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Hydrocortisone Arthropathy—An Experimental Investigation

ROBERT B. SALTER, M.D., M.S., F.R.C.S.[C], F.A.C.S.,*
ALLAN GROSS, M.D.† and J. HAMILTON HALL, M.D.,‡
Toronto

DESPITE the prevalent clinical use of intra-articular hydrocortisone in the treatment of various types of chronic joint disease there have been relatively few published reports of undesirable side effects in the joints so treated. Chandler and Wright,[1] in 1958, reported clinical and radiographic deterioration in specific joints of patients with rheumatoid arthritis following repeated intra-articular injections of hydrocortisone. In 1959, Chandler *et al.*[2] reported similar deterioration in the hip joints of a patient with osteoarthritis following repeated intra-articular injections of hydrocortisone and referred to the condition as "Charcot's arthropathy". Subsequently, reports by Sweetman, Mason and Murray,[3] Steinberg, Duthie and Piva,[4] Zachariae,[5] and Miller and Restifo[6] have implicated intra-articular injections of hydrocortisone as a cause of subsequent joint deterioration.

There is, as yet, no absolute proof that the reported deterioration of human joints following repeated intra-articular injections of hydrocortisone is caused by the hydrocortisone. Since all of the joints so treated were already involved by a pathological process, it could be argued that any deterioration following such injections might be part of the natural course of the underlying disease process. Nevertheless, these clinical case reports are disturbing and merit scientific investigation.

EXPERIMENTAL DESIGN AND MATERIALS

The present experimental investigation was designed to determine the effects of repeated intra-articular injections of hydrocortisone—and of the suspending medium alone—on the living articular cartilage of the knee joints of adult rabbits.

New Zealand white rabbits, varying in weight from 2000 to 2500 grams, were used throughout the experiments. Hydrocortisone was obtained commercially as Hydrocortone-T.B.A. (Hydrocortisone tertiary-Butylacetate) (17-hydroxycorticosterone-21-tertiary-butylacetate) (Merck Sharp & Dohme). Hydrocortone-T.B.A. is a very slightly soluble ester of hydrocortisone. The hormone is prepared as a 25 mg. per ml. suspension. The formula of the suspending medium is as follows: 0.9% benzyl alcohol, 0.1% polysorbate 80, 0.01% benzalkonium chloride, 0.25% sodium citrate, 45.00% sorbitol and water for injection q.s. ad 100%.

In the first group of 45 adult rabbits, Group A, the left knee joints received an injection of 1 ml. of Hydrocortone-T.B.A. once a week for periods varying from 2 to 10 weeks. The right knee joint of each experimental animal received an injection of 1 ml. of sterile normal saline once a week for the same period of time.

In the second group of 10 adult rabbits, Group B, the left knee joints received an injection of 1 ml. of the suspending medium alone, once a week, for periods varying from 2 to 10 weeks.

The intra-articular injections into the suprapatellar pouch of the knee joints were performed under general anesthesia. The animals were allowed to run free until the time of sacrifice, which was one week after the final intra-articular injection.

Postmortem studies of the dissected experimental and control knee joints included gross examination of the joint structures as well as examination under the dissecting microscope. The lower ends of the femora and the upper ends of the tibiae were then decalcified, sectioned, stained by various methods (hematoxylin and eosin, periodic acid-Schiff, and toluidine blue) and examined microscopically.

EXPERIMENTAL RESULTS

Group A

All knee joints that received two or more injections of the hydrocortisone ester revealed both gross and microscopic abnormalities, the severity of which varied directly with the number of injections.

The gross changes, which were consistently most marked on the medial side of the tibial joint surface, included loss of the normal lustre of the surface of the cartilage, generalized thinning of the cartilage, fissuring as well as fibrillation of the cartilage and multiple small white deposits deep to the joint surface within the

From the Department of Surgery and the Research Institute, The Hospital for Sick Children and the University of Toronto.
*Surgeon-in-Chief, The Hospital for Sick Children, and Professor, Department of Surgery, University of Toronto.
†Research Fellow, Division of Surgical Research, Research Institute, The Hospital for Sick Children.
‡Research Fellow, Division of Surgical Research, Research Institute, The Hospital for Sick Children.
Reprint requests to: Dr. R. B. Salter, Department of Surgery, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario.

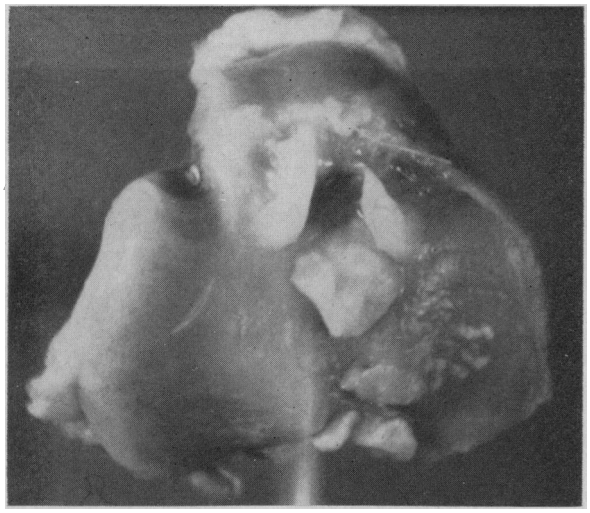

Fig. 1.—Upper tibial joint surface of the left knee of a rabbit which had received eight intra-articular injections of Hydrocortone-T.B.A. at weekly intervals. Note the multiple small white deposits below the surface of the articular cartilage on the medial tibial plateau (right side of the photograph).

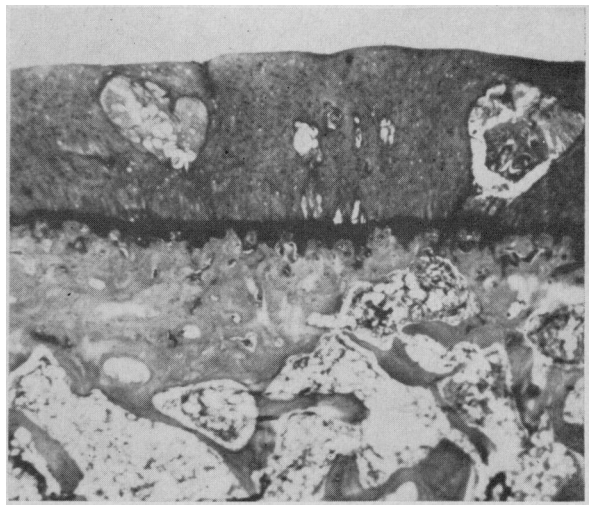

Fig. 3.—Low-power photomicrcgraph showing multiple cystic lesions within the matrix of articular cartilage from the medial side of the upper tibial joint surface of a rabbit which had received 10 intra-articular injections of Hydrocortone-T.B.A. at weekly intervals. These lesions were found to contain calcium.

substance of cartilage (Fig. 1). The latter were seen only after six or more injections.

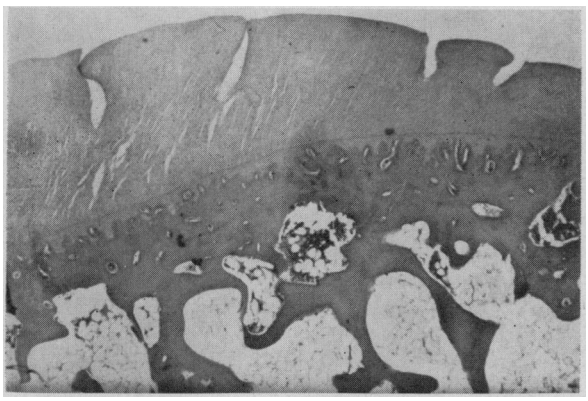

Fig. 2.—Low-power photomicrograph showing marked fissuring of the articular cartilage from the medial side of the upper tibial joint surface of a rabbit which had received eight intra-articular injections of Hydrocortone-T.B.A. at weekly intervals.

The aforementioned gross lesions were confirmed by microscopic examination. The fissuring of the cartilage was striking (Fig. 2). The PAS- and toluidine blue-stained sections demonstrated loss of metrachromasia. The white deposits within the cartilage were found to represent cystic areas of degeneration within the middle zone of the cartilage matrix (Figs. 3 and 4). Preliminary histochemical studies of the contents of these cystic areas in undecalcified specimens revealed the presence of calcium.

The control knee joints, which received a comparable number of injections of sterile normal saline, were grossly and microscopically normal.

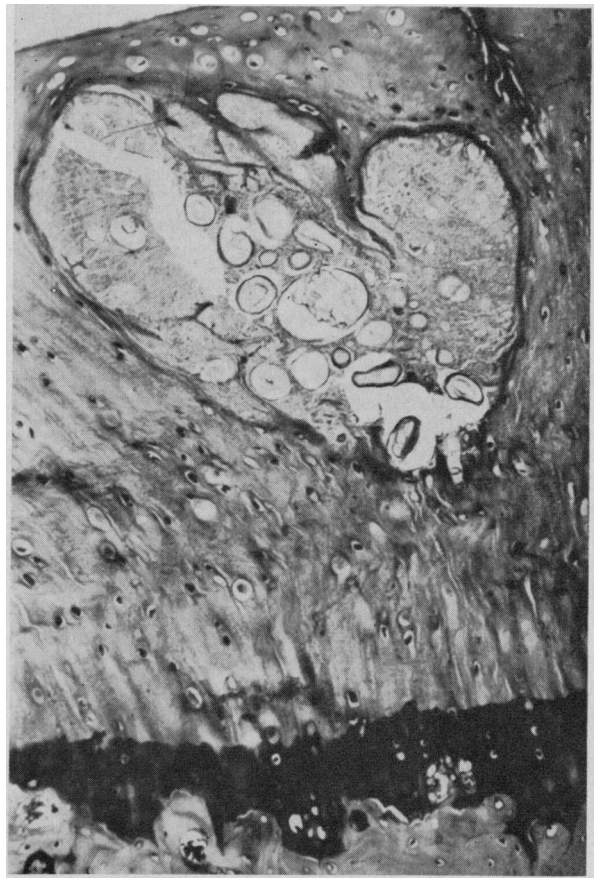

Fig. 4.—High-power photomicrograph of the large cystic lesion shown in the left upper corner of Fig. 3.

Group B

The knee joints which received repeated injections of the suspending medium alone were also grossly and microscopically normal.

DISCUSSION

The animal experiments in Group A have demonstrated consistent lesions in articular cartilage due to repeated injections of Hydrocortone-T.B.A. The absence of lesions following the repeated injections of the suspending medium alone in Group B clearly indicates that the lesions in Group A are due to the hydrocortisone rather than to any component of the suspending medium. Furthermore, since the severity of the lesions varied directly with the number of injections, the deleterious effects of the hydrocortisone would seem to be cumulative.

While the present investigation was in progress, Mankin and Conger[7] using glycine-^{3}H incorporation in rabbit articular cartilage, reported a reversible biochemical lesion following a single intra-articular injection of Hydrocortone-T.B.A. They concluded that glycine-^{3}H incorporation can be equated with protein synthesis and that the effect of the Hydrocortone-T.B.A. was "a decrease in matrix synthesis during the period of its effect". The biochemical lesion following a single intra-articular injection was gradually reversible over a period of two weeks.

It is not surprising that repeated intra-articular injections of Hydrocortone-T.B.A., once a week over a period of several weeks, should produce a progressively severe morphological, or anatomical, lesion in articular cartilage. It seems probable that the clinical and radiographic deterioration reported in human joints following repeated intra-articular injections of hydrocortisone is primarily due to a specific deleterious effect of the drug on the metabolism of cartilage. Less probable is the explanation suggested by the term "Charcot arthropathy", namely, that the deterioration may be due to relief of painful inflammation in the joint and resultant increased trauma to already damaged articular cartilage with increased use. Nevertheless, the latter may at least be a secondary cause of the phenomenon under discussion.

Since, in clinical practice, repeated intra-articular injections of hydrocortisone are administered for various forms of chronic joint disease in which the articular cartilage is already abnormal, further animal experiments are planned to determine the effects of repeated intra-articular injections of Hydrocortone-T.B.A. on previously damaged articular cartilage. Furthermore, because of the possibility of species variation in sensitivity to hydrocortisone, the present experiments will be repeated in another species.

At present, however, the aforementioned clinical reports,[1-6] the biochemical lesion demonstrated by Mankin and Conger,[7] and the progressive morphological lesions demonstrated in the present experimental investigation, when combined and correlated, justify a warning signal regarding the potential danger of repeated intra-articular injections of hydrocortisone in any given human joint over a long period of time. While it is unlikely that a single intra-articular injection of hydrocortisone is harmful, multiple intra-articular injections of hydrocortisone in a given joint are probably deleterious to the articular cartilage and should be avoided in order to prevent the iatrogenic complication of hydrocortisone arthropathy.

Summary Published clinical reports of joint deterioration following repeated intra-articular injections of hydrocortisone stimulated the authors to conduct an experimental investigation in living rabbits.

Progressive morphological lesions were demonstrated in the articular cartilage of all joints that received two or more intra-articular injections of Hydrocortone-T.B.A. at weekly intervals. These lesions included loss of the normal lustre of the surface of the cartilage, thinning, fissuring, fibrillation of the cartilage and cystic lesions containing calcium within the cartilage matrix. Injections of saline and injections of the suspending medium alone produced no lesions in the cartilage.

The morphological lesions are most reasonably explained on the basis of a specific biochemical effect of hydrocortisone on articular cartilage, namely a decrease in matrix production, as suggested by Mankin and Conger.[7] It is suggested that repeated intra-articular injections of hydrocortisone in a given joint over a long period of time have a deleterious effect on the articular cartilage —not only in the rabbit, but probably also in man.

Résumé La publication de rapports sur la détérioration des articulations à la suite d'injections intra-articulaires répétées de hydrocortisone, a poussé les auteurs à poursuivre des recherches expérimentales sur des lapins.

Des lésions morphologiques progressives se sont manifestées dans le cartilage de toutes les articulations ayant reçu deux injections intra-articulaires ou plus d'hydrocortone-T.B.A. à intervalles d'une semaine. Parmi ces lésions on peut citer la disparition du lustre normal de la surface cartilagineuse, l'affaiblissement du cartilage par amincissement, fissuration et fibrillation et l'apparition de lésions cystiques calcaires dans la matrice cartilagineuse. Aucune lésion ne fut occasionée par des injections salines ou du fluide de suspension.

L'explication la plus raisonnable de ces lésions morphologiques serait un effet biochimique spécifique de l'hydrocortisone sur le cartilage articulaire, soit une diminution de la production matricielle,

selon les suggestions de Mankin et Conger.[7] Il est suggéré que des injections intra-articulaires d'hydrocortisone dans une articulation quelconque, répétées sur une période prolongée, ont un effet nocif sur le cartilage articulaire, non seulement chez le lapin mais probablement également chez l'homme.

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Single Total-Dose Intravenous Infusion of Iron-Dextran

D. T. LEE, M.D., F.R.C.S. and S. C. ROBINSON, M.D., F.A.C.O.G.,
Halifax, N.S.

THE vast majority of persons with iron deficiency are best treated by oral iron. With adequate dosage and sufficient time, this route is effective. It is also simple, inexpensive and safe.

On the other hand, there are clear indications for using parenteral iron, and these have been outlined previously.[5] Briefly, these indications are: (1) iron deficiency associated with intolerance to oral iron, or unwillingness to take such medication; (2) to build iron stores rapidly and effectively; (3) severe iron deficiency with marked anemia requiring rapid treatment—e.g. late pregnancy; (4) in patients with defective iron absorption; and (5) in gastrointestinal disorders precluding the ingestion of iron.

It is apparent that large amounts of parenteral iron are being used today.[1, 3-6, 8] Not so apparent are the common side effects of mild degree and the rare side effects of a serious or dangerous nature. These range from local pain and discolouration, through phlebitis, abscess and arthropathy to severe anaphylactoid reactions. No sarcomas in humans have been reported, but a fatal anaphylactic reaction was recently described.[2]

Iron-sorbital-citric acid complex (Jectofer) given intramuscularly appears to be less likely than intramuscular iron-dextran (Imferon) to produce local reactions,[5] but overdosage can easily occur and inadvertent intravenous injection may be dangerous.[5] Although 30% of iron-sorbital citric-acid complex is lost in the urine, this preparation appears to have some real advantages for parenteral use by the intramuscular route. However, local pain and the inconvenience of repeated intramuscular injections have stimulated the re-examination of the intravenous use of iron preparations.

In 1962, one of us described the intraperitoneal administration of iron-dextran given as a single dose calculated to replace the iron deficit.[7] These experiments in humans were done after the safety of the method had been established in animals. Owing to the strong chelation of the iron to the dextran, the high blood levels did not cause iron toxicity. Despite this, the manufacturer advised us not to proceed with the intravenous use of this material. However, numerous reports have now appeared in the European literature concerning the intravenous use of iron-dextran.[1, 4, 6, 8] The first reports concerned the use of this material for measuring circulation time and blood volume by the Fick principle, but more recently workers have described single total-dose intravenous infusions to replace body iron deficit.[1, 4, 6, 8] All agree on the effectiveness of this mode of administration, but all describe significant side effects. Because of the great convenience of single-dose administration, we determined to study the safety, efficiency and suitability of single total-dose intravenous infusion of iron-dextran.

Iron-dextran (Imferon) is a stable chelate with a molecular weight in the 180,000 range. It is sterilized in the vial and contains 50 mg.

From the Department of Obstetrics and Gynecology, Dalhousie University, Halifax, Nova Scotia.
Reprint requests to: Dr. S. C. Robinson.