vaccination course in these children was eventually resolved by a decision to give inactivated (Salk) vaccine.

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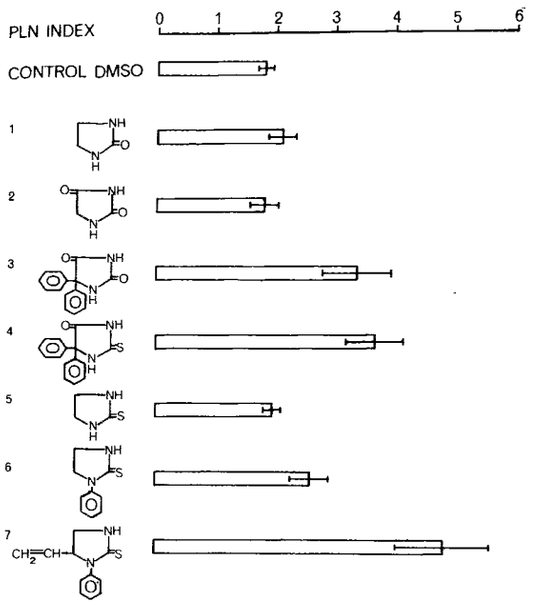
SPANISH TOXIC OIL SYNDROME AND CHEMICALLY INDUCED GRAFT-VERSUS-HOST-LIKE REACTIONS

SIR,—In our letter of May 26 (p 1174) we pointed to the strong clinical and pathological parallels between Spanish toxic oil syndrome, human graft-versus-host-disease (GVHD), and chemically induced GVHD-like symptoms. We proposed a role for 1-phenyl-5-vinyl-2-imidazolidinethione (phenylvinyl-IZT) (figure, no 7) in the pathogenesis of toxic oil syndrome. In the presence of aniline, this heterocyclic thiourea compound can be formed from 2-hydroxylated isothiocyanates in unrefined, industrial rapeseed oil.

Dr H. and Dr E. Gleichmann (June 30, p 1474) have pointed out that the similarity between GVHD and phenytoin-induced immunological side-effects is not confined to the clinical and laboratory features, but applies to the pathogenesis as well. The popliteal lymph node (PLN) assay, developed by W. L. Ford and colleagues as a model for locally induced GVH reactions, has been used to investigate[1] the immune dysregulation caused by phenytoin (figure, no 3). Phenytoin injected into the footpad of mice elicited PLN enlargement, characterised by obliteration of the lymph node architecture, diffuse lymphocyte proliferation, blast transformation, and angiogenesis. This immunoblastic lymphadenopathy, which can be considered as the first, proliferative phase of GVHR, is seen in patients on hydantoin therapy,[2] in autoimmune diseases,[3] and in GVHD[4]—and in the early phase of toxic oil syndrome.[5]

Phenylvinyl-IZT induces PLN enlargement (figure, no 7) histologically comparable with that observed after phenytoin treatment. As with hydantoins the immunological reactions of mice to the IZT derivatives require the presence of at least one lipophilic phenyl ring (figure). Furthermore, the introduction of the vinyl ($CH_2=CH-$) group in phenylvinyl-IZT potentiates the immunological reaction to the molecule considerably (figure, nos 6 and 7). This parallels the importance of the α-methylene group in the plant allergen α-methylene-γ-butyrolactone, reduction of which to methyl leads to a loss of immunological reactivity.[6] As suggested by others,[7] syndromes very similar to toxic oil syndrome can be caused by vinyl chloride[8] and trichloroethylene.[9]

In drug-induced GVHD-like immunological disorders and in toxic oil syndrome as well, severe immunological side-effects are observed in susceptible individuals only. Genetic factors (HLA-DR)[7] may determine the course of the syndrome. In the toxic oil syndrome only about 10% of patients (mainly women) had severe late phase symptoms, similar to the biphasic course of GVHD.[4]



Popliteal lymph node (PLN) reactions seven days after injection of related compounds (7·3 mmol).

Expressed as the ratio of the PLN weight of test side divided by PLN weight of contralateral, non-injected side. The bars represent the arithmetic mean ±SEM of PLN indices of groups of 5–6 Balb/c Cpb mice.

Control dimethylsulphoxide (solvent); (1) 2-imidazolidone; (2) 2,4-imidazolidinedione (hydantoin); (3) 5,5-diphenylhydantoin; (4) 5,5-diphenyl-2-thiohydantoin; (5) 2-imidazolidinethione (IZT); (6) 1-phenyl-2-imidazolidinethione (phenyl-IZT); (7) 1-phenyl-5-vinyl-2-imidazolidinethione (phenylvinyl-IZT).

"Margarine disease" in the Netherlands shared several clinical features with the early phase of toxic oil syndrome[10] and resembled an ethylphenylhydantoin induced syndrome.[11]

In view of the thiourea group present in phenylvinyl-IZT, propylthiouracil, and methimazole antithyroidal activity might, on our hypothesis, have been expected in toxic oil syndrome patients, as pointed out by Dr Paterson (June 23, p 1411). However, the basic IZT molecule is about 27 times less active in rats than propylthiouracil.[12] Large substituents (phenyl group) decrease antithyroid potency even more.[12] Moreover, those affected by contaminated oil will have been exposed to the putative toxic factor for no more than 40 days or so[6,10]—too short a period for the development of a clinically manifest goitre.

Although hard evidence for cyclic thiourea compounds as the cause of toxic oil syndrome must come from analysis of the oil and from animal studies, our results do support a possible aetiological role for phenylvinyl-IZT.

We thank Dr H. W. A. Biessels, Dr J. K. Terlouw, and Mr H. Verhaar (departments of organic and analytical chemistry, University of Utrecht) for the synthesis and purification of 1-phenyl-IZT and 1-phenyl-5-vinyl-IZT.

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FITNESS OF NORTH SEA DIVERS

SIR,—We agree with Dr Crosbie (Aug 25, p 471) that the difference in mean values for aerobic power between the divers and the sedentary men we studied (July 14, p 107) is significant statistically but, as we pointed out, the difference is of no biological significance. The error of the measurement of maximum aerobic power is about 10%, which almost completely covers the difference between the means. Furthermore, the individual values for the divers were all below the mean plus 2 SD for the sedentary group. Crosbie's implication that the divers were actually fitter than the sedentary group is statistical pedantry. If the official view in the Employment Medical Advisory Service is that the fitness of North Sea divers is no cause for concern it may need to be changed in the light of our analysis of the latest group of ten divers, studied in August, 1984. They had a mean aerobic power of $43 \cdot 8 \pm 4 \cdot 5$ ml O_2 kg^{-1} min^{-1}, which is not significantly different from that for sedentary men on Tayside. We hesitate to suggest that the divers are getting less fit, though Crosbie could well be forced to this statistical *reductio ad absurdum*, since the latest group of divers is not statistically different from the sedentary population while the previous group was.

Crosbie seems confused by our reference to recreational sportsmen in Tayside. The divers were much less fit than the sportsmen (maximum aerobic power of $60 \cdot 3 \pm 8 \cdot 6$ ml kg^{-1} min^{-1}) but we gave the range of values to demonstrate that no diver had an aerobic power approaching the upper values found in men whose lives are unlikely ever to depend on their fitness.

We are asked for more information about the populations studied. The divers are currently diving; they are very experienced and have been chosen by their employers to attend a paramedical course for divers at Ninewells Hospital; they come directly from their diving duties, not from leave; all course participants were measured (there was no selection). From the group of sedentary men we excluded any taking regular exercise; as far as possible the men were recruited randomly from local business organisations although, as with most population studies on volunteers, we cannot exclude a positive bias in their fitness.

Crosbie refers to the Diving Operations at Work Regulations 1981 and stresses overall physical and psychological fitness, as decided by the examining doctor. He apparently distrusts the measurement of aerobic power, preferring certification of fitness to dive to be based on qualities that are notoriously difficult to assess objectively. This is surprising since the Health and Safety Executive's (HSE) document (MA1) on the medical examination of divers refers to standards for blood pressure and forced expiratory volume. As physiologists, we do not accept that the only objective measurement of cardiovascular fitness recommended by the HSE (the Army's step-up test) is as sensitive a measure of cardiovascular fitness as is our treadmill test, with its continuous measurement of heart rate and oxygen consumption. In any case, UK divers know that step tests are not done routinely. If they were or, better still, if measurement of aerobic power were part of the routine assessment of divers, as is now required by law for divers in Norwegian waters, we might have fitter divers, less at risk during their day-to-day work of failing to perform well in a life-threatening emergency. Surely the current good safety record of the diving industry could only be improved were divers to be fitter.

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PSITTACOSIS OF NON-AVIAN ORIGIN

SIR,—We agree with your editorial (Aug 25, p 442) that "traditional ideas of the source of *C psittaci* require reappraisal, and that non-avian sources and human-to-human transmission must be considered", but what is the real dimension of the problem? When a patient with psittacosis has no evidence of exposure to avian sources of infection the possibility of a false-positive diagnosis and/or a false-negative epidemiological investigation must be excluded before different modes of spread are hypothesised.

Psittacosis is diagnosed serologically by a complement-fixation (CF) test detecting group-specific chlamydial antigen but different diagnostic criteria are used. We define a confirmed case as one with a compatible illness plus a four-fold or greater change in the CF titre; a presumptive case as a compatible illness and a single or a stable titre of 128 or more; and a suspected case as a compatible illness and a single or stable titre of 32 or 64. The influence of diagnostic criteria on the results of the epidemiological investigation is shown in the table, summarising a hospital-based study in 1982–83 in an area of central Italy (about 500 000 people). Exposure to birds (poultry and domestic pigeons especially) was recorded in 83% of confirmed cases, in 78% of presumptive cases, but in only 62% of suspected ones. When reliability of diagnosis decreases, the traditional exposures become less frequent.

EXPOSURE TO BIRDS IN 56 CASES OF PSITTACOSIS

Exposure to avian sources	Diagnosis of psittacosis		
	Confirmed	Presumptive	Suspected
Confirmed	25 *(83%)*	14 *(78%)*	5
Not confirmed	5 *(17%)*	4 *(22%)*	3

False-negative epidemiological investigations can arise because a delayed and/or incomplete inquiry may fail to detect occasional exposure to avian sources. Questions must be asked promptly via direct interviews with the patient by trained personnel using questionnaires. In our experience the hospital notes of patients affected by psittacosis rarely contain detailed epidemiological information—indeed the diagnosis usually follows the patient's discharge.

The influence of diagnostic criteria and epidemiological approach may in part explain the striking differences between data from the Centers for Disease Control (USA) and the Public Health Laboratory Service (England and Wales); in 1979 116 cases of psittacosis were reported in the USA and for 87% of them the type of avian exposure was known,[1] while in the same year 140 cases were reported in England and Wales but only for 36 of these illnesses (21%) was a bird contact stated.[2]

Last, but not least, if a serologically confirmed case of psittacosis has no evidence of traditional exposure, explanations to be considered, apart from non-avian animal or human origin, are: (1) that the four-fold or greater rise in CF titre is due to *C trachomatis*, a suspected cause of community-acquired pneumonia in adults;[3] (2) that the four-fold or greater rise in CF titre is an anamnestic response; or (3) that the avian source of infection is a bird without close contact with people but still able to contaminate the environment with its excreta (eg, wild birds or semi-domestic pigeons). The first hypothesis can be evaluated by a diagnostic test specific for *C trachomatis*[4] and the second by titrating antibodies against other agents causing acute infections of the lower respiratory tract; the third possibility can be only roughly explored.

Psittacosis of non-avian origin is a real problem—but its size is very difficult to define.

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