DISORGANISATION OF THE KNEES FOLLOWING INTRA-ARTICULAR HYDROCORTISONE INJECTIONS

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Despite reports of severe arthropathy after its use, the injection of steroids into joints is still widely practised. The following case history adds to the evidence against this practice and has prompted a review of the theoretical and practical objections to its continued use.

CASE REPORT

A seventy-three-year-old woman was first seen in January 1968. Four years before, she had felt pain of gradual onset beginning in the left knee and later in the right. She had no other joint pains. In May 1965 she had had a moderate effusion in both knees and the right one had shown varus deformity of 10 degrees. Radiographs showed moderate osteoarthritic changes in the medial compartment and patello-femoral compartment of the right knee, and similar but less marked changes in the left knee (Fig. 1). Treatment by heat and quadriceps exercises, with phenylbutazone 100 milligrams three times a day for nine months, had given slight relief.

In March 1966 indomethacin 50 milligrams three times a day was used to replace the phenylbutazone. Radiographs in June 1966 showed slightly more advanced osteoarthritis and resorption of the medial tibial condyle in the right knee. The left knee showed slightly more medial joint lipping than before (Fig. 2).

In October 1966 a course of twelve injections of 50 milligrams hydrocortisone at weekly intervals had been given into the left knee joint. This gave marked symptomatic improvement.
In view of the success with the left knee a course had been begun of 50 milligrams hydrocortisone into both knees, repeated every two weeks for twenty injections. This amounted to a total of thirty-two injections into the left knee and twenty injections into the right knee in fourteen months. Progress—In January 1968 the patient began to have severe pain, day and night. She was able to walk only with difficulty, unable to ascend or descend stairs and confined to the house. The left knee was more painful than the right. She was then a healthy, energetic woman of seventy-three years. She stood with a varus deformity of 20 degrees and fixed flexion deformity of 20 degrees on the right and 15 degrees of valgus and 20 degrees of fixed flexion on the left.
There were slight effusions and moderate thickening in both knees, with marked crepitus on movement. The range of flexion was from 10 to 100 degrees on the right and from 20 to 60 degrees on the left. The left knee showed 10 degrees of valgus instability and 20 degrees of varus instability from the neutral. The hips, ankles and feet were normal. No neurological or circulatory defect was present in the legs.

Radiographs of both knees, taken with the patient standing, showed the deformities and a dramatic change in the extent of joint damage in the fourteen months (Fig. 3).

**Investigations**—Haemoglobin was 88 per cent (12.6 g.) and erythrocyte sedimentation rate was 34 millimetres in the first hour (Westergren). The total white cell count was 6,800 per cubic millimetre with a normal peripheral blood film. Latex fixation test for rheumatoid arthritis was negative and uric acid level was normal on three occasions. The Wassermann and Kahn reactions were negative. Examination of aspirate from the right knee revealed only a straw-coloured fluid containing red blood cells and scattered lymphocytes and neutrophils.

**Findings at operation**—The suprapatellar pouch, intercondylar notch and lateral recesses of the joint were filled with a green-brown, cheese-like material (Fig. 4). The articular surfaces of the femoral condyles, tibial condyles and patella were denuded of cartilage and stained green. The menisci and cruciate ligaments had disappeared.

**Histological examination**—This revealed extensive degenerative changes affecting the femoral, tibial and patellar surfaces with loss of articular cartilage. The exposed bone was in some places sclerotic and showed evidence of osteoelastic activity. In other areas the bone had been irregularly fractured and fragmented and fibrous granulation tissue had grown from the marrow spaces to cover the bone ends (Fig. 5). The joint debris contained haemosiderin and minute bone fragments, the abundance of the latter suggesting that rapid bone destruction had occurred.

**COMMENT**

It is seldom possible to provide absolute proof of the destructive effect of intra-articular steroid injections. In rheumatoid arthritis and osteoarthritis the joints are progressively destroyed anyway, and at a rate which is not accurately predictable. In these diseases the sequelae of steroid therapy may be attributed to the agency of other drugs, to accidental infection or merely coincidence.

We believe that the changes we have described in our patient cannot reasonably be explained other than by the repeated injections. Radiographs taken at an interval of one year before the course of injections showed a slowly progressive osteoarthritis. In the right knee there were indeed cystic changes in the medial condyle of the tibia and the lateral condyle of the femur, which might imply impending collapse of the bone, but in the left knee there were no such signs. Other drugs cannot reasonably be implicated, because the second set of
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radiographs was made after the completion of courses of treatment with phenylbutazone and indomethacin. Nor was there any evidence of accidental infection.

That the patient's initial symptoms arose from degenerative osteoarthritis and no other form of arthritis seems certain from the typical radiographic appearances and the negative serological tests. Yet the macroscopic and microscopic findings at operation were quite different from those seen in advanced osteoarthritis. It is notable, too, that the left knee of our patient, the one which received more injections, was eventually the worse affected, though it had been the better of the two.

Chandler and Wright (1958) first drew attention to a rapidly progressive arthritis and destruction of the knee joint in ten out of eighteen patients with rheumatoid arthritis treated in this manner, and they noted the similarity to Charcot's arthropathy. They considered that hydrocortisone released the joint from the normal protective inflammatory response associated with arthritis, permitting damaging movement. Sweetnam, Mason and Murray (1960) and Steinberg, Duthie and Piva (1962) described further cases of hydrocortisone-induced arthropathy in the hip and knee respectively.

The mechanism of production of the arthropathy was not understood initially, but Cohen (1961) warned of the danger of softening the subchondral bone in the neighbourhood of a joint injected with hydrocortisone, a complication which had already been reported with systemic steroid therapy (Duperrat, Pringuet and Puissant 1961). Hydrocortisone inhibits the formation of ground substance in mesenchymal tissue generally, including articular cartilage, and Thomas (1964) showed experimentally that the effect of hydrocortisone depended on the state of the articular cartilage. If it is intact then hydrocortisone stabilises the lysosomes within the chondrocytes and inhibits breakdown of the cartilage, but if it is already damaged, as in arthritis, hydrocortisone inhibits repair.

Fig. 5
Photomicrograph of the upper end of the left tibia removed at operation (×10.) The articular surface is denuded of cartilage. Fractured bone trabeculae are seen and on the left side of the specimen fibrocartilage is seen emerging from the bone space to cover the surface.

VOL. 51 B, NO. 3, AUGUST 1969
Mankin and Conger (1966) measured glycine \( ^{3}\text{H} \) incorporation into rabbit articular cartilage and demonstrated that the effect of hydrocortisone was to decrease matrix synthesis. Salter, Gross and Hall (1967) injected hydrocortisone into normal rabbits' knees and produced fissuring of articular cartilage, and loss of metachromasia, with cystic lesions within the cartilage. These effects were most marked in the animals which had received the greatest number of injections.

Two papers (Holden and Kendall 1961; Bain, Jacomb and Wynn 1967) have indicated that greater symptomatic relief may be obtained with steroids that remain in the joint for a longer period than hydrocortisone after injection, such as prednisolone and Depo-Medrone. However, McCluskey and Thomas (1959) showed that prednisolone was even more effective than hydrocortisone in preventing cartilage repair.

There are good theoretical reasons for supposing that intra-articular injections of steroids might damage an arthritic joint, and some evidence from clinical practice that this does in fact occur.

Only the most obvious disasters will be reported, because the signs of less severe damage are difficult to distinguish from the natural progression of the original disease.

The case against multiple injections is so strong that the practice should, in our opinion, be discarded, which implies that even a single injection requires strong justification.

Our thanks are due to Mrs J. A. Herbert who typed the manuscript and Mr R. Emanuel who made the illustrations.

REFERENCES


