We did not observe any significant S-T segment changes in the two patients with angina pectoris who developed chest pain. One (case 13) had only "mild discomfort" and produced no significant haemodynamic changes, while the other (case 11) was forced to stop his car quickly because of pain (fig. 9). A sudden increase in arterial pressure, particularly the diastolic value, occurred with the subjective appreciation of pain, but the electrocardiogram remained normal. We have observed similar changes in attacks of angina pectoris in other circumstances (Littler *et al.*, 1973).

The studies of Hoffman (1963), Bellet *et al.* (1968), and Taggart *et al.* (1969) all showed S-T segment and T-wave changes in a number of their patients with ischaemic heart disease during driving—in Taggart's series as many as 59% of the total—however, only two patients (8%) developed frank angina pectoris. We accept that our lead system may not have detected the ischaemic change in these instances (Littler *et al.*, 1972).

Heart rate changes were not obviously different in our three groups of patients who in this respect responded to driving in the same way.

Few observations have been made on the behaviour of the arterial pressure during motor car driving. From this laboratory Beven *et al.*, (1969), using an earlier version of the present method for measuring direct arterial pressure, reported that there was no significant change in arterial pressure during short-term journeys in three patients, one of whom had malignant hypertension. We have not been able to find any other such observations. Our observations confirm that arterial pressure remains remarkably stable during driving. We are not able to comment on its behaviour during busy "rush hour" traffic such as occurs in London. However, most of our patients did drive from outside and through the city of Oxford where the traffic density creates real problems, the traffic on the roads leading into the city being at times dense and occasionally hazardous. There were occasional surges in arterial pressure (figs. 2 and 8) while related to such things as overtaking, but these were short-lived, and overall arterial pressure was little different at the end of a journey as compared with its beginning. Patients with hypertension behaved in a similar way to normotensives. An interesting example of the effect of being driven by another person can be seen in fig. 6. This was atypical: other patients who were driven tended to behave in a similar fashion to that while driving. It should be remembered, however, that the levels achieved during this episode (fig. 6) were no higher than when the patient was driving himself.

Of two patients who developed chest discomfort while driving, one (case 13) had no significant pressure change while the other (case 11) began to show pressure changes *after* pain started. This pattern has been noted in other cases of anginal pain (Littler *et. al.*, 1973) and suggests that this rise of pressure reaction is an effect rather than the cause of the pain.

Recently Aronow and his colleagues (1972) have suggested that the occurrence of angina pectoris during motor car driving may be related to increased levels of arterial carboxyhaemoglobin produced by atmospheric carbon monoxide pollution from car exhaust fumes. These workers studied 10 patients with angina in the resting state, after being driven for 90 minutes during heavy morning "freeway traffic," and two hours after return. The study was repeated 24 hours later while breathing "compressed purified air." Exposure to heavy freeway traffic increased arterial carboxyhaemoglobin levels causing angina to develop sooner after less cardiac work, presumably on the basis of reducing myocardial oxygen tension. S-T segment depression occurred in three patients while breathing freeway air but not after breathing compressed purified air.

It is interesting to note that these workers found no significant difference in resting systolic and diastolic arterial pressures or resting heart rate immediately after the period of driving as compared to the control period or two hours later; findings which are in keeping with our own observations.

Thus it would appear that the arterial pressure of people driving motor cars is much more stable than might have been expected.

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# Sarcoma after Injection of Intramuscular Iron

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### Summary

**Two cases are presented of sarcomata arising at the site of previous iron dextran injections. One of the tumours showed a histological pattern associated with iron dextran administration in animal experiments.**

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### Introduction

The development of fibrosarcoma in animals after iron dextran injections was first reported by Richmond (1957, 1959) and subsequently by other workers (Golberg *et al.*, 1960; Fielding, 1962; Haddow *et al.*, 1964; Roe *et al.*, 1964; Roe and Haddow, 1965; Carter *et al.*, 1968). Tumours of other histological types have also been reported (Roe *et al.*, 1964; Langvad, 1966, 1968; Carter *et al.*, 1968). In man neoplasia has twice been recorded in association with iron dextran therapy. One was a fibrosarcoma (Robinson *et al.*, 1960), the other a secondary deposit from a squamous cell carcinoma (Crowley and Still, 1960). The present report concerns two patients, one developing a reticulum cell sarcoma, the other a pleomorphic sarcoma.

## Case 1

A 56-year-old widow first received iron injections in 1963. She was given three injections of iron sorbitol citric acid complex but developed a febrile reaction, and the treatment was changed to an eight-day course of iron dextran totalling 800 mg followed by a six-month course of oral iron. The injections were given into each buttock alternately.

In October 1969 her family doctor started a course of 10 weekly injections of iron sorbitol citric acid complex, again administered into alternate buttocks. After her ninth injection a painful subcutaneous swelling developed in the right buttock associated with inguinal lymphadenopathy. She also complained of pain in the adductor region of the thigh after a fall. An *x*-ray picture showed the soft tissue shadow in the buttock and healing fractures of the right pubic rami. The swelling was thought to be an infected injection-site haematoma, but after treatment with antibiotics for two weeks had produced no improvement the lesion was explored.

The subcutaneous tissue was thickened and oedematous, containing white tumour-like tissue. The histological appearances, however, were interpreted as those of an inflammatory lesion following an episode of fat necrosis. The patient was next seen six weeks later during which time several cutaneous lesions, from 2·5 to 15 cm in diameter, had developed in the buttock (fig. 1) and the inguinal nodes had become further enlarged. The chest *x*-ray film was clear, but an *x*-ray picture of the pelvis showed erosion at the previous fracture sites. A sternal marrow biopsy showed nothing abnormal.

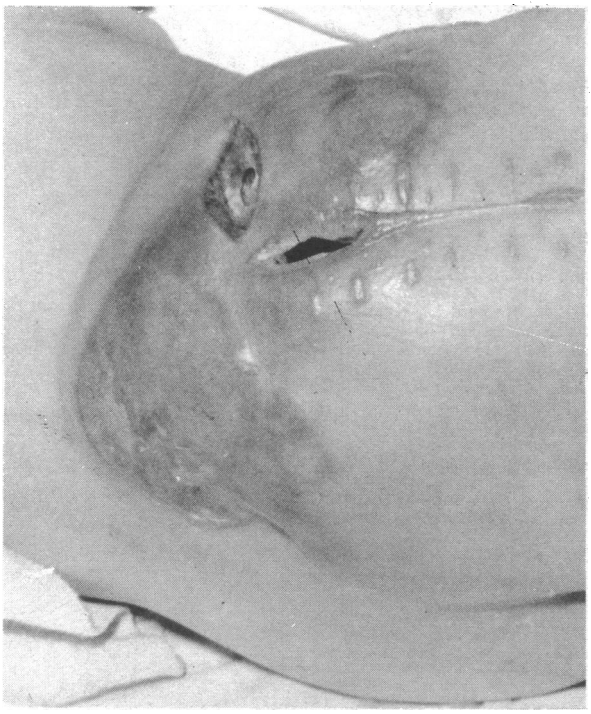

FIG. 1—Case 1. Reticulum cell sarcoma before radiotherapy.

A further biopsy specimen of the tumour was taken and a histological diagnosis of a malignant lymphoid neoplasm of reticulum cell sarcoma type was made (fig. 2). It showed a pleomorphic cellular infiltrate, and in places the cells were elongated and spindle-shaped but elsewhere they were more polygonal. Nuclear morphology was variable and mitotic figures were numerous. There was no evidence of stainable iron within the tumour cells. The first biopsy was reviewed and thought to be compatible with the final diagnosis. A course of radiotherapy produced a good response in both soft tissue and skeletal lesions. Four weeks later the patient developed intestinal obstruction. At laparotomy she was found to have faecal peritonitis from which she died.

Necropsy findings showed peritonitis due to perforation of abnormal bowel. Both the small and the large intestine showed extensive ulceration. Microscopy showed that no tumour was present and

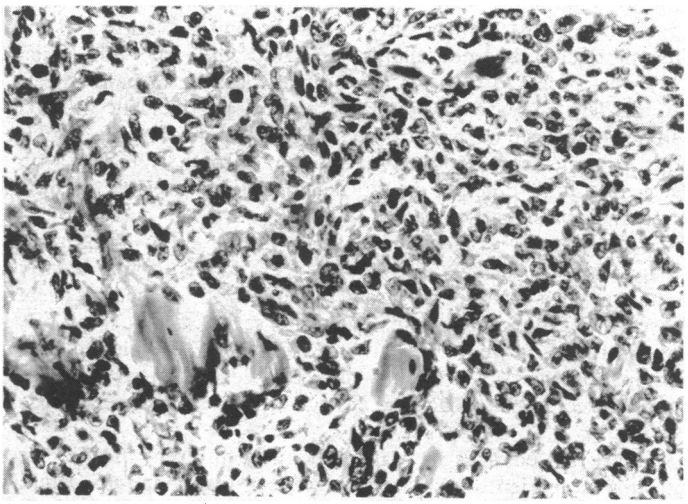

FIG. 2—Microscopal features of tumour in case 1. (×340.)

suggested that these lesions might be due to radiation injury. No viable tumour was detected in the buttock, the pelvis, or any distant site.

## Case 2

A 25-year-old housewife first received a course of iron dextran injections in May 1967 after the birth of her second child. In 1970 she had a further course of iron dextran after her third child. Records of these injections are incomplete, but the total dose was probably 500-1,000 mg in each case. The injections were given into each buttock alternately.

The patient remained well until August 1972 when she presented with a swelling of the right buttock (fig. 3). Two weeks previously she had bruised this area. On examination there was a large, fluctuant swelling of the whole of the right buttock. This was thought to be a haematoma and was treated symptomatically.

The swelling had not diminished in size four weeks later and was therefore incised. At operation it was found to consist of a mass of

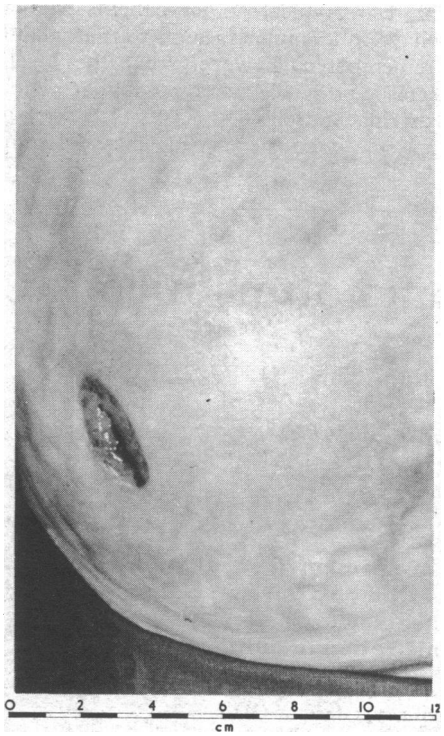


FIG. 3—Case 2. Pleomorphic sarcoma before radiotherapy.

necrotic tissue, and histological examination showed a tumour composed of bizarre pleomorphic cells with a high mitotic rate. Multinucleate giant cells were prominent, but other cell types were present varying from small round cells in a myxomatous stroma to bundles of elongated strap cells. This was thought to be a pleomorphic sarcoma of uncertain histogenesis (fig. 4).

Curative surgery was thought impracticable and a course of local radiotherapy was given but with little response. Despite this the patient remained free from distant metastasis at the time of writing.

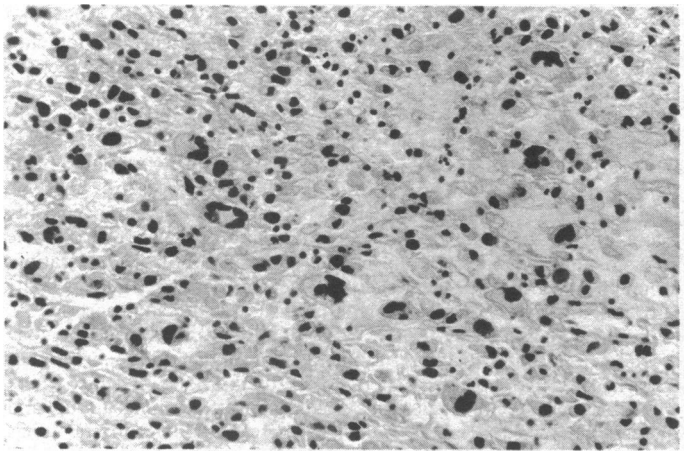

FIG. 4—Microscopal features of tumour in case 2. (×340.)

## Discussion

The possible hazard of tumour induction by iron dextran has been discussed often in the past and was reviewed by Roe (1967). In animals a variety of local tumours have been induced, usually fibrosarcomas (Golberg *et al.*, 1960; Fielding, 1962; Haddow *et al.*, 1964; Roe *et al.*, 1964; Roe and Haddow, 1965; Carter *et al.*, 1968), and, less commonly, fibromas (Roe *et al.*, 1964; Carter *et al.*, 1968). Primary tumours distant from the injection site may be no more frequent than in controls (Roe *et al.*, 1964). Langvad (1966, 1968), however, reported a highly significant incidence of both local and distant primary tumours, the commonest lesion being a reticulosarcoma. Studies of human tissue after iron dextran injection by Baker *et al.* (1961) and Foye and Feichtmeir (1961) failed to show any malignant change.

Several factors may influence the development of these tumours, including dose, species of animal, and life span. The dose of iron dextran may be important either in relation to the total body weight (Baker *et al.*, 1961) or in terms of the amount injected at any one site (Haddow and Horning, 1960; Roe and Lancaster, 1964). Roe and Carter (1967) showed an increase in the degree of malignancy of induced tumours related to the dose administered. The ease with which tumours can be induced is dependent on the species and this may be related to histological differences in the muscle (Baker *et al.*, 1961). The induction time for local sarcomas is about one-third to one-half of the animal's life span, and for lymphoreticular tumours it is over half. By extrapolation tumour induction in man might take over 20 years.

It is difficult to decide how far the above results of animal experiments are relevant to human disease. The association in our present cases between parenteral iron therapy and subsequent neoplasia may well be fortuitous. The tumours, however, developed at the site of injection and one showed a histological pattern commonly associated with iron dextran administration in Langvad's (1966) animal experiments. At necropsy no other primary site was found, which suggests that this was not a secondary tumour.

In case 1 the neoplasm arose during a course of injections of iron sorbitol citric acid complex, and it is conceivable that this may have been involved in tumour induction by altering the patient's immunological mechanism.

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