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 toluene 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.

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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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warfarin was found in the plasma. This is difficult to explain since diazepam and paracetamol do not usually depress warfarin absorption or accelerate its metabolism (Breckenridge, 1972). From day 155 to day 164 when she was taking co-trimoxazole (two tablets twice daily) for a urinary tract infection the plasma warfarin levels increased, producing the expected effect on prothrombin activity. Interestingly the co-trimoxazole appeared to exert its effect by inhibition of warfarin metabolism rather than by displacement from protein binding.

Anticoagulant resistance has been reported by other workers. O'Reilly *et al.* (1964) gave the first report of a kindred of patients exhibiting inherited (probably autosomal dominant) resistance. In such patients the resistance is present at the start of treatment and is believed to occur as a result of altered enzyme or receptor site affinity for vitamin K or the drug. Other patients have been described in whom resistance was due to increased drug metabolism resulting in normal blood levels despite large oral doses (Lewis *et al.*, 1967). We have found only one reference to patients gradually developing tolerance to anticoagulant drugs though the actual doses attained were not exceptional (Soulier, 1961). Our patient gradually acquired resistance to several drugs but adequate control was not achieved even with high doses.

We feel that the anticoagulant resistance in our patient was

not related to reduced absorption (normal rate of appearance of warfarin in the plasma after ingestion) or to increased warfarin metabolism (high plasma levels and normal plasma half life). It was more likely to be due to a gradually developing altered affinity such as that discussed by O'Reilly *et al.* (1964).

The precise cause of our patient's recurrent embolic episodes was not elucidated though we are at present considering further cardiological investigations.

We are grateful to Dr. E. W. J. Gumpert, Professor R. Kilpatrick, and Mr. A. G. Norman for permission to report details of this patient, and to Dr. A. Breckenridge (Royal Postgraduate Medical School) for plasma warfarin measurements and helpful criticism.

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Endocarditis due to *Actinobacillus actinomycetemcomitans*

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There is only one report of a case of endocarditis due to *Actinobacillus actinomycetemcomitans* from the United Kingdom (Mitchell and Gillespie, 1964) though several have been described elsewhere. (Kayser and Bircher, 1967; Underhill, 1968; Vandepitte *et al.*, 1970; Block *et al.*, 1973). The rarity with which this organism is isolated, and thus recognized, may result from the fastidious nature of its growth requirements. We describe here these requirements and emphasize the importance of beginning treatment in clinically probable cases of bacterial endocarditis even if blood cultures are initially negative.

Case Report

A 55-year-old local authority officer was referred as an outpatient in March 1974 with a three-month history of general malaise and a weight loss of 28 lb (12.7 kg). For three weeks he had also noticed night sweats. His previous health had been good, but as a child he had not been allowed to play school games because of a heart murmur. He had been unfit for military service because, he had understood, of severe myopia. There was no history of rheumatic fever or chorea. He had not received any antibacterial chemotherapy before his referral.

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On examination he looked unwell, but not obviously anaemic, and was sweating with an axillary temperature of 37.8°C. His pulse was regular at 120 beats/min and there was a loud (grade 3/4) pansystolic murmur at the apex, which was not displaced. There were no signs of heart failure, the spleen and liver were not palpable, and no splinter haemorrhages, Osler nodes, or retinal lesions were observed. His teeth and gums were healthy. Haemoglobin was found in the urine (Labstix). He was immediately admitted to hospital with a presumptive diagnosis of infective endocarditis.

In the ward his temperature varied between 37°C and 38°C and rose to 39°C on two evenings out of three. Urine microscopy showed red cells with granular and red-cell casts. Initial investigations: appearances on chest radiography and screening were normal, and plasma urea was 7.6 mmol/l (46 mg/100 ml); creatinine 141 µmol/l (1.6 mg/100 ml); and haemoglobin 11.1 g/dl with normochromic and normocytic red cells. The W.B.C. was $10.3 \times 10^9/l$ ($10\,300/mm^3$) (71% neutrophils, 26% lymphocytes, 3% monocytes) and E.S.R. was 123 mm/h. Serum albumin was 27 g/l; globulin 42 g/l; bilirubin 6.8 µmol/l (0.4 mg/100 ml); SGOT 27 IU/l; alkaline phosphatase 100 K.A. units/l. The serum β_1A -globulin was 0.78 g/l (normal 1-1.5 g/l). No evidence of brucellosis or psittacosis was found. Fifteen blood samples were cultured for bacteria and fungi and all showed no growth at 48 hours.

On the third day in hospital a high-pitched diminuendo, early diastolic murmur was noted at the left sternal edge in the fourth intercostal space and the plasma urea was 9.5 mmol/l (57 mg/100 ml) with a creatinine of 168 µmol/l (1.9 mg/100 ml). Treatment was started with benzylpenicillin 18 MU daily by intermittent intravenous infusion, and he was digitalized. On the fifth day of treatment his temperature had fallen to a steady 37°C. Echocardiography at this stage showed mitral regurgitation.

By the 16th day of therapy 11 of the 15 blood samples taken before chemotherapy was started had grown a gram-negative coccobacillus when subcultured under carbon dioxide. After antibiotic sensitivity tests on this organism therapy was changed to ampicillin 4.5 g/day by intravenous injection.

On the 19th day of treatment the patient developed nocturnal dyspnoea with basal crepitations and raised jugular venous pressure; a chest radiograph showed small bilateral pleural effusions. These symptoms and signs responded rapidly to an increase in digoxin and a daily dose of frusemide 40 mg. The haemoglobin concentration had slowly fallen to 9.4 g/dl, and three units of packed cells were given.

The diastolic murmur gradually diminished in intensity and was inaudible after the 43rd day of therapy. Two weeks of intravenous penicillin had been followed by four weeks of ampicillin intravenously, and a 10-day course of streptomycin 0.5 g twice daily by intramuscular injection was added as a final sterilization procedure in case cell-wall-defective forms of the organism had survived the ampicillin. All chemotherapy was then stopped, and as the patient