

IgA-induced Anaphylactic Transfusion Reactions: A Report of Four Cases

By Juhani Leikola, Jukka Koistinen, Marja Lehtinen, and Martti Virolainen

Anaphylactic reactions after transfusion of a small amount of red cell compatible blood is described. Typical manifestations were substernal pain, dyspnea, and severe normovolemic shock. All the four patients lacked IgA and were found to have antibodies to IgA with titers from 500 to 16,000, as determined by a passive hemagglutination assay. In immunodiffusion against IgA, a single precipitation line was produced by three of the four serums. The antibodies were shown to be IgG by ultracentrifugation, gel filtration, immuno-

electrophoresis, and ion exchange chromatography. The antigen-antibody complexes were able to fix complement. Lack of cell-bound immunity was suggested by the failure of IgA to stimulate lymphocytes from one patient. Two of the patients received IgA-deficient blood or plasma; both tolerated the transfusion without ill effects. Twice-washed erythrocytes from normal blood provoked a reaction in the third patient, but after three additional washings, no reaction was observed.

IN RECENT YEARS, considerable attention has been paid to isoimmunization to IgA, which may cause severe transfusion reactions.¹⁻⁹ Class-specific antibodies to IgA, occurring in subjects who lack IgA,^{1,4} may be responsible for such reactions. There are only five reported patients with IgA deficiency and strong anti-IgA antibodies who experienced anaphylactic transfusion reactions on challenge with intravenous IgA.⁵⁻⁸ Two of these patients had precipitating antibodies to IgA.^{6,8} However, in one of the patients a manyfold concentration of the serum was required to demonstrate a precipitation with IgA. In the present study, we report four additional IgA-deficient patients, three of whom had precipitating antibodies against IgA and all of whom experienced severe transfusion reactions due to IgA.

CASE REPORTS

Case No. 1 (K.S.)

A 40-yr-old man had pernicious anemia treated with vitamin B₁₂ injections since the age of 25. He had never received blood or plasma products. For 4 yr he had had recurrent respiratory infections, and in September 1970, he was found to have gastric cancer. In

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immunoelectrophoresis and single radial immunodiffusion no IgA was found in his serum. The IgM level was 9 mg/100 ml, and IgG was 235 mg/100 ml.

In October 1970, the tumor was removed by radical gastrectomy. Prior to the operation, a unit of red cell compatible blood was given, and after a few seconds the patient felt severe epigastric pain, dyspnea, and paresthesiae in the hands and feet. No pulse could be felt; the patient's anxiety was marked. The transfusion was interrupted immediately, and the blood pressure was elevated with vasopressors. The reaction subsided within a few hours, and no anuria occurred.

Later, while under general anesthesia, the patient was given a twice-washed red cell concentrate. A similar but milder reaction developed that was easily managed by intravenous administration of hydrocortisone. Subsequently, the patient tolerated 30 ml of five times washed red cell concentrate.

Case No. 2 (M.H.)

A 72-yr-old unmarried woman with no children had had rheumatoid arthritis for 2 yr. In May 1971, she was admitted to the hospital because of anemia; hemoglobin was 8.8 g/100 ml.

One unit of whole blood was given, and within 1 or 2 min, the patient became restless and complained of nausea, chest and lumbosacral pain. The transfusion was interrupted immediately, but the patient developed diaphoresis, hypotension, and cyanosis. Emergency measures for anaphylactic shock were started immediately, but the patient's signs of anaphylaxis persisted. The patient developed anuria during the next few hours, which subsided within 24 hr. A left-sided paresis was noted afterward, but improved during the following months.

There were no erythrocyte antibodies in the patient's serum before or after the transfusion. Low titers of leukocyte antibodies were found 1 mo after the anaphylactic reaction but not in a sample taken immediately following transfusion. In later investigations, absence of IgA was found in the patient's serum; IgG was 1520 mg/100 ml, and IgM was 35 mg/100 ml.

Case No. 3 (J.M.)

A 49-yr-old woman with two children had had no allergic symptoms and had received no transfusions. In August 1971, she was admitted to the hospital because of macrocytic anemia and thrombocytopenia. The Schilling test was abnormally low and improved with intrinsic factor. In immunoelectrophoresis and radial immunodiffusion no IgA was detected; IgG was 1.330 mg/100 ml, and IgM was 160 mg/100 ml.

A transfusion with a red cell concentrate was started but was followed almost immediately by severe anaphylactic symptoms. The patient experienced intense substernal pain, dyspnea, and hypotension within a few seconds. She was treated with vasopressors and steroids in high doses and recovered in 10 hr. No evidence for a hemolytic transfusion reaction was found, and leukocyte antibodies were not demonstrable.

Her pernicious anemia was successfully treated with vitamin B₁₂. Three months later, she had completely recovered from the complications of transfusion. At this time she was given a 20 ml test dose of blood group compatible plasma lacking IgA, which she tolerated well without ill effects.

Case No. 4 (P.J.)

A 43-yr-old man had had recurrent anemia since 1956 that had been treated with parenteral iron and blood transfusions. In 1970, absent IgA and malabsorption were demonstrated. In July 1971, the patient was found to have a large abdominal tumor. He was not anemic, and no iron was demonstrable in the bone marrow. No serum IgA could be found. The other immunoglobulins were: IgG 750 mg/100 ml and IgM 60 mg/100 ml.

Because other investigations failed to disclose the nature of the abdominal tumor, an exploratory laparotomy was performed. Before the operation, a 20 ml test dose of blood

group compatible normal plasma was given. After a few seconds his skin became red, and he experienced substernal pain and dyspnea. A fall in blood pressure or change in the heart rate were prevented by administration of hydrocortisone intravenously. The abdominal operation was then undertaken without blood transfusions, and a benign jejunal fibromyoma was removed.

In later investigations, no antibodies to erythrocytes or leukocytes were found. After having recovered from the operation he was transfused with 1 U of blood lacking IgA, which he tolerated well.

MATERIALS AND METHODS

Passive Hemagglutination Assay

A slight modification of the chromic chloride method of Gold and Fudenberg¹⁰ for coating red cells was used. One volume of washed human group O erythrocytes was mixed with one volume of protein solution at a concentration of 1 mg/ml, and one volume of 0.05% CrCl₃ was added. Tris-HCl-buffered saline (pH 7.2) was used as a diluent. The protein coats consisted of six isolated IgA myeloma proteins (four of them IgA subtype 1 and two of subtype 2),¹¹ normal human IgG isolated from pooled serum, and six IgM proteins from patients with Waldeström's macroglobulinemia. After 5-min incubation at room temperature, the coated red blood cells were washed four times and were used for the assay. This was carried out in Microtiter (Cooke) plates, as described previously.¹ Each time, normal human serum (NHS) was used as a negative control and a human serum with known anti-IgA antibodies was used as a positive control.

Gel Diffusion

These experiments were carried out in 1% agarose (L'Industrie Biologique Française S.A., Gennevilliers, France) that was dissolved in 0.15 M phosphate-buffered NaCl, pH 7.2, (double diffusion and single radial diffusion) or in 0.05 M barbital pH 8.2 (immunoelectrophoresis). For the detection of IgA, the standard Ouchterlony microtechnique with rosettes of six peripheral and one central well was employed. An antihuman IgA serum was prepared in rabbits by immunizing them with several IgA myeloma proteins and absorbing the resulting antiserum with a human serum lacking IgA. This specific antiserum was used both undiluted and diluted 1:5. Immunoelectrophoresis and Mancini's single radial immunodiffusion were done according to the standard methods.

To show the precipitation reaction of human anti-IgA in agarose, a large central well with the antiserum was used with small peripheral wells containing the antigen (Fig. 1). The precipitation bands were best seen after 48 hr. Prior to the diffusion experiments, the serums were cleared of lipids by centrifuging them at 26,000 g for 15 min.

Complement Fixation

One of our antisera (J.M.) was tested in the following manner. First, the antibody-antigen complexes were prepared by mixing anti-IgA serum J.M. with NHS in five different proportions. To 1 ml of J.M. was added serial fourfold dilutions of NHS starting from 0.32 ml and ending to 0.00125 ml in the fifth tube (mixtures No. 1-5 in Table 2). The mixtures were kept overnight in a refrigerator, and in the following morning, a faint turbidity had developed in the fifth tube indicating a precipitation reaction.

The consumption of complement was measured by diluting the mixtures in twofold series. Guinea pig complement (2 U) was added. The tests were done in duplicates; one series was incubated for 60 min in a 37°C water bath, and the other series was incubated overnight at 4°C. Thereafter, 2% sheep red cells sensitized with rabbit hemolytic antibodies were added, and the results were read visually after 30 min at 37°C.

Fractionation of the Serums

Ultracentrifugation. The serums were run in sucrose gradient from 10% to 40% at 125,000 g for 16 hr using a swinging bucket head in a preparative centrifuge (Beckman

Spinco). Nine successive fractions were collected by puncturing the tube bottom in a fractionating apparatus (Beckman). The fractions were not dialyzed before testing.

Gel filtration. A Sephadex G-200 (Pharmacia) column with Tris-HCl-buffered saline, pH 8.0, as solvent was used at +5°C. Three main protein peaks, corresponding to the 19S, 7S, and 4.5S fractions, were recovered from the serums. The fractions within each peak were pooled, concentrated, and dialyzed before testing.

Ion exchange chromatography. DEAE-cellulose (Whatman DE 52) was equilibrated with 0.02 M phosphate buffer, pH 7.0. Two elutions with this buffer were carried out in a column using 0.02 M and 0.2 M phosphate buffers, pH 7.0. Both eluates were concentrated and dialyzed against 0.15 M NaCl before using.

Tests With "Diagnostic" Anti-Rh Sera

Four "diagnostic" incomplete anti-Rh sera (Ripley, Wiklinska, Heyman, Bakos) were used.¹² Group O Rh-positive erythrocytes were incubated with 1 to ¼ volumes of the respective anti-Rh serum at 37°C for 60 min and then were washed five times. To ascertain the sensitization, a pool from high-titered rheumatoid serums was used as a positive control. The serums from our patients were tested for agglutination of these sensitized cells using the Microtiter plates.

Lymphocyte Cultures

The peripheral lymphocytes from one patient (J.M.) were cultured as described previously.¹³ The cells were grown in the presence of either normal human plasma, autologous plasma, IgA-deficient plasma, or isolated myeloma proteins that were able to inhibit the humoral anti-IgA antibody of the same patient. Control cells from a normal person were cultured in similar conditions.

RESULTS

The first suggestion of an IgA-related transfusion reaction was obtained when immunoelectrophoresis with antisera to whole human serum and specifically to IgA revealed no IgA in any of the four patients. The same deficiency was observed by single radial immunodiffusion and by double diffusion when two dilutions of the specific antiserum was used. The sensitivity of the latter method was about 5 µg/ml of IgA, and accordingly, the serums were severely deficient of IgA.¹⁴ Whether the deficiency was absolute or relative could not be shown by methods available to us.

To show anti-IgA antibodies, the serums were tested in the hemagglutination assay with different IgA coats (Table 1). IgM and IgG proteins were used as controls. The IgA-coated cells were all agglutinated to a high titer, whereas the others remained unagglutinated. No significant difference in agglutination patterns was found between the various IgA proteins. This shows the class specificity of the antibodies. The reaction was inhibited by each IgA myeloma protein, as well as by normal human serum. The patient K.S. did not have anti-IgA antibodies in the sample collected immediately after transfusion reaction, and an IgA-induced transfusion reaction was not initially suspected.

To be certain that the serums did not contain anti-Gm or other anti-IgG antibodies, the serums were tested with "diagnostic" anti-Rh sera. If red cells are sensitized by these IgG anti-Rh antibodies, they are readily agglutinated by various kinds of anti-IgG antibodies.¹² None of our anti-IgA serums produced agglutination to any degree.

In double diffusion experiments, a single line of precipitation developed

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Table 1. Agglutination of IgA-coated Red Blood Cells by Human Anti-IgA Serums

Serum Samples	IgA Subtype 1			IgA Subtype 2		
	IgA(1)	IgA(2)	IgA(3)	IgA(4)	IgA(5)	IgA(6)
Case 1, K.S. (Reaction Oct. 3, 1970)	<8	<8	N.D.*	N.D.	<8	<8
Case 2, M.H. (Reaction June 2, 1971)	2,000	2,000	N.D.	N.D.	1,000	500
Case 3, J.M. (Reaction Aug. 28, 1971)	4,000	4,000	2,000	1,000	2,000	500
	8,000	8,000	4,000	8,000	16,000	8,000
	16,000	8,000	8,000	8,000	16,000	16,000
	16,000	16,000	N.D.	N.D.	N.D.	N.D.
	16,000	8,000	N.D.	N.D.	N.D.	N.D.
Case 4, P.J. (Reaction Sept. 21, 1971)	4,000	2,000	2,000	2,000	1,000	N.D.
	2,000	1,000	2,000	1,000	1,000	N.D.
	4,000	1,000	1,000	1,000	500	N.D.

*N.D., not done.

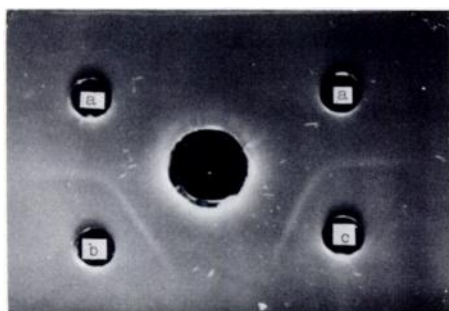


Fig. 1. Reaction of IgA with anti-IgA in agarose. (A) Rabbit antihuman IgA, diluted 1:5; (B) isolated myeloma IgA, 80 μ g/ml; (C) NHS, diluted 1:20. Center well anti-IgA (J.M.)

between serum J.M. and human IgA (Fig. 1). The line was identical with that formed by rabbit anti-IgA diffusing against IgA antigen. A similar line was observed if normal human serum was used instead of isolated myeloma IgA. No line was formed against serums with IgA deficiency.

A similar, but somewhat fainter line of precipitation was also produced by the serum M.H. The presence of anti-IgA precipitins in serum K.S. could be shown only after concentration. This was done by precipitation of the globulins of serum K.S. by 45% saturated $(\text{NH}_4)_2\text{SO}_4$ and by redissolving the precipitate into a small volume of saline. Despite this five times concentration, we did not find precipitins in serum J.S.

Table 2 shows the fixation of complement by IgA-anti-IgA complexes. The serum J.M. was used as a source of antibody. This reaction was dependent on the size of immune complexes; the maximal complement consumption was obtained in slight antigen excess where no visible precipitation was formed. The complement fixation was slight at 37°C but was marked in the cold. This reaction pattern is typical for IgG antibodies.¹⁵

As shown by ultracentrifugation and by gel filtration on Sephadex G-200, the antibodies did not migrate with macroglobulin fraction and, thus, were not IgM. Serums from all four patients were fractionated this way; a typical example is given in Fig. 2.

One serum (J.M.) was fractionated on a DEAE-cellulose column, and the antibodies were recovered only from the eluate that was obtained with 0.02 M phosphate. When a concentrated globulin preparation of this serum was ana-

Table 2. Complement Fixation by Human IgA—Anti-IgA Complexes of Serum J.M.

IgA—anti-IgA Mixtures	Reaction at +37°C					Reaction at +4°C				
	1:1	1:2	1:4	1:8	1:16	1:1	1:2	1:4	1:8	1:16
1*	++	+	+	+	+	+	+	+	+	+
2	+	+	+	+	+	+	+	+	+	+
3	+	+	+	+	+	+	+	+	+	+
4	(+)	+	+	+	+	0	0	0	(+)	+
5	+	+	+	+	+	(+)	+	+	+	+

*No. 1 represents heavy antigen excess; No. 5 represents zone of equivalence.
t, +, complete hemolysis; (+), partial hemolysis; 0, no hemolysis.

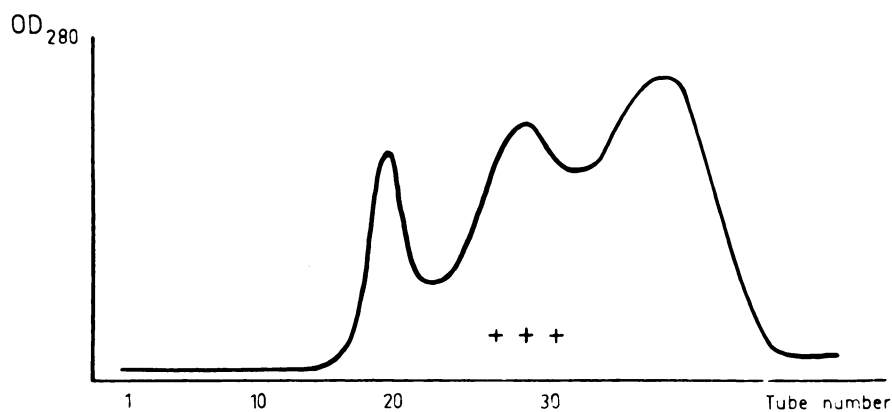


Fig. 2. Gel filtration on Sephadex G-200 of serums from one (J.M.) of the patients. +: Fractions containing anti-IgA.

lyzed by immunoelectrophoresis, a single arc was formed in the cathodal region (Fig. 3). These findings suggest the IgG nature of the antibodies.

It was not known whether the patients had cellular immunity to IgA, although the mode of transfusion reaction suggested a humoral mechanism. Because of the risk of skin lesions, skin tests were not done, but lymphocytes from one patient (J.M.) were cultured in the presence of IgA. Normal human serum containing IgA, or 2 $\mu\text{g}/\text{ml}$ purified myeloma IgA, did not induce blast transformation. Ten to 100 $\mu\text{g}/\text{ml}$ IgA in the presence of the patient's own plasma or control plasma slightly stimulated both the patient's lymphocytes and control lymphocytes (0.3%–0.8% blasts on the sixth day, controls without IgA less than 0.1%). Therefore, the effect of isolated IgA on the lymphocytes from J.M. was probably nonspecific.

DISCUSSION

Although immunization of persons lacking IgA is possible, the mechanism of immunization itself remains obscure. Three of the present cases can be explained by isoimmunization due to transfusion or pregnancy, but the fourth patient (K.S.) had no clear history of IgA exposure. Schmidt et al.,⁶ as well as Bjerrum and Jersild,⁸ also found no evidence of previous transfusion or pregnancy in their patients. One reasonable explanation seems to be an immunization of the fetus to maternal IgA.³

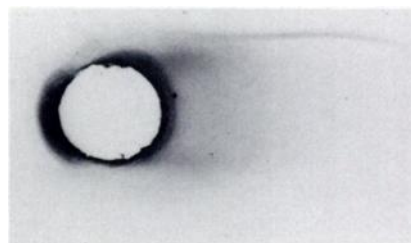


Fig. 3. Immunoelectrophoresis of concentrated globulins of serum J.M. Upper trough NHS, diluted 1:8, lower trough: serum with absent IgA, diluted 1:8.

According to the literature and to our own cases, the antibodies to IgA class-specific determinants have high titers as determined by passive hemagglutination assay.¹⁻⁷ They may even precipitate the antigen. These potent anti-IgA antibodies, which seem to belong to the IgG class, readily form antibody-antigen complexes that fix complement. This makes it conceivable that after the initial immunization has taken place, a new challenge of intravenously administered soluble antigen precipitates anaphylactic shock. In those three of our cases (J.M., M.H., K.S.) where the actual transfusion complication had taken place, the reaction was almost fatal, despite immediate cessation of the transfusion.

Our fourth patient (P.J.), fortunately avoided the most severe form of reaction because the clinical staff had been informed about the possibility of IgA-connected transfusion reactions. Previously, the patient had been found to be deficient of IgA, and a trial with a small amount of normal plasma was done prior to an unavoidable abdominal operation. A test dose of plasma provoked a typical reaction, and the operation was carried out with special precaution as to the blood loss. Later on, red cell compatible blood lacking IgA became available, and the patient's anemia was treated with this, with no side effects. The other patient (J.M.) had her anemia cured otherwise. To determine the compatibility of IgA-deficient plasma, 20 ml of this was injected to her intravenously. No reaction was observed this time either.

The detection of class-specific antibodies is simple by passive hemagglutination. For convenience, we used the chromic chloride technique,¹⁰ which has proved to be an increasingly important serologic tool. The major advantages of this method are its simplicity and low consumption of the protein that is fixed on the indicator cells. The use of precipitation techniques alone is unsatisfactory.

Antibodies to IgA that are not class specific but are directed to only a part of the molecule, and accordingly may occur in persons with normal IgA level, have also been claimed to be responsible for transfusion reactions.^{2,5} However, in most cases the reaction has been urticarial or febrile, and concomitant leukocyte antibodies were a frequent finding. In addition, the titer has been low (except anti-Am antibodies),^{16,17} and it can be argued whether low titers with a sensitive method are of any major significance in this respect. We think that the real relationship of transfusion reactions and these low-titered antibodies is still unresolved. Similar anti-IgG or anti-IgM antibodies do not cause transfusion reactions.^{18,19}

It is notable how a small amount of plasma can cause the reaction. The patient J.M. had received only a few milliliters of red cell concentrate, and, nevertheless, the reaction was indeed very serious. An ordinary washing of red cells, which does not remove all the plasma, is not sufficient to provide a safe transfusion if the patient with antibodies needs blood. We do not have experience on the use of frozen, thawed, and washed red blood cells in these cases, but if large amounts of blood are not needed they may be cautiously tried. Since these patients can be transfused with IgA-free blood, the Finnish Red Cross Blood Transfusion Service has established a national register of IgA-deficient blood donors.

To prevent immunizations, IgA preparations (and gamma globulin containing traces of IgA) should not be used for treatment of patients with IgA deficiency. If a person is found lacking IgA, it should be determined by a sensitive method whether he has anti-IgA antibodies. Even if anti-IgA is not present, and IgA-free blood is not available, only thoroughly washed red blood cells should be used if the patient needs transfusion.

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REFERENCES

1. Vyas GN, Holmdahl L, Perkins HA, Fudenberg HH: Serologic specificity of human anti-IgA and its significance in transfusion. *Blood* 34:573, 1969
2. Vyas GN, Fudenberg HH: Isoimmune anti-IgA causing anaphylactoid transfusion reactions. *N Engl J Med* 280:1073, 1969
3. Vyas GN, Levin A, Fudenberg HH: Intrauterine isoimmunization caused by maternal IgA crossing the placenta. *Nature (Lond)* 225:275, 1970
4. Vyas GN, Fudenberg HH: Immunobiology of human anti-IgA: A serologic and immunogenetic study of immunization to IgA in transfusion and pregnancy. *Clin Genet* 1:45, 1971
5. Vyas GN, Perkins HA, Fudenberg HH: Anaphylactoid transfusion reaction associated with anti-IgA. *Lancet* 2:312, 1968
6. Schmidt AP, Taswell HF, Gleich GJ: Anaphylactic transfusion reactions associated with anti-IgA antibody. *N Engl J Med* 280:188, 1969
7. Miller WV, Holland PV, Sugarbaker E, Stroeber W, Waldmann TA: Anaphylactic reaction to IgA: A difficult transfusion problem. *Transfusion* 54:618, 1970
8. Bjerrum OJ, Jersild C: Class-specific anti-IgA associated with severe anaphylactic transfusion reactions in a patient with pernicious anemia. *Vox Sang* 21:411, 1971
9. Kunkel HG, Jerry LM, Smith WK: Selective deficiency of γ A-globulins, occurrence of γ A-antibodies and their specificities, in Miescher PA (ed): *Immunopathology*. Basel-Stuttgart, Schwabe, 1971, p 151
10. Gold ER, Fudenberg HH: Chromic chloride: Coupling reagent for passive hemagglutination reactions. *J Immunol* 99:859, 1967
11. Vaerman JP, Heremans JF: Subclasses of human immunoglobulin A based on difference in the alpha polypeptide chains. *Science* 153:647, 1966
12. Aho K, Harboe M, Leikola J: Studies of the antibody nature of the rheumatoid factor. Reaction of the rheumatoid factor with sheep erythrocytes sensitized with human anti-sheep cell antibodies and with O Rh-positive cells sensitized with incomplete anti-Rh antibodies. *Immunology* 7:403, 1964
13. Virolainen M: Blast transformation in vivo and in vitro in carbamazepin hypersensitivity. *Clin Exp Immunol* 9:429, 1971
14. Claman HN, Merrill DA, Peakman D, Robinson A: Isolated severe gamma A deficiency: Immunoglobulin levels, clinical disorders, and chromosome studies. *J Lab Clin Med* 75:307, 1970
15. Cunniff RV, Stollar BD: Properties of 19S antibodies in complement fixation. I. Temperature dependence and role of antigen structure. *J Immunol* 100:7, 1968
16. Vyas GN, Fudenberg HH: Am(1), the first genetic marker of human immunoglobulin A. *Proc Natl Acad Sci USA* 69:1211, 1969
17. Kunkel HG, Smith WK, Joslin FG, Natvig JB, Litwin SD: A genetic marker of the γ A2 subgroups of γ A immunoglobulins. *Nature (Lond)* 223:1247, 1969
18. Pretty HM, Fudenberg HH, Perkins HA, Gerbode F: Anti- γ globulin antibodies after open heart surgery. *Blood* 32:205, 1968
19. Leikola J, Fudenberg HH, Vyas GN, Perkins HA: Isoantibodies to human IgM: Serological and immunochemical investigations. *J Immunol* 106:1147, 1971



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