IMPLANTATION OF PLACENTAL TISSUE IN PATIENTS WITH RHEUMATOID ARTHRITIS*†

PRELIMINARY REPORT

BY

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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 Couadeau, 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.

TABLE I
PATIENTS CLASSIFIED ACCORDING TO SEVERITY OF RHEUMATOID PROCESS AND CLASS OF FUNCTIONAL CAPACITY

Class	Stage				
	I	II	III	IV	Total
I	—	—	—	—	—
II	—	1	7	2	10
III	—	1	11	6	18
IV	—	2	2	3	7
Total ..	—	4	20	11	35

‡ 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.

Functional impairment shown in four classes: Class I, all usual duties without handicap; Class II, normal activities despite discomfort or limited motion; Class III, few duties of usual occupation or self care; Class IV, largely or wholly incapacitated.

Response of rheumatoid activity to therapy, based entirely on objective findings, given in four grades: Grade I, complete remission; Grade II, major improvement; Grade III, minor improvement; Grade IV, no improvement.

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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 3½ 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

TABLE II
RESPONSE OF PATIENTS RECEIVING PLACENTAL IMPLANTATION

Case No.	Sex	Age	Duration of Disease (yrs)	Stage of Severity	Functional Class	Erythrocyte Sedimentation Rate	Date of Implant	Grade of Improvement
1	M	54	12	IV	III	90	18/6/49	III
*2	F	48	1	III	III	108	12/7/49	II
3	F	22	8	III	III	18	5/11/49	IV
4	F	62	19	IV	II	68	11/11/49	IV
5	F	45	1½	II	IV	59	12/11/49	IV
6	F	37	7	IV	IV	92	12/11/49	IV
7	M	70	3/12	II	II	66	22/11/49	II
8	M	34	1	IV	IV	12	29/12/49	II
9	M	63	8/12	III	III	104	21/3/50	II
10	M	51	12	III	IV	88	2/6/50	IV
11	M	46	21	III	IV	48	14/8/52	II
12	F	40	1	II	III	32	14/8/52	IV
13	F	58	5	III	III	48	29/9/52	IV
14	F	36	20	IV	III	61	31/10/52	III
15	F	30	8	IV	II	30	31/10/52	II
*16	M	46	2	II	IV	88	31/10/52	IV
17	F	39	3	III	III	61	28/11/52	II
18	M	51	16	III	II	58	12/12/52	IV
19	F	53	10	III	II	54	12/12/52	II
20	F	46	3½	III	III	64	27/1/53	II
21	F	63	35	III	III	102	27/1/53	III
22	M	26	10	III	III	73	6/2/53	IV
23	M	40	7	III	II	42	6/2/53	II
24	F	33	7½	III	III	35	20/2/53	IV
25	F	40	7	IV	III	57	13/3/53	II
26	F	66	50	IV	III	60	20/3/53	IV
27	F	30	18	III	II	37	20/3/53	II
28	F	62	5	III	III	35	27/3/53	II
29	M	35	24	III	IV	72	27/3/53	IV
30	F	48	12	IV	IV	92	3/4/53	II
31	F	45	10	IV	III	82	3/4/53	IV
32	F	35	5	IV	III	51	10/4/53	II
33	F	51	11	III	II	94	10/4/53	III
*34	F	37	15	III	II	34	17/4/53	II
35	M	64	19	III	III	95	17/4/53	IV

* See Text.

ankles of 1 year's duration. The shoulders and hips were also painful on motion. The pain had become progressively worse, so that sitting down or rising from a chair was done with extreme difficulty. She managed to descend a flight of steps by walking slowly backwards.

Examination revealed warm, swollen, tender knees that were painful on motion. The ankles were similarly involved. Motion of both shoulders and elbows was limited because of pain. The wrists were swollen and tender, and limited motion produced pain. The metacarpal-phalangeal joints and the proximal inter-phalangeal joints were swollen, warm, and tender; flexion of the fingers was incomplete. The erythrocyte sedimentation rate (Westergren) was 108 mm. in 1 hour. The rheumatoid arthritis was classified as Stage III, Class III.

Placental tissue implantation was done on July 12, 1949; 2 days later there was decrease in swelling of all involved joints except the right ankle, motion of the joints was less painful, and the range of motion was improved. Improvement was progressive over a period of 2 weeks and has been maintained to date. The therapeutic result was 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 with no 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 codein.

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.

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, *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 reservations, the method may be investigated further to assess its relative significance in the treatment of rheumatoid arthritis.

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Greffe de tissu placentaire chez des malades atteints d'arthrite rhumatismale

RÉSUMÉ

On présente une série préliminaire d'observations sur l'emploi de greffes de tissu placentaire dans l'arthrite rhumatismale. Sur 35 malades atteints d'arthrite rhumatismale, 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 connaît 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, enthousiasme 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.

Injerto de tejido placentario en enfermos con artritis reumatoide

SUMARIO

Se presenta una serie preliminar de observaciones sobre injertos de tejido placentario en la artritis reumatoide. 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 tratase 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 inertos, 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 avaluar su importancia relativa en el tratamiento de la artritis reumatoide.