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dysgammaglobulinemia
immunoglobulins
infection, recurrent
lymph node
lymphocytes
lymphocytotoxicity

# Immunologic Amnesia

## Study of an 11-Year-Old Girl with Recurrent Severe Infections Associated with Dysgammaglobulinemia, Lymphopenia and Lymphocytotoxic Antibody, Resulting in Loss of Immunologic Memory

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*Extract*

A female child with a life-long, remarkable susceptibility to bacterial and fungal infections is presented. She was shown to be incapable of manifesting delayed hypersensitivity reactions, anamnestic antibody response and second set allograft rejection. The failure of these lymphocyte-dependent functions was attributed to the presence of a lymphocytotoxic antibody in the patient's serum, particularly associated with her serum γA globulins. She manifested recurrent, profound lymphopenia in association with infection.

*Speculation*

The pathogenesis of undue susceptibility to infection in an 11-year-old female child has been compared with and related to the immunologic deficit produced by the administration of antilymphocyte antiserum to experimental animals. Further characterization of the 'autoantibody' is needed to clarify its role in lymphocytotoxicity and its suppression of normal lymphocyte function.

### *Introduction*

A number of experimental approaches designed to clarify the role of the lymphocyte in immunological phenomena have recently implicated the central function of this cell in homograft rejection, delayed hypersensitivity and immunologic 'memory'. The experimental manipulations have involved: depletion of lymphocytes by chronic thoracic duct drainage [6]; administration of antilymphocyte antiserum [24]; and neonatal thymectomy [5, 12]. It is apparent from these experiments that the lymphocyte conveys certain specific immunologic information but the molecular basis of the specificity is not known.

A group of inherited disorders in which there is a failure of normal embryogenesis of the thymus gland closely resembles experimentally produced defects which are observed in neonatally thymectomized rodents. In both situations there is profound lymphopenia, aplasia of peripheral lymphoid structures, impairment of delayed hypersensitivity and an inability to reject allografts [14].

The present study concerns a child with an immunologic abnormality in lymphocyte function. This patient has recurrent lymphopenia and a circulating lymphocytotoxic antibody. She is capable of initiating responses which are lymphocyte-dependent but has no immunologic 'memory'. Her defect resembles that observed in experimental animal models to which antilymphocyte antiserum has been administered.

*Case History*

R.D. was born on May 30, 1956. The antenatal and natal history were normal. Birth weight was 7 lbs, 7 oz. The patient was well until 2 months of age, when eczema was first noted. It has persisted in varying degrees up to the present time. She received routine immunization against poliomyelitis, diphtheria, tetanus and pertussis during the first year of life. She has never been vaccinated.

Between 5 and 18 months of age, the patient had 6 upper respiratory infections complicated by otitis media. At age 21 months she was seen for the first time in the outpatient department because of an eczematous rash in the axillae and flexor surface of the knees, seborrheic dermatitis of the scalp and a 'fungus' infection of the feet. The patient was stated to be allergic to penicillin and wool. Hydrocortisone ointment was ineffective in treatment of the eczema. At 23 months of age the patient developed a secondary infection of the eczema; $\beta$-hemolytic streptococci and *Staphylococcus aureus* were cultured from the skin pustules. At the same time, the patient had bilateral otitis media; the same microorganisms were cultured from the suppurative material drained from the ears. In the following month she developed cellulitis of the left foot and an abscess in the left axilla. Staphylococci were again cultured from the pus. At 25 months of age another abscess developed in the left buttock. A variety of antibiotics were used to treat these infections.

The patient was subsequently lost to follow-up and was not seen again until age $5\,^{9}/_{12}$ years. During this interval she had persistent eczema and onychomycosis, several episodes of otitis media and pyuria. At 2½ years of age, a tonsillectomy and an adenoidectomy were performed. At age 5 she had the mumps, without untoward complication.

The patient was seen again at the Children's Hospital because of orbital cellulitis and bilateral serous otitis media. She was successfully treated with erythromycin and chloramphenicol. In the following month the patient sustained a bout of chickenpox without complication. During the next 3 months, she had 3 episodes of bilateral otitis media. At age $6\,^{7}/_{12}$ she had measles marked by severe, persistent hyperpyrexia (105°–106°F) for 3 weeks. After this time, the course of her illness became very complex; the list of her infections is given in table I.

The patient has remained in the 3rd percentile for height and weight. Following a severe pulmonary infection in December, 1965, her vital capacity fluctuated between 50 % and 60 % of normal. X-rays of the chest showed increased bronchial markings at both bases. These findings have persisted. Immunologic investigations of the patient were undertaken in April, 1964, at a time when the patient had an episode of monilial pneumonia accompanied by profound lymphopenia.

*Table I.* Summary of clinical course after the age of 6 ½ years

| | |
|---|---|
| 1963 | |
| January | Measles |
| March | Pneumonia |
| | Vaginitis and cystitis |
| April | Pneumonia |
| October | Pneumonia |
| December | Pneumonia |
| 1964 | |
| January | Bilateral otitis media |
| | Pneumonia |
| | Dental abscess |
| February | Bilateral otitis media: S. *aureus* |
| April | Bronchopneumonia: Monilia |
| October | Septicemia: H. *influenzae* |
| | Pneumonia: S. *hemolyticus*, group A |
| November | Right otitis media |
| | Septicemia: D. *pneumoniae* |
| December | Impetigo: S. *hemolyticus*, group A |
| 1965[1] | |
| January | Conjunctivitis: H. *influenzae* |
| April | Pneumonia |
| May | Right otitis media: D. *pneumoniae* |
| July | Bilateral otitis media: D. *pneumoniae* |
| | Pneumonia |
| December | Pneumonia |
| 1966 | |
| April | Pharyngitis |
| June | Pneumonia |
| July | Right otitis media |
| August | Pneumonia: S. *aureus*, coag.+ |
| November | Pneumonia: S. *aureus*, coag.+ |
| | Paronychia: S. *aureus*, coag.+ |
| 1967 | |
| January | Pneumonia |
| February | Pharyngitis |
| March | Pneumonia |
| May | Right otitis media |
| July | Pyelonephritis: P. *vulgaris* |

[1] During 1965, patient received 0.6 ml/kg of $\gamma$-globulin, intramuscularly, at monthly intervals.

*Methods*

The patient's serum was electrophoresed in 1 % agarose [9]. The patterns were stained with bromphenol blue. Immunoelectrophoresis was performed by the micromethod of SCHEIDEGGER [19]. Goat and rabbit antisera to $\gamma$G, $\gamma$A and $\gamma$M globulins, all three immunoglobulins, and $\varkappa$ and $\lambda$L chains were obtained from Hyland Laboratories or prepared in our laboratory. Immunoglobulin levels were estimated by radial diffusion [3] or quantitative precipitation [4].

Hemagglutinating antibody titers to diphtheria and tetanus toxins [22] and to O antigens of *Salmonella typhosa* were determined as previously described [11].

Delayed hypersensitivity was assessed with commercially available antigens by intradermal injection of 0.1 cc of appropriate amounts of various antigens [20].

To determine the lymphocytotoxic effect of the patient's serum the following assays were performed [17]. A 10 ml sample of blood was drawn into sterile heparin (Panheparin) and the cells were allowed to sediment in the upright syringe for one to two hours. The leukocyte-enriched plasma was expressed from the syringe, and the buffy coat was obtained by centrifugation of the plasma for 5 to 10 minutes at 4° and $50 \times g$. The buffy coat was suspended in Medium 199 with 10 % inactivated calf serum and subsequently washed three times in Medium 199. The concentration was adjusted to approximately $30 \times 10^6$ cells/ml. The differential count consistently yielded 60 % lymphocytes from the cell donors. A 0.3 ml aliquot of the cell suspension, 0.3 ml of serum to be tested for lymphocytotoxic effect, and 0.2 ml of reconstituted lyophilized guinea pig complement were mixed and incubated in a sterile test tube. The cell culture was incubated at 37° for one hour with constant gentle agitation. Total cell counts and differential cell counts were performed prior to and at the termination of the experiment. The number of vital cells was determined by observing the uptake of eosin red dye [7]. The percentage of killed lymphocytes was expressed by determining the number of vital lymphocytes at the end of the incubation time divided by the total vital lymphocyte count at the beginning of the experiment and subtraction of the ratio from 100 %.

$\gamma$A and $\gamma$G globulins were separated from the patient's plasma by gel filtration on Sephadex G 200. The $\gamma$A globulin, which was present in relatively large amounts in the patient's plasma, was pooled from the fractions between the '19S' and '7S' peaks. The protein from this portion of the eluate did not contain detectable $\gamma$G globulin. It was not determined whether the $\gamma$A preparation was contaminated with $\gamma$D globulin. The '7S' peak of the eluate was again eluted from DEAE cellulose with a phosphate buffer at pH 6.8, $\mu$ 0.007. This $\gamma$G preparation from the patient's serum was contaminated with 0.6 % $\gamma$A globulin and no detectable $\gamma$M globulin.

*Results*

*Immunoglobulins.* The patient's serum exhibited a persistent elevation of $\gamma$A globulin concentration and a significant diminution of $\gamma$M globulin during three years of repeated observations (fig. 1 a). Serial estimations of the patient's immunoglobulin levels are shown in table II. The patient's serum contained increased amounts of $\gamma$D globulin [16]. A transient rise in the $\gamma$M globulin concentration to normal levels occurred during a two-month period in 1966 when the patient was receiving a variety of antigenic stimuli to test her ability to synthesize specific antibodies (figs. 1 b and 2).

The distribution of $\varkappa$ and $\lambda$ determinates on the light chains of her $\gamma$G and $\gamma$A globulins was normal (table II).

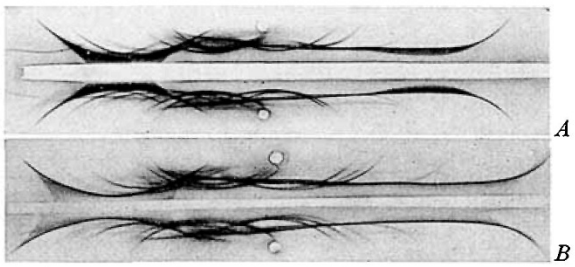



*Fig. 1.* 1. Immunoelectrophoresis of patient's serum (top well) and normal serum (bottom well). Patterns developed with equine antihuman serum. Anode is to the left. *A.* Serum drawn at a time when $\gamma$M globulins could not be detected and *B.* when the serum $\gamma$M concentration was 104 mg %.

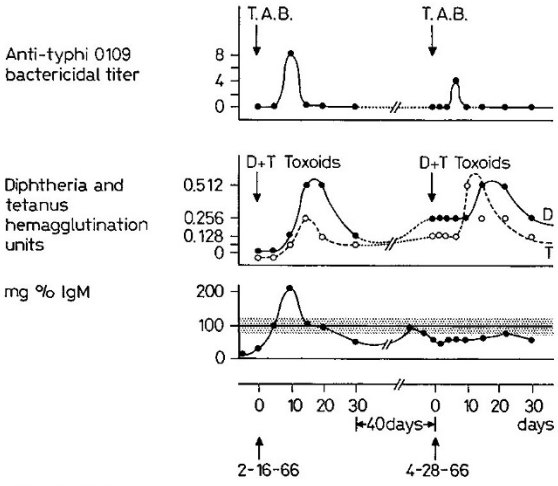



*Fig. 2.* Primary and secondary responses to salmonella 0109 (bacteriocidal titers) and diphtheria and tetanus toxoid (hemagglutinating titers), with simultaneous IgM levels.

*Table II.* Immunoglobulins in serum (mg %)

| Date | IgG | IgA | IgM | IgD | $\varkappa$ L chains | $\lambda$ L chains |
|---|---|---|---|---|---|---|
| 9–8–64 | 1200 | | | | | |
| 10–14–64 | | 580 | 30 | | | |
| 10–30–64 | | 1200 | 48 | | | |
| 12–29–65 | 1650 | 470 | 5 | | | |
| 2–16–66 | 2000 | 990 | 23 | | | |
| 2–26–66 | 1600 | 1400 | 210 | 170 | 1550 | 630 |
| 3–6–66 | 2000 | 1050 | 103 | | | |
| 4–28–66 | 3100 | 1100 | 55 | | | |
| 6–13–66 | 3500 | 1180 | 42 | | | |
| 9–21–66 | 1250 | 1100 | 38 | 110 | 2250 | 830 |
| 10–31–66 | 1700 | 780 | 17 | | | |
| 2–6–67 | 6000 | 340 | 35 | | | |

As her $\gamma$G globulin serum concentration became progressively more elevated, the $\gamma$G band assumed a scalloped appearance (fig. 3) and four M compounds were found upon electrophoresis of her serum in agarose (fig. 4). The M components were found to contain both $\varkappa$ and $\lambda$ L chains and all four types of H chains except for the most anodal one, which was found to contain a predominance of type $\lambda$ L chains and type b $\gamma$ H chains [23].

Urine from the patient, at a time when her serum $\gamma$A globulin concentration was 1100 mg %, was found to contain 0.8 mg % of $\gamma$A globulin or 6.4 mg of $\gamma$A per 24-hour urine collection. At the same time, the urine contained 2.9 mg % of $\gamma$G globulin or 23.2 mg/24 hours. The urine $\gamma$A globulin gave a reaction of complete identity with serum $\gamma$A globulin using a goat antiserum to human $\gamma$A globulin. No Bence-Jones protein was detected.

Saliva obtained from the patient at this time contained 6.8 mg % of $\gamma$A, or approximately twice the normal expected concentration. Saliva of the patient contained 16 mg % of $\gamma$G globulin (fig. 5).

*Antibody formation.* Despite repeated stimulation with diphtheria and tetanus toxoids, the patient was unable to exhibit a secondary or anamnestic response to these antigens. At the time of maximal response, 15 days after the stimulus, her serum contained 0.5 hemagglutinating units to the respective antigens (fig. 2). She also had a minimal response to repeated injections of a typhoid-paratyphoid A and B vaccine; peak response occurred 10 days after the stimulus (fig. 2).

The patient had no detectable antibodies to poliovirus or H. pertussis despite three previous immunizations with DPT and Salk vaccine during the first 2 years of life. She also had no heterophile antibody or antibody to influenza viruses of types A and B. Her serum agglutinated type B red cells in a titer of 1:64 when her $\gamma$M globulin was in the normal range (fig. 2). The isohemagglutinin titer was reduced to 1:4 by treatment of serum with 0.2 M mercaptoethanol. During September of 1964, the patient had a $\beta$ hemolytic streptococcal infection and her ASLO titer rose to 1:500.

*Delayed hypersensitivity responses.* The patient was unresponsive to intradermal injections of PPD at second and intermediate strengths, Battey strain antigen, *Neisseria catarrhalis*, diphtheria toxoid, mumps virus and streptodornase-streptokinase (Varidase) on repeated occasions of testing from 1964 through 1966. The patient was repeatedly unresponsive to Monilia antigen at four different times using dilutions of 1:1000, 1:100 and 1:10. In May, 1964, one month after the patient had Monilia pneumonia, she showed a transient weak response to a Monilia antigen. The patient was sensitized with dinitro-fluorobenzene in vesicant doses (5 %) in December, 1964 and again in December, 1965.

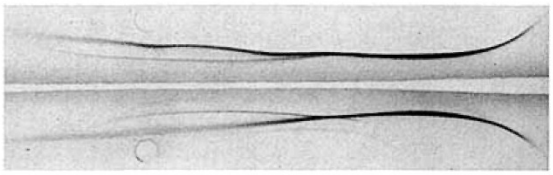


*Fig. 3.* Immunoelectrophoresis of patient's serum (top well) and normal serum (bottom well). Pattern was developed with goat antihuman immunoglobulin antiserum. Anode is to the left.

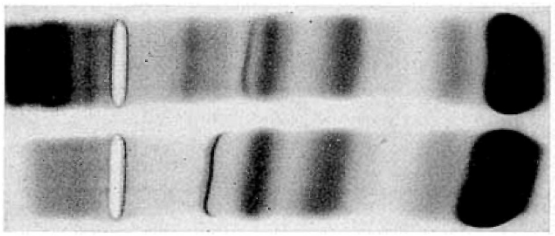


*Fig. 4.* Electrophoresis in agarose of patient's serum (top) and normal serum (bottom). Anode is to the right.

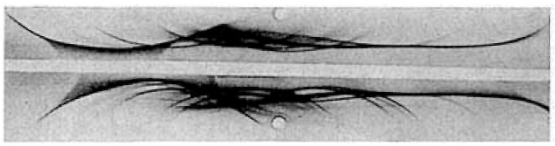


*Fig. 5.* Immunoelectrophoresis of patient's saliva (top well) and her serum (bottom well). Pattern developed with horse antihuman antiserum. Anode is to the left.

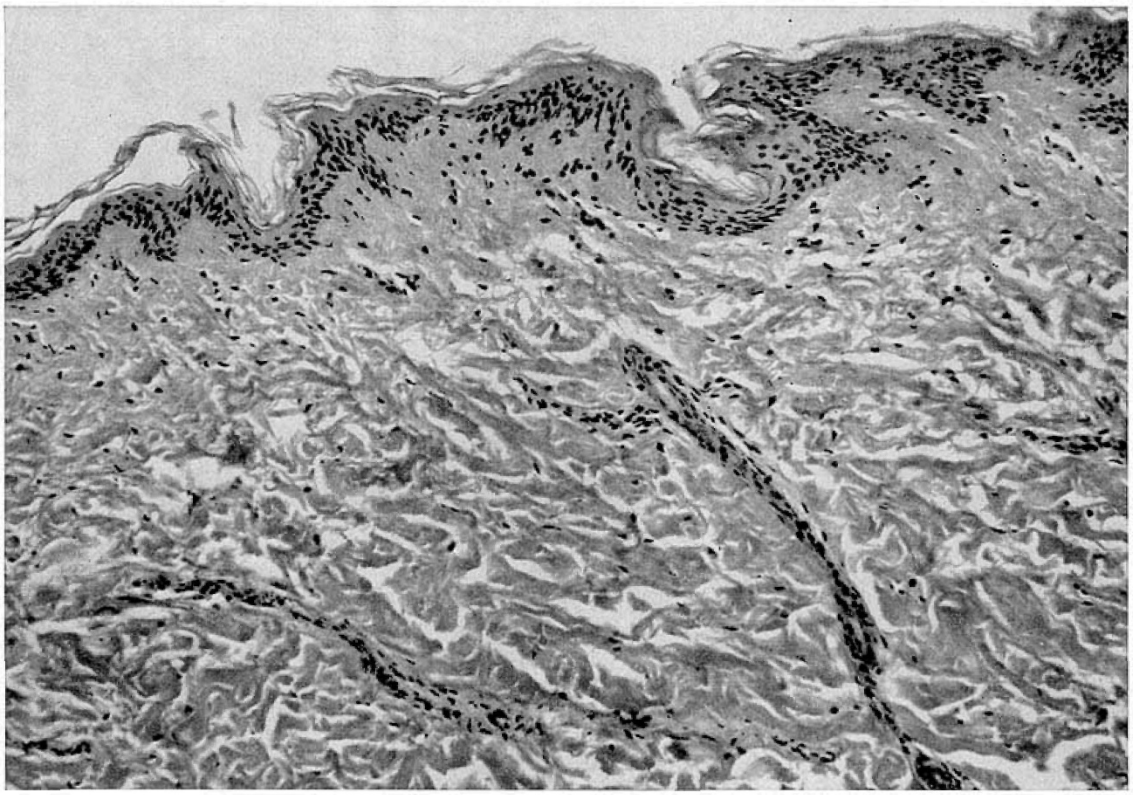
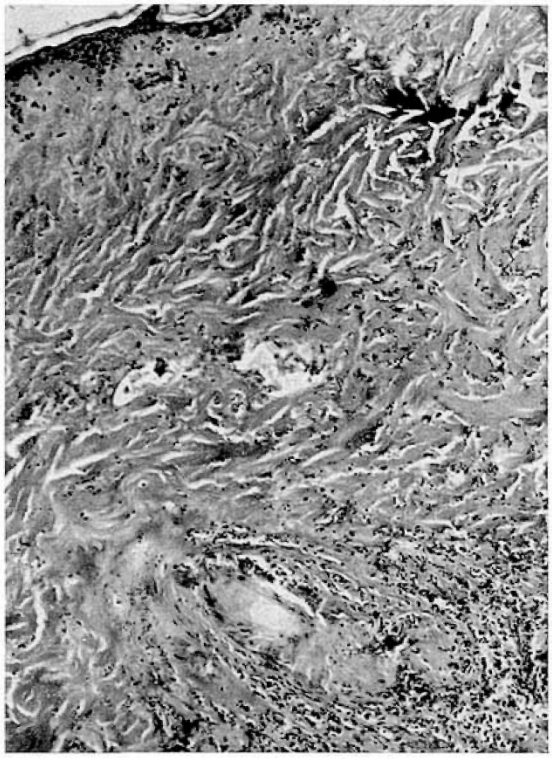


*Fig. 6.* Biopsy of first set skin allograft at 7 days. ▶

*Fig. 7.* Biopsy of first set skin allograft at 15 days.



She was unresponsive upon challenge by 1:1000 and 1:100 dilutions of the sensitizing dose. In December, 1966, the patient was given 0.1 ml of heat-killed vaccinia virus by intradermal injection. Fifteen and 45 days after provocation, she was unresponsive to the vaccinia virus up to 96 hours after intradermal challenge.

*Leukocyte function.* The leukocytes of the patient gave a normal reduction of nitroblue-tetrazolium during phagocytosis of latex particles.

*Allograft rejection.* A full thickness skin graft measuring $6 \times 1$ cm, taken from a normal unrelated male donor, was placed on the patient's lower abdomen and held in place by two silk sutures at both ends of the allograft. Seven days later, a biopsy of the graft showed pyknosis of epithelial cells, absence of epithelial regeneration, massive hyalinization and necrosis of the dermis and little infiltration with round cells (fig. 6). Another biopsy, at the fifteenth day when the graft exhibited obvious macroscopic rejection, showed necrosis of the epithelium and dermis with a mixed infiltrate of polymorphonuclear and mononuclear cells in the dermis (fig. 7).

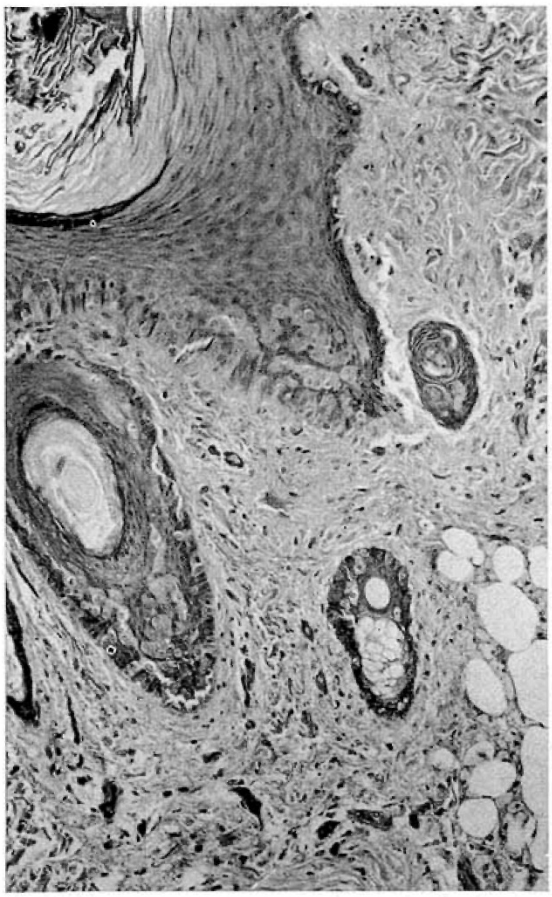


*Fig. 8.* Biopsy of second set skin allograft at 7 days.

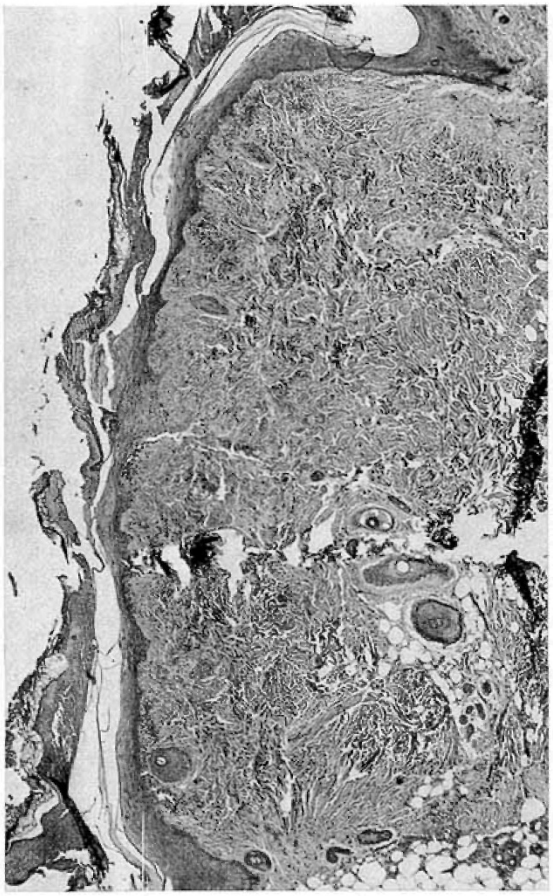


*Fig. 9.* Biopsy of second set skin allograft at 16 days.

Ten months after the initial grafting, a full thickness skin graft measuring $3 \times 0.6$ cm, from the same normal unrelated male donor was placed on the anterior surface of the patient's right thigh. Sixteen days after grafting, a biopsy of the graft showed excellent preservation of the epithelium and dermis. No evidence of necrosis was present and minimal inflammatory exudate was observed (figs. 8 and 9). When last observed, 160 days after the placement of the second graft, there was no evidence of rejection and hair follicles were apparent in the graft.

The patient failed to exhibit a second set rejection of the donor skin. The graft had survived wholly intact for 100 days, when a third skin graft from a second unrelated male donor measuring $3 \times 0.8$ cm was placed on the anterior aspect of the patient's left thigh. Biopsy of the graft, taken at 18 days, showed pyknosis of epithelial cells, absence of epithelial regeneration, massive hyalinization and necrosis of the dermis and massive round cell infiltration, predominantly with mononuclear cells. During this rejection of skin from the second donor, the second graft of the first donor remained intact, and when last observed, 60 days after the third grafting attempt and 160 days after the first graft was placed, continued to survive.

*Histologic studies.* A lymph node biopsy showed normal lymphoid architecture with adequate numbers of lymphocytes, plasma cells and germinal centers. Bone marrow aspiration on two occasions in 1964 and 1966 revealed no abnormality of the differential count of bone marrow cells. Examination of peripheral blood lymphocytes by electron microscopy did not reveal any morphologic abnormality.

*Lymphocytotoxicity studies.* Continuous observation of the patient and her peripheral white blood counts starting in 1964 revealed that her episodes of severe infection were accompanied by absolute lymphopenia (fig. 10). The possibility that the serum of the patient contained

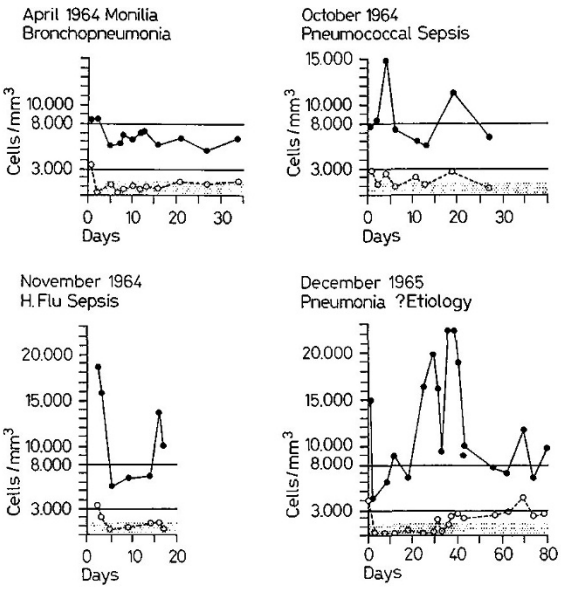



*Fig. 10.* Absolute white blood cell and lymphocyte counts during four episodes of severe infection.

*Table III.* Lymphocytolytic tests *in vitro*

| Experiment No. | Cell donor | Serum donor | % lymphocytes killed in 1 hour |
|---|---|---|---|
| 1 | patient | patient[1] | 55 |
| 2 | normal | patient[1] | 63 |
| 3 | patient | patient[2] | 10 |
| 4 | normal | patient[2] | 31 |
| 5 | patient | normal | 14 |
| 6 | normal | normal | 12 |

[1] Serum drawn when patient's blood contained 50 lymphocytes/mm³.
[2] Serum drawn when patient's blood contained 4000 lymphocytes/mm³.

*Table IV.* Lymphocytolytic tests *in vitro*

| Experiment No. | Antibody source | % lymphocytes killed in 1 hour |
|---|---|---|
| 1 | patient's serum[1] | 50 |
| 2 | 0.33 mg % $\gamma$A | 68 |
| 3 | 0.55 mg % $\gamma$A | 80 |
| 4 | 1.1 mg % $\gamma$A | 61 |
| 5 | normal serum | 0 |

[1] 3.3 mg of $\gamma$A and 10.5 mg of $\gamma$G were contained in 0.3 ml of patient's serum used in test.

a circulating lymphocytotoxic antibody was investigated. The serum of the patient, drawn at a time when she was profoundly lymphopenic and upon two occasions when the absolute lymphocyte count in the peripheral blood was normal, was tested for lymphocytotoxicity against the patient's own lymphocytes and against those from a normal donor. The serum of the patient obtained when her lymphocyte count was either profoundly depressed or normal manifested cytotoxic activity against lymphocytes from normal donors (table III). A significant effect was observed against her own cells when the serum tested was drawn during a lymphopenic episode. No effect was observed on the patient's own cells with serum drawn at a time when her lymphocyte count was normal and the effect on normal cells was less striking (table III).

The $\gamma$A and $\gamma$G globulins were isolated from the patient's serum (fig. 11). The lymphocytotoxic effect of the patient's serum was found to be associated primarily with the $\gamma$A globulin of her serum (table IV).

*Family studies.* The immunoglobulin levels were estimated in serum samples from the patient's mother, father, brother and sister and were found to be normal.

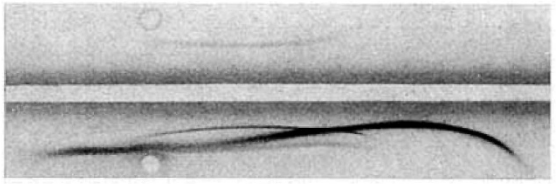


*Fig. 11.* $\gamma$A globulin isolated from patient's serum (top well) and normal serum (bottom well). Pattern developed with goat antihuman serum immunoglobulins. Anode is to the left.

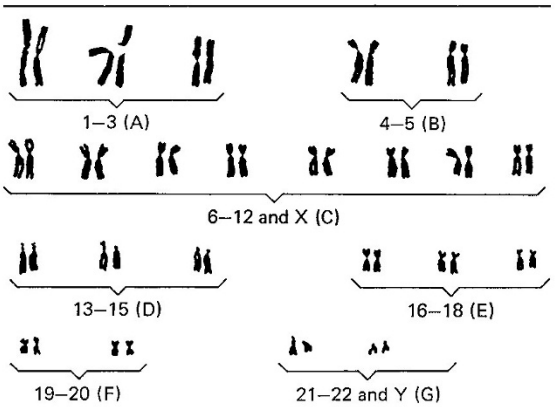



*Fig. 12.* Karyotype from the patient's peripheral blood cells stimulated with phytohemagglutinin.

These individuals also gave a positive skin reaction to a Monilia antigen. The patient, her mother and two siblings were found to have a Gm (1,3,5,–2) phenotype of their $\gamma$G globulins. The father of the patient had agglutinators against Gm (1), Gm (2) and Gm (5). Only the Gm (3) determinant could be detected in his $\gamma$G globulin. The patient, her father and her brother had Inv (2) $\varkappa$ chains while the mother and sister were Inv (–2).

A culture of peripheral blood lymphocytes of the patient in the presence of phytohemagglutinin revealed the presence of a giant satellite in the D group of chromosomes. The father of the patient had a similar abnormality.

*Discussion*

This report describes an 11-year-old girl who has had remarkable susceptibility to bacterial and fungal infections during her whole life. These infections have involved the upper and lower respiratory and genitourinary tracts and skin. Although antibiotic therapy has been successful in terminating these infections, several of them have been life-threatening and, at present, her pulmonary function is severely compromised. Administration of gamma globulin prophylaxis (0.6 ml/kg/month) during her ninth year of life was of no benefit.

Repeated examination of the patient's serum revealed persisting immunoelectrophoretic abnormalities consisting of marked elevation of the $\gamma$G, $\gamma$A and $\gamma$D globulin concentrations and variable, but usually diminished concentration of $\gamma$M globulin. It is conceivable that the low $\gamma$M globulin concentration in her serum was a consequence of the elevated concentrations of the other immunoglobulins. Such a reciprocal relation in the concentration of the serum immunoglobulins has been observed in experimental models [18] and in patients with type I dysgammaglobulinemia [2]. Immunoglobulin alterations similar to those found in this patient have been observed in infants with the Wiskott-Aldrich syndrome [25] and, indeed, many of the clinical features of her illness resemble those of this well-known entity. The patient described here, however, never had thrombocytopenia. Furthermore, the Wiskott-Aldrich syndrome is known to be transmitted as an X-linked affection.

Another interesting aspect of the patient's immunoglobulin abnormalities was the presence in her serum of multiple, narrowbanded M-components. These were shown to consist of a normal population of molecules in contrast to the homogeneity of M-components found in the sera of patients with myelomatous disease. The presence of multiple M-components is commonly observed in the sera of patients with diffuse hypergammaglobulinemia due to, for example, cirrhosis of the liver and lupus erythematosus [1].

Another, and perhaps more significant, aspect of this patient's immunologic deficiency is her lack of persisting cellular immunity. She was capable of rejecting first set allografts but incapable of second set rejection. In fact, the prolonged acceptance of a second set allograft suggested that she had either become tolerant to histocompatibility antigens of the graft, or that she had developed a state of so-called enhancement, as described by KALISS [8]. She was also incapable of manifesting a delayed hypersensitivity reaction to a number of antigens to which normal individuals exhibit hypersensitivity [20, 21], and she could not be actively sensitized with dinitro-fluorobenzene or killed vaccinia virus. The patient never exhibited a secondary or anamnestic rise in antibody titers to a variety of antigens with which she had been repeatedly stimulated. In summary, the patient was capable of immunologic response following the stimulation provided by an allograft or by certain antigens, but she was incapable of amplifying and maintaining these responses despite repeated stimulation; it appeared that the patient had no immunologic memory. Both functionally and histopathologically, the afferent pathway of her immunologic response was intact. Conversely, she appeared to have a severe deficit in the efferent 'limb' of her immune capacity.

The immunologic capacities which are deficient in this patient have been shown to be perpetrated by small lymphocytes. These cells convey certain specific information which is critical in the phenomena of allograft rejection, delayed hypersensitivity and immunologic memory. The patient under study was defective in her ability to manifest these three types of immunologic functions. Close observation of her peripheral white cell population revealed recurrence of profound and prolonged lymphopenia, particularly in association with infection. These periods of absolute lymphopenia were more exaggerated than one would anticipate in association with septic infection. This observation prompted us to examine her serum for a lymphocytotoxic factor. This was detected and found to be associated with her immunoglobulins, particularly the $\gamma$A globulin fraction of her serum proteins. Because of the limited availability of blood from the patient, it was not possible to determine whether or not this lymphocytotoxic factor was specific for any genetic polymorphism. Insofar as the serum and its immunoglobulins were tested, this factor proved to be lymphocytotoxic for lymphocytes obtained both from the patient herself and from normal donors.

Several experimental approaches to define the function of lymphocytes have employed heterologous antiserum to lymphocytes [10, 13, 24, 26]. Administration

of this antiserum to various animal species has resulted in suppression of allograft rejection, graft-versus-host reaction and primary antibody responses. MEDAWAR [10] has noted that such antisera 'are able to weaken the reactive capabilities of already sensitized animals to a degree that approaches a complete erasure of immunologic memory'. It has been observed that antilymphocyte serum can be effective without necessarily causing lymphopenia, and thus the reversion of lymphocytes from a committed to a pristine state does not necessarily involve the destruction of these cells.

The immunologic deficiency of the patient described in this study closely resembles that obtained in experimental manipulations with antilymphocyte antiserum. The presence of a lymphocytotoxic antibody in the serum of the patient might explain her inability to maintain a commitment of her lymphocytes with consequent failure of delayed hypersensitivity response, second set rejection and immunologic memory.

A child observed by ROSSI *et al.* in Bern, Switzerland, has findings which coincide in every detail with those of the patient reported here. This male child recently died and was found to have a normal thymus gland at autopsy [15]. An identical chromosomal abnormality was observed in both cases, but interpretation of this finding is difficult at present.

### *Note Added in Proof*

In 1962 STOOP *et al.* presented a 7-month-old female child with recurrent infections and the presence in the serum of $\gamma$G-M components. As in the case of ROSSI [15] three other siblings were similarly affected. In retrospect these reports probably describe a common disease entity. (STOOP, J.W.; BALLIEUX, R.E. and WEYERS, H.A.: Paraproteinemia with secondary immune-globulin deficiency in an infant. Pediatrics *29:* 97 [1962].)

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