IMPLANTATION OF PLACENTAL TISSUE IN PATIENTS WITH RHEUMATOID ARTHRITIS*†

PRELIMINARY REPORT

BY

ROBERT M. LINTZ

From the Second (Cornell) Medical Division, Bellevue Hospital, and the Department of Medicine, Cornell University Medical College, New York, N.Y.

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Many factors have an influence on rheumatoid arthritis. Since 1938 the favourable effect of pregnancy in most instances of this disease has been accepted (Hench, 1938). Subsequent to this observation, preparations associated with pregnancy have been employed for the treatment of rheumatoid arthritis with indifferent success. In recent years rheumatoid arthritis has been treated with transfusions of blood from pregnant women (Barsi, 1947; Watson, 1953), with serum from placental blood (Tufts, 1953; Aronson and others, 1952), and with postpartum plasma (Granirer, 1951; Neustadt and others, 1953), and conflicting reports as to the efficacy of these methods have been published.

Filatov (1944, 1945, 1946), the Russian ophthalmologist, has written extensively on the use of tissue implants. Though primarily concerned with diseases of the eye, he reported its use in many conditions, including arthritis.

Following these reports, a considerable interest in this form of therapy was shown in various parts of Europe (Tinozzi and others, 1951; Pflüger, 1952; Armand and Coutadeau, 1950). A rather extensive literature exists on the treatment of retinitis pigmentosa with placental implantation; as one might expect, there is a marked variance in the reported results of the different investigators. Other workers cited the use of tissues, including placenta, in diseases in which the eye was not primarily involved. Thyroid gland implantation in a large series of patients with arthritis has been reported from Vienna (Mandl and Gyri, 1952), and from Paris (Etienne-Martin and others, 1952). Workers in Sweden (Edström and Thune, 1951) and Denmark (Wassmann, 1952) have implanted the anterior lobes of pituitary glands of pigs or calves in patients with rheumatoid arthritis with interesting results.

Material

Thirty-five patients with rheumatoid arthritis, classified according to the criteria of the American Rheumatism Association (Steinbrocker and others, 1949), were studied. The patients were taken at random and included twelve males and 23 females, varying in age from 22 years to 70 years. In six patients the disease had been present for periods of 3 months to 2 years, in five patients from 3 to 5 years, and in the remaining 24 patients from 6 to 50 years. With few exceptions the patients had previously received various forms of therapy, including gold salts and cortisone. In four patients the disease was classified: Stage II, in twenty Stage III, and in eleven Stage IV. The functional capacity was Class II in ten, Class III in eighteen, and Class IV in seven (Table I). The x-ray findings in each case were consistent with the stage of the disease, and in all but two patients the erythrocyte sedimentation rate was elevated.

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* Severity of disease classified in four stages according to clinical and radiological changes: Stage I, early; Stage II, moderate; Stage III, severe; Stage IV, terminal status with ankylosis.

† This study was aided by a grant from the New York Chapter of the Arthritis and Rheumatism Foundation.
ANNALS OF THE RHEUMATIC DISEASES

Method

Placental tissue not more than 24 hours old was obtained from women who gave a negative history for jaundice and in whom the history and serological tests for syphilis were negative. About 25 g. of tissue (the equivalent of a 2-cm. cube) was cut into small pieces. The material was immersed in a 1 per cent. aqueous solution of Brilliant Green for 1 hour, this tissue becoming permeated with the dye. The excess solution was poured off and the tissue was thoroughly rinsed a number of times with sterile distilled water in order to remove some of the remaining dye. Placental tissue prepared in this manner was sterile on incubation in broth and on agar media.

Under local procaine hydrochloride anaesthesia, an incision about 10 cm. long was made on the lateral aspect of the thigh through the subcutaneous fat down to the fascia and a pocket was made by undermining the fat. The small pieces of treated placenta were placed in the pocket and the incision closed with sutures. The patients were maintained on antibiotics for 4 to 7 days.

There were no unfavourable systemic reactions to the tissue implantation, but several patients had a slight elevation of temperature attributable to the procedure. The incisions did not heal by primary union and the wounds drained liquified material for a number of days and remained partially open for 3 to 5 weeks after the implant before healing by granulation. In one patient it was necessary to re-open the wound because it had closed without drainage.

Results

Of the 35 patients studied, fifteen showed no improvement (Grade IV), four were Grade III, sixteen Grade II, and none Grade I (Table II). Those who improved were aware of symptomatic improvement within a period of 2 to 10 days after the implant with increased mobility of some of the involved joints. Objective signs of improvement were manifested by decrease in heat, reduction in joint swelling, and improvement in range of motion. Both subjective and objective improvement were progressive over a period of 2 to 6 weeks, by which time the maximum benefits from the procedure usually were noted. The patients who were improved have maintained their improvement to date. This group includes two whose duration of improvement is 4 years, two 3 1/2 years, and one more than 3 years. The remainder show a duration of improvement ranging from 2 to 10 months. This difference in time is due to the fact that the study was interrupted for a period of 2 years. With few exceptions, some decrease in sedimentation rate was noted in the Grade II patients following wound healing; this fall was not apparent immediately, but was noted over a period of from 4 to 12 weeks.

Case Reports

Case 2, 48-year-old white woman, gave a history of pain and swelling of fingers, wrists, elbows, knees, and

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* See Text.
Joints of the arthritis remission similar the occurrence of exfoliative dermatitis. The patient had significant relief of symptoms for a 2-year period while on cortisone, but it had become necessary to stop this medication because of significant oedema. Butazolidin was also effective but was discontinued because of the occurrence of a duodenal ulcer. Her arthritis then became progressively worse, so that in an effort to relieve pain she was taking Demerol several times a day in addition to aspirin and codeine.

At the time of examination the fingers, wrists, elbows, shoulders, knees, ankles, toes, and jaw showed changes characteristic of advanced rheumatoid arthritis, and the erythrocyte sedimentation rate (Westergren) was 34 mm in 1 hour. The disease was classified as Stage III, Class II.

Placental implantation was carried out on April 17, 1953. The patient noted subjective improvement 3 days later, and was able to get out of a chair and out of bed with greater ease without analgesics. There was decreased swelling and tenderness of the involved joints. Subjective and objective improvement continued over a period of 2 weeks and the improvement has been maintained to date. The therapeutic response is classified as Grade II.

Case 16, 46-year-old white man, gave a history of complete invalidism for 2 years because of arthritis. All the peripheral joints were actively involved, but the x-ray revealed only minimal cartilage destruction. The erythrocyte sedimentation rate was 88 mm in 1 hour. His rheumatoid arthritis was classified Stage II, Class IV.

He had been placed on oral cortisone with a daily maintenance dose of 100 mg., and on this regimen was free from all joint pain and interested in finding a job. When cortisone was withdrawn after a gradual reduction in dosage, all the symptoms returned and the objective findings were comparable to those present before cortisone.

Gelfoam, prepared in the manner described for placenta, was then implanted without change in the patient's condition. Thyroid gland tissue similarly treated was then employed and no improvement was noted. Placental implantation was carried out, and 3 days after the implant the patient stated that he felt comfortable.

On the 4th day he stated that he was free of all pain. On examination there was decrease in swelling of the involved joints, and a complete range of motion of all joints without pain; stairs were negotiated in a normal manner. This clinical remission lasted for 9 days, after which there was a sudden relapse and the patient rapidly reached his pre-treatment status. A second and third placental implantation were without benefit. With the fourth placental implant, the patient experienced a clinical remission similar to that following the first, but again the remission was short-lived, lasting only 9 days. The therapeutic result was classified as Grade IV because of the relapse. This case is reported in detail because of the significant, although short-lived, improvement.

Case 34, 37-year-old white woman, had had rheumatoid arthritis for 15 years. Gold salts therapy had been instituted 6 years ago, but had been stopped because of the occurrence of exfoliative dermatitis. The patient had significant relief of symptoms for a 2-year period while on cortisone, but it had become necessary to stop this medication because of significant oedema. Butazolidin was also effective but was discontinued because of the occurrence of a duodenal ulcer. Her arthritis then became progressively worse, so that in an effort to relieve pain she was taking Demerol several times a day in addition to aspirin and codeine.

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Discussion

Experimental evidence indicates that ACTH (Opsahl and Long, 1951), gonadotropin and oestrogens (Stewart, 1951) are secreted by the placenta. Progesterone can be extracted from the placenta, but evidence of its secretion by this tissue is inconclusive. It seems most unlikely that any of the material that was implanted in this group of patients was active after the wound healed. The reason for this assumption is the discharge of liquified material which occurred before wound closure. Filatov believed that there was no hormonal action induced by this procedure, but thought that any beneficial effect that might be obtained was due to the elaboration of disintegration substances which he termed "catalysts" or enzymes. However, this does not preclude the possibility of some short-lived initial hormonal stimulus from the implanted material. Hench (1949) has stated that the activity of rheumatoid arthritis, "a basic biochemical disturbance of unknown type", is potentially reversible at any stage. He points out that although the pathological anatomy is largely irreversible, the pathologic physiology may be reversed. He suggests that powerful corrective forces lie dormant awaiting proper stimulation.

Summary

A preliminary series of observations in the use of placental tissue implants in rheumatoid arthritis is presented. In a group of 35 patients with rheumatoid arthritis, there was evidence of Grade II improvement in sixteen patients following subcutaneous implantation of human placental tissue; this
improvement has been maintained until the present
time. The mode of action of this procedure is not
known, but it is not considered to be due to any
sustained hormonal elaboration by the implanted
placenta. Many factors are known to influence
favourably the course of rheumatoid arthritis,
\textit{e.g.} surgery, placebos, injection of inert
materials, the natural course of the disease, the enthusiasm
of the physician, and the will of the patient to get well.
Psychological stimuli must be eliminated in assessing
the value of any new procedure. With these reserv-
ations, the method may be investigated further to
assess its relative significance in the treatment of
rheumatoid arthritis.

REFERENCES

5, 195.
J. med. Sci.}, 223, 144.
Diseases}, 10, 163.
Etienne-Martin, —, Klepping, C., Troubat, M., Klepping, J., and
— (1945). \textit{Ibid.}, 2, 484.
Neustadt, D., Geiger, J., and Steinbrocker, O. (1953). \textit{Annals of the
Rheumatic Diseases}, 12, 350.
24, 199.
\textit{J. Amer. med. Ass.}, 140, 659.
(Napoli)}, 65, 681.
Watson, R. J. (1953). Personal communication.

\textbf{Greffe de tissu placentaire chez des malades
atteints d'arthrite rhumatismale}

On présente une série préliminaire d'observations sur
l'emploi de greffes de tissu placentaire dans l'arthritis
rhumatismale. Sur 35 malades atteints d'arthrite rhuma-
tismale, 16 présentèrent des signes d'amélioration du
2-ème degré après une greffe souscutanée de tissu
placentaire humain; cette amélioration se maintient
toujours. On ne connaît pas le mode d'action de ce
procédé et on ne croit pas qu'il s'agisse d'une élaboration
hormonale soutenue des greffes placentaires. On connait
beaucoup de facteurs qui influencent favorablement
l'évolution de l'arthrite rhumatismale, tels que remèdes
factices, injections de produits inertes, interventions
chirurgicales, évolution naturelle de la maladie, enthous-
iasme du médecin et volonté de guérir du malade. En
déterminant la valeur de tout procédé nouveau il faut
éliminer l'incitation psychologique. A ces restrictions
près, cette méthode mérite des recherches ultérieures
afin d'évaluer son importance relative dans le traitement
de l'arthrite rhumatismale.

\textbf{Injerto de tejido placentario en enfermos
con artritis reumatoide}

\textbf{SUMARIO}

Se presenta una serie preliminar de observaciones
sobre injertos de tejido placentario en la artritis reuma-
toide. En un grupo de 35 enfermos con artritis reumatoide,
16 presentaron signos de mejoría de grado II después
del injerto subcutáneo de tejido placentario humano;
esta mejoría se mantiene todavía. No se conoce el modo
de acción de este procedimiento y no se cree que se
trate de una elaboración hormonal sostenida de los
injertos placentarios. Se conocen muchos factores que
ejercen un efecto favorable en el curso de la artritis
reumatoide, tales que cirugía, remedios facticios,
inyecciones de productos inertes, evolución natural de
la enfermedad, entusiasmo del médico y la voluntad de
mejorar del enfermo. Al determinar el valor de un
procedimiento nuevo hay que eliminar la estimulación
psicológica. Con estas reservas, el método merece
investigación ulterior para evaluar su importancia
relativa en el tratamiento de la artritis reumatoide.
Implantation of Placental Tissue in Patients with Rheumatoid Arthritis: Preliminary Report

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