

HUMAN MATERIALS AND STUDY OF POLLUTANTS

SIR,—Miller¹ has indicated the possible use of stored umbilical cords as a biological dosimeter for chronological changes in the level of pollutants. His suggestion is ingenious because old cords are readily available in some countries. Stored human tissues other than umbilical cord could also be used. For example, fixed human organs are preserved in every anatomical institution. Nishimura² determined the methyl-mercury levels in fixed fetal organs obtained through induced abortions from healthy mothers who resided in urban districts of central Japan. He found that the levels of the compound in the fetal organs (cerebrum, liver, and kidney) were comparable with or rather lower than the corresponding values in the old fetal organs which had been stored in formalin for more than 52 years. This result ruled out the chronologically increased contamination of human tissues, and was relevant to the experience of inhabitants of the Minamata area where a severe neurological disorder due to methyl mercury (Minamata disease) became epidemic.³ Further studies with various populations under different living conditions are needed for comparison of the levels of pollutants in human tissues.

To investigate the direct exposure of human conceptuses to embryotoxic agents, human embryonic tissue proper should be studied. For this purpose, therapeutically induced abortions could be utilised. However, only a limited number of such studies have been conducted.^{4,5} We determined the concentrations of polychlorinated biphenyls (P.C.B.s) in human embryonic and fetal tissues and compared them with the corresponding values in adults' organs.⁶ The levels of P.C.B.s in the embryos and fetuses were much lower than those in the adults' tissues. The concentrations of the compound in the human conceptuses were also lower than the lowest embryotoxic tissue level estimated from animal experiments.

Induced abortion is now legal in many countries. If tissue from aborted embryos and fetuses were preserved by deep freezing, they could be analysed any time in future, and such data could be compared for populations at different times or in different places. If systematic surveys were done, epidemics of puzzling diseases due to chemical contamination might be sought more easily and, possibly, be prevented.

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THE OGADEN FAMINE

SIR,—The article from the Murrays⁷ on the impact of Somali food shelters on the health of nomads raised several interesting points, many of which I hope will be enlarged upon by those better qualified than myself. However, as a short-term emergency medical relief worker in the Ogaden in May and June, 1975, I would like to comment on their conclusions about psychosomatic illness and social and moral disruption caused by camp life.

We found that the mothers of very malnourished and sick children were initially reluctant to bring them for intensive feeding and medical treatment. Their attitude was a mixture of despairing resignation and suspicion. We thought this was due to their total unfamiliarity with Europeans and Western medicine. They became cooperative, and their enthusiasm

spread to others. One wonders how much the nomads' apparent indifference to the very ill and exhausted was due to ignorance and, possibly too, to the grim necessity not to allow the weak to jeopardise their movements in their desperate search for water and pasture.

I wonder also whether the subsequent demand for treatment of minor and imaginary ills was not due to the curiosity, boredom, and acquisitiveness so familiar in a camp existence. Professor Murray and his colleagues describe camp apathy well. I did not get the impression of the more sophisticated psychosomatic illnesses so familiar in my general practice in Britain.

The nomads' small unsociable groups were in striking contrast to the community sense of the Ethiopian Amharic peasants in camps during the Wollo famine of 1973. The nomads' small family groupings and clan rivalries in securing forage and water could have exacerbated their social isolation in the strange camp surroundings in contrast with the Amharic village culture.

"Refeeding disease" is a fascinating concept of which I have not been previously aware, and I shall await further comment with interest.

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ANAPHYLACTIC REACTION TO APROTININ

SIR,—We wish to report a case of severe anaphylaxis complicating therapy with aprotinin ('Trasylol'). A previously fit 67-year-old woman came under our care with acute pancreatitis. She was treated from the time of admission under the protocol of the current Medical Research Council trial of trasylol and glucagon in this condition. About 8 days after admission she had a diffuse urticarial rash; the ampicillin she was then receiving was stopped, and the rash gradually faded. She was also suspected of having a pancreatic pseudocyst.

She recovered and was allowed home, only to be readmitted 2 weeks later with relapsing acute pancreatitis. Her general condition was poor, and she was treated with intravenous tetracycline and a 6-hourly infusion of trasylol 200 000 kallikrein-inactivating units. About half an hour after this infusion began she became nauseated, hypotensive, and severely pyrexial, and developed a diffuse punctate erythematous rash, especially of the trunk. It was felt she had an endotoxaemia and colistin sulphate and metronidazole were added to the drug regimen. She received corticosteroids and oxygen for the acute period of this reaction. Her temperature subsided and her blood-pressure returned to normal. Nevertheless she was transferred to the intensive-care unit where trasylol is usually given by very slow direct intravenous injection. About 30 s after this second dose began she had a similar reaction culminating in a cardiorespiratory arrest resulting in severe irreversible brain damage. No further trasylol was given. She died 2 weeks later and post-mortem examination confirmed the presence of very severe pancreatitis. The code of the trial had previously been broken after the acute anaphylaxis and she had received trasylol on the first admission and trasylol was the only drug common to both admissions.

In the past, trasylol has been regarded as a safe drug¹ and the 1975 data sheet states: "Other than three mild skin reactions, no side effects have been reported". It goes on to mention the possibility of anaphylaxis but adds that no such cases have been reported. The 1976 data sheet has been modified to give a slightly stronger warning of the possibility of anaphylaxis, but the literature supplied with the drug merely states that if allergy exists, antihistamines should be given before the drug.

In fact there have been several published cases of anaphylaxis with trasylol,²⁻⁴ and deaths have been reported.^{1,2} Our

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4. Chaube, S., Nishimura, H., Swinyard, C. A. *Archs envir. Hlth*, 1973, 26, 237.

5. Nishimura, H., Hirota, S., Tanaka, O., Ueda, M., Uno, T. *Biol. Neonat.* 1974, 24, 197.

6. Nishimura, H., Shiota, K., Tanimura, T., Mizutani, M., Matsumoto, M., Ueda, M. *Pediatrician* (in the press).

7. Murray, M. J., Murray, A. B., Murray, M. B., Murray, C. J. *Lancet*, 1976, i, 1283.

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2. Baden, H., and others. *Scand. J. Gastroent.* 1969, 4, 291.

3. Bauer, J., Futterman, S., Dreiling, D. A. *Am. J. Gastroent.* 1971, 56, 542.

4. Siegel, M., Werner, M. *Dt. med. Wschr.* 1965, 90, e1712.

examination of the literature has not been exhaustive, and it is therefore possible that other cases exist. Anaphylaxis to trasylol may occur with the first course of treatment.³

Trasylol may turn out to be a useful drug in acute pancreatitis. The manufacturer's indications for trasylol are very wide, and we would remind all users of the drug to bear in mind that its use carries definite risks. These risks will become more apparent if the drug becomes more widely used. The drug is still under evaluation by the M.R.C. so it cannot be considered to be of proven value. Thus particular care in its use is advisable, and we recommend that if there is any doubt about potential allergy intradermal skin testing should be carried out.⁵ In view of the fact that allergy may appear on a first course there is probably a case for skin-testing all patients before administering the drug. We also suggest that the data sheet and prescribing information supplied with the drug be revised.

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TRANEXAMIC ACID AND INTRACRANIAL THROMBOSIS

SIR,—Fibrinolysis is the process by which fibrinogen and fibrin are degraded by the proteolytic enzyme plasmin, promoting the resolution of thrombi. Activators in the plasma and in vessel walls convert plasminogen to plasmin. Antifibrinolytic drugs might upset this mechanism by their inhibitory effect on the activation of plasminogen. Theoretically, therefore, the administration of antifibrinolytic agents could facilitate the development of a thrombosis.

We have seen two cases of intracranial arterial thrombosis in young women taking the antifibrinolytic drug tranexamic acid ('Cyklokapron'). In both cases the drug had been prescribed for menorrhagia and had been taken during the days of bleeding.

Case 1

A 31-year-old woman, previously healthy, developed uterine myomas with menorrhagia, resulting in severe anaemia. For one year she had been taking tranexamic acid (3–4.5 g/day) during the days of blood-loss. In the middle of June, 1975, the patient was treated with doxycycline ('Vibramycin') for bronchopneumonia. Her menstruation started on June 18 and from June 19 she took tranexamic acid continuously until June 27. On June 20 she experienced a transitory weakness of her left hand, lasting a few minutes. On June 27 she woke to find that she could not move her left arm and leg. The skin sensibility on the same side was also impaired. On admission to hospital on the same day the symptoms had already regressed considerably, but paraesthesia and numbness in her left cheek persisted for several days. An E.E.G. on arrival confirmed a right-sided cerebral lesion, and showed clear regression when repeated 3 days later. Carotid angiography on July 16 revealed circulatory impairment within one of the posterior peripheral branches of the right middle cerebral artery. The results of relevant laboratory tests on admission were: Hb 9.2 g/dl, E.S.R. 67 mm in 1st h, thrombocytes $700 \times 10^9/l$, C.S.F. normal. Coagulation tests on July 8, including a test of thrombocyte function, revealed a slight increase in fibrin-degradation products, 10–20 mg/l (normally less than 10 mg/l), indicating fibrinolysis. This was interpreted as a physiological response to the vascular lesion. Otherwise coagulation tests were normal. The patient's hospital course was uneventful. She was discharged after 1 month with no residual symptoms. Hb at that time was 10.2 g/dl, E.S.R. 37 mm in 1st h and platelet-count $252 \times 10^9/l$. She has remained well and has now had a hysterectomy.

Case 2

A 32-year-old woman, with no previous illnesses apart from migraine since puberty, had been taking 0.5–1 g tranexamic acid/day during her menstrual periods for about a year. At midcycle in June, 1975, she woke up one night with a severe headache, and her left arm and leg felt "numb". The next day she developed a left-sided hemiparesis and a homonymous hemianopia to the left. Carotid angiography revealed thrombosis of the right posterior cerebral artery. C.S.F. was normal. Thrombocytes 1 week later were $540 \times 10^9/l$, otherwise the laboratory findings were normal. In September, 1975, some left-sided weakness, dysaesthesia, and hemianopia still persisted. At that time her laboratory tests, including thrombocytes ($184 \times 10^9/l$), were normal.

Both our patients had an initial thrombocytosis which in itself could have predisposed to thrombosis. The anaemia and bronchopneumonia in case 1 might have explained the reversible thrombocytosis. In neither case did we find evidence of any underlying disease that could have been thrombogenic.

The connection between the taking of tranexamic acid and the vascular lesions in these patients may have been fortuitous. So far we have been unable to find any earlier reports of cerebral lesions in young women taking antifibrinolytic drugs. When given after a subarachnoid haemorrhage, however, they have been reported to increase the risk of "ischæmic complications".¹

Tranexamic acid, at least in Sweden, is given to an increasing number of young women routinely to prevent uterine bleeding in connection with intrauterine contraceptive devices (I.U.D.s). Ironically one reason for a change from oral-contraceptive drugs to I.U.D.s is the fear of side-effects of the pill, mainly thromboembolic diseases.

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CORTICOSTEROIDS, SALBUTAMOL, AND R.D.S.

SIR,—I wish to contribute to the discussion opened by Weiss and Pugh² about the prevention of respiratory-distress syndrome (R.D.S.) by corticosteroids and/or beta-sympathomimetic drugs.

In a 24-year-old nullipara, whose pregnancy had been induced by human menopausal gonadotrophin, twins were diagnosed by ultrasound echography at 15 weeks' gestation. A previous hystero-graphy had revealed an incompetent cervix, and Shirodkar's technique had been done at 16 weeks' gestation. The patient was followed up twice a month and the pregnancy proceeded normally until the 29th week, when spontaneous rupture of the membranes occurred. An intramuscular dose of 12 mg of betamethasone was given immediately and repeated 48 h later. High doses of salbutamol were also administered intravenously for 3 weeks, to a total dose of 210 mg.

The patient went into labour at 32 weeks gestation. The first twin was a 1620 g girl with no respiratory problem. The second twin, whose amniotic sac was intact, weighed 1990 g and developed R.D.S. (state 2).

In this case neither corticosteroids nor high doses of a beta-sympathomimetic drug administered continuously for 3 weeks were able to prevent R.D.S. in the second twin. On the other hand there is strong evidence that prolonged rupture of the amniotic membranes of the first twin induced fetal lung maturation and that this does prevent R.D.S.³

This case does not permit any conclusions to be drawn about the efficacy of corticosteroids in the prevention of R.D.S. (the

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3. Rouvillois, J. L., Papiernik, E., Amiel-Tison, C. *J. Gynec. Obstet. Biol. repr.* 1973, 2, 271.