

Attention should be concentrated on the real female risk factors. Multiple pregnancies, abortions, and early menarche lead to a greater risk of cholelithiasis, and could explain why women get more gallstones than men. Eating meat is also a factor, since vegetarian women have only half the gallstone prevalence of omnivores.³ We do not understand the mechanisms involved, and this is where attention and research should focus.

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FATAL HYPOKALAEMIA ASSOCIATED WITH IFOSFAMIDE/MESNA CHEMOTHERAPY

SIR,—We have recently seen four patients in whom severe hypokalaemia (fatal in one case) developed after cytotoxic chemotherapy with ifosfamide/mesna. Three patients received 5 g/m² of ifosfamide with 9 g/m² of mesna, and a fourth patient received 4 g/m² and 8 g/m², respectively. The ifosfamide was infused in 3 l of dextrose saline [without added potassium] over 24 h.¹ Mesna was administered concurrently with the ifosfamide and continued for 8-12 h after the ifosfamide infusion. One patient received ifosfamide as a single agent, and the other three received combination chemotherapy (table). Plasma potassium concentration was measured because of a confusional state in three patients, attributed to ifosfamide encephalopathy,² and muscle weakness in the fourth (patient 3). No patient had any other identifiable cause for hypokalaemia³ and in particular none had received diuretics or had protracted vomiting or diarrhoea.

CLINICAL DETAILS OF FOUR PATIENTS WHO RECEIVED IFOSFAMIDE/MESNA AND WHO HAD HYPOKALAEMIA

Patient	Tumour	Other cytotoxic agents	Plasma potassium concentration (mmol/l)		Time of onset (days)
			Before ifosfamide	After ifosfamide	
1	Non-Hodgkin's lymphoma	Etoposide, mitozantrone	3.6	2.6	2
2	Squamous carcinoma bronchus	Doxorubicin, vindesine	4.2	1.8	3
3	Oat cell carcinoma bronchus	..	3.5	1.7	5
4	Oat cell carcinoma bronchus	Methotrexate, etoposide	4.8	2.4	12

Plasma potassium concentration at the time of presentation ranged from 1.7-2.6 mmol/l (table). Plasma bicarbonate concentration was normal or raised in all patients, and plasma calcium and magnesium concentrations were normal in the patients whose levels were measured. No patient had renal failure. In three patients plasma potassium concentration returned to normal after several days of intravenous potassium replacement. Patient 3 had a fatal cardiac arrest one day after admission at a time when his plasma potassium concentration was 2.2 mmol/l.

Ifosfamide is a widely used cytotoxic agent, but serious hypokalaemia has not been reported.⁴ The occurrence of hypokalaemia shortly after ifosfamide/mesna infusion in four patients, in the absence of any other adequate cause, suggests that the association was causative. The pathophysiology is uncertain. Ifosfamide is tubulotoxic in animals.⁴ One patient developed adult Fanconi syndrome, with proximal renal tubular acidosis and renal failure, after high dose ifosfamide (8 g/m²) and mesna.⁵ Renal tubular damage to a lesser extent is a probable explanation of hypokalaemia in these patients. The use of intravenous fluids without potassium supplementation may have contributed to

hypokalaemia occurring on the second day, though the infusion of 4 l of potassium-free intravenous fluid over 36 h would not normally be expected to cause either severe or prolonged hypokalaemia.

We cannot comment on the frequency of occurrence of hypokalaemia after ifosfamide/mesna chemotherapy. The relation between hypokalaemia and ifosfamide encephalopathy is unclear, since in our experience correction of the plasma potassium concentration is not usually associated with rapid resolution of the confusional state.

We conclude that severe, sometimes fatal, hypokalaemia is a complication of cytotoxic chemotherapy with ifosfamide/mesna. Further investigation of the frequency, pathophysiology, and prevention of this complication is required.

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ALLERGIC REACTIONS TO CUTTLEFISH IN DEEP-SEA FISHERMEN

SIR,—Allergic reactions to animal products, including crab and fishmeal,¹ are well known. We report on such reactions to cuttlefish in fishermen.

In 1980-81 Polish fishermen began to catch and process cuttlefish in the South Atlantic. Soon afterwards doctors on the factory ships began to report cases of bronchial asthma and spastic bronchitis in fisherman, and they suspected that the allergy was associated with contact with cuttlefish. The fishermen are medically examined pre-employment and periodically after that, and asthmatics are not employed at sea.

We have investigated the problem by collecting information retrospectively and by alerting ship's doctors and captains to the possibility of allergic reactions in crew members. We asked them to provide data on suspected cases during the 1987 fishing season in the waters around the Falklands. On the average, there is a doctor employed on every other large Polish trawler/factory ship in that area. To investigate the problem on the spot one of us (Z. W.) worked as a ship's doctor during the 1987 season.

Retrospective and prospective data are summarised in tables I and II.

Cuttlefish is hand and machine processed aboard trawlers, mainly by fishermen employed in the processing plant. Sometimes they are also hand sorted and processed on deck, by other members of the crew. People engaged in this work are encouraged to wear protective gloves and spectacles, but many of them do not.

Among cases listed in table I as "bronchial asthma and spastic bronchitis" 8 also had skin manifestations of allergy; and in 5 cases conjunctivitis accompanied respiratory signs and symptoms. All cases except 3 (who received medical advice by radio) were seen by

TABLE I—ALLERGY TO CUTTLEFISH IN CREWS OF POLISH SHIPS OPERATING IN THE SOUTH ATLANTIC, 1983-87

Allergy*	Year					Total
	1983	1984	1985	1986	1987	
Resp	1	9	8	7	36	61
Other	0	0	0	0	5	5
Total	1	9	8	7	41	66

*Resp = atopic bronchial asthma, spastic bronchitis; other = dermatitis, conjunctivitis, Quincke's oedema

TABLE II—TYPE OF WORK DONE BY CREW MEMBERS WITH ALLERGIC REACTIONS TO CUTTLEFISH

Work	No
Fisherman, processing plant	57
Fisherman, on deck	1*
Chief, processing plant	1
Mechanic, processing plant	2
Mechanic, cold room	1
Fishmeal storeroom keeper	1
Fishmeal plant worker	2
Cook	1*

*Processed cuttlefish.

ship’s doctors. All 66 cases were crew members who handled cuttlefish.

In 1987, the estimated incidence of allergic reactions described was about 1% annually, after adjustment to the 4-month long cuttlefish catching season, and the proportion of the crew on board who handle cuttlefish (about three-quarters of a trawler’s crew).

In the years 1983–86, 5 fishermen with severe bronchial asthma or status asthmaticus were evacuated from ship to shore and later on repatriated to Poland. In 1987 there were 2 such cases.

These allergic reactions are important because asthma on a ship without a doctor is difficult to treat. Status asthmaticus developed in some cases treated by doctors, and some patients had to be brought home from distant fishing grounds.

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PROGNOSTIC FACTORS IN HODGKIN’S DISEASE

SIR,—In the prognosis of Hodgkin’s disease (HD), Dr Gobbi and colleagues (March 26, p 675) show that erythrocyte sedimentation rate (ESR), stage, histological subtype, and age at diagnosis are, in decreasing order, the major determinants influencing survival. In contrast, albumin concentration, sex, mediastinal bulk, haemoglobin levels, and constitutional symptoms at diagnosis had less or no prognostic value. Gobbi et al devise an equation for predicting survival time in individual patients.

To verify whether this set of prognostic variables had the same influence on survival in the population of HD patients observed at our institution, we reviewed staging and survival data of 440 patients who were diagnosed as having HD from January, 1969, to March, 1987 (median follow-up 51 months). All patients underwent similar evaluation as in Gobbi and colleagues’ study, although treatment patterns (radiotherapy in 123 cases, chemotherapy in 228, and combined therapy in 89) differed in some respects. Information about the nine prognostic variables at diagnosis was available. Variables were coded according to Gobbi and colleagues’ table II. Multivariate analysis of survival was done by the proportional hazards model.¹

The results of our survival analysis are summarised in the table. Our findings confirmed the prognostic value of age and histological subtype but revealed no significant influence of ESR and stage, which were the two most important predictors of survival in Gobbi and colleagues’ study. Additionally our analysis indicated that age at diagnosis and presence of constitutional symptoms are important for prognosis; Gobbi et al found that constitutional symptoms were not so important.

Although Gobbi et al used more complex statistical techniques, their data combined with ours offer a wide and composite picture of the main variables influencing the prognosis of HD. To explain why different sets of prognostic variables were found in the two analyses, we would say that follow-up was much shorter in our study and our patient series was more “recent”. Also the treatments differed

VARIABLES INFLUENCING SURVIVAL IN 440 PATIENTS WITH HD

Second level of variable*	Multiple hazards coefficient	p	Relative risk (95% confidence interval)†	No of patients
Age ≥ 45 yr	0.77	0.0004	2.16 (1.41–3.31)	164
Symptoms present	0.53	0.022	1.71 (1.08–2.69)	180
Histological subtype				
MC or LD	0.45	0.043	1.57 (1.0–2.43)	237
Male sex	0.40	0.070	1.49 (0.96–2.30)	250
Mediastinal bulk present	0.42	0.16	1.52 (0.85–2.72)	67
Stage III or IV	0.22	0.31	1.25 (0.81–1.95)	222
Albumin > 3.5 g/dl	–0.11	0.63	0.90 (0.57–1.40)	293
Haemoglobin > 11 g/dl	0.04	0.86	1.04 (0.68–1.57)	303
ESR > 45 mm/h	0.02	0.95	1.01 (0.64–1.61)	136

*First levels are not shown and are the opposite of second level, except for histological subtype where first level = lymphocyte predominance or nodular sclerosis, and for stage where first level = stage I or II.

†In accordance with statistical model relative risk and 95% confidence interval indicated only for second level of prognostic variable compared with first level (relative risk = 1). MC = mixed cellularity; LD = lymphocyte depletion.

between the two studies, especially for patients in stages IIA and IIIA. While Gobbi et al selected therapy mainly on the basis of unfavourable histology (MC or LD), in our study this criterion was not used since chemotherapy was added to radiotherapy in stage IIA patients with mediastinal bulk, and was the only treatment in stage IIIA.²

Our findings show that the prognostic value of some patients’ variables at diagnosis can be affected by a series of factors which are difficult to identify but which probably depend on the treatments in the patient population studied. Previous studies in selected groups of HD patients have shown that post-staging factors related to treatment, such as the early response to chemotherapy,³ can be more important for prognosis than staging variables.

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A TALMUDIC HANGOVER

SIR,—Julia Littlewood and colleagues (March 12, p 558) may be interested to know of a very severe headache secondary to red wine described in the *Babylonian Talmud*, written almost seventeen centuries ago.¹ A Roman matron had said to Rabbi Judah, whose face was always red and shining: “You are a sage and yet you are a drunkard!”. The rabbi replied: “You may well believe me that I taste no wine besides that of Kiddush and Havdalah, and the four cups of Passover, on account of which I have to bind my temples from Passover until Pentecost (seven weeks later)”. Kiddush and Havdalah refer to the ushering in of the Sabbath on Friday evening and the conclusion of the Sabbath on a Saturday night. Although the colour of the wine is not specified, Jewish law states that red wine is always to be preferred for ceremonial occasions, and it is inconceivable that the great Talmudic sage used anything but red wine to fulfil these obligations.

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1 Tractate Nedarim 49b. In: Babylonian Talmud London: Soncino Press, 1936.