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Association of Antibodies to Gm and Antibodies to Australia Antigen in Adolescent Drug Addicts (37810)

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Recent literature indicates a striking frequency of occurrence of anti-gamma globulins in the sera of drug addicts (1). The specific nature of these antiglobulins and their etiology have not been elucidated. Blumberg and associates (2) found a significant association between anti-Gm and antibody to Australia antigen in patients with thalassemia who had received many transfusions. On the basis of this observation they advanced several hypotheses, including: (i) anti-Au and anti-Gm are associated in other populations; and (ii) the presence of antibodies to Gm antigens is in some cases caused by infection with Au antigen and also agents similar to it. The present study defines the anti-gamma globulins of the addict in terms of Gm specificity and supports the hypotheses of Blumberg *et al.* derived from their analysis of patients with thalassemia.

Methods. The study group was derived from a juvenile detention facility for adolescents and consisted of 298 youngsters between the ages of 12 and 17 yr addicted to heroin. The male to female ratio was 3:1. A nonaddicted control group of 103 adolescents with a male to female ratio of 2:1 was selected from the same institution. The serum of each patient was initially tested for gamma globulin antibodies of the Gm (a), Gm (b), and Gm (f) specificities.[1] The method used for Gm typing has been described elsewhere (3). A Gm phenotype for Gm (a), Gm (b) and Gm (f) was established for each subject possessing anti-Gm gamma globulins in the serum. Additionally, latex fixation reactivity (4) was determined in those sera to distinguish Ragg (rheumatoid) from SNagg (nonrheumatoid) Gm agglutinators. Au antigen and antibody were measured by the radioimmunoassay of Coller *et al.* (5). Antibodies against red blood cells were identified by a sensitive agglutination method utilizing polybrene particles (6).

Results. Anti-gamma globulins of the Gm specificities studied were found in 23 of 298 addicted individuals as compared to 1 in 103 nonaddicted adolescents. In 4 instances, 2 Gm antibodies were identified in the same subject (Table I). Antibody titers ranged from 1:2 to 1:512. Latex fixation reactivity was found in 11 of the 23 anti-Gm positive sera (40%). Four of the 11 latex positive sera demonstrated Gm antibodies directed against the Gm phenotype of the individual. None of these patients, however, manifested clinical evidence of rheumatoid arthritis.

Sera from the 23 addicts with anti-Gm and from 80 other addicts who did not have anti-Gm were tested for the presence of Au and anti-Au. Antibody to Au was found in 18 of these sera and Au antigen in 8 of them. There was a significant association of anti-Au and anti-Gm: 8 of the 23 sera con-

TABLE I. Distribution of Gm Antibodies.

	Addicts	Controls
Anti-Gm (a)	14	1
Anti-Gm (b)	9	1
Anti-Gm (f)	4	0
Total Gm antibodies	27 (in 23 subjects)	1
Total no. subjects studied	298	103
% anti-Gm positive	7.7	0.9

[1] Gm (a) = Gm (1); Gm (b) = Gm (5); Gm (f) = Gm (4).

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TABLE II. Au Antibody and Gm Antibody in Addict Sera.

	Anti-Au (+) sera	Anti-Au (−) sera	Totals
Anti-Gm (+) sera	8	15	23
Anti-Gm (−) sera	10	70	80
Totals	18	85	103

Probability
Fisher's exact 2 × 2
P (this and more extreme) = 0.018844967

taining anti-Gm also contained anti-Au while only 10 of the 80 sera which did not contain anti-Gm had anti-Au [$P = 0.02$] (Table II). There was no apparent association between the presence of anti-Gm and Au antigen.

Red blood cell antibodies were found in 7 of the 298 addicts (2.3%) and in 3 of 103 controls (2.9%).

Discussion. Several possibilities could explain the genesis of Gm antibodies in heroin addiction. These include: (i) Repeated contamination with blood introduced by needles, syringes and/or droppers, used in common by addicts, results in gamma globulin isoimmunization. (ii) Heroin or other materials in the injected "street mixture" directly stimulates Gm antibody formation. (iii) Repeated inoculations of infectious agents, particularly the hepatitis agent(s) associated with Australia antigen are responsible for induction of anti-Gm. The first possibility was investigated by attempting to identify other isoantibodies in the blood specifically directed against red blood cells. No differences were found between the study and control groups. Further, isoimmunization fails to explain the existence of those Gm antibodies with autoimmune characteristics. These observations, therefore rule against the first possibility. Owing to the lack of information on the constituents of the "street mixture" it is not possible to draw any conclusions about the second possibility except indirectly by exclusion of the first and third proposals. However, the data on the association of anti-Au and anti-Gm are compatible with the third possibility and support the hypothesis generated by the thalassemia study.

Blumberg *et al.* (7) have suggested that Australia antigen has characteristics of both an infectious agent and a serum protein polymorphism capable of producing antibodies in individuals infected with this agent. Thus, Gm antibodies may be the result of the injection of IgG protein, as part of the Au antigen particle (8), which differs from that of the infected host. They have termed Australia antigen or presumed infectious agents similar to it "Icrons" (7) and further suggest that the interactions between the infectious agent and the putative host (i.e., development of Au antibody, or of persistent antigenemia) relates to inherited antigenic specificities of the host; that is, polymorphisms of the host. With regard to the Gm system, information arising from the thalassemia study indicates that those individuals who have fewer Gm antigens and are therefore prone to Gm antibody formation are more likely to produce Au antibody; whereas those who are better endowed with Gm antigens and unlikely to produce Gm antibodies manifest persistent Au antigenemia (2).

This concept invokes IgG isoimmunization as a basis for the association of Au and Gm antibodies. But again, the presence in some individuals of anti-Gm with what appears to be the same Gm specificity as the host suggests that factors other than simple isoimmunization are operating. In each instance these Gm antibodies were associated with positive latex fixation reactions in the serum. The finding of Gm antibodies in rheumatoid arthritis has long been appreciated, though it is poorly understood. The occurrence of latex reactivity in serum, in the absence of rheumatoid disease, has been noted in patients with hepatocellular disorders (9) and in drug addiction as well (10).

The findings presented in this study are compatible with the explanation that in an addict population Gm antibody stimulation may result from infection with the hepatitis agent associated with Australia antigen, though the mechanism for this stimulus remains as yet unclear. An analogous situation may be found in the induction of anti-A and anti-B blood group antibodies by bacterial (11) and viral antigens (12). Infec-

tion with Au antigen might help explain, in part, the presence of Gm antibodies in otherwise normal individuals who have not been known to be sensitized by the administration of incompatible Gm gamma globulin.

Summary. A 7.7% incidence of antibodies directed against Gm (a), Gm (b) and Gm (f) antigens of IgG was noted in 298 adolescent drug addicts, as compared to 0.9% in a nonaddicted control group. Isoimmunization as a stimulus for Gm antibody production in addicts was indirectly excluded. A significant association between anti-Au and anti-Gm in the sera of drug addicts was found, which suggests that the hepatitis agent associated with Australia antigen may be responsible for the induction of Gm antibodies in this group.

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