detected until it had resulted in cardiac arrest. This can easily happen; I have reported^{1,2} several fatalities from this cause with specialist anaesthetists.—I am, etc.,

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¹ Bourne, J. G., *Anaesthesia*, 1970, 25, 473.

² Bourne, J. G., *Lancet*, 1973, 1, 35.

X-Trisomy Associated with Hodgkin's Disease

SIR,—X-trisomy is not connected with any characteristic clinical syndrome. Many 47,XXX women have no clinical abnormality, gynaecological or otherwise, and are even fertile. Others are mentally retarded.^{1,3}

We should like to report a case of X-trisomy associated with Hodgkin's disease. An 18-year-old girl (whose mother was aged 42 and father aged 45 at the time of her birth) had generalized lymph node enlargement which had appeared one month previously. Biopsy of a lymph node showed Hodgkin's disease. The patient was of medium growth and had menstruated regularly since the age of 14. Gynaecological examination showed a slightly hypoplastic uterus. Her mental development was normal (I.Q. not estimated).

The cells obtained directly from the lymph node and from culture of peripheral lymphocytes contained 47 chromosomes, the additional one being the size of a member of group C. The presence of an extra chromosome in group C in a patient without phenotype anomalies suggested that it was an X chromosome. This suggestion was supported by the occurrence of double Barr's bodies in cells from buccal mucosal smears (fig. 1). Thus the 47,XXX karyotype was

Fig. 1.—Lymph node cell with a 47,XXX karyotype. Inset—Buccal epithelial cell with double Barr's bodies.

established. Mitoses from the peripheral blood showed a short-arm deletion of a G chromosome, probably 22 p-, in 30% of the cells counted. A similar anomaly was described by Gunz and Fitzgerald in lymphatic leukaemia.⁴ The fact that this anomaly was not seen in lymph node cells in our case is difficult to explain. Tetraploid cells were an almost constant feature in cases of Hodgkin's disease observed by Coutinho *et al.*,⁵ though in some cases chromosomal abnormalities were not found in lymph node cells.

It is known that constitutional chromosome anomalies may predispose to neoplasia.⁶ On the other hand the results of O'Riordan

*et al.*⁷ indicate that (with the exception of Down's syndrome) there is no increased susceptibility to cancer in general among persons who carry autosomal rearrangements or sex chromosome aneuploidy.—We are, etc.,

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- Dewhurst, C., *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 1971, 78, 1058.
- Lucas, M., Dewhurst, C. J., Hurley, R., Anderson, S., and Blunt, S., *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 1971, 78, 1087.
- MacLean, N., Court Brown, W. M., Jacobs, P. A., Mantle, D. J., and Strong, J. A., *Journal of Medical Genetics*, 1966, 5, 165.
- Gunz, F. W., Fitzgerald, P. H., and Adams, A., *British Medical Journal*, 1962, 2, 1097.
- Coutinho, V., Bottura, C., and Falcao, R. P., *British Journal of Cancer*, 1971, 25, 789.
- Koller, P. C., *The Role of Chromosomes in Cancer Biology* (Recent Results in Cancer Research No. 38). London, Heinemann, 1972.
- O'Riordan, M. L., Langlands, A. O., and Harnden, D. G., *European Journal of Cancer*, 1972, 8, 373.

Cauda Equina Syndrome in Ankylosing Spondylitis

SIR,—The association between the cauda equina syndrome in ankylosing spondylitis and posteriorly projecting diverticula from the lumbosacral canal confirmed by Dr. D. J. Thomas and others (26 January, p. 148) has been fully established. Since reporting my original cases¹ I have seen one further example and have been sent details of two other cases. Similar findings have been reported by other observers^{2,3} who have commented on the widening of the canal often seen. These diverticula will not be seen if myelography is performed in the usual prone position as they do not extend posteriorly but excavate the laminae and spinous processes.

How these remarkable destructive lesions arise and how they could be responsible for the cauda equina lesion is quite unknown, but indeed very little seems to be known about the state of the meninges and the spinal canal in this disease in the absence of this neurological complication.—I am, etc.,

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- Matthews, W. B., *Journal of Neurological Sciences*, 1968, 6, 561.
- Rosenkranz, W., *Journal of Neurosurgery*, 1971, 34, 241.
- Russell, M. L., Gordon, D. A., Ogryzlo, M. A., and McPhedran, R. S., *Annals of Internal Medicine*, 1973, 78, 551.

Histidine for Treatment of Uraemic Anaemia

SIR,—Professor C. Giordano and his colleagues in Naples have recently presented data suggesting that histidine supplements improve the anaemia associated with chronic renal failure.¹ But there are some inconsistencies in their work on this subject which make it difficult to interpret the results.

The data from 20 of the 28 patients whom they discuss in this recent paper were previously reported at the European Dialysis

and Transplant Association (E.D.T.A.) meeting in Vienna in June 1973.² These 20 patients were then stated to have received no iron supplements, whereas according to the recent paper¹ the 28 patients were given iron and folic acid. As patients on haemodialysis are sometimes iron-deficient it is important to know whether or not the patients were given iron. The protocol of the study described in the abstract³ of the E.D.T.A. communication was different from that of the study which was subsequently published.^{1,2} In both studies patients on maintenance haemodialysis were given histidine supplements. According to the abstract³ the reticulocyte count rose significantly after histidine, whereas in the most recent paper¹ there was a significant fall in reticulocytes by the end of two months' treatment with histidine.

The patients' diet is described in the two papers^{1,2} as a "free diet" without the protein intake being specified. The protein content of the diet is of immediate relevance in a study in which it is claimed that amino-acid supplements are necessary. There is some evidence that the patients were eating a low-protein diet. Fifty per cent. of the patients received only 12-15 hours of haemodialysis per week. But in spite of being underdialysed their predialysis blood urea levels varied from only 75 to 110 mg/100 ml. This suggests that the patients were eating a low-protein diet, perhaps because of habit or advice or because of the anorexia associated with underdialysis. It is possible, therefore, that the low plasma histidine levels before histidine treatment were due in part to deficiency of protein and therefore of histidine. It would seem more reasonable to correct this deficiency by increasing the protein intake and, if necessary, the hours of dialysis than to attempt to correct with histidine supplementation what is probably a generalized amino-acid deficiency.

Professor Giordano suggests that there should be an extensive controlled trial of histidine treatment for the anaemia associated with chronic renal failure. Before this suggestion is acted upon it would be of great help if the data concerning iron supplements, reticulocyte response, and dietary protein intake could be clarified.—We are, etc.,

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- Giordano, C., *et al.*, *British Medical Journal*, 1973, 4, 714.
- Giordano, C., *et al.*, *Proceedings of the European Dialysis and Transplant Association*, 1973, 10, 160.
- Giordano, C., De Santo, N. G., Rinaldi, S., Esposito, R., and Acone, D., *Kidney International*, 1973, 3, 4A.

Oral Contraceptives and Thromboembolism

SIR,—I was rather surprised to read the paper by Mrs. May A. Badaracco and Dr. M. P. Vessey (9 February, p. 215) which draws important conclusions about oral contraceptives from what appears to be slender evidence from the patients involved.

In your leading article (p. 213) you are happy to accept this evidence. You quote Drill,¹ who reported on 15 prospective studies each involving more than 1,000 woman-years of use of the contraceptive pill.

While these may not all have been statistically watertight studies, they did show a reduced rather than an increased incidence of thromboembolic disease. Hougie² in an excellent review article quotes the Puerto Rican study³ designed especially to determine the effects of oral contraceptive agents on the incidence of thromboembolic disease in which 9,898 patients were randomly allocated to the contraceptive pill or to other contraceptive methods and followed up. This very large prospective study also failed to show an increased risk of thrombophlebitis among pill users. It may be argued that these surveys are dealing with different population groups, but it is by no means proved that "clotting [is] provoked by oral contraceptives."—I am, etc.,

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- 1 Drill, V. A., *Journal of the American Medical Association*, 1972, **219**, 583.
- 2 Hougie, C., *American Heart Journal*, 1973, **85**, 538.
- 3 Fuertes-de la Haba, A., Curet, J. O., Pelegrina, I., and Bangdiwala, I., *Obstetrics and Gynecology*, 1971, **38**, 259.

Anaemia in Beta-thalassaemic Carriers

SIR,—We are very interested in the question of anaemia occurring in heterozygous beta-thalassaemic subjects. Thus we are grateful to Dr. H. H. M. Knox-Macauley and his colleagues (21 July 1973, p. 150), who report a reduced haemoglobin level in beta-thalassaemic carriers. Two of us had already reported similar results in heterozygous beta-thalassaemic children of both sexes.¹ Nevertheless, we think that neither report proves whether symptomless beta-thalassaemic subjects are anaemic or not, since the study of Dr. Knox-Macauley and his colleagues was concerned with patients referred to hospital and ours related to a child inpatient population. Similarly, no conclusive evidence is provided by a recent investigation performed in Thailand,² since no information concerning the age of the subjects examined is given. We have therefore determined the haemoglobin levels of groups of symptom-free heterozygous beta-thalassaemic males (age 15–60 years) and females (15–52 years) compared with normal controls. The results are given in the table.

These data show a significant decrease in the mean haemoglobin level in beta-thalassaemic carriers of both sexes. According to one authority³ the lower limits of normal haemoglobin content at sea level (as in the present investigation) are 14 and 12 g/100 ml for males and females respectively. The haemoglobin level in 86 of the 87 beta-thalassaemic males examined by us was below 14 g/100 ml, while in 61 of the 70 beta-thalassaemic females it was less than 12 g/100 ml. Our study therefore leads to the conclusion that anaemia is quite a common finding in beta-thalassaemic carriers.

In our opinion this pattern of anaemia could be related to the reduced mean corpuscular haemoglobin content¹ brought about by a decrease of both alpha- and beta-chain production,⁵ with impaired haem biosynthesis⁶ and increased haemolysis.⁷—We are, etc.,

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- 1 Castaldi, G., and Zavagli, G., *Lancet*, 1972, **2**, 1254.
- 2 Pootrakul, P., Wasi, P., and Na-Nakorn, S., *British Journal of Haematology*, 1973, **24**, 703.
- 3 Committee on Iron Deficiency, *Journal of the American Medical Association*, 1968, **203**, 407.
- 4 Kan, Y. W., and Nathan, D. G., *Journal of Clinical Investigation*, 1970, **49**, 635.
- 5 Kan, Y. W., Nathan, D. G., and Lodish, H. F., *Journal of Clinical Investigation*, 1972, **51**, 1906.
- 6 Lyberatos, C., et al., *Acta Haematologica*, 1972, **47**, 164.
- 7 Mazza, U., Gallo, E., Ricco, G., Pich, G., and Stratta, O., First Meeting of European Division of International Society of Haematology, Milan, 1971 (abstracts, p. 36).

Steroid Aerosols in Asthma

SIR,—The disturbing incidence of candida infections of the pharynx and the larynx reported by Dr. M. K. McAllen and others (2 February, p. 171) is not universal. I have treated 149 patients with an aerosol of beclomethasone dipropionate and in 80 the period of observation has been for 20–30 months.¹ In five cases sore throat, huskiness, or hoarseness was reported. In one case *Candida albicans* was grown but quickly disappeared with treatment with nystatin lozenges. The patient has continued for a further 12 months with a dose of 400 µg of beclomethasone daily without trouble. In the remaining four cases postnasal swabs were negative but symptoms disappeared after the dose of aerosol had been decreased to 300 or 200 µg per day. Despite careful questioning, none of the other patients has complained of a sore throat or hoarseness.

Other findings may be of interest. After 18 months of treatment with the aerosol five patients have been weaned completely without relapse of asthma, but in 25 others the symptoms recurred and they have had to continue, usually at a dose of 200–300 µg daily. Seventeen patients claim that they have had more frequent attacks of purulent bronchitis than before treatment; 11 have had to have occasional courses of oral prednisolone and antibiotics together, but have continued with good function between attacks. Four patients who had originally been well controlled have relapsed and failed to respond to further treatment and are maintained now on oral steroids. Originally 47 out of 75 patients who had been maintained on systemic steroids pre-

viously were weaned successfully from oral steroids and received at least equal benefit from the aerosol. Two only of these patients have relapsed and have had to resume oral steroids daily. No other untoward effects have been noted. Serum cortisol levels have remained normal in all patients who had not previously received oral steroids and in the 45 completely weaned successfully from oral steroids.

Regular use of the beclomethasone aerosol remains a significant advance in the safe management of asthma as long as (1) the dose is kept to the minimum required and (2) the patient is carefully instructed how to use the aerosol, otherwise most is expended in the mouth and throat.—I am, etc.,

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- 1 Pines, A., *Practitioner*, 1973, **211**, 86.

Clinical Diagnosis of Reye's Syndrome

SIR,—Your leading article on this subject (11 August, p. 308) is timely and emphasizes the need to consider Reye's syndrome in any child with an encephalopathy of no apparent cause.

Of great concern to clinicians in establishing the diagnosis of the disease are the guidelines advocated in your article, which are largely drawn from the prospective studies of Glasgow *et al.*^{1–3} In these studies of patients with encephalopathy and fatty visceral degeneration in Thailand no mention is made of the presence or lack of toxic quantities of aflatoxin in the urine of the patients or in the tissues in fatal cases. In a series of earlier articles from Thailand on the epidemiology, toxicology, and clinical study of a Reye's-like syndrome the toxin of *Aspergillus flavus* was implicated as the aetiological factor.^{4–7} A striking clinical, biochemical, and pathological corollary to the human disease can be produced in the juvenile monkey by the administration of a purified toxin derived from cultures of fungi contaminating foodstuffs ingested by victims.⁸

Clarification of this point about the presence or absence of toxic amounts of aflatoxin in the fluids and tissues of affected patients is of fundamental importance before criteria developed for the aflatoxin-related diseases are adopted for the diagnosis of a disorder not due to aflatoxins. Differentiation of these two syndromes can be made not only on toxicological grounds but also pathologically and clinically. While there are many similarities, clinical differences can be found, especially the precipitous course in the Thai disorder, which is often heralded by seizures, which progressed to status epilepticus in about 50% of one series of 67 cases.⁴ Hypoglycaemia is also more frequent in the Thai disease, being found in 75% in one series¹ and in 99% in another.⁴ In three of Glasgow *et al.*'s 43 cases consciousness was regained on administration of intravenous glucose^{1–3} and in several others improvement such as increased pupillary responses were seen. From these observations they concluded that hypoglycaemia played an important role in the development of the encephalopathy in their patients. The hypoglycaemia in Reye's syndrome is not influenced by infusions of

	No. of cases	Haemoglobin (g/100 ml) (mean ± S.D.)	P
Heterozygous beta-thalassaemic males	87	11.72 ± 1.29	
Control males	650	15.04 ± 1.33	<0.001
Heterozygous beta-thalassaemic females	70	10.62 ± 1.30	
Control females	261	13.38 ± 1.00	<0.001