers (mean and S.D.) and 6 male non-smokers (mean).