

MEDICAL MEMORANDA

Formalin Asthma in Hospital Staff

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Few cases of airways obstruction attributable to inhaled formaldehyde have been reported, though it has been suggested that the presence of formaldehyde contributes to the aggravation of chest diseases caused by air pollution (Kotin and Falk, 1964). Occupational "formalin asthma" has been described in a worker in a match factory (Vaughan, 1939) and in workers employed in the tanning and rubber industries (Popa *et al.*, 1969). We report here the use of inhalation provocation tests to investigate the relevance of inhaled formalin fumes to airways obstruction in two hospital staff members continually exposed to this substance in the course of their work.

Case 1

This patient was a 41-year-old nursing sister who began working with formalin in a renal dialysis unit in 1969. She developed a persistent dry cough and episodic attacks of wheezing within a few months which were not improved when she stopped smoking. On two occasions wheezing began four to five hours after exposure for five to 20 minutes to spilled undiluted formalin B.P.C. (34-38% solution of formaldehyde in water w/w). There were no other obvious provoking factors. In 1973 her wheezing, accompanied by increasing breathlessness and rhinitis, became persistent and her cough became productive. Treatment with antibiotics and bronchodilators brought little relief and in June 1973 she was obliged to take sick leave, during

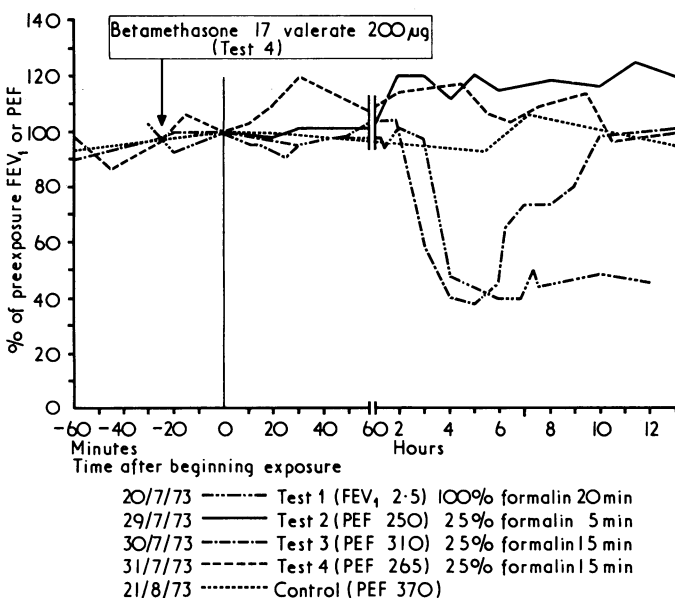


FIG. 1—Case 1. Results of inhalation provocation tests. Values in parentheses are readings obtained immediately before each exposure.

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which she slowly recovered. A chest x-ray film showed inflammatory changes in the apical segment of the right lower lobe. The haemoglobin was 13.4 g/dl and the W.B.C. was $13.1 \times 10^9/l$ ($13\ 100/mm^3$), of which $2.1 \times 10^9/l$ ($2100/mm^3$) were eosinophils. Routine skin prick tests with 12 common allergens proved negative.

Inhalation provocation tests were begun one month later, when she was receiving no medication. She simulated occupational exposure by "painting" formalin on identical cardboard pieces on different mornings within a confined space. A nose clip prevented her recognizing 25% but not 100% formalin. Ventilatory function was monitored by measurement of forced expiratory volume in one second (FEV₁) using a dry spirometer (Vitalograph) or peak expiratory flow (PEF) using a Wright's meter. The results, expressed as % change, are shown in fig. 1. The late asthmatic reaction seen in test 1 persisted for some days and like that of test 3 showed little objective response to inhaled salbutamol. It was inhibited by prior inhalation of betamethasone 17-valerate 200 µg (test 4). There was no febrile response or significant change in W.B.C. or eosinophil count after any of these tests.

After these studies extractor fans were fitted to the dialysis unit, and undiluted formalin was handled more carefully. The nurse avoided unnecessary exposure and, in particular, no longer cleared up spilled undiluted formalin herself. With these measures her symptoms were completely relieved and she needed no medication.

Case 2

A 59-year-old pathologist had suffered mild asthma as a child and hay fever from the age of 19. Airways obstruction had recurred in 1970 and been slowly progressive ever since. He smoked a pipe and had worked with formalin continually for 17 years. He thought that prolonged exposures worsened his symptoms during the evening after. Routine investigations showed an eosinophilia of $1.19 \times 10^9/l$ ($1188/mm^3$), and a skin-prick test produced a positive reaction to grass pollen. There was no other abnormality.

Inhalation provocation tests were conducted as in case 1. Increasing exposures to formalin produced no febrile or haematological response and no significant change in the pattern of ventilatory function from that shown on a control day (fig. 2). The exposure of test 4 was thought to have exceeded the daily maximum encountered naturally in the course of his work. He may consequently be regarded as a control to case 1.

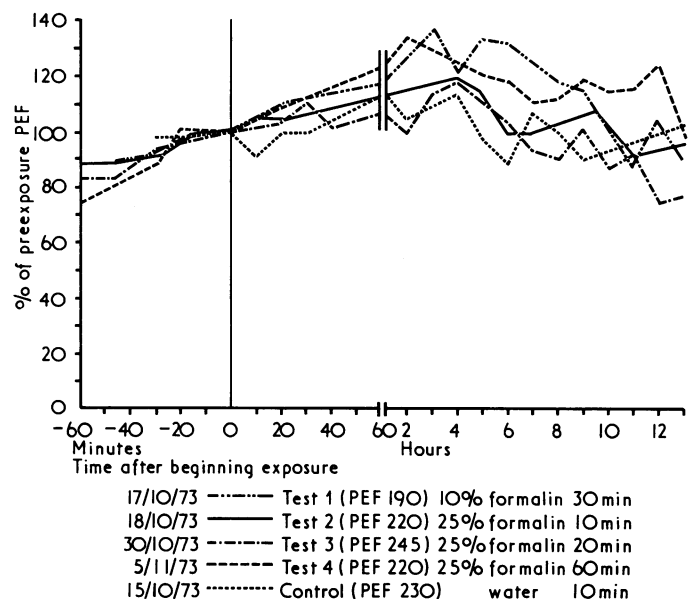


FIG. 2—Case 2. Results of inhalation provocation tests. Values in parentheses are readings obtained immediately before each exposure.

Comment

The value of inhalation provocation tests as an adjunct to a carefully taken occupational history in the investigation of airways obstruction is well illustrated by these two cases. The suspected aetiological role of formalin was confirmed in one patient but excluded in the other. As a result measures of environmental control were introduced where appropriate, with good effect.

The responses observed in case 1 seemed to be specific asthmatic reactions to formalin fumes. They began between two and four hours after exposure was begun. The greater the exposure the longer the reaction persisted, though the maximum percentage fall in ventilatory function was similar, provided exposure was sufficiently prolonged to provoke a positive response. Similar late asthmatic reactions have been described after the inhalation of fumes of other chemicals, including tolylene di-isocyanate (Pepys *et al.*, 1972) and aminoethyl ethanol-

amine (Sterling, 1967; Pepys and Pickering, 1972). Such reactions may be inhibited by the prior inhalation of corticosteroid aerosols (Pepys *et al.*, 1974), and this was confirmed in our patient though subsequent treatment did not in the event prove necessary.

We thank the medical illustration department, Radcliffe Infirmary, for the illustrations.

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Anticoagulant Resistance: An Unusual Case

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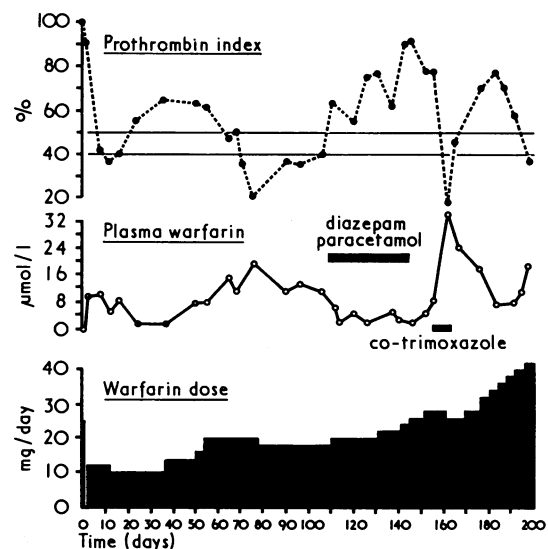
True oral anticoagulant resistance is rare (Paterson, 1972). We report a case of resistance to both coumarin and indanedione derivatives which developed gradually during treatment in a patient with a long history of cerebral embolic episodes.

Case Report

The patient, a woman aged 44, first presented in 1955 with a history of recurrent neurological disturbances and a diagnosis of atypical multiple sclerosis was made. Her neurological state fluctuated until 1966, when she was admitted in cardiac failure, having an apical systolic murmur and persistent tachycardia. The possibility of recurrent emboli from an atrial myxoma was then considered and cardiac catheterization was carried out, showing nothing abnormal. In 1968 after further apparent emboli the procedure was repeated, again with a negative result. On that occasion Osler's nodes and splinter haemorrhages were noted. Blood cultures grew no pathogens, and in view of the possibility of thrombus embolization she was started on anticoagulant therapy. Attempts were made to stabilize her on phenindione but doses up to 400 mg daily gave inadequate control.

In 1969 because of persistent recurrent neurological and cardiac abnormalities cardiomy was performed despite the negative catheter studies and a small atrial myxoma was removed from the mitral valve. Anticoagulation was then restarted because of further cerebral emboli, and over the next two years (until 1971) control was attempted with warfarin (up to 50 mg daily), phenindione (up to 800 mg daily), and nicoumalone (up to 30 mg daily). Resistance developed gradually with all these drugs.

In 1973 a further major cerebral embolus occurred. Warfarin anticoagulation was reattempted, this time with pharmacokinetic studies. All relevant investigations gave normal results before the start of treatment. Phenazone half life studies showed normal liver metabolism



Warfarin dosage, plasma levels, and prothrombin index in patient studied.

Conversion: SI to Traditional Units—Plasma warfarin: 1 µmol/l. \approx 0.3 µg/ml.

before and after six months of warfarin therapy. Warfarin absorption and half life (32 hours) were within the normal ranges. Slowly developing resistance was again seen (fig.).

The patient continues on warfarin 80 mg daily with fluctuating anticoagulant control.

Comment

The most important mechanisms of anticoagulant resistance are (1) decreased absorption of the drug, (2) increased destruction or metabolism of the drug, and (3) the presence of enzymes or receptor sites with altered affinity for vitamin K or the drug.

Our patient showed resistance to the effects of both the coumarin group and the chemically dissimilar indanediones. This resistance was not present at the start of treatment but gradually developed over several months with each drug despite eventual high dosage.

To check the correct ingestion of warfarin plasma levels of the drug were measured (see fig.). These corresponded to dosage. The patient was taking other medication on only two occasions. From day 110 to day 145 she was taking diazepam 10-30 mg daily) and paracetamol (2-4 g daily), and at that time little

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