sensitivity to P.P.D. (Field and Caspary, 1971a) yet negative Mantoux reaction also has a high level of serum depressive factor.

The inhibitory factor is not specific, in so far as M.S. or sarcoid serum will also interfere with unrelated antigen-lymphocyte interaction. For example, serum (1:60) from a patient with other neurological disease and two M.S. sera reduced a mixed lymphocyte reaction by 23·1, 28·6, and 41·5% respectively. Likewise M.S. serum (1:60) reduced the interaction between bovine serum albumin and lymphocytes in a case of erythema nodosum by 54·8% and for egg albumen by 48·1%. A full account of these studies will be given elsewhere, but it is already clear that the development of lymphocyte sensitization (as indicated by the capacity to interact with a particular antigen) seems to be associated with the appearance in the serum of a depressant factor and that this factor is more effective against its own lymphocytes than those from another individual. In view of the many reports of depressive factor referred to in the introduction, it may be that the present study of M.S. and other neurological disease is but a special instance of a general phenomenon—the simultaneous development of lymphocyte responsiveness and a serum-mediated "damping mechanism." If further studies support this view, then we have another example of a biological "brake-accelerator" mechanism, operating this time in immunological reactivity. The suppressor element might indeed be the "feedback factor" postulated in several modern schemata involving lymphocyte activity—for example, that of Mackler (1971).

It is legitimate to speculate that disease may result from imbalance between lymphocyte reactivity on the one hand and suppressive activity of serum on the other, so that it would be reasonable to attempt therapeutic control of lymphocyte activity (either in positive or negative direction) by increasing or reducing the suppressive factor. Thus autoimmune diseases (if they exist) presumably result from a runaway activity of lymphocytes and might be treated by augmenting the level of suppressor factor. On the other hand, where lymphocyte activity is being held in check physiologically and where its greater exercise might be beneficial—for example, in resistence to cancer—it might be possible to eliminate or reduce suppressor activity. As a first step it is necessary to isolate and characterize the suppressor factor. Its relation to the factor isolated by Cooperband, Bondevik, Schmid, and Mannick (1968) is being explored, but it is already clear that it occurs in the same α2-globulin fraction in normal, M.S., and cancer serum.

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MEDICAL MEMORANDA

Muscle Fibrosis and Contractures in a Pethidine Addict

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Myopathy complicating intramuscular administration of some drugs is well recognized. The repeated intramuscular injection of chloroquine, for example, induces intense necrosis and phagocytosis at the injection site (Aguayo and Hudgson, 1970). Pethidine is usually injected intramuscularly, and it is perhaps surprising that there has been only one report of myopathy developing in those addicted to it (Aberfeld *et al.*, 1968). We believe that the case described here was of this kind.

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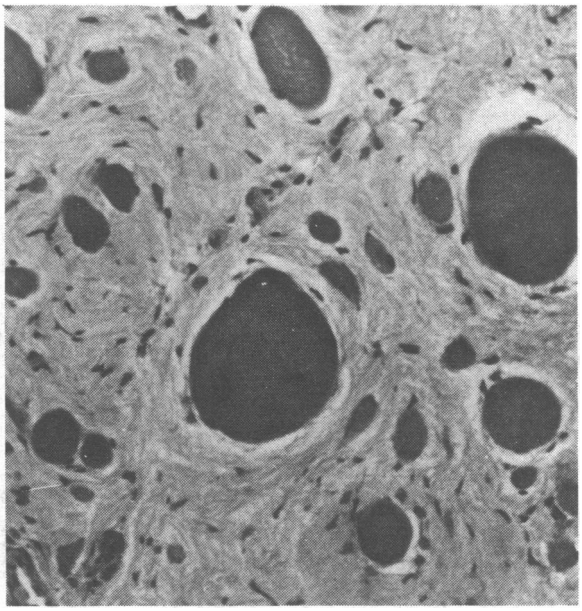
Case Report

The patient was a 60-year-old Indian who had emigrated to England in 1968. When first seen in December 1968 he complained that for 18 months he had experienced increasing difficulty in flexing his elbows fully and for eight months a similar difficulty with his knees. He had had a cholecystectomy in 1954 and a calculus removed from the common bile duct in 1963. He was given pethidine first in 1961 for biliary colic and he continued to inject the drug with increasing frequency until the second laparotomy in 1963. After that he remained in hospital for three months, receiving pethidine 100 mg every two or three days. On leaving hospital he had continued to inject himself in steadily increasing doses up to 1,000 mg daily. At first he injected the drug only into the triceps muscles, but in 1967 he developed an abscess in the left triceps and began to inject the drug into the fronts of both thighs. When they became "woody" he used the medial aspect of the thighs and the buttocks. He did not sterilize the needles, which were about 3·7 cm long, and changed them only every two or three weeks. Since coming to England he had been persuaded by his son to stop the drug, and apart from a feeling of restlessness and insomnia he had suffered no untoward effects.

On examination many needle marks were present on the lateral aspects of both upper arms and of the thighs. Both triceps muscles were indurated, particularly where there were most needle marks, and the skin was also thickened. There was pronounced induration of both thighs, particularly of the rectus femoris and vastus medialis muscles and to a less extent of the vastus lateralis and tensor fasciae latae, particularly on the right. There was severe contracture of both triceps muscles, and elbow flexion was limited to 85° on the left. There were also severe contractures of both quadriceps, knee flexion being restricted to 45° on the right and 35° on the left. There was no demonstrable weakness of these muscles. Triceps and knee jerks were absent but the other reflexes were present. There were no sensory abnormalities in the extremities. There was moderate enlargement of the inguinal lymph nodes but no other lymphadenopathy.

The serum adolase and aspartate and alanine transaminase levels were all raised (10·7 mU/ml, 132 Karmen units, and 200 Karmen units respectively) but the serum creatine kinase level was normal. Radiographs of the arms and thighs showed no soft tissue calcification. Considerable resistance was met in the right triceps and rectus femoris muscles on introducing the needle electrode for electromyography. In the triceps there were occasional fibrillation potentials as well as spontaneous discharges of high frequency which were abrupt in onset and termination. On voluntary contraction brief polyphasic potentials of low amplitude appeared, and the interference pattern on maximal effort was much reduced in density and amplitude. Only distant activity of low voltage was recorded in the quadriceps.

The most striking feature in sections of biopsy material from the left rectus femoris and right triceps muscles was the presence of gross, widespread interstitial fibrosis which had almost completely



Triceps biopsy. Severe loss of muscle fibres with fibrous tissue around the remaining fibres which show excessive variation in size and internal nuclei. (Haematoxylin and eosin. × 208.)

replaced the muscle fibres in some areas, and broad bands of mature collagen with a few atrophic muscle fibres distributed in a random fashion were all that could be seen (Fig.). In all the fibrotic areas the muscle fibres showed typical chronic myopathic changes—that is, rounded fibres, some of which contained internal nuclei, considerable variation in fibre diameter, and fibre splitting. Apart from the areas into which the pethidine had presumably been directly injected, however, the muscle fasciculi and individual fibres were substantially normal apart from slight perimysial and endomysial fibrosis. No other histological abnormalities were found and histochemical study failed to show any evidence of selective fibre-type atrophy or of any other metabolic disturbance.

The patient failed to complete a course of oral penicillamine, given in the hope of arresting the fibrosis, but notwithstanding made a remarkably good functional recovery with physiotherapy alone. When last examined (August 1970) his right elbow could be flexed to 140°, his left to 100°, his right knee to 180°, and his left to 110°. He had not resumed injecting himself with pethidine, so far as was known.

Comment

Aberfeld *et al.* (1968) described extensive induration of skin and fibrosis of multiple limb muscles in a mother and daughter who suffered from porphyria and had been addicted to pethidine for periods of 12 and 5 years respectively. As in the present case the pattern of muscle involvement did not conform to that of any recognized myopathy, and the parts involved were those accessible to self-administration of the drug. The serum aldolase and creatinine kinase were raised in one case and normal in the other. No electrical activity could be recorded from the indurated areas of muscle in either. The biopsy in their first case showed disorganization of muscle architecture with areas of connective tissue proliferation, haemorrhage, and infiltration with mononuclear cells. They believed that the muscle lesions were most likely due to the combination of repeated needle trauma, chemical irritation, and local infection. Certainly the production of focal areas of muscle fibre destruction by hypodermic needles and electromyographic needle electrodes has been shown in the experimental animal (Engel, 1967; Hathaway *et al.*, 1969).

It might be expected therefore that the repeated intramuscular injections in these patients would produce degeneration of large numbers of muscle fibres. Disruption of the sarcolemma and the endomystial sheaths of muscle fibres would also render abortive any regenerative attempts, and newly-formed muscle fibres would also be exposed to subsequent needle trauma, contributing thereby to an overall loss. Low grade infection probably played a part in the development of the muscle lesions in the present patient. The possibility that pethidine itself has a local myotoxic or sclerosing action must also be considered. Though induration of skin at the site of subcutaneous injection of pethidine is known to occur (Goodman and Gilman, 1970) the effects of intramuscular injection of the drug have not been reported.

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