Diabetes and rheumatoid factor

IRWIN ORESKES* AND HARRY SPIERA

From the Clinical Research Center, and the Department of Medicine, Mount Sinai School of Medicine, City University of New York

Previous work from this laboratory (Oreskes and Spiera, 1966) as well as that of many other investigators (Bartfeld, 1969) has shown that the anti gamma globulin antibodies, otherwise known as rheumatoid factor (RF), are found in many persons with a wide variety of diseases other than rheumatoid arthritis. Indeed, it appears that a majority of individuals exhibiting RF activity do not have rheumatoid arthritis (Oreskes and Spiera, 1966, 1967). Presence of RF has been noted in the aged (Heimer, Levin, and Rudd, 1963), and this observation has been associated with higher levels of chronic disease in such groups, notably parkinsonism and diabetes (Litwin and Singer, 1965). In some individuals RF production appears to be due to immune stimulation by isologous γ G immunoglobulin. Thus multiple transfusions (Vierucci, 1965), vaccination (Aho, Konttinen, Rajasalmi, and Wager, 1962), and transplacental transfer of γ G from mother to child (Steinberg and Wilson, 1963), or child to mother (Fudenberg and Fudenberg, 1964), have all been implicated in the stimulation of RF activity.

Diabetic individuals maintained on insulin therapy are perforce subjected to repeated 'immunization' by a foreign protein. Production of anti-insulin-antibodies by many such individuals appears likely (Berson and Yalow, 1966). In view of the findings cited above, as well as the possibility that circulating antigen-antibody complexes may also stimulate RF production, it was considered that individuals receiving injections of exogenous insulin might exhibit an increased frequency of RF activity as compared to control groups. Formation of RF-like antibodies has been noted in rabbits after hyperimmunization with bacterial antigens (Abruzzo and Christian, 1961) or ovalbumin (Aho and Wager, 1961).

Material and methods

To test this hypothesis, 101 ambulatory clinic outpatients with a confirmed diagnosis of diabetes mellitus were tested for RF activity in their serum by means of the slide latex test (SLT) and the tanned sheep cell test (TSC). Details of these procedures were published some years ago (Oreskes and Spiera, 1966; Oreskes and Plotz, 1965).

Positive sera were taken as those exhibiting a 1+ or higher degree of agglutination in the SLT and a titre of 1:20 or more in the TSC test. Sera examined with the TSC test were first adsorbed overnight with an equal volume of packed washed tanned unsensitized sheep cells to remove heterophil activity.

Subjects with a current or previous history of rheumatoid arthritis or other diseases known to be associated with a significant frequency of RF activity were excluded. Serological results were grouped in two categories:

- (1) Those from patients who had received multiple injections of insulin;
- (2) Those from patients who had never received insulin and who were instead maintained on dietary or oral hypoglycemic (Orinase) regimens.

These two groups exhibited closely similar sex and age distributions.

Results and discussion

The results are summarized in the Table. In the non insulin group, RF activity was found in 10.7 per cent. of cases. This value is not significantly different from 10.2 per cent., the frequency of positive RF tests previously found in a group of patients with osteoarthritis of similar ages (Oreskes and Spiera, 1966). However, in the insulin group, RF activity was found in

Table Frequency of positive rheumatoid factor tests in patients with diabetes

Insulin	Sex	No. of cases	RF Positive	
			No.	Per cent.
Given	Male	17	4	23.5
	Female	28	9	31.1
	Total	45 (a)	13 (b)	28.9
Not given	Male	22	1	4.5
	Female	34	5	14.7
	Total	56 (c)	6 (d)	10.7

Age distribution (yrs)	Mean	(a)	(b)	(c)	(d)
	Median	55.2	57.1	59.0	58.6
Sex (per cent.)	Male	53.0	56.0	56.0	57.0
	Female	37.8	39.3	39.3	39.3

28.9 per cent. of cases. Comparing the insulin and non insulin groups by the χ^2 test, this difference in frequency of RF positive tests was found to be statistically significant. ($\chi^2 = 4.27$; $0.05 > P > 0.02$).

In both groups TSC titres were low with a median value of 1:160. This is in agreement with the situation usually observed in nonrheumatoid disease, and is in contrast to the higher titres usually encountered in rheumatoid arthritis (Oreskes and Siltzbach, 1968).

There was no correlation between RF activity, age, sex or general clinical condition.

In patients who had received insulin, no relation between duration of therapy or dose level and RF activity could be established.

These results suggest that, in some individuals, the presence of RF activity is associated with chronic antigenic stimulation by a foreign protein due to therapeutic injection of insulin.

Summary

Study of 45 insulin-treated diabetics revealed a statistically significant 2.7-fold increase in positive tests

for rheumatoid factor (RF) as compared to 56 diabetics on dietary or oral hypoglycaemic (Orinase) therapy, or to forty patients with osteoarthritis. Frequency of RF was not significantly different in the Orinase and osteoarthritis groups. Age was not a factor in these results, since all three groups were of about the same age (mean and range). In the insulin-treated group, RF activity was twice as common among females as among males. No relation between duration of insulin therapy, dose level, or duration of disease, and RF activity was established.

These results suggest that, in some individuals, the presence of RF activity is associated with chronic antigenic stimulation by a foreign protein due to therapeutic injection of insulin.

The technical assistance of Mrs. Evelyn Eason is gratefully acknowledged. We also wish to thank Dr. John Bookman for permission to study his patients, and Dr. Henry Dolger for valuable comments.

This work was aided by National Institutes of Health Grant, RR 71, and by grants from the New York Chapter of the Arthritis Foundation.

References

- ABRUZZO, J. L., AND CHRISTIAN, C. L. (1961) *J. exp. Med.*, **114**, 791 (The induction of a rheumatoid factor-like substance in rabbits)
- AHO, K., KONTTINEN, A., RAJASALMI, M., AND WAGER, O. (1962) *Acta path. microbiol. scand.*, **56**, 478 (Transient appearance of the rheumatoid factor in connection with prophylactic vaccinations)
- AND WAGER, O. (1961) *Ann. Med. exp. Fenn.*, **39**, 79 (Production of anti-antibodies in rabbits)
- BARTFELD, H. (1969) *Ann. N. Y. Acad. Sci.*, **168**, 30 (Distribution of rheumatoid factor activity in nonrheumatoid states)
- BERSON, S. A., AND YALOW, R. S. (1966) *Amer. J. Med.*, **40**, 676 (Insulin in blood and insulin antibodies)
- FUDENBERG, H. H., AND FUDENBERG, B. R. (1964) *Science*, **145**, 170 (Antibody to hereditary human gamma-globulin (Gm) factors resulting from maternal-fetal incompatibility)
- HEIMER, R., LEVIN, F. M., AND RUDD, E. (1963) *Amer. J. Med.*, **35**, 175 (Globulins resembling rheumatoid factor in serum of the aged)
- LITWIN, S. D., AND SINGER, J. M. (1965) *Arthr. and Rheum.*, **8**, 538 (Studies of the incidence and significance of anti-gamma globulin factors in the aging)
- ORESKEs, I., AND PLOTZ, C. M. (1965) *J. Immunol.*, **94**, 567 (Autoinhibition of rheumatoid factor reactivity demonstrated by a block hemagglutination procedure)
- AND SILTZBACH, I. E. (1968) *Amer. J. Med.*, **44**, 60 (Changes in rheumatoid factor activity during the course of sarcoidosis)
- AND SPIERA, H. (1966) *J. Amer. med. Ass.*, **198**, 384 (Use of fingertip blood in detection of rheumatoid factor)
- , — (1967) *Excerpta Medica Int. Congr. Series No. 143* (Rheumatoid factor in rheumatoid arthritis and other diseases)
- STEINBERG, A. G., AND WILSON, J. A. (1963) *Science*, **140**, 303 (Hereditary globulin factors and immune tolerance in man)
- VIERUCCI, A. (1965) *Vox. Sang.*, **10**, 82 (Gm groups and anti-Gm antibodies in children with Cooley's anaemia)