least one macrophage per 100 lymphocytes. The macrophages of our patients restored this response to PPD. In addition, a soluble factor (CMRF) collected from macrophage cultures of both patients, as described by Bach et al., also reconstituted the response of purified lymphocytes to PPD. These studies indicate that macrophages in severe combined immunodeficiency are capable of 1) restoring the response of purified lymphocytes to PPD and 2) synthesizing CMRF (conditioned medium reconstituting factor). They also confirm Bach et al.'s observation that CMRF can replace the macrophage in its interaction with purified lymphocytes.

Incompatible bone marrow transplantation in lymphopenic immunologic deficiency. REBECCA H. BUCKLEY, D. BERNARD AMOS, WILLIAM P. KREMER, and DELFORD L. STICKEL. *Duke Univ. Sch. of Med., Durham, N. C.*

Fatal graft-versus-host (G-V-H) disease has been an invariable accompaniment of incompatible bone marrow transplantation in infants with lymphopenic defects. This report describes an approach which permitted circumvention of this complication. Histocompatibility studies demonstrated no HL-A compatible donors for a female infant with lymphopenic agammaglobulinemia (very low IgG, absent IgA, IgM, and IgE). Serum from her mother (para 16) contained antibodies (1:64 titer) to paternal HL-A antigens inherited by the patient. Maternal lymphocytes were not stimulated by paternal or infant's leukocytes in mixed leukocyte culture in media containing maternal plasma. Immunologic enhancement was attempted at age 5 months by pretreating the infant with cell-free maternal plasma I.V. 24 hours before the I.V. infusion of 5×10^6 immature albumin-gradient-separated maternal marrow cells. Appetite and growth increased dramatically during the first 3 months, thrush and pneumonia cleared, and no overt signs of G-V-H were noted. Delayed cutaneous responsiveness to *C. albicans* was seen by the 13th day and persists. Lymph node biopsy at 90 days contained plasma cells which stained with fluoroscein-conjugated anti-IgG, IgA, IgM or IgE. A second maternal marrow transplant was given at age 11 months, again without overt G-V-H. This 19-month-old infant has gained 4 kg and grown 20 cm since the first transplant 14 months ago. A normal serum IgA concentration and somewhat low but constant levels of IgG and IgM are present now 5 months after the last plasma infusion. These findings suggest possible usefulness of immunologic enhancement in future attempts when compatible donors are unavailable.

Transfer factor in the treatment of chronic mucocutaneous candidiasis. MARTIN L. SCHULKIND, WILLIAM H. ADLER, III, WILLIAM A. ALTEMEIER, III, and ELIA M. AYOUB. *Univ. Fla. Coll. Med., Gainesville, Fla.*

The use of "transfer factor" to correct a partial defect in cellular immunity to *Candida albicans* was studied in an 8-year-old girl with chronic granulomatous mucocutaneous candidiasis.

The patient first presented at age 5 years with extensive deforming encrusted lesions on her face, head, trunk and extremities. No evidence of endocrinopathy or antibodies to endocrine tissue was found. Her general humoral immunity was intact. She had a normal complement of granulocytes and lymphocytes. Candida aggregation activity was present in her serum. Her skin test response to *C. albicans* extract was consistently negative. Her lymphocytes underwent blastogenesis to PHA, diphtheria toxoid and *C. albicans* extract. However, in the presence of exogenous transfer factor, blastogenesis to candida increased. Transfer factor extracted from her cells did not transfer immunity to non-sensitized cells.

Amphotericin B therapy cleared her skin lesions temporarily, but neither fresh frozen plasma injections nor 5-fluorocytosine was effective. Following 2 injections of transfer factor, she developed a positive skin test response to *C. albicans* extract, and her lymphocytes produced leukocyte inhibition factor (LIF) to candida. After a third injection there was appreciable clearing of the skin lesions.

These findings indicate that exogenous transfer factor can restore cellular immunity to candida in a patient with chronic mucocutaneous candidiasis and may be an effective treatment for this disease.

A primitive immunologic marker of intrauterine virus infection. JOSEPH W. ST. GEME, JR., CATHERINE W. C. DAVIS, and LLOYD F. VAN PELT. *UCLA Sch. of Med., Harbor Gen. Hosp., Torrance, Calif.*

Retrospective and prospective studies of the human have suggested that intrauterine mumps virus infection evokes an incomplete immunologic response of delayed hypersensitivity, without humoral antibody. Experimental infection of the subhuman primate during the first third of pregnancy also leads to the development of only cellular immunity in the infant offspring. The significance of delayed hypersensitivity as an immunologic marker of fetal infection is strengthened by the observation of an anamnestic neutralizing antibody response in 2 of 4 infant monkeys following a second skin test. Repeated skin testing of 5 seronegative adult monkeys failed to induce a primary antibody response.

Intrauterine mumps virus infection illustrates the phylogenic and ontogenic concept that cellular immunity is the most primitive immunologic response. Experimental infection of 9 monkeys between the 25th–40th day of gestation, with subsequent cesarean section after 1, 2 and 3 weeks, has demonstrated that virus multiplies in the young fetus for only 1 week. Fetal interferon response does not occur, so the termination of viral replication seems to result from transplacental distribution of abundant 7S maternal neutralizing antibody. This conclusion is supported by the restrictive effect of antibody on mumps virus replication in vitro.

Thus, the immature fetus confronts minimal antigenic mass and accrues immunopoietic instruction for only the more primitive response of delayed hypersensitivity.

Demonstration and replacement of a functional defect of the fifth component of complement in newborn serum. A major tool in the therapy of neonatal septicemia. MICHAEL E. MILLER. *Univ. of Pennsylvania, Philadelphia, Pa.*

Previous studies from this and other laboratories have shown a relative deficiency in the opsonic activity of neonatal serum. The nature of this deficiency has been incompletely understood. The studies now reported show that the impairment of opsonic activity in neonatal serum involves a *functional* deficiency of the fifth component of serum complement (C5). (1) Opsonic activity of neonatal sera towards baker's yeast phagocytosis (Miller, 1969) was restored to normal by the addition of sera from mice with normal amounts of C5 (B10D2 new line) but not by addition of sera from a co-isogenic strain lacking C5 (B10D2 old line); (2) Utilizing highly purified human C3 & C5, re-constitution of

opsonic activity of neonatal sera occurred only when C5 was added; (3) 5-day-old stored, ACD bank plasma was markedly deficient in re-constituting opsonic activity of neonatal serum. Fresh (<24 hrs) ACD plasma, however, effected significant reconstitution. The deficiency of 5-day-old plasma in opsonic reconstitution of neonatal sera was *completely corrected* by the addition of C5 containing mouse serum, or by purified human C5, but *not* by C5 deficient mouse serum.

These studies demonstrate that the opsonic deficiency of neonatal serum involves a functional deficiency of C5 and that restoration of opsonic activity can be brought about by infusion of *fresh* plasma, which contains functionally active C5. A rationale is, therefore, presented for the use of fresh plasma in therapy of neonatal septicemia.

Immunological abnormalities in Job's syndrome. HENRY F. PABST, BEULAH HOLMES, PAUL G. QUIE, HENRY GEWURZ, GLENN RODEY, and ROBERT A. GOOD. *Variety Club Heart Hospital, Univ. of Minnesota, Minneapolis, Minn.*

A 9-year-old girl was investigated with Job's syndrome to establish the underlying pathogenesis. Recurrent large but "cold" staphylococcal abscesses in skin, kidney and abdomen were unaccompanied by fever, pain and signs of acute inflammation. Normal parameters of the immunological investigation were: cellular, delayed hypersensitivity type of immunity as demonstrated by: 1) skin test response to staphylococcal protein A, SKSD, Candida and challenge with 2,4-DNFB; 2) transformation of lymphocytes with phytohemagglutinin and with staphylococci; 3) skin homograft rejection in 10 days; immunoglobulin levels other than IgE; complement component levels and function; heat stable and labile opsonin activity; in vitro phagocytosis by polymorphonuclear leukocytes of several types of staphylococci including the patient's (P.S.); respiratory enzyme activity of these cells during phagocytosis; in vitro chemotaxis of her leukocytes as generated by P.S. in the Boyden chamber; endogenous pyrogen production by her granulocytes in presence of P.S. The striking abnormalities were: 1) marked scarcity of neutrophilic granulocytes in staphylococcal abscesses; 2) heavy eosinophilic infiltration of the surrounding tissue, 3) basophilic granulocyte accumulation in inflammatory cycle studies using P.S., and 4) extremely elevated serum IgE level. It is concluded that in vivo chemotaxis for neutrophilic granulocytes is defective in this syndrome.

Acrodermatitis enteropathica with dysgammaglobulinemia. O. RENNERT, R. JULIUS, M. SCHULKIND, and T. SPRINKLE. *Univ. Fla., Coll. Med., Gainesville, Fla.*

In 1942 Danbolt and Closs described the association of diarrhea, eczematoid rash and alopecia. These physical findings constitute the triad essential for the diagnosis of this autosomal recessive disease. The demonstration of the efficacy of Diodoquin therapy in this otherwise fatal disease was by Dallaha and Lorincz in 1953. Reports since then indicated partial success utilizing this agent, breast milk or a combination of the two. The major cause of death has been overwhelming infection. This sequellous has been ascribed to the marasmic status of the children. The case described is an 8-month-old boy who demonstrated the classic triad of this syndrome in association with total absence of humoral IgA and IgG, and normal levels of IgM. Autopsy revealed sparse lymphoid elements and supported the diagnosis of dysgammaglobulinemia. Arachidonic acid was detectable at extremely low levels in serum. Metabolism of tryptophan was normal. The association of acrodermatitis and dysgammaglobulinemia may represent the occurrence of two distinct disease entities or suggest a pathogenetic relationship. Our experience with this patient supports the view that halogen-substituted-8-hydroxyquinolins specifically affect the skin manifestations in this syndrome but may be ineffective against the malabsorptive component. Both these features were well controlled by therapy with Diodoquin and breast milk.

Altered reactivity to respiratory syncytial virus: Antibody response to RSV antigens and studies of the pathogenesis of atypical RSV illness in recipients of inactivated vaccine. JERRY J. ELLER, VINCENT A. FULGINITI, ARTHUR A. ROBINSON, HITOSHI NAGAHAMA, JAMES SHIRA, and DANIEL C. PLUNKET. *U.S. Army Med. Res. and Nutrition Lab., and Univ. of Colo. Med. Ctr., Denver, Colo.*

The vaccine, in contrast to natural infection, failed to produce significant serum IgA antibody. Kinetic experiments revealed no defect in the quality of IgG antibody produced by the vaccine. Arthus and precipitating antibodies were not demonstrable in post-vaccine sera. The mean percent blastoid formation and uptake of radiouridine were greater in vaccinees than in controls in vitro lymphocyte stimulation tests. A delayed dermal hypersensitivity reaction could be demonstrated in guinea pigs and African Green monkeys after multiple injections of adjuvanted RSV vaccine. Immediate wheal and flare reactions were not detected. A positive delayed skin test was still present in the monkeys 12 months after immunization. An African Green monkey previously immunized developed a temperature elevation above 106° and rales in the lungs, but no wheezing, lasting about 48 hours, beginning 9 days after intranasal challenge with live 11th MK passage RSV. The vaccine was shown to contain a disproportionate amount of soluble, CF antigens compared to surface, viral antigens. Evidence indicates that the vaccine overstimulated delayed hypersensitivity and IgE in young atopic children. Enhanced delayed hypersensitivity may account for the high fever, rash and some pulmonary infiltration, and the IgE-mediated response for the marked wheezing seen in atypical illness.

A new test of delayed hypersensitivity to measles virus *in vitro*. RICHARD J. LABOWSKIE, ROBERT EDELMAN, MARY C. BIUNDO, and JOSEPH A. BELLANTI. *Georgetown Univ. Med. Ctr., Washington, D. C.*

The purpose of these studies was to develop an in vitro method for the demonstration of delayed hypersensitivity to measles virus. Using cell lines chronically infected with measles virus, a lymphocyte-target cell interaction was studied, using morphology or Cr^{51} release as an end point. Preliminary morphologic studies employing control and chronically infected HeLa cells indicated a greater cytotoxic effect with lymphocytes from children previously immunized with live measles vaccine than in unimmunized controls. All subsequent studies employed two human fibroblast lines, one infected (WI-M1) and one normal (WI-38). The WI-M1 carries measles antigen at the cell surface in steady state replication. Modifying the cytotoxic method of Holm and Perlmann, lymphocytes purified by glass bead adsorption were added to Cr^{51} labelled target cells in a ratio of 100:1. The release of Cr^{51} in excess of background was interpreted as a measure of lymphocytotoxic factor. The percentage release of Cr^{51} from WI-M1