of E.B. virus titres 4-fold or more and the development of positive heterophil reactions were observed in all patients following the infusion of lymphoid cell lines.

All available protective procedures must be used in laboratories using human cell cultures, but the use of laminar-flow hoods without a method of sterilising the exhaust air stream is not a major safety improvement in my opinion. Methods for the restriction of viruses to sterilisable vessels or working chambers are probably a more practical and attainable goal, albeit not satisfactory at the present time. It is imperative to perform complete physical, biochemical, and hæmatological examinations on all employees in cell and virus laboratories on a regular basis, and to store serum samples from new employees for future reference.

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TETRAPLOIDY IN AMNIOTIC-FLUID CELLS

SIR,—Dr. Kohn and Dr. Robinson (Oct. 10, p. 778) raise the question of the significance of tetraploidy in cultured amniotic-fluid cells. They found tetraploidy in the cultured amniotic-fluid cells of three fetuses, one of which was aborted and subsequently shown to have a normal karyotype.

About a year ago we first observed tetraploidy in our amniotic-fluid-cell cultures. In a series of twenty consecutive cases for clinical diagnosis we have found variable tetraploidy (0–43%) in cultured amniotic-fluid cells obtained through amniocentesis at 14–16 weeks' gestation. So far, ten of the twenty cases have been delivered and are phenotypically normal infants. No clear association has emerged in this group between the tetraploidy observed and previous ingestion of oral contraceptives.

Observations made on the basis of sex-chromatin studies and cellular D.N.A. determinations have indicated that tetraploid cells occur naturally in the human amnion.[1] Schlegel et al.,[2] studying structurally normal aborted amnions, also found tetraploidy in 10% of the total cells counted. While the origin of the cells becoming tetraploid may well be amnion, the reason for the wide variation in the percentage of tetraploidy remains unclear.

Our findings will be reported in full elsewhere. At present, however, it appears that the occurrence of tetraploidy even in most metaphases in amniotic-fluid-cell cultures is consistent with the birth of a child with a normal karyotype.

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ANTICONVULSANT DRUGS AND CHROMOSOMES

SIR,—The letter from Dr. Márquez-Monter and his colleagues (Aug. 22, p. 426) prompts me to report data obtained in a study of anticonvulsant drugs and chromosome damage in vitro.

Repeated cultures of leucocytes from a mentally retarded boy revealed an unusually high frequency of chromosome and chromatid breaks and gaps (36·2% of the cells).[3] At that time our patient had received 500 mg. ethotoin ('Peganone', Abbott) daily for 8 months. The preponderance of the chromosome anomalies (40% of chromosome, 68·4% of chromatid) were in chromosome 3. This is similar to the pattern found by Ayraud et al.[4] in a girl who had been exposed to an anticonvulsant agent during intrauterine life. A similar aberration pattern was found in the mother. The in-vitro effect of ethotoin on chromosomes was therefore investigated.

Phytohemagglutinin-stimulated whole-blood cultures in medium TC199 with 20% human serum were used. Demecolcine was added two hours before harvesting. After hypotonic treatment with 0·95% sodium-citrate solution the cells were fixed in methanol/acetic acid, flattened by air-drying, and stained with orcein. 100 metaphases were examined from each culture. In the first experiment ethotoin was added as the commercially available peganone pill; subsequently pure ethotoin was used. The in-vitro concentration of 50–100 μg. per ml. is comparable to the in-vivo plasma concentration obtained with therapeutic doses.

Thirteen cultures were treated for 12–24 hours with doses from 0·5 to 500 μg. per ml. Between 5% and 18% of the leucocyte metaphases were damaged (controls 10–16%). The chromosome damage consisted predominantly of chromatid and chromosome constrictions and gaps. Some breaks and fragments, one exchange, and one endoreduplication were observed. In control cultures in this laboratory, between 1% and 15% of cells have aberrations of these kinds with a similar distribution of types. These results suggest that the anticonvulsant drug ethotoin does not induce chromosome aberrations in vitro.

I am indebted to Abbott Laboratories, North Chicago, U.S.A., for a gift of ethotoin, and to Eva Enersen for skilful technical assistance.

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PSYCHOSIS DUE TO L.S.D.

SIR,—The title and the major thrust of the article by Dr. Hatrick and Dr. Dewhurst (Oct. 10, p. 742) are directed at showing a cause-and-effect relationship between the taking of L.S.D. and the occurrence of two acute psychotic reactions. To make such an inference is as unsound as concluding that homocides are "due to" good Irish whiskey, simply on the evidence that two convicted murderers had a history of having imbibed Irish at some time before their criminal act.

The fact that two psychotic girls were found to have taken L.S.D. in the recent past is interesting. But that fact in no way implies a causal relationship between the two events. Before drawing such a conclusion, I would want to know the expected incidence of acute psychotic events in the general population. I would like to know the frequency of lysergic-acid injection between a psychotic group of individuals and a non-psychotic group similar to the study group in as many respects as possible. It would also like to know the difference between the psychosis occurrence rate in "normal" people who have experienced a single dose of L.S.D., and other "normal" people who have not had the exposure. Finally, I would not assign "proof" until a tightly controlled "double-blind" experimental study with the drug had been carried out. The experiment will never be done. But the retrospective analysis of acute psychotics, and the prospective study of L.S.D. users might bear interesting results which would strengthen, or weaken, the hypothesis that L.S.D. causes acute psychotic reactions.

Too many decisions in medicine are based on anecdotal information rather than scientifically determined fact. That *The Lancet* should encourage the process by publishing an article as prejudicial as the one by Hatrick and Dewhurst is disturbing. Lysergic acid may be "one of the most dangerous drugs in the pharmacopœia", but as physicians

1. Klinger, H. P., Schwarzacher, H. G. *J. biophys. biochem. Cytol.* 1960, 8, 345.
2. Schlegel, R. J., Neu, R. L., Leao, J. C. et al. *Cytogenetics*, 1968, 5, 430.
3. Brøgger, A. *Ann. Acad. scient. fenn. Ser. A IV*, 1968, 128, 36.
4. Ayraud, N., Kermarec, J., Martinon, J. *Ann. Genet.* 1968, 11, 253.

and scientists we have a responsibility to draw these conclusions from soundly derived data, not from uncontrolled case studies which serve only to expose the reader to isolated bits of information which may stimulate the formulation of researchable hypotheses.

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WEIGHT GAIN AS SIGN OF IMPROVEMENT IN ASTHMA

SIR,—Assessment of the response to treatment of patients with asthma is difficult because of the variability of symptoms and of the spontaneous variability of functional abnormality that can be measured. In studies on the use of disodium cromoglycate ('Intal') observations have been made on the patient's subjective response and on any change in respiratory function. Improvement in symptoms, however, is not always accompanied by improvement in function measured.[1,2] At the London Chest Hospital we noticed that patients who showed improvement in asthmatic symptoms after treatment with disodium cromoglycate often gained weight, and this was investigated further.

57 adult patients were selected from those attending the London Chest Hospital outpatients. All were considered to have asthma because of recurrent attacks of wheezing. All had been inhaling disodium cromoglycate for at least three months and a complete record of their weights and clinical progress was available. All were being treated with corticosteroids, or sympathomimetic amines, or both. They were weighed on attendance at outpatients on a steelyard scale under standard conditions. An increase in weight of 5 lb. (2·27 kg.) was chosen as significant. The response to disodium cromoglycate was classified as "good" when the dose of corticosteroid or sympathomimetic amine could be reduced or the drug stopped; "fair" when the doctor was satisfied that the patient had responded; or "nil" when no improvement was observed.

RESPONSE TO DISODIUM CROMOGLYCATE IN RELATION TO WEIGHT GAIN*

Response to disodium cromoglycate	Weight increase	No weight increase	Total
"Good"	17	18	35
"Fair" and "nil" ..	1	21	22
Total	18	39	57

*$P < 0.0005$.

18 of the 57 patients increased in weight by 5 lb. (2·27 kg.) or more. The range of increase was 5–25 lb. (2·27–11·35 kg.). 7 other patients gained 5 lb. or more but this was considered to be a response to other drugs, and these patients are not included in the weight-gain group (see below). Of the remaining 32 patients 12 put on less than 5 lb. (2·27 kg.) in weight, 15 fluctuated, and 5 lost weight.

The response to disodium cromoglycate was assessed as "good" in 35 patients, "fair" in 13, and "nil" in 9. The difference in numbers who gained weight in the "good" as opposed to the "fair" and "nil" groups is significant (see table).

There was a record of the previous weights of 41 patients. There was no relationship between weight at the start of treatment in comparison to previous weights and subsequent gain in weight; this is not surprising, for if weight change does follow variation in intensity of asthma it must be remembered that these patients were not necessarily at their worst when disodium cromoglycate was started.

1. Howell, J. B. L., Altounyan, R. E. C. *Lancet*, 1967, ii, 539.
2. Robertson, D. G., Epstein, S. W., Warrell, D. A. *Br. med. J.* 1969, i, 552.

7 patients gained 5 lb. (2·27 kg.) or more in weight but were excluded from the weight-gain group because they had been having other drugs. In 5 the weight gain seemed related to prednisone, in 1 to corticotrophin, and in 1 to nortriptyline and isocarboxazid. 12 other patients who gained weight significantly had been taking corticosteroids for some time before the start of treatment with disodium cromoglycate. 5 of these patients were able to reduce the dose and 7 were able to stop taking corticosteroids.

Two-thirds of those taking disodium cromoglycate, including all those who showed no improvement, did not gain a significant amount of weight. Because of this, and because those whose response was "good" had more chance of gaining weight, it is thought that the increase is due to improvement in the asthma rather than to an effect of the drug itself. No weight change was found in animal experiments with disodium cromoglycate other than a loss at extremely high (toxic) doses.[3]

In conclusion, about a third of a group of patients who had been taking disodium cromoglycate for at least three months put on 5 lb. or more in weight. This was thought to be due to decreased breathlessness causing an increased intake of food. Weight gain can be a good objective sign of improvement in asthma.

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OCCUPATIONAL HEALTH: THE NEXT MOVE ?

SIR,—Your arguments (Oct. 3, p. 701) for delaying the development of an Employment Medical Advisory Service by the Department of Employment are based on two assumptions—first that the proposed service is inadequate, and second that it would be likely to put back any move towards the Department of Health and Social Security assuming responsibility for all health services. The second assumption is hypothetical. It could equally well be argued that the E.M.A. service would be a more attractive prospect for integration with the N.H.S. than the present Appointed Factory Doctor Service. We have yet to devise a health service without serious defects. The E.M.A. service is no exception, but it is a considerable advance on the present system, which falls a long way short of meeting urgent needs, particularly for those people employed in workplaces without their own occupational health services. It would be unwise to abandon or delay the E.M.A. service because of its shortcomings and to neglect an immediate need for the sake of an ideal.

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APLASTIC ANÆMIA AND INFECTIOUS HEPATITIS

SIR,—Dr. Hilton (Oct. 17, p. 826) reports that no cases of infectious hepatitis were found to precede the development of aplastic anæmia in a review of 183 case-notes at Manchester Royal Infirmary. The rarity of the association prompts me to report the case of a twelve-year-old boy admitted to All Saints Hospital, Chatham, on Dec. 27, 1966. He had been jaundiced for five weeks. Investigation revealed hepatic dysfunction consistent with infectious hepatitis and an abnormal depression of the peripheral-blood picture—hæmoglobin 14 g. per 100 ml., and total white-cell count 2700 per c.mm. with 57% neutrophils. The hospital course was one of rapid deterioration, with the development

3. Wardell, G. Personal communication.