Acta orthop. Scandinav. *36*, 127–136, 1965.

From Orthopaedic Hospital Copenhagen, Dep. I – II and IV.
Chiefs: A. Bertelsen, E. Hj. Larsen and K. Bang Rasmussen.

DELETERIOUS EFFECTS OF CORTICOSTEROIDS ADMINISTERED TOPICALLY, IN PARTICULAR INTRA-ARTICULARLY

By

LIS ZACHARIAE

INTRODUCTION

Cortisone and its derivatives exert an indubitable clinical effect in rheumatoid arthritis and other disorders of the mesenchymal tissues, both when administered systematically and topically. One of the conditions in which topical treatment has gained most ground is osteoarthritis. At the outset, numerous reports were published on the excellent therapeutic effect (*Hollander* 1951, 1953, *Kearsley* 1952, *Egelius* 1953, *Zachariae* 1954, and many others). Gradually, however, various complications began to be noticed, first infections and their sequelae, but more important still are the degenerative conditions which may develop in such a cortisone-treated joint. *Chandler et al.*, in 1958, reported Charcot-like changes in a hip joint treated with local injections of hydrocortisone acetate, and others have subsequently published similar findings (*Chandler & Wright* 1958, *Sweetnam et al.* 1960, and *Steinberg et al.* 1962). The author will report a few of her own cases which illustrate these changes and thereafter, on the basis of the previous and present experience, try to arrive at an acceptable explanation by considering the essential mechanism of the effect of these hormones.

CASE REPORTS

Case 1. A male, aged 68, had been suffering for one year from osteoarthritic symptoms with moderate radiological changes (Fig. 1). In the course of the next year he received 50 injections of various cortisone preparations into the hip and, at the same time, systemic Butazolidin medication. This resulted in temporary improvement which was, however, replaced by exacerbation, and X-rays showed that

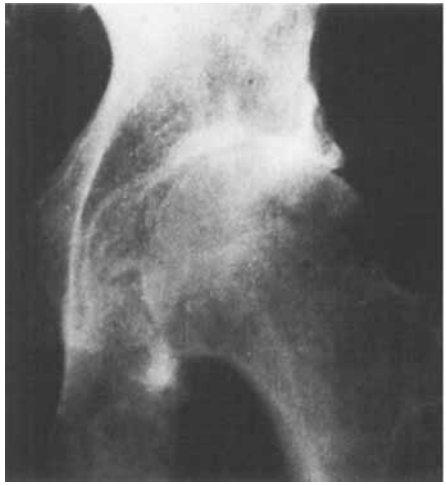

Fig. 1.

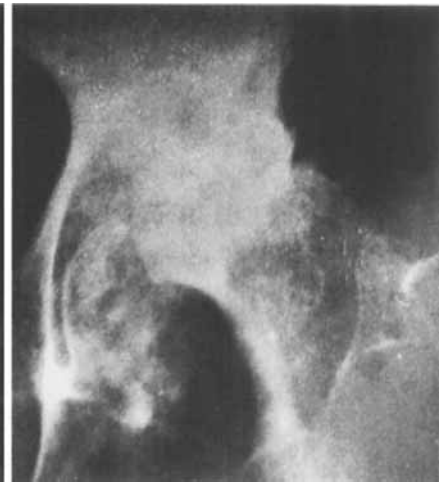

Fig. 2.

Fig. 1. (Case 1). Hip with moderate osteoarthritic changes.

Fig. 2. (Case 1): Same hip one year later. Severe destruction of the femoral head has occurred during topical cortisone therapy.

the lesion had become considerably worse, with destruction and dislocation of the femoral head (Fig. 2).

Case 2. A female, aged 57. Ever since youth, she had suffered from symptoms in both hips, mainly the right. When the medication was instituted, X-rays revealed subluxation and incongruence of both hips with distinct osteoarthritic changes on the right, while on the left there was but moderate osteoarthritis. She received a series of hydrocortisone acetate injections into both hips. After one of the injections into the left hip, she developed violent pain which persisted and became intensified, making the left hip more painful than the right. Seven years later the patient was so disabled that she was unable to walk. X-rays now showed that the lesion in the right hip had progressed steadily, while in the left hip there was extensive destruction; in fact, the entire upper part of the femoral head had been destroyed.

Case 3. A female, aged 60, with a long history of various articular symptoms. As she began to suffer from increasing pain in the right hip and X-rays revealed osteoarthritis, she was given one intra-articular injection of hydrocortisone acetate. This elicited severe pain which persisted, and X-rays 6 months later showed marked progression of the lesion.

Case 4. A female, aged 75, had increasing osteoarthritic complaints from one knee. Within a couple of years she received repeated injections of hydrocortisone acetate. The injections were administered in part intra-articularly and in part at the pes anserinus which was tender (Fig. 3). The symptoms persisted, and X-rays revealed a progressing lesion at the medial tibial condyle (Fig. 4). Operation showed a small, detached chip of bone to which the medial semilunar cartilage was attached. Both were removed, but without major effect upon the complaints.

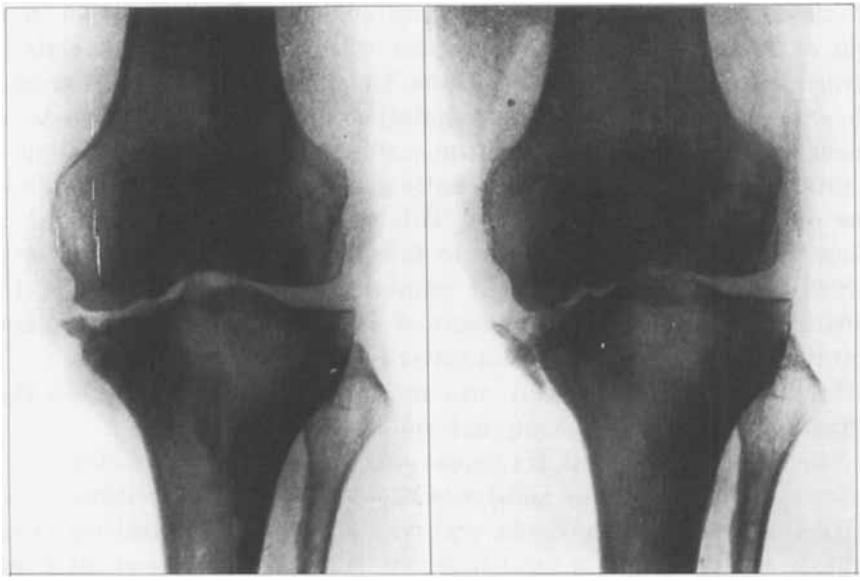

Fig. 3. *Fig. 4.*

Fig. 3. (Case 4): Knee joint shortly after the institution of topical hydrocortisone acetate therapy.

Fig. 4. (Case 4): Same knee, 6 months later, after several topical injections of hydrocortisone acetate, showing a progressing bony lesion at the medial tibial condyle.

DISCUSSION

These case histories illustrate the degenerative changes which may develop in joints treated topically with cortisone preparations and which do not differ from those reported previously in the literature. However, the author has tried to report a few typical examples which will be discussed below. That such complications may occur must be considered definitely proved, and it now remains to find the explanation and to decide whether it is justified at all to treat osteoarthritis with topical injections of cortisone. *Hollander*, who has a wide experience of this treatment, reported in 1960 that about 1 per cent of the treated joints became unstable. This might be due to the disease itself, as the ligaments had been stretched for so long by effusion in the joint, but it might also have been caused by the treatment.

Chandler et al. (1958, 1959) interpret these degenerative changes as being of the "Charcot type", *i.e.* that cortisone renders the joints painless, so that they are more apt to get worn. In a study from 1958

Chandler & Wright found radiological evidence of deterioration in 13 out of 25 knee joints after treatment with hydrocortisone acetate or hydrocortisone tertiary butyl acetate. On comparing these two groups, they found in the one showing radiological exacerbation after the treatment a significant improvement in walking time and an alleviation of pain, somewhat, but not significantly greater than in the group showing no radiological exacerbation. This supports the "Charcot" theory. *Sweetnam et al* (1960) incline to this theory, while *Steinberg et al.* (1962) express doubt. In their opinion, the analgesic effect of the cortisone preparations is not marked enough for such a mechanism, but they are unable to suggest a better explanation.

In the present cases there was no striking relief of pain, so that Chandler's theory is probably not applicable in this series.

The purely mechanical, traumatic effect which may be exerted by the injection of a crystalline substance should not be under-estimated. In Case 4 a purely local necrosis occurred after sub-periosteal injection, and Case 3 developed a local necrosis of the femoral head after one painful injection which may simply have injured a vessel and caused an infarction. Case 1 received 50 topical injections in one year, and this may be imagined to harm any joint. A few of the named complications may simply be traumatic, but it has been clearly demonstrated by the studies of *Chandler & Wright* (1958) and by the present investigations that in the great majority of cases they are probably due to another mechanism. Any osteoarthritis progresses in "jumps", but presumably we need not consider the possibility that these degenerative changes might be due exclusively to this natural progression.

How, then, do these cortisone preparations act in the joints? Various theories have been advanced, but the problem cannot be considered as solved. Cortisone preparations injected intra-articularly disappear with striking rapidity from the synovial fluid. However, the prednisolone derivatives appear to linger somewhat longer (*Will & Murdoch* 1960). The explanation is partly that some absorption takes place to the entire organism (*Shuster & Williams* 1961) and partly that the cortisone derivatives have to be transformed into certain metabolites to exert their activity (*Wilson* 1956).

In osteoarthritic joints the synoval fluid is abnormal, the degree of polymerization of hyaluronic acid being much lower than in normal synovial fluid. This has been demonstrated *int. al.* by *Sundblad* (1953) and *Kulonen* (1955) by viscosimetry. *Hedberg & Morits* (1958) demonstrated in tissue cultures that hyaluronic acid is produced by the cells

in the synovial membrane and in the periarticular tissue which contain numerous, large mast cells (*Asboe-Hansen* 1950, 1951). In other words, it must be presumed that under pathological conditions the synovial membrane produces a low-molecular hyaluronic acid and that the injected steroids, or metabolitis thereof, influence the cells to produce a more normal, high-molecular hyaluronic acid. *Jessar et al.* (1953) also feel that the hyaluronic acid in the most important fraction of the synovial fluid, despite the fact that it is a relatively small fraction. They found that hydrocortisone acetate exerted no effect upon the protein fraction in the synovial fluid, while *Kulonen* (1955) did find certain changes in the synovial proteins following injection of hydrocortisone acetate. The investigations of *Jensen & Zachariae* (1959) into the osmotic tension in the synovial fluid during treatment with hydrocortisone acetate supports the theory on the role of hyaluronic acid.

The mechanism outlined above may explain part of the clinical analgesic effect of the cortisone derivatives, since the accumulation of fluid subsides because the more high-molecular hyaluronic acid binds less water, so that tension and pain subside.

Other studies on wound healing and formation of granulation tissue have demonstrated, however, that cortisone inhibits the new-formation of connective tissue, as the synthesis of ground substance is inhibited, presumably through an action upon the mast cells which are prevented from producing normal hyaluronic acid (*Asboe-Hansen* 1950, 1952, *Moltke & Zachariae* 1954). On the face of it, it would seem unlikely that the same cells could be favourably influenced in certain articular diseases and unfavourably in wound-healing granulations by the same cortisone preparations. This phenomenon might perhaps be imagined to be due to enzymatic processes, but in treating osteoarthritis with cortisone preparations a given equilibrium would have to be obtained, as an overdosage would give rise to the necrotic lesions illustrated by the previous reports and by the present case histories.

Whether the essential mechanism of cortisone is one or the other, it must be established that it inhibits the new-formation of connective tissue. *Ragan et al.* (1949) were the first to demonstrate the inhibitory effect of cortisone upon the formation of granulation tissue, and innumerable studies on this subject have been carried out since then. Summing up, it may be said that when administered systemically, and even more when administered topically, cortisone preparations exert their effect upon the mesenchymal tissue, inhibiting its new-formation (*Schiller & Dorfmann* 1957). Under the influence of cortisone, the

tissue shows a reduced fibroblastic activity, a reduced fibrocyte count, inhibited endothelial regeneration, inhibited formation of collagen fibrils, and reduced vascularization. In addition, there will be a reduced capillary permeability, a reduced leukocyte and macrophage count, an action upon the reticulo-endothelial cells, and a reduced quantity of fibrin. All this is possibly due to changes in the ground substance whose synthesis is disturbed (*Asboe-Hansen* 1956).

In all tissues, and in an osteoarthritic joint, there is a constant degradation of tissue and simultaneous reparative processes, *i.e.* building-up of new connective tissue. In a normal joint, these processes are in equilibrium, but in an osteoarthritic joint this equilibrium is disturbed for some reason or other. At times, the breakdown predominates, resulting in the so-called "dry joints" in which the cartilage gradually disappears; at other times, regeneration predominates, resulting in the hypertrophic, exudative varieties. If corticosteroids are administered topically, the regeneration, but not the breakdown, will be inhibited. This may, for a time, be beneficial in the case of hypertrophic osteoarthritis. Gradually, however, nothing is left but breakdown, and the result is the complicating necrosis. Although *Trueta et al.* (1953) believe that the symptomes and the articular changes in osteoarthritis are due rather to the reparative, reactive hyperaemia produced by the primary cartilaginous degeneration than to these degenerative changes as such, a certain amount of regeneration must be necessary at all times. No doubt, certain varieties of osteoarthritis would be highly suited for short- or longer-lasting treatment corticosteroids, but how can we pick out these cases clinically and determine the dosage so that it accurately establishes the correct equilibrium between breakdown and regeneration?

In actual fact, there are no doubt many different types of what we call osteoarthritis, and it is a common finding that it is impossible to decide beforehand, on the basis of the clinical features, whether a patient is going to benefit by intra-articular injections of cortisone derivatives. It has been demonstrated that in osteoarthritis the joint temperature is elevated, presumably because of hyperaemia (*Fletscher* 1954). During treatment with hydrocortisone acetate *Hollander* (1956) has studied the temperature in the knee joints of patients with osteoarthritis, patients with rheumatoid arthritis, and in a control group. After the treatment he found a fall in the temperature in the group with rheumatoid arthritis, a slight increase in the control group, and a marked increase in the osteoarthritic group. *Hollander* concluded that

changes in temperature depend upon the type of joint condition present. To this may be added *Selye's* (1953) statements after applying the granuloma-pouch technique in studying the effect of hydrocortisone upon tissues. In his opinion, there is a negative correlation between inflammation and necrosis, meaning that the more an irritant stimulates to inflammation, the more is the tissue protected against necrosis, as inflammation is the defence reaction of the organism against the necrotizing agent. Reversely, if the protective inflammation is inhibited, *e.g.* by cortisone, there is a greater likelihood of tissue necrosis.

This statement is in keeping with the clinical findings of *Jonash* (1962). Operating on a patient with bursitis, who had received a total of 9 injections of hydrocortisone acetate during the preceding 7 months, he found distinct changes in the surrounding connective tissue which was yellowish and showed, on microscopic examination, necrotic areas with mucoid degeneration.

CONCLUSION

Cortisone preparations exert a clinically beneficial effect upon osteoarthritis, but in a number of cases radiological exacerbation with degenerative articular changes results. These changes are not explicable by the natural progression of the disease and only partially by the trauma caused by the injection. A possible explanation is that cortisone renders the joints painless, so that they will get more worn, as Charcot joints, but this is not the only possible explanation. In osteoarthritis the normal equilibrium between degeneration and regeneration of tissue is disturbed. In some cases degeneration predominates and in others regeneration. Administration of cortisone, which is known to inhibit the regeneration of connective tissue, gives the degenerative processes a violent preponderance.

SUMMARY

Four cases of radiologically demonstrable degenerative changes in osteoarthrtic joints following topical application of hydrocortisone preparations are reported. On the basis of previous publications and the present findings, the author tries to elucidate the mechanism of this phenomenon. The changes are probably not due to the natural progression of the disease, but perhaps to some extent to the trauma of the injection, especially in the event of numerous injections or injections into tight tissue. Chandler's theory that the joints get severely worn because they have rendered painless by the injections is discussed. It

is emphasized that cortisone is known to inhibit the new-formation of connective tissue apart from exerting other possible specific effects on the joints. The theory is advanced that cortisone, injected into osteoarthritic joints, inhibits regeneration, thus lending preponderance to the degenerative processes which constitute an important link in the disease.

RESUME

Sont rapportés quatre cas de modifications dégénératives démonstrables radiographiquement dans des articulations ostéoarthritiques à la suite de l'application topique de préparations d'hydrocortisone. Sur la base de publications antérieures et des trouvailles présentes, l'auteur essaie d'élucider de mécanisme de ce phénomène. Les modifications ne sont probablement pas dues à la progression naturelle de la maladie, mais peut-être dans une certains étendue au trauma de l'injection, spécialement dans le cas de nombreuses injections ou d'injections dans des tissus compacts. Il est discuté de la théorie de Chandler d'après laquelle il se produit une grave usure de l'articulation du fait qu'elle a été rendue indolore par les injections. Il est souligné que la cortisone est connue pour enrayer la nouvelle formation de tissu conjonctif en plus qu'elle empêche peut-être d'autres effets spéfifiques sur l'articulation. Il est avancé la théorie que la cortisone, injectée dans des articulations ostéoarthritiques entrave la régénération, donnant le prépondérance au processus dégénératif qui constitue un élément important de cette maladie.

ZUSAMMENFASSUNG

Über vier Fälle von röntgenologisch nachweisbaren degenerativen Veränderungen in osteoarthitischen Gelenken, die nach örtlicher Verwendung von Hydrocortisonpräparaten auftraten, wird berichtet. Auf Grund vorangehender Veröffentlichungen und den gegenwärtigen Befunden versucht der Verfasser den Mechanismus dieses Phänomens zu erklären. Die Veränderungen sind wahrscheinlich nicht auf das natürliche Fortschreiten der Erkrankung zurückzuführen, sondern vielleicht bis zu einem gewissen Grade auf das Trauma der Injektion, besonder im Falle von zahlreichen Injektionen oder Injektionen in straffes Gewebe. Chandlers Theorie, dass die Gelenke aufs schwerste abgenutzt werden weil sie durch die Injektion schmerzlos werden, wird diskutiert. Es wird hervorgehoben, dass das Cortison bekanntlich die Neubildung

von Bindegewebe hindert, abgesehen davon, dass es möglicherweise auch andere spezifische Wirkungen auf die Gelenke hat. Die Theorie, dass Cortison, wenn in Gelenke injiziert, die Regeneration hindert und somit zu einem Überwiegen von degenerativen Prozessen, die eine wichtige Erscheinung der Krankheit darstellen, führt, wird aufgestellt.

REFERENCES

Asboe-Hansen, G.: The Origin of Synovical Mucin. Ann. rheum. Dis. *9*: 149, 1950.

Asboe-Hansen, G.: Om Bindevævets Musinøse Substanser. Disputats, København 1951.

Asboe-Hansen, G.: The Mast Cell an Object of Cortisone Action on Connective Tissue. Proc. Soc. exp. Biol. & Med. *80*: 677, 1952.

Asboe-Hansen, G.: Hormonal Control of Connective Tissue. Proc. III. Rheumatol. Congr. 114, 1956.

Chandler, G. N. & Wright, V.: Deleterious Effect of Intraarticular Hydrocortisone. Lancet *II*: 661, 1958.

Chandler, G. N., Jones, D. T., Wright, V. & Hartfall, S. J.: Charcot's Arthropathy Following Intra-Articular Hydrocortisone. Brit. med. J. *I*: 952, 1959.

Egelius, N., Hävermark, N. G. & Jonsson, E.: Behandling av Ledaffektioner med Hydrocortison (Comp. F.). Svenska Läkartidningen, Marts, 677, 1953.

Egelius, N., Jonsson, E. & Sundblad, L.: Action of Hydrocortisone and Other Substances on the Hyaluronic Acid of Joint Fluids in Rheumatoid Arthritis. Proc. III.Rheumatol. Congr. 142, 1956.

Fletcher, E., Jacobs, J. H. & Rose, F. C.: The Effect of Periarticular Procaine Infiltration on Joint Temperature. Ann. Phys. Med. 2: 123, 1954.

Harrison, H. M., Schajowicz, F. & Trueta, J.: Osteoarthritis of the Hip: A Study of the Nature and Evolutions of the Disease. J. Bone Jt Surg. *35 B*: 598, 1953.

Hedberg, H. & Moritz, U.: Biosynthesis of Hyalurone Acid in Tissue Cultures of Human Synovial Membrane. Proc. exp. Biol. & Med. *98*: 90, 1958.

Hollander, J. L.: Intra-Articular Hydrocortisone in Arthritis and Allied Conditions. J. Bone Jt Surg. *35 A*: 983, 1953.

Hollander, J. L., Brown, E. M., Jessar, R. A. & Brown, C.: Hydrocortisone and Cortisone Injected into Arthritic Joints. J. amer. med. As.. *147*: 1629, 1951.

Hollander, J. L. & Moore, R.: Studies in Osteo-Arthritis Using Intra-Articular Temperature Response to Injection of Hydrocortisone Acetate and Prednisone. Ann. rheum Dis. *15*: 320, 1956.

Jensen, C. E. & Zachariae, L.: The Contributions from Hyaluronic Acid and from Protein to the Colloid Osmotic Pressure of Human Synovial Fluid. Acta rheum. Scand. *5*: 18, 1959.

Jessar, R. A., Ganzell, M. A. & Ragan, Ch.: The Action of Hydrocortisone in Synovial Inflammation. J. clin. Invest. *32*: 480, 1953.

Jonash, E.: Nil Nocere!: Ist die lokale Anwendung von Cortisonen und ihrer Derivate immer ungefärlich. Münch. med. Wschr. *104*: 1638, 1962.

Kersley, G. D.: Intraarticular Hydrocortisoneacetate in Rheumatic Arthritis. Lancet *II*: 269, 1952.

Kulonen, E. & Mäkinen, P.: An Orientating Study in the Synovial Fluid with Reference to the Effect of Compound F. Acta rheum. scand. *1*: 1, 1955.

Ragan, Ch,, Howes, E. L., Plotz, Ch. M., Meyer, K. & Blunt, J. W.: Effect of Cortisone on Production of Granulation Tissue in the Rabbit. Proc. Soc. exp. Med. *72*: 718, 1949.

Ragan, Ch., Howes, E. L., Plotz, Ch. M., Meyer, K., Blunt, W. & Lattes, R.: The Effect of ACTH and Cortisone on Connective Tissue. Bull. N. Y. Accord. Med. *26*: 251, 1950.

Schiller, S. & Dorfman, A.: The Metabolism of Mucopolysaccharides in Animals: The Effect of Cortisone and Hydrocortisone on Rat Skin. Endocrinology *60*: 376, 1957.

Shuster, S. & Williams, I. A.: Adrenal Suppression due to Intraarticular Corticosteroid Therapy. Lancet *II*: 171, 1961.

Selye, H.: On the Mechanism Through which Hydrocortisone Affects the Resistance of Tissues to Injury. J. amer. med. Ass. *152*: 1207, 1953.

Soto-Hall, R. & Haldemann, K. O.: The Diagnosis of Neuropathic Joint Disease (Char-Joint). J. amer. med. Ass. *114*: 2076, 1940.

Sundblad, L.: Studies on Hyaluronic Acid in Synovial Fluids. Acta Soc. Med. Uppsal. *58*: 113, 1953.

Steinberg, Ch. le Roy, Duthie, R. B. & Piva, A. E.: Charcot-Like Arthropathy Following Intra-Articular Hydrocortisone. J. amer. med. Ass. *181*: 851, 1962.

Sweetnam, D. R., Mason, R. M. & Murray, R. O.: Steroid Arthropathy of the Hip. Brit. Med. J. *13*: 1392, 1960.

Will, G. & Murdoch, W. R.: Persistence of Intra-Articular Steroid. Brit. med. J. *1*: 94, 1960.

Wilson, H., Glyn, J., Scull, E., McEwen, C. & Ziff, M.: Rate of Disappearance and Metabolism of Hydrocortisone and Cortisone in the Synovial Cavity in Rheumatoid Arthritis. Proc. Soc. exp. Biol. & Med. *83*: 648, 1953.

Wilson, H., Fairbanks, R., Scialabba, D., McEwen, C. & Ziff, M.: Metabolites of Hydrocortisone and Cortisone in Synovial Fluid in Rheumatoid Arthritis. J. clin. Endocrin. *16*: 86, 1956.

Zachariae, L.: 17-Hydroxycorticosteron-21-Acetat anvendt intraarticulært ved Arthroser. Nord. Med. *51*: 479, 1954.

Zachariae, L.: Hydrocortisons lokale Virkning på Bindevæv. Disputats, København 1956.

Zachariae, L. & Moltke, E.: Influence of Hydrocortisone on Mast Cells of Normal Skin and Healing Wounds in the Rabbit. Acta Endocrin. *16*: 300, 1954.