Possible practical outcomes of these findings are discussed.

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ABSENCE OF RESPONSE TO CORTISONE

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Complete absence of clinical response of rheumatoid arthritis to massive doses of cortisone is rare, though relative lack of response is not uncommon. The following case, which failed to respond to 500 mg. of cortisone a day, 100 mg. of A.C.T.H. intravenously, or to hydrocortisone ("compound F") intra-articularly, answers some of the questions raised in the annotation in the *British Medical Journal* of May 10 (p. 1016), discussing the paper by Kellgren and others on the same subject (p. 997).

Case Report

The patient was a man aged 38. A brother had had rheumatic fever.

January, 1949.—Acute rheumatoid arthritis started in the left wrist, and shortly afterwards both ankles became involved. He was treated with gold, which was stopped owing to a slight rash, from which he soon recovered.

August, 1950.—On admission to the Royal National Hospital for the first time his general condition was good; there was swelling of the wrist and ankles. The sedimentation rate was 27 mm. (Westergren); haemoglobin 94%. Hypoglycaemic treatment was without benefit.

February, 1951.—He was readmitted to hospital in very similar condition: sedimentation rate 26 mm. (Westergren); Wassermann reaction negative; plasma cholesterol, 69 mg. per 100 ml. For a short period 100 mg. A.C.T.H. daily and, later, 200 mg. cortisone daily was given without benefit. Deep *x*-ray treatment to the feet was without result.

June, 1951.—A slight rash appeared on the legs, from below the knees to above the ankles, and cleared up within a month.

July, 1951.—He was again admitted to hospital. His general condition was still quite good, but affected joints were more painful. The sedimentation rate was 57 mm. (Westergren); haemoglobin, 97%; glucose and insulin tolerance normal. Histamine-fast achlorhydria was present. He was again treated with A.C.T.H., the dosage being increased to 400 mg. a day, given in four doses. There was no decrease in pain or joint swelling or increase in joint movement. The urinary 17-ketosteroids increased slightly, but there was no obvious change in corticoids. After a rest period 500 mg. of cortisone was given daily by injection, again with no clinical improvement, but there was a slight decrease in 17-ketosteroids with a slight increase of corticoids. Intravenous A.C.T.H., 20 mg. and then 100 mg., given in eight-hour drips, again produced no clinical effect. Throughout treatment the eosinopenic response was normal, the fall being 70, 77, and 42%. The effect of A.C.T.H. was not potentiated by ascorbic acid or thyroxine. There was no clinical evidence of adrenal insufficiency, and the Kepler test gave a normal result.

March, 1952.—The patient's condition had definitely deteriorated, his hands, wrists, elbows, feet, ankles, and right jaw being affected. The sedimentation rate was 23 mm. (Westergren); haemoglobin, 87%. Thyroid function was investigated, using I^{131}, and was found to be within a low range of normal. (Slope uptake 1.3×10^{-2}; 48-hour excretion 51.2%; thyroid index 2.6). The 17-ketosteroids were 8.3 mg. in 24 hours.

Two injections of 2 ml. (50 mg.) intra-articular cortisone into the left wrist gave no relief of symptoms, and then two injections of 50 mg. of hydrocortisone were given into the same joint, again without any benefit. There was no depression of the circulating eosinophils.

April, 1952.—The patient was transferred temporarily

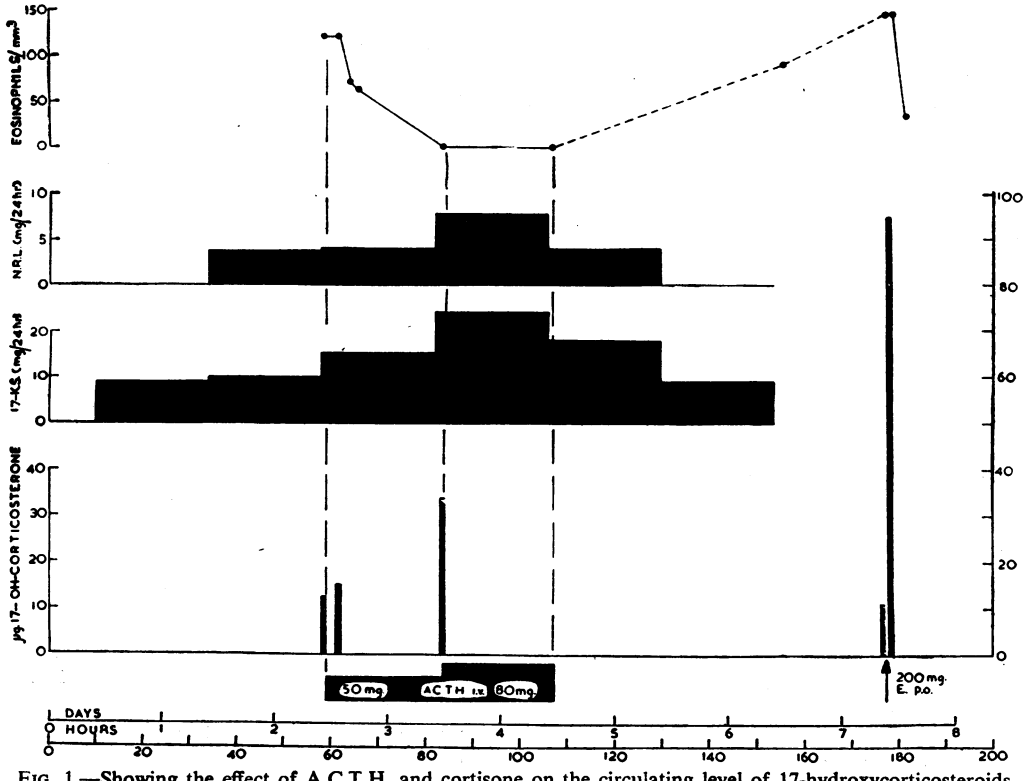

FIG. 1.—Showing the effect of A.C.T.H. and cortisone on the circulating level of 17-hydroxycorticosteroids (μg./100 ml. plasma), on the urinary excretion of 17-ketosteroids and neutral reducing lipids, and on circulating eosinophils.

to Hammersmith Hospital, under the care of Dr. R. I. S. Bayliss, for investigation of adrenocortical function. A.C.T.H., 50 mg. given in a 24-hour intravenous drip, caused a 100% fall in circulating eosinophils; the plasma concentration of circulating 17-hydroxycorticosteroids (compound F) rose from a normal value of 10.5 μg./100 ml. plasma to 34.2 μg.; and the urinary excretion of 17-ketosteroids and neutral reducing lipids (N.R.L.) also increased (Fig. 1). A.C.T.H., 80 mg. in a 24-hour intravenous drip, caused a further rise in the urinary excretion of adrenocortical hormones. Oral administration of 200 mg. of cortisone on the seventh day of observation produced within four hours a 75% fall in eosinophils and a very marked rise in plasma circulating 17-hydroxycorticosteroids. The patient was given 400 mg., 300 mg., and then 100 mg. of cortisone orally for three more days with no signs of improvement in the joints. He then returned to the Royal National Hospital, and on April 27 the left knee became painful and swollen for the first time.

On May 2 a synovial biopsy was performed on the left knee and also on the left wrist, where the disease had been present for over three years; the findings were as follows.

Knee-joint.—There was marked superficial fibrinoid necrosis of the whole free surface of the membrane in the specimen. It varied in depth from a thin layer to a broad band 0.5 mm. in depth. There was a fibroblastic reaction, but the membrane was not obviously thickened. A focal and diffuse lymphocytic reaction was associated with plasma cells and polymorphs. The latter were unusually numerous and were aggregated under the points where necrosis was most pronounced. There was some congestion. No abnormalities were seen in the vessels.

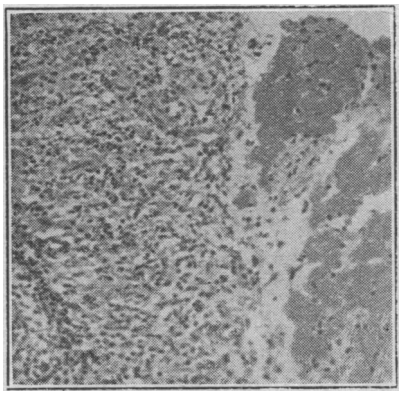

FIG. 2.—Left knee. Showing superficial necrosis, with fibroblastic reaction and marked infiltration by lymphocytes and polymorphonuclear leucocytes. (H. and E. ×85.)

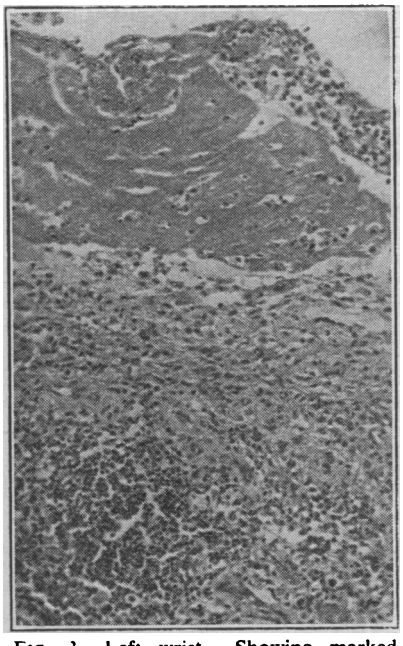

FIG. 3.—Left wrist. Showing marked superficial necrosis and fibrin deposition. The membrane is infiltrated by lymphocytes and polymorphs. (×85.)

Wrist.—Superficial tissue. This was a "carbon copy" of the knee synovia except that there was more fibrous thickening. The proportions of lymphocytes, plasma cells, and polymorphs were the same, as was the amount of superficial necrosis.

Deep Tissue.—Fibro-fatty tissue showing paravascular lymphocytic foci; marked thickening of arterioles was present. The resemblance between the two specimens (knee and wrist) was striking, both showing an acute destructive form of rheumatoid arthritis.

On May 4 Astwood's cellulose-purified and concentrated corticotrophin was administered in a dosage of 1 mg. subcutaneously eight-hourly for two days; the dose was then increased to 1.5 mg. eight-hourly for three days, but with no relief of symptoms. The ketosteroid excretion, however, rose from 5.9 to 12.7 mg. in 24 hours.

Finally, a course of 200 mg. oral cortisone, together with tolazoline hydrochloride ("priscol"; 2-benzyl-imidazoline hydrochloride), 50 mg. intravenously and 25 mg. orally, was given daily for two days, during which time there was actually an increase in joint pain.

Comment

This case of typical active rheumatoid arthritis, proved by synovial biopsy, failed to show any clinical improvement with several batches of A.C.T.H. given in doses of 400 mg. a day intramuscularly and 100 mg. intravenously in an eight-hour drip. Thyroid and ascorbic acid failed to potentiate the A.C.T.H. Likewise the patient did not respond to Astwood's purified corticotrophin in doses of 1.5 mg. eight-hourly. He also did not derive any benefit from cortisone in doses of 500 mg. a day given intramuscularly. There was no clinical improvement when cortisone was given with tolazoline, used to produce vasodilatation in an endeavour to aid its distribution to the affected tissues. Direct application of cortisone and hydrocortisone to the diseased tissues by intra-articular injection was also ineffective.

The patient showed no clinical or biochemical evidence of adrenocortical insufficiency and the eosinopenic response was normal to systemic A.C.T.H. and cortisone, a fall of 92% occurring with intravenous A.C.T.H. 50 mg. A.C.T.H. given in an intravenous drip over 24 hours caused a threefold increase in the level of blood hydrocortisone. The thyroid activity, using labelled iodine, was within the lower range of normal.

It seems, therefore, that in this case the failure to respond to A.C.T.H. cannot be explained by inadequate dosage, by inadequate absorption from the site of intramuscular injection (as it was equally ineffective intravenously), by failure to stimulate the adrenal glands (as there was an adequate fall of eosinophils, and a threefold rise in the level of blood hydrocortisone on intravenous administration), or because of the type of A.C.T.H. used (as several batches and purified A.C.T.H. were all ineffective). Similarly, the lack of response to cortisone cannot be explained by inadequate dosage, by failure to reach the target organ (as it was ineffective when combined with tolazoline hydrochloride and also when given locally), or by the lack of conversion to hydrocortisone (as this was ineffective locally). It therefore seems that the fault, in this case, must lie primarily in the end-organ or affected tissues.

In connexion with the diseased joint tissues, it is interesting that in this case histological examination of biopsy material from a wrist-joint which had been affected for three years gave results strikingly similar to those from a knee-joint affected for only five days. Both specimens showed typical acute rheumatoid arthritic changes, those in the knee being strikingly characteristic and advanced considering the very short time since symptoms were first felt at that site.

Acknowledgment is made to Dr. R. I. S. Bayliss for investigating adrenocortical function and the data contained in Fig. 1, and to Dr. Max Reiss for the investigation of thyroid function. We are indebted to Professor Astwood for his supply of purified corticotrophin, and to Dr. H. J. Gibson for assistance with the histology.

ADDENDUM.—The patient has now received 200 mg. of cortisone daily, with 50 mg. tolazoline hydrochloride orally for 30 days without any sign of improvement or toxicity. There was no increase in activity of the rheumatic state on withdrawal of the cortisone. A marked improvement however occurred in a swollen knee after an injection of hydrocortisone, though whether *post* or *propter hoc* is uncertain.