RHEUMATOID ARTHRITIS OF MENOPAUSAL WOMEN TREATED WITH INSULIN HYPOGLYCAEMIAS

BY

Z. Z. GODLOWSKI,* and H. PATERSON
*From the Department of Pathology, Edinburgh University,
and Ballochmyle Hospital, Edinburgh*

(RECEIVED FOR PUBLICATION DECEMBER 27, 1951)

A favourable response to insulin hypoglycaemias (I.H.) or adrenaline infusions, in one case of rheumatoid arthritis and in two cases of non-articular rheumatism, has already been described (Godlowski, 1949). Since then Kersley and others (1950) have found in a series of forty cases of various aetiological types of rheumatoid arthritis treated with I.H., a significant improvement in 31, no response at all in eight, and a definite deterioration while under treatment in one. In their further observations (Kersley and others, 1951), they showed that the 44 per cent. of cases showing initial marked improvement diminished to 10 per cent. in the course of a 6-months' follow-up. Greif and others (1950) found clinical remission in three out of four cases of rheumatoid arthritis with I.H., but in the fourth a clinical deterioration took place during treatment.

The present series of ten cases deals only with rheumatoid arthritis in menopausal or post-menopausal women.

Method

Material.—All ten patients were women whose menopause began from one to 20 years ago. The duration of the symptomatology of rheumatoid arthritis varied from a few months to 18 years, the onset of the articular pathology having been more or less closely related to the beginning of menopausal symptoms. In none was there any history of rheumatic fever or episodes of rheumatoid arthritis before the onset of the menopause.

Routine Investigations.—For two control weeks of hospitalization each patient was kept in bed without any treatment, and the following investigations were carried out:

Weekly: measurement of bodyweight, erythrocyte sedimentation rate (Westergren), circulating eosinophil count (Randolph, 1944);
haemoglobin and erythrocyte count;
leucocytosis.

24-hourly: measurement of urinary output of 17-ketosteroids and 11-oxycorticoids (Tompsett and Oastler, 1946, 1947);
urinary output of creatinine (Folin, 1914), and of uric acid (Benedict and Franke, 1922).

In the next 2 to 4 weeks, during the actual treatment, this series was repeated twice.

In the last 2 weeks of withdrawal each patient again remained without any treatment, and the same series of investigations was repeated at the end of the period.

Insulin Hypoglycaemia.—This was produced by a subcutaneous injection of soluble insulin at 8 a.m. to a fasting patient. The dosage of insulin fluctuated between 20 and 80 units, and caused well-developed clinical symptoms of hypoglycaemia (Godlowski, 1946). The discontinuation of I.H. was carried out by giving the patient a tumbler of highly-sugared water followed by a meal rich in carbohydrates. The I.H. was applied daily for a period of from 14 to 28 days.

* Research Fellow of the Carnegie Trust for the Universities of Scotland, Edinburgh.

Results

The most constant and significant improvements obtained by insulin hypoglycaemia therapy in this series were as follows:

- (i) definite increase in bodyweight in nine out of ten cases.
- (ii) diminution of pain, stiffness, oedema, and atrophy in nine out of ten cases.
- (iii) striking improvement in muscular strength in the hands in six out of the nine positive cases.

During and immediately after treatment the erythrocyte sedimentation rate fell significantly in eight out of ten cases, although only in three did it return to normal levels (all these three had a relapse within 2 months of discontinuing the treatment). Of the eight cases which showed initial improvement in the erythrocyte sedimentation rate estimations, three showed a significant increase by the end of the withdrawal period. The haemoglobin and red blood count, if materially subnormal, either returned to normal levels or showed a tendency towards it (no iron therapy was given). The circulating eosinophils in all nine positive cases were significantly diminished during the period of I.H. treatment and returned to their initial level in the withdrawal period. The 24-hr excretion of steroids and nitrogen in the urine showed no significant change.

All the cases relapsed, three with significant deterioration of the whole clinical picture, in the course of a ten-months' follow-up period.

Although the one negative case made some progress during the period of I.H. treatment (mainly in bodyweight and muscular strength), the rest of the signs and symptoms persisted in their initial intensity at the end of the treatment and further deterioration was noticed in the follow-up period; thus this case is regarded as not responding to the treatment at all, and such insignificant improvement as did occur may be ascribed merely to hospitalization.

Discussion

Ten cases of rheumatoid arthritis in menopausal or post-menopausal women were treated daily with I.H. for a period of 2 to 4 weeks, with a significant improvement in nine cases. In the 2 weeks of the withdrawal period this improvement still persisted, and in some cases further improvement occurred. The erythrocyte sedimentation rate in all nine positive cases was reduced, but returned to normal levels in only three. The slowing down of the erythrocyte sedimentation rate may be interpreted as showing that the cause of its acceleration was only partially and temporarily affected by I.H.; in other words, if increased erythrocyte sedimentation rate signifies the activity of the morbid process, so I.H. only partially and temporarily affected the primary aetiological factor of rheumatoid arthritis of menopausal type.

In view of the early relapsing of the full symptomatology of all nine positive cases, and in view of the persistence of a high, though slightly reduced, erythrocyte sedimentation rate, the positive results obtained by I.H. should be regarded as a conditional elimination of the aetiological factor and not as a permanent modification of the primary agent operating in the morbid process. The lack of

permanent improvement with I.H. therapy in the menopausal type of rheumatoid arthritis should not be taken to apply to all the aetiological types of the disease, because this represents a separate entity in which the primary pathogenic factor initiating the articular pathology has probably an individual mode of action.

Further investigations of the mechanism of the beneficial action of I.H. in the conditional alleviation of menopausal and other types of rheumatoid arthritis, and in various anaphylactic conditions, are in progress.

Summary

(1) Nine out of ten cases of rheumatoid arthritis in menopausal or post-menopausal women treated with insulin hypoglycaemias responded with clinical remission; one case showed no significant clinical change.

(2) Nine cases relapsed in the course of the next 10 months, and in some the articular pathology progressed more rapidly than in the pre-treatment period.

(3) The results obtained by insulin hypoglycaemia in the treatment of this type of rheumatoid arthritis should be regarded as a temporary slowing down of the pathological processes.

(4) Since all the treated cases relapsed, this form of treatment should be regarded as having only a conditional and temporary effect.

We wish to thank J. Fitzpatrick, B.Sc., A.R.I.C., biochemist to the Ayr County Laboratory, Central Hospital, Irvine, for the estimations of the urinary steroids, uric acid, creatinine, etc.

REFERENCES

- Benedict, S. R., and Franke, E. (1922). *J. biol. Chem.*, **52**, 387.
 Folin, O. (1914). *J. biol. Chem.*, **17**, 469.
 Godlowski, Z. Z. (1946). *Brit. med. J.*, **1**, 717.
 — (1949). *Annals of the Rheumatic Diseases*, **8**, 285.
 Greif, S., and Moro, E. (1950). *Wien. med. Wschr.*, **100**, 603.
 Kersley, G. D., Mandel, L., Jeffrey, M. R., Bene, E., Taylor, K. B. (1951). *Brit. med. J.*, **2**, 574.
 —, —, Desmarais, M. H. L., and Bene, E. (1950). *Ibid.*, **2**, 855.
 Tompsett, S. L., and Oastler, E. G. (1946). *Glasg. med. J.*, **27**, 281.
 —, — (1947). *Ibid.*, **28**, 349.

Arthrite rhumatoïdale au cours de la ménopause traitée par l'hypoglycémie insulínique

RÉSUMÉ

(1) Neuf cas sur dix d'arthrite rhumatoïdale durant ou après la ménopause traités par l'hypoglycémie insulínique, accusèrent une amélioration clinique; dans le dixième cas il n'eut pas de modification clinique significative.

(2) Neuf cas ont eu une rechute avant que dix mois se soient écoulés, et pour certains d'eux la pathologie articulaire s'avança plus rapidement qu'avant le traitement.

(3) Les résultats obtenus dans le traitement de ce type d'arthrite rhumatoïdale doivent être considérés comme un ralentissement temporaire des processus pathologiques.

(4) Tous les malades traités ayant eu des rechutes, cette forme du traitement doit être considérée incapable de produire un effet autre que conditionnel et temporaire.

Artritis reumatoide de menopáusicas tratada con hipoglicemia insulínica

SUMARIO

(1) De diez casos de artritis reumatoide menopáusica o postmenopáusica tratados con hipoglicemia insulínica, nueve respondieron con mejoría clínica y el décimo quedó sin cambio clínico significativo.

(2) Los nueve casos tuvieron una recaída en el curso de los diez meses que siguieron el tratamiento y en algunos de ellos la patología articular progresó más rápidamente que antes del tratamiento.

(3) Los resultados obtenidos en el tratamiento con hipoglicemia insulínica de este tipo de artritis reumatoide deben estimarse como retardación pasajera de los procesos morbosos.

(4) A la vista de tantas recaídas, esta forma de tratamiento debe considerarse capaz de producir tan sólo efectos condicionales y pasajeros.