Agammaglobulinemia: An Approach to Homovital Transplantation*

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THE CLINICAL ESTABLISHMENT of enduring homovital grafts has long been a heady challenge to medical science. The facts, however, are that haphazard organ transplants between persons (with the exception of monozygotic twins), despite initial acceptance, ultimately are rejected by the host. Our inability to solve this provocative problem has significantly retarded medical progress in this era of technical facility with certain mechanical aspects of vascular anastomosis. The key to the resolution of this predicament is not evidently at hand, but we have been encouraged by the intriguing possibilities demonstrable in that experiment of nature: congenital agammaglobulinemia.

The immunological theory of antigenicity in the donated organ provoking an antibody reaction-rejection in the host has more current support than other hypotheses. While its categorical proof is still lacking, the weight of investigative testimony favors that concept in clarifying for man the predictable destruction of homotransplants. Although the initial phases of healing involving the homograft may grossly simulate the appearance about an autograft, long term survival is eventually denied this foreigner. Medawar and his associates[4, 11-13] have provided us with much of the experimental evidence supporting the immunologic theory for such failures. These conclusions may be summarized as follows:

(1) The time required for rejection of homotransplants is approximately the same as that required for antibody formation.

(2) Under precise experimental conditions, the rate of transplantation rejection becomes a function of the dose of "antigen."

(3) Circulation (blood or lymph) without a barrier to antibody contact is essential for the rejection of homotransplants.

(4) Evidence for an anamnestic reaction towards homotransplants exists.

(5) An agent decreasing antibody formation (cortisone) prolongs the survival time of homotransplants.[2]

(6) The rejection of skin transplants is accompanied by the appearance in the blood of antibodies against donor cells.[1]

The opportunity and obligation to test clinically the validity of this reasoning from their experimental data was recognized by us to exist in that congenital malformation known as agammaglobulinemia. This condition was first described as an an entity by Bruton[3] in 1952, and has since been extensively studied by Janeway[9] as well. From the work of these men, it can now be characterized as a congenital defect, sex linked (males only) as a recessive trait, appearing as an immunological paralysis associated with secondary inability to create gamma globulin.[5-7] Other portions of the protein spectrum appear to be spared, and are in normal concentrations. Moreover, there is no accelerated decay rate for parenterally introduced

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TABLE I. *Homotransplantation of Skin to Patients with Agamma Globulinemia.*

Patient	Age	Sex	Form of Agamma globulinemia	Type of Graft	Fate of Graft
E. S.	7 yrs.	M	Congenital	Split Thickness	100% Initial Take 100% Survival 1 year.
				Full Thickness	100% Initial Take 100% Survival 1 year.
W. A.	6 yrs.	M	Congenital	Split Thickness	100% Initial Take 100% Survival 3.5 mo.
				Full Thickness	80% Initial Take 100% Survival 3.5 mo.
F. H.	58 yrs.	M	Acquired	Split Thickness	Initial Failure 0% Take
				Full Thickness	100% Initial Take Complete Rejection—16 weeks.
J. S.	9 mos.	M	Transient	Full Thickness	100% Initial Take Complete Rejection in 41 days.

TABLE II. *Homotransplantation of Skin from Patients with Agamma Globulinemia to Immunologically Normal Persons.*

Patient	Age	Sex	Source of Skin	Fate of Graft
J. D.	3	F	Congenital Agammaglobulinemia Patient	1. 100% Initial Take. 2. Complete Rejection at 37 days.
K. D.	5	F	Congenital Agammaglobulinemia Patient	1. 80% Initial Take. 2. Complete Rejection at 30 days.
M. O.	20	M	Acquired Agammagolbulinemia Patient	1. 60% Initial Take. 2. Complete Slough at 24 days.
H. B.	33	M	Acquired Agammaglobulinemia Patient	1. 100% Initial Take. 2. Complete Slough at 25 days.

TABLE III. *The Relation of Homograft Survival and Serum Gamma Globulin Level.**

Patient	Serum Gamma globulin Concentration mg.%	Graft Size	Present State of Graft
E. S.	13.1	8 × 3.5 cm.	100% survival at 1 year. 8.8 × 3.3 cm.
W. A.	4.4	8 × 4 cm.	100% survival at 3.5 mo.† 8 × 5 cm.
F. H.	>75	10 × 2.5 cm.	Complete rejection 4 mo.
J. S.	400	3 × 2 cm.	Complete rejection 41 days.

* The normal serum gamma globulin is 800 to 1200 mg. per cent.

† There was an 80 per cent initial take of one half of this graft which was full thickness.

gamma globulin in these children. It is a likely presumption that very few of these tots survived long in the pre-antibiotic days since they harbored this increased susceptibility to infections. They are incapable of creating antibodies and have none circulating; they are, therefore, most vulnerable to bacterial infections. Although an uncommon disease, its actual rarity in any pediatric clinic with a modest patient load is quite likely inversely proportional to the case finding attention given any child periodically ravaged by bacterial infection.

A quite different form of agamma globulinemia can be recognized in adults. Here, the patient will describe the development

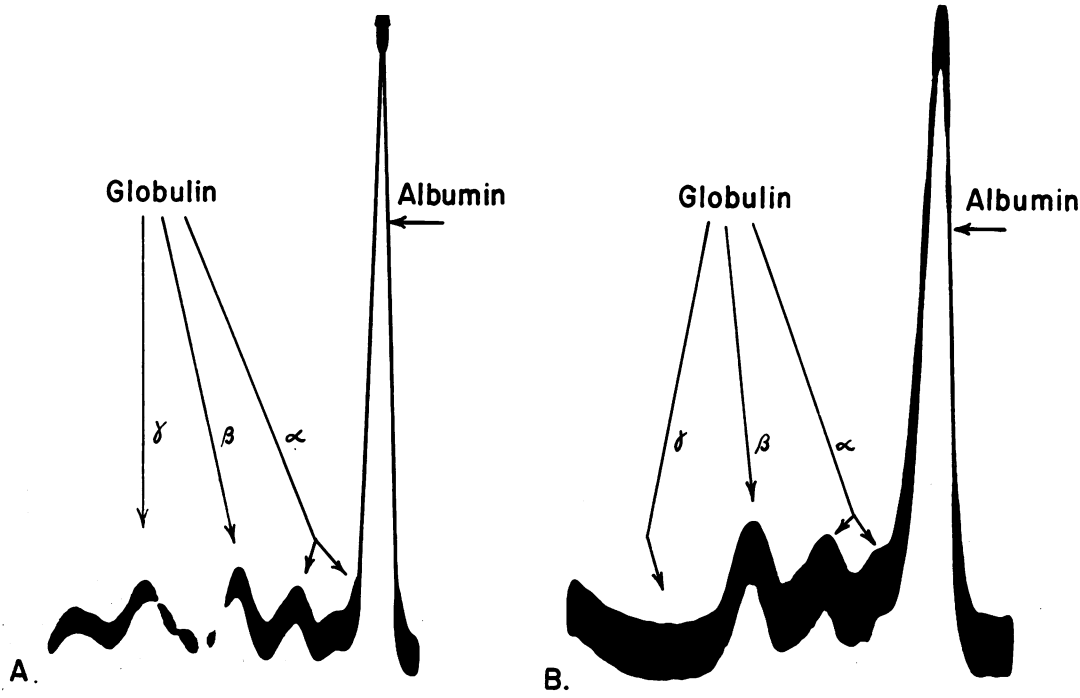


FIG. 1. (A) Normal electrophoresis pattern. (B) Electrophoresis pattern of an agammaglobulinemic patient without discernible gamma globulin.

of a decreased resistance to infections, as contrasted with either normal adults or with his own childhood. The surmise is reasonable that this may be an acquired condition. Both sexes may exhibit this phenomenon, and it can come on at any time during adult life. In addition, although these people are without demonstrable gamma globulin electrophoretically, they can be shown immunologically to have an amount greater than that identifiable in the congenital form of the disease. If the latter group of individuals can be described as having immune paralysis, then the former have an immune paresis. The significance of this latter consideration will be emphasized in the case of F. H., to be described in the text.

The immunity handicap was broadly studied in the first child (E. S.) selected for homografting. The results of these studies have been reported, along with those from several other congenital agammaglobulinemics, as a portion of the detailed exploration of this problem.[5-8] The responsibility for submitting this boy to the risk and distress of an operation as required for grafting was carefully weighed and appreciated by all parties involved. Our decision to proceed arose from the prevailing need for acquiring critical evidence about the mechanisms of homotransplant failures in man. Equally important, should this graft prove to be an acceptable replacement for that tissue lost, conceivably we might then be able to introduce tissues capable of correcting the deficit in the child's protein synthesizing mechanism. The choice of graft favored skin primarily because of the ease of visual evaluation of its integrity at frequent intervals, along with the ready availability of that site for biopsy and for photographs. Cutaneous tissue was also deemed preferable to serve as an orthotopic skin graft (*i.e.*, one into a position formerly occupied by skin) because of its demand for precise immunological requirements. Although the tissues adjacent

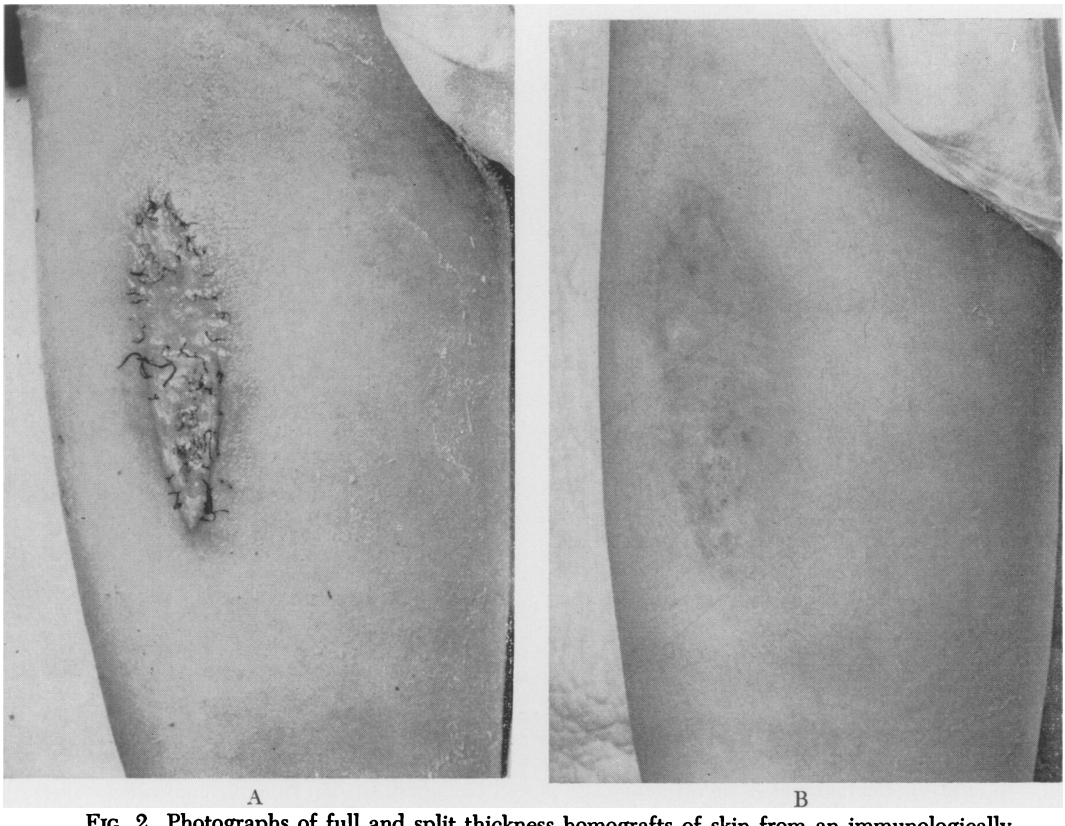


FIG. 2. Photographs of full and split thickness homografts of skin from an immunologically normal, unrelated adult, of different blood group placed on a six-year-old patient with congenital agammaglobulinemia (E. S.). (A) One month following grafting. (B) Four months following grafting. The graft at 13 months exhibits no inflammatory reaction nor decrease in size. It has, in fact, grown somewhat.

to the grafting of a tumor or of an endocrine gland may be tolerant of such strangers, these same surroundings can exhibit marked inhospitableness for transplanted skin derived from the same donor. As Medawar[14] has vigorously stated: "If skin grafts can be made to succeed, their hosts are most unlikely to raise immunological objections to the grafting of other tissues." Longmire[10] and his associates have concerned themselves with and made significant contributions along these lines.

To date, four persons with gamma globulin deficits of varying magnitudes have received skin grafts from an unrelated eugammaglobulinemic adult person of dissimilar blood type. These homotransplants were half split and half full thickness grafts. This latter hemisegment was lightly tattooed with India ink after removal and before implantation. The skin, always full thickness, removed from the agammaglobulinemic person preparatory to securing a site for the homograft, was comparably marked for handy, subsequent identification. This agammaglobulinemic skin, usually as a full-thickness graft, was placed onto the clean granulating surface of a burned patient, in most instances. The details of these procedures are presented in the case reports to follow. In brief, it may be stated, however, that all patients accepted kindly these grafts. The uniform amount of take was almost 100 per cent. Each child with a total amount of gamma globulin less than 15 mg. per cent (E. S. and W. A.) has continued to maintain

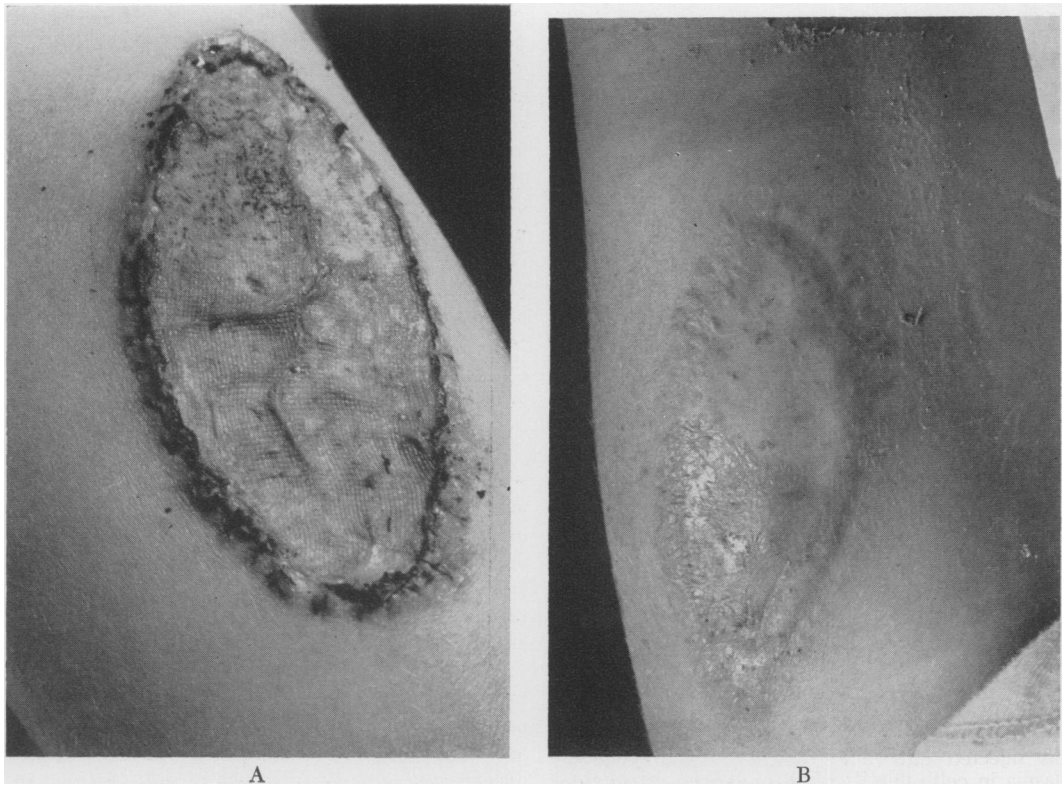


FIG. 3. Photographs of an orthotopically placed homograft of skin from an immunologically normal, unrelated adult of different blood group to an agammaglobulinemic patient (W. A.). (A) Two weeks following grafting. (B) Ten weeks following grafting. There is no decrease in size from original dimensions.

the integrity of this grafted cutaneous layer for 13 months, and for 3.5 months, respectively. The other child with approximately 400 mg. of gamma globulin, and the adult with the acquired form of this disease and approximately 75 mg. of gamma globulin, after the initial "take," have slowly rejected this alien tissue.

CASE REPORTS

Case 1. E. S. is a 7-year-old boy born in Germany of Latvian parents who are unrelated. He was well until 7 months of age, at which time he developed severe diarrhea complicated by pneumonia. He was treated with sulfadiazine and seemed to recover completely. However, during the first 4 years of life, he suffered repeated episodes of respiratory infection with high fever, otitis media, and pneumonia. He responded well to chemotherapy and antibiotics, but was in almost constant trouble with recurrent episodes of bacterial disease. During the next 3 years this boy suffered from bacterial meningitis on 3 occasions, bacterial pneumonia 3 times, severe life-threatening laryngotracheobronchitis, septicemia twice, bacterial infection of the urinary tract, and numerous episodes of bacterial infection of the respiratory tract, usually with frank otitis media. For several weeks during 1953 when he was free of overt infection, the observation was made that he possessed low levels for the neutrophil count. This hematological abnormality persisted for approximately one month. In a number of instances the etiological agent responsible for the infections was specifically identified. Two episodes of meningitis were due to the pneumococcus and one to *hemophilus influenza,* Group B. Several episodes of pneumonia were attributed to pneumococci, and one urinary infection was caused by a proteus. In every instance the infections responded well to antibiotic therapy. There was no doubt in the minds of the responsible physicians that antibiotic therapy had been lifesaving many times. Attempts to vaccinate this patient against smallpox were carried out 3 times and no

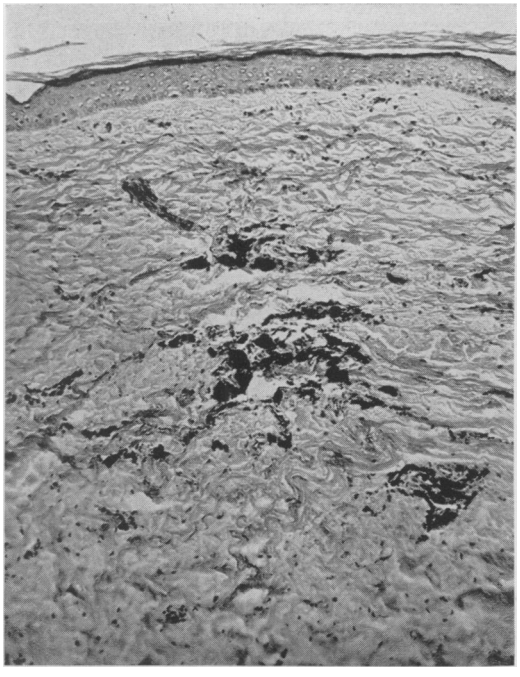


FIG. 4. Microscopic section removed by punch biopsy from a healed persistent skin homograft on an agammaglobulinemic patient, pigment in dermis injected into donor tissue. Note absence of plasma in cell infiltration, characteristic of reaction to homografted tissue in normals (*i.e.*, Fig. 7).

reaction whatever was produced. He was given diphtheria toxoid several times, but remained Schick positive. Upon admission to the University of Minnesota Hospitals, an electrophoretic pattern of the serum proteins was performed and a diagnosis of agammaglobulinemia was made (Fig. 1). Subsequent study revealed an absence of iso-agglutinins against heterologous blood group substances, a deficiency of plasma cells in the hematopoietic tissues, and failure of plasma cellular development from reticulum in response to antigenic stimuli and an absence of circulating or tissue antibody in any form.

On March 9, 1954, homografts of split and full thickness skin from an unrelated patient of different blood group were transplanted orthotopically to this boy. The dimensions of the transplanted skin were 3.5 by 8 cm. The full thickness graft was tattooed prior to transplanting. Both grafts have persisted without reaction for 1 year. The tattooed area of the full thickness graft has remained visible (Fig. 2 A and B).

Case 2. W. A., a 6-year-old white male, born after a normal gestation terminated by a normal delivery, was troubled with skin disease, thought to be infected eczema, between 3 and 6 months of age. He developed meningitis at 9 months of age, which responded to treatment with penicillin and sulfadiazine. When 13 months old, he developed peritonitis, abdominal abscess and septicemia, which responded after a prolonged period of broad spectrum, intensive, antibiotic therapy. At 18 months of age, he underwent an interval appendectomy but no evidence of previous appendicitis was found. During the next 3 years he had at least 7 attacks of pneumonia, and repeated attacks of otitis media and mastoiditis. On several occasions during the course of the infections it was noted that the granulocyte count was very low, and a diagnosis of agranulocytosis was entertained. The granulocytopenia proved to be transient in each instance.

In January 1953 the patient had a febrile illness, with headache followed by severe paralysis of both legs. A diagnosis of Guillain-Barré syndrome was made in retrospect, but the history and residual manifestations are strongly suggestive that the disease was poliomyelitis. During 1953 he suffered recurrent upper respiratory infections and several episodes of pneumonia.

It was found that bronchiectasis existed, and a lobectomy was performed. In spite of the surgical procedure, pulmonary infections continued to occur and bacterial pneumonia developed on several additional occasions. In July 1954 he was admitted to the University of Minnesota Hospitals and laboratory studies revealed an absence of gamma globulin. Roentgenologic studies, including bronchograms, revealed bronchiectasis in the remaining portions of the right lung. The left lung was normal. This patient also displayed a failure to develop plasma cells on antigenic stimulation, had no iso-agglutinins against heterologous blood groups nor detectable antibody against Schick or Dick toxins or streptolysin, streptococcal hyaluronidase or desoxyribonuclease.

Full and split thickness homografts from an unrelated patient with a dissimilar blood type were placed orthotopically on this boy on December 10, 1954. The dimensions of the homografted skin measured 8 x 4 cm. The split thickness graft took initially 100 per cent; 80 per cent of the full thickness took initially. Both grafts have persisted without rejection until the present time, 4 months later (Fig. 3 A and B).

Case 3. J. S., a 7-month-old male child was well until 3 months of age, when he developed pneumonia. Recovery occurred with antibiotic therapy and he was well until 5 months of age, when he again developed pneumonia. A third severe respiratory infection diagnosed as pneumonia occurred at 6 months of age. The family history was of interest in that several members of the family

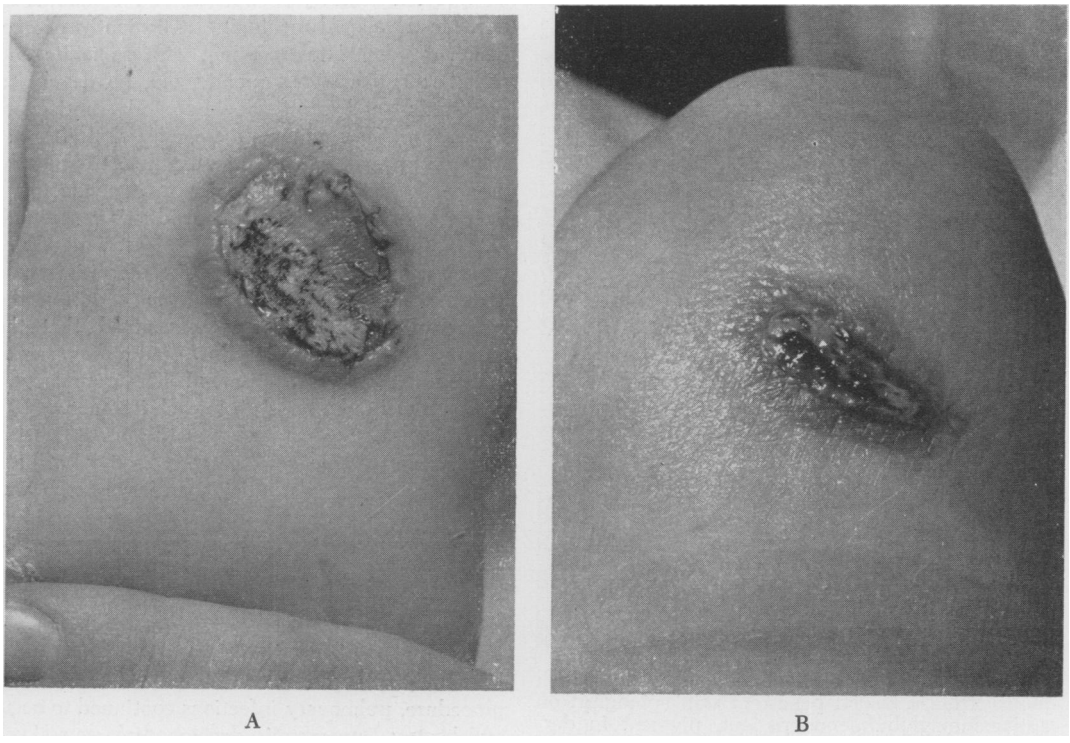


FIG. 5 A and B. Photographs of homografted skin on a patient with transient agammaglobulinemia, but with a normal immune mechanism (J. S.). Complete slough occurred in six weeks. (A) Two weeks following grafting. (B) Four weeks following grafting.

were troubled with asthma, eczema or hay fever. The child was a large, healthy infant having no physical abnormalities. Routine laboratory workup was negative. The zinc turbidity reaction was zero, the baby was blood group O, and possessed no antibody against heterologous blood groups. Both free and paper electrophoretic patterns showed complete absence of gamma globulin at this time.

Subsequently a homotransplant of skin measuring 3 x 2 cm. was placed on this child and after a complete initial "take," it sloughed at about 6 weeks (Fig. 5). Re-study of the circulating gamma globulin at this time revealed now a normal immune mechanism. The agammaglobulinemia observed at 7 months of age was of a transient nature and had not been a persistent deficit of production as observed in the first 2 cases. The etiology of this type of transient depression of gamma globulin production remains unknown to us.

Case 4. F. H., a 58-year-old male, was well until 4 years prior to admission, when he developed pneumonia for the first time. Chest roentgenogram at that time revealed a large mass in the superior mediastinum. Exploration of the tumor which proved to be a thymoma was delayed several months because of recurrent respiratory infections, including another episode of pneumonia. The respiratory disease responded to treatment with sulfadiazine and penicillin. On November 6, 1951, a 540 Gm. benign thymoma was excised. A serum protein determination performed on November 6, 1951, just prior to the operation, revealed the low total serum protein concentration of 5.4 Gm. per cent. During the next 4 years, the patient had 17 attacks of pneumonia. With these bouts occurring with greater and greater frequency, he was admitted to the University of Minnesota Hospitals for study. Electrophoretic analysis of the serum proteins revealed an absence of gamma globulin. In the course of study it was discovered that this patient lacked circulating eosinophils, and that there was a failure of plasma cell development to antigenic stimulation and a great paucity of plasma cells in the bone marrow. He did show a low titer response to heterologous blood groups, indicating the presence of some antibody. This capacity was inadequate to develop antibodies against the bacterial antigens, typhoid, paratyphoid and pneumococcal polysaccharide.

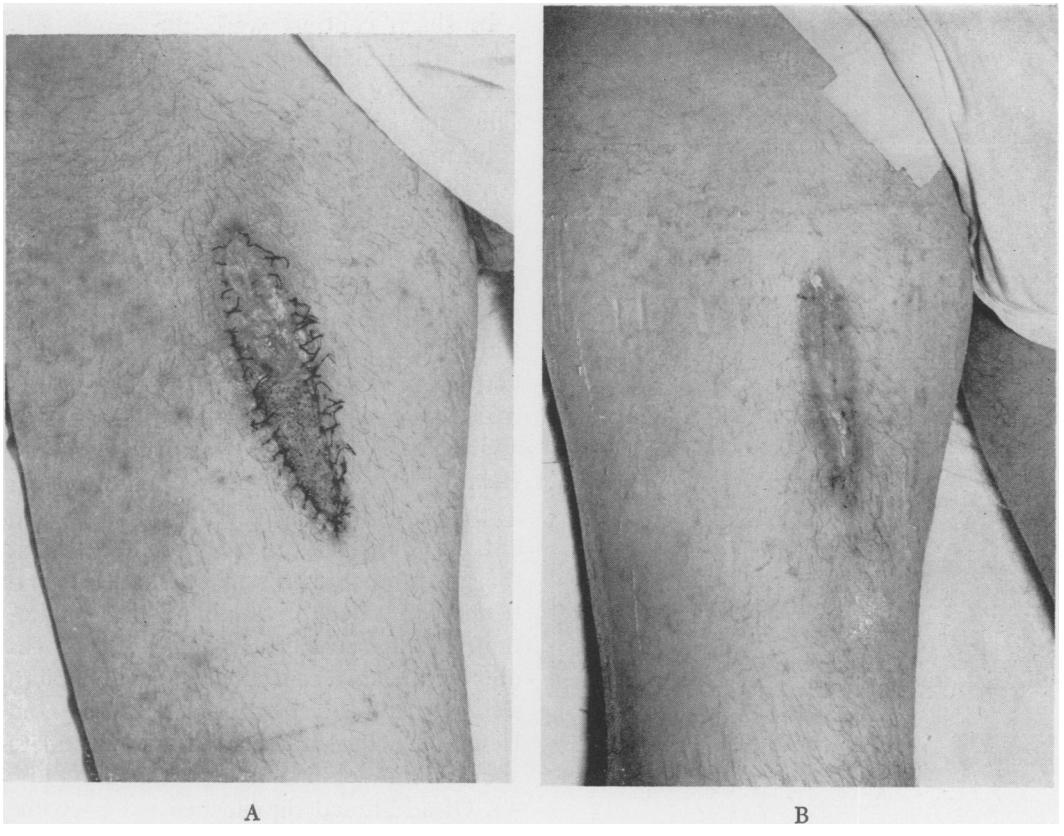


FIG. 6. Photograph of homografted skin on a patient with incomplete, acquired agammaglobulinemia. Complete slough occurred in four months. (A) Two weeks following grafting. (B) Eleven weeks following grafting.

Skin grafts, measuring a total of 10 x 2.5 cm., both full and split thickness, were applied on June 4, 1954, accepted virtually 100 per cent by the host, persisted for 16 weeks, only to slough ultimately and completely (Fig. 6 A and B).

On December 11, 1954, definite icterus was noted. The liver was not palpable nor tender, and no known hepatitis existed in the patient's community. On December 18, 1954, a right upper quadrant mass was palpated. Gastro-intestinal roentgenograms suggested an extrinsic mass in the region of the first and second portions of the duodenum. The patient became anuric, developed hematemesis with hypotension, and failed to respond to treatment with ACTH, metaraminol, (Aramine -R), whole blood transfusions, antibiotics, and vitamin K. Terminally the patient developed ascites and peripheral edema, and expired on December 25,1954. The postmortem studies revealed death to be due to acute yellow atrophy of the liver. One other case of agammaglobulinemia is known to have had hepatitis, which in this instance resulted in severe chronic liver disease. The extrinsic mass pressing on the duodenum appeared to be hemorrhage into the omental bursa, which was thought to be secondary to the hypoprothrombinemia produced by the hepatitis.

DISCUSSION

Spacial limitations permit but a brief reference to several interesting points relevant to this clinical study in immunology. A minimum of description has been devoted to the more intimate aspects of the operative technic, for no unusual maneuvers were involved. The skin preparation of the donor area and the recipient site to be excised received the usual initial care with alcohol and then ether before being finally cleansed with pHisoHex.® All grafts were fastened in place circumferentially with fine silk sutures, car-

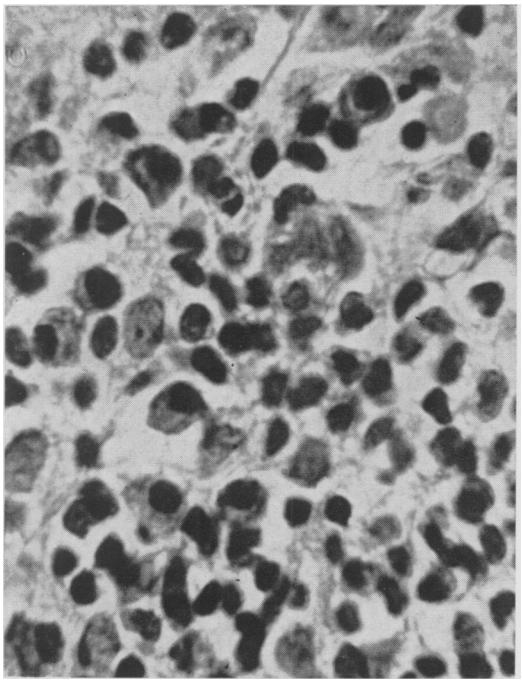


FIG. 7. Photomicrograph showing plasma cell reaction in an area of homograft rejection in an immunologically normal individual.

ried perforations (pie crusting) to permit serum escape through the medial aspects, and were held snugly in place under a xeroform impregnated fine gauze stint. This latter was then covered with an occlusive dressing for at least 12 to 14 days before the initial inspection.

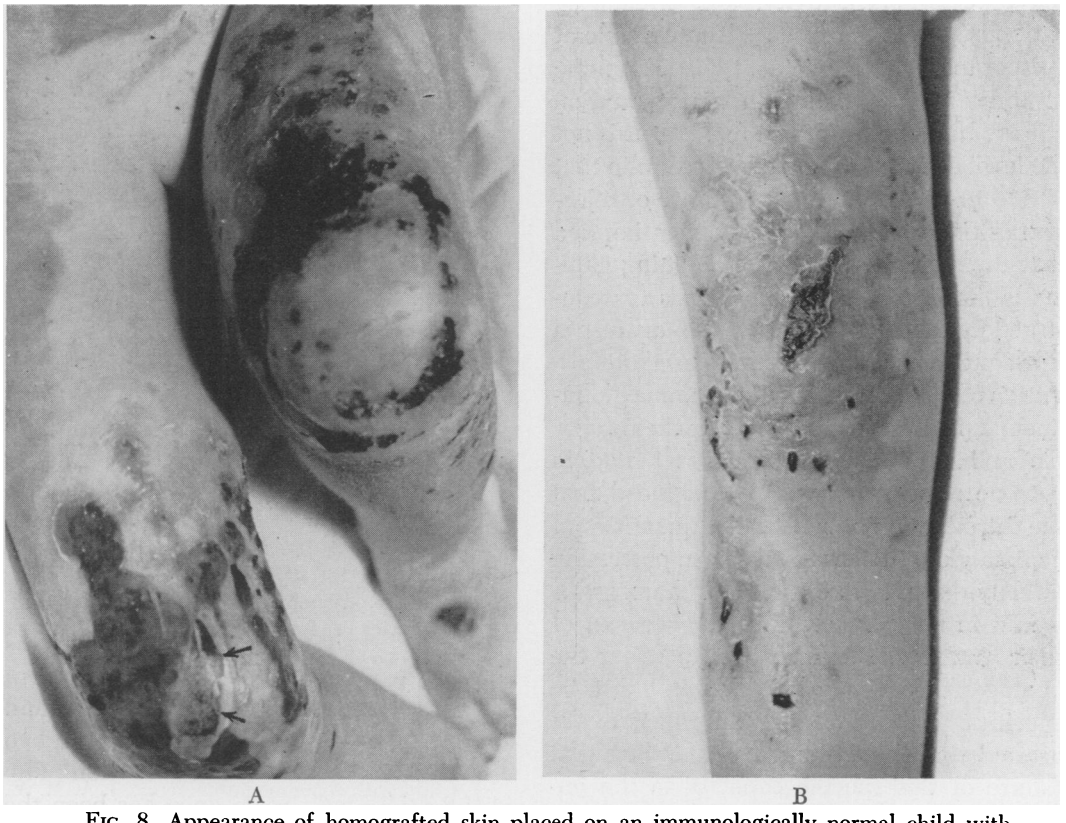
Observations have been presented indicating that homotransplantation of skin has been possible in two children suffering from congenital agammaglobulinemia. In both of these patients extensive immunological studies have been carried out which permit designation of the underlying deficiency as an immunological paralysis. Delayed rejection of a skin homotransplant occurred in an adult who was suffering from acquired agamma globulinemia, featured by an incomplete immunological paralysis.*

* Rejection of a homograft in an immunologically normal individual is characterized by an intensive plasma cell infiltrate (Fig. 7).

In sharp contrast were the results obtained when skin from agammaglobulinemic patients was transplanted to immunologically normal persons who were accepting autotransplants with facility (Fig. 8 A and B). In each of the latter studies the grafts took well at first, and then began to slough between 14 and 21 days after application. In all four instances the destruction and rejection of the homograft was complete by the 40th day after its application. It is conceded that absolute proof that the graft sites continue to be occupied by tissue obtained from an unrelated donor has not been presented. However, the maintenance of tattoo marks in the skin and careful clinical observation of the grafted skin site strongly indicate that the grafts in the agammaglobulinemic patients represent successful homotransplantation. Further support for this concept was obtained when a centrally located area biopsied from the oldest graft (E. S.) was found to contain abundant black pigment and to show no signs of inflammatory reaction (Fig. 4). Of additional significance has been the prompt ingrowth of skin from the area adjacent to the defect created by the punch biopsy. Further study of the regenerated area is proposed for the future.

The "true" identity of this tissue grown to fill an excised area, and very specifically also the entire graft, excites speculation. Let us conceive of it being returned to the individual from which it came. Has it lost genetic specificity for that person? Who is the "donor" now? Can despeciation ever occur, or what are its temporal dimensions? These and so many other answers to our queries are critical to the natural growth of knowledge about this captivating problem. Assuredly, it would be most worthwhile to know when and if this stranger eventually became an expatriate, or if he remained as a visitor on permanent visa.

Perhaps the most important evidence favoring the concept that this is a well tolerated homograft arises from the day to day examination of the transplant site. Once the



A B

FIG. 8. Appearance of homografted skin placed on an immunologically normal child with burns, showing: (A) initial take; (B) imminent slough in 3 weeks, with acceptance of autografts surrounding the test area.

clinician has familiarized himself with the appearance of an initial "take" and its subsequent rejection by the host, the process can hardly fail to be recognized. It is difficult to confuse with the benign course taken by the tolerated homograft. With many observers representing several different clinical disciplines watching the homografts in the agammaglobulinemic patients at frequent intervals, there was no disagreement or uncertainty about the status of the graft in any instance. To be sure it could be contended that the natural history of the process of rejection may merely be extended under these circumstances over a tremendous length of time, and hence that these grafts will ultimately disintegrate or be replaced during the course of the next few years. This may be true, but the evidence to date denies that theory, for the homotransplant sites in E. S. and W. A. are currently at least as large or somewhat larger than their initial dimensions, suggesting that they have grown as the child has grown during the subsequent months. To the contrary, when grafted skin has finally been declined by the host under other circumstances, including F. H. and J. S., the homograft has shrunk steadily, and about this focus there is puckering and drawing of the tissues adjacent to the region, into a scar of the smallest dimensions consistent with the size of the original defect.

It is worthy of special emphasis that we consider the prime factor in the ultimate successful transplant of a homograft to be the incapacity of the host to respond specifically to the antigens of the homograft. Our observations that these patients fail to develop immunological reactions of all three forms, *i.e.*, reagenic hypersensitivity, bacte-

rial type hypersensitivity, and circulating antibody production, makes it impossible at present to determine which type of immune response is associated with transplantation failure. In other words, we feel that it is not the level of circulating gamma globulin that is vital to the long term acceptance or rejection of tissue, although it has been implied that the mere presence of circulating gamma globulin is all the body needs for construction of specific antibodies against a subsequently introduced antigen. Administration of gamma globulin to agamma globulinemic patients does not render them capable of immunological reactivity. Stated in yet one more way, we are convinced that the introduction of substantial quantities of gamma globulin into the children possessing already long term "takes" of homografts would in no way prejudice the survival of their grafts. We believe that to reject the homograft the immune response must be specifically directed toward antigens in the grafted tissue. It is our understanding that failure of this specific capacity in the immunological paralysis associated with agammaglobulinemia permits successful homotransplantation. Our interest in arousing immunological capacity in the agamma globulinemic child has led us to try to transplant tissue capable of achieving this goal. These studies which are intimately bound with the development of "curative" procedures for this condition, to date have supported this hypothesis *(vide supra)*, and will constitute the substance of an early report.

In conclusion, we have expressed, via these case reports, our interest in this fascinating experiment of nature. We candidly hope thereby that many inquiring workers will be keenly aroused by these immunological challenges, and by virtue of greater interest bring sooner to successful practice, clinical, homovital organ grafting. Such an accomplishment represents a maturation of surgery that is a bright vista to contemplate.

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