IMMUNOLOGICAL ASPERMATOGENESIS IN MAN

II. RESPONSE TO CORTICOSTEROIDS IN CASES OF NON-OBSTRUCTIVE AZOOSPERMIA WITH A POSITIVE BLASTOID TRANSFORMATION TEST

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Summary. Corticosteroids were used in the treatment of a group of eighteen non-obstructive azoospermic or severely oligospermic patients showing a positive lymphocyte blastoid transformation test in response to a seminal antigen. A control group of eleven similarly affected patients with negative blastoid transformation tests was given the same treatment. Response was noticed in nine of the positive test group (50%), and one patient's wife conceived. None of the control group showed any response.

The value of this trial therapy is discussed.

INTRODUCTION

An immunological reaction was demonstrated in a group of infertile males with non-obstructive oligospermia or azoospermia (El-Alfi & Bassili, 1970). The present paper reports the findings in the same group of patients when subjected to corticosteroid therapy.

MATERIAL

Eighteen of the twenty-one patients who showed a positive lymphocyte blastoid transformation test were given corticosteroids orally. The remaining three patients were not available at the time of the trial. The ages of the men receiving corticosteroids ranged from 25 to 50 years, with an average of 38.5 years, and the number of years during which they had been known to be infertile ranged from 1 to 29 with an average of 8.7 years. Thirteen patients were completely azoospermic during the period before treatment, while the remaining five gave reports varying from severe oligospermia to azoospermia before the trial therapy.

Six patients had a history of previous testicular injury in the form of trauma, biopsy or orchitis. Twelve had bilateral small, soft testes while the remaining six had testes of normal size and consistency (Table 1).

As controls, eleven patients were chosen at random from the group of patients with non-obstructive azoospermia who had a negative blastoid transformation test. Their ages ranged from 20 to 55 years with an average of

TABLE 1
HISTORY OF TESTICULAR INJURY AND SIZE AND CONSISTENCY
OF TESTES IN EIGHTEEN INFERTILE MEN WITH POSITIVE
LYMPHOCYTE BLASTOID TRANSFORMATION TESTS TREATED
WITH CORTICOSTEROID

Case No.	History of testicular injury			Size and consistency of testes	
	Infection	Trauma	Biopsy	Small and soft	Normal
8	—	—	+	—	+
21	—	—	+	+	—
25	—	—	—	+	—
27	—	—	—	+	—
28	—	—	—	+	—
48	—	—	—	+	—
50	—	+	—	+	—
51	—	—	—	+	—
54	—	—	—	+	—
85	—	—	—	—	+
113	+	—	—	+	—
120	+	—	—	+	—
121	—	—	—	—	+
123	—	—	—	—	+
131	+	—	—	—	+
134	—	—	—	+	—
145	—	—	—	—	+
160	—	—	—	+	—

TABLE 2
HISTORY OF TESTICULAR INJURY AND SIZE AND CONSISTENCY
OF TESTES IN ELEVEN CONTROL PATIENTS

Case No.	History of testicular injury			Size and consistency of testes	
	Infection	Trauma	Biopsy	Small and soft	Normal
42	—	—	—	+	—
62	—	—	—	+	—
72	+	—	—	+	—
74	—	—	—	—	+
82	+	—	—	+	—
86	+	—	—	+	—
96	—	—	—	—	+
107	—	—	—	+	—
114	—	—	—	—	+
116	—	—	—	—	+
126	—	—	—	+	—

34.2 years and they had been known to be infertile for 1 to 25 years (average 9.5 years). Six patients gave a history of complete azoospermia, and the remaining five a history of alternating oligospermia and azoospermia, before the start of the trial. A history of previous testicular injury was recorded for three of

TABLE 3
SEMEN CHARACTERISTICS OF EIGHTEEN INFERTILE MEN WITH POSITIVE BLASTOID TRANSFORMATION TESTS TREATED WITH CORTICOSTEROIDS

Case No.	Maximal semen characteristics												Peak of response
	Before treatment				During treatment				After treatment				
	Semen vol. (ml)	Sperm conc. (10^6 /ml)	Motility (%)	Normal morphology (%)	Semen vol. (ml)	Sperm conc. (10^6 /ml)	Motility (%)	Normal morphology (%)	Semen vol. (ml)	Sperm conc. (10^6 /ml)	Motility (%)	Normal morphology (%)	
27	1.5	0.5	10	60	2.5	6.5	45	85	2	4.5	45	85	10th week of treatment
28	2.5	—	—	—	4	2.6	20	60	4	10	20	70	6 months after treatment
51	1	0.6	—	—	2	5	—	—	2	12.5	5	50	8 months after treatment
145	4.5	0.5	5	60	4.5	40	50	80	3.5	33	55	80	8th week of treatment
8	2	1 to 2/HPF*	—	—	4	0.1	30	70	3.5	0.8	60	70	6 months after treatment
21	1.5	—	—	—	1.5	—	—	—	1.5	2 to 3/HPF	—	1/HPF	9 months after treatment
54	0.5	—	—	—	1	2 to 3/HPF	—	1/HPF	0.5	2 to 3/HPF	—	1/HPF	12th week of treatment
113	2	—	—	—	3	0.75	—	30	2.5	0.75	—	20	4th week of treatment
120	1	—	—	—	2.5	—	—	—	3	3 to 4/HPF	—	1/HPF	6 months after treatment
25	0.5	—	—	—	0.5	—	—	—	0.5	—	—	—	—
48	1.5	—	—	—	2	—	—	—	2	—	—	—	—
50	1.0	—	—	—	1.5	—	—	—	1.5	—	—	—	—
85	2	—	—	—	2	—	—	—	3	—	—	—	—
121	1	—	—	—	2	—	—	—	2	—	—	—	—
123	2	1 to 2/HPF	—	—	1.5	1 to 2/HPF	—	—	2	1 to 2/HPF	—	—	—
131	2	—	—	—	3	—	—	—	2.5	—	—	—	—
134	2.5	—	—	—	3.5	—	—	—	3.5	—	—	—	—
160	3	—	—	—	3.5	—	—	—	3.5	—	—	—	—

* HPF, high power field.

them. Seven patients had bilateral small, soft testes and in the remaining four, the testes were normal (Table 2).

Treatment

The corticosteroid dose (prednisone, 5-mg tablets) was standardized for all patients by giving 40 mg/day for 2 weeks, followed by a gradual reduction over a 9-week period. The prednisone used was a synthetic product, and contained no traces of testosterone.

The patients were checked carefully for hypertension, peptic ulcer, chest affections, diabetes, Cushingoid manifestations and any mental troubles before giving prednisone.

All the men were treated as out-patients. They had to report every week for clinical checking, and for semen examination following a 5-day period of continence.

RESULTS

Of the eighteen patients treated, four showed a good response both during and after treatment, five showed a poor response and nine showed no response.

TEXT-FIG. 1. Sperm concentration in four infertile men showing good response to corticosteroid therapy.

Of the four patients showing a good response (Table 3), three continued to maintain good sperm counts 8 to 12 months after the end of treatment. The sperm counts of the fourth patient (Case No. 28), started to decline 10 months after the end of treatment, and he is now azoospermic again (Text-fig. 1).

The motility of the spermatozoa was good (40 to 50% active) in two of these patients, and poor in the remaining two (Table 3). Three patients had alternating azoospermia and severe oligospermia, while the fourth was completely

TABLE 4
SEMEN CHARACTERISTICS OF ELEVEN INFERTILE MEN WITH NEGATIVE BLASTOID TRANSFORMATION TESTS (CONTROLS) TREATED WITH CORTICOSTEROID

Case No.	Maximal semen characteristics									
	Before treatment					During treatment				
	Semen vol. (ml)	Sperm conc. (10^6 /ml)	Motility (%)	Normal morphology (%)	Semen vol. (ml)	Sperm conc. (10^6 /ml)	Motility (%)	Normal morphology (%)	Semen vol. (ml)	After treatment
42	2.5	1 to 2/HPF*	—	—	3	—	—	—	2	1 to 2/HPF
62	2	—	—	—	1.5	—	—	—	2	—
72	3	2	20	50	3	1.5	20	50	3.5	2
74	2	—	—	—	1.5	—	—	—	2.5	—
82	3.5	0.5	10	50	3	0.25	5	30	3	0.25
86	3.5	2 to 3/HPF	—	—	2.5	1 to 2/HPF	—	—	3	3 to 4/HPF
96	3	—	—	—	3.5	—	—	—	3.5	—
107	2	—	—	—	1.5	—	—	—	2.5	—
114	2.5	—	—	—	2	—	—	—	2	—
116	3	—	—	—	2.5	—	—	—	3	—
126	1.5	2 to 3/HPF	—	—	2	1 to 2/HPF	—	—	1.5	1 to 2/HPF

* HPF, high power field.

azoospermic before treatment. There was no history of testicular injury in any of these patients but three had bilateral small, soft testes. In the fourth (Case No. 145), the size and consistency were normal. This patient showed the best results. His total sperm count rose from 2.25 million before, to 180 million during treatment and his wife became pregnant. Her first missed period occurred 3 months after the onset of treatment.

The five patients who responded poorly to treatment (Table 3) did show a slight increase in their sperm counts, but their spermatozoa were mostly sluggish or immotile. This small improvement appeared during treatment in two patients, and after treatment in three patients (Table 3). Four had azoospermia, and one severe oligospermia before the start of treatment. Four gave a history of testicular injury (Table 1), and the testes were soft and small in four and of normal size and consistency in one.

Of the remaining nine patients with a positive blastoid transformation test who showed no response to corticosteroid therapy, eight had azoospermia and one oligospermia before the start of therapy. Two had a history of testicular injury. Bilateral small, soft testes were found in five and testes of normal size and consistency in four (Table 1).

None of the control patients showed any improvement in their pre-treatment counts (Table 4).

There was no significant change in the accessory organs of any of the treated patients.

DISCUSSION

Treatment of infertility resulting from an auto-immune disorder in the male has not yet been greatly successful. Wilson (1956) tried donor insemination which resulted in a successful pregnancy. Rozin (1960) suggested the *in vitro* substitution of normal centrifuged acellular seminal plasma from donors for the agglutinin-rich seminal plasma of infertile husbands who still have good sperm counts, but an azoospermic or severely oligospermic husband cannot be helped by such a line of treatment. The present group of eighteen patients all had non-obstructive azoospermia or severe oligospermia, and all gave evidence of an immunological disorder manifested by a positive lymphocyte blastoid transformation reaction to a seminal antigen. The increase in sperm count recorded here for nine (50%) patients in response to corticosteroid therapy gave some encouragement to a number of infertile males for whom, as yet, there had been no successful treatment. The good response of some patients to the corticosteroid therapy supports the hypothesis of auto-immune aspermato-genesis as a cause of infertility in man and the absence of any response in the controls strongly supports the reliability of the blastoid transformation test in the detection of such cases (El-Alfi & Bassili, 1970).

It is believed that in the case of the three patients who showed a good rise in their sperm counts (Case Nos. 27, 28 and 51) but whose wives did not become pregnant, and probably also in the case of some of the patients who showed a poor response to corticosteroids but some increase in sperm count, artificial insemination of the husband's semen (AIH) is worth a trial, particularly since the rise in the sperm counts might not be long lasting. The sperm

count of one patient (Case No. 28) showed a gradual rise to 10·4 million during treatment, and 40 million 6 months afterwards, but the counts gradually declined to zero level 12 months after the termination of treatment. Another point in favour of AIH is that the rise in the total sperm count may not reach a level that would allow normal conception.

It is difficult, in a group of patients like the present one, to give an individual prognosis. Changes in the degree of blastoid transformation could not be correlated with rise in sperm count. Corticosteroid therapy suppressed the blastoid transformation reactions whether or not the testicular tubules responded to suppression of the auto-immune process. Similarly, a changing titre of circulating antibodies could not be taken as a criterion for prognosis. It appears from Table 3 that individuals who are severely oligospermic before therapy probably have a better chance of responding to corticosteroids than those with a history of prolonged azoospermia. However, some of those with prolonged complete azoospermia did respond, while other similar cases failed to respond. It is possible that in the latter group, the testicular tubules were so damaged that even after the suppression of the auto-immune process, spermatogenesis could not be resumed.

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