ABSTRACTS

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IMMUNOHEMATOLOGY


From a retrospective analysis of 1000 cases of Rh-erythroblastosis, the authors reached several conclusions: 1) Significant anemia in the absence of jaundice may be associated with early death, attributable in part to delay in initiating therapy. 2) Anemia at birth was the one finding best correlated with mortality, (24 per cent) and with pathologic evidence of liver necrosis and/or extramedullary hemopoiesis. 3) Conjugated hyperbilirubinemia also was correlated with a fairly high mortality (17 per cent). Regurgitation of direct-reacting bilirubin was not associated with increased pathologic evidence of cholestasis and was interpreted as resulting from delayed maturation, or impaired efficiency, of the transport system responsible for transferring conjugated bilirubin from the hepatic cell to the canalculus.—J. B. S.

EXPERIENCE WITH A NEW ISOVOLUMETRIC EXCHANGE TRANSFUSION METHOD. G.J.A. Cropp. From the University of Colorado Medical Center, Denver, Col. J. Pediat. 71:332-341, 1967.

Isovolumetric exchange transfusion is recommended, particularly for small, high-risk newborns, or in rapid exchange of large volumes of blood in older children and adults. Results of studies in models, animals, and in patients suggest that the method is efficient and less taxing. Several technics for achieving isovolumetric exchange are described.—J. B. S.


A 63 year old female had an acquired Coombs positive hemolytic anemia for 2½
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The autoantibody was of the incomplete warm gamma type. In the narrow, plasma cells were absent. Quantitative estimation by radial immunodiffusion yielded very low values: $\gamma\text{-G} = 180$ mg per cent, $\gamma\text{-A} = 15$ mg, $\gamma\text{-M} = 25$ mg. The patient had suffered from multiple bouts of pneumonia as a child and young adult, but did not display other signs of antibody deficiency. There was no sign of systemic disease such as chronic lymphatic leukemia. The anemia responded to corticosteroid therapy, while the Coombs test remained positive and the hypogammaglobulinemia persisted.

—K. B.


A male patient with “Swiss type” hypogammaglobulinemia with a life-threatening uncontrollable infection was treated by injection of 200 ml of his mother's blood and suspensions of fetal thymic and liver cells. Shortly thereafter, the patient’s peripheral lymphocyte count rose, a previously established skin allograft was rejected, and his infection was controlled. A graft versus host reaction, however, then ensued and he died within 24 hours or 3 weeks after birth and then X-irradiated. Thymectomized-irradiated rabbits showed a reduced capacity for production of humoral antibodies to sheep red cells and conalbumin, but not to Salmonella typhi. These findings indicated that thymectomy produced only a limited impairment of immunity. Antibody levels following primary stimulation were usually much lower in appendectomy-irradiated than in irradiated controls. The cellular immune response, development of delayed tuberculin hypersensitivity and skin homograft immunity were impaired in thymectomized and thymectomized-appendectomy-irradiated rabbits than in irradiated controls. The immune response was suppressed more strongly in thymectomized-appendectomy-irradiated than in thymectomized rabbits. The immune response was observed in the sera of some thymectomized and/or appendectomy-irradiated rabbits and not in irradiated controls. One or more sharp narrow bands within the gamma G region were observed in the sera of some thymectomized and/or appendectomy-irradiated rabbits.

The authors inferred that mononuclear cells have specific surface receptors for IgG, and that these are critical to the mechanism whereby red cells coated with antibody are apprehended and destroyed in vivo. (Abstractor's note: These results help to explain the spherocytosis observed frequently in patients with Coombs positive hemolytic anemias, despite the absence of morphologic changes noted when incomplete antibodies are added to red cells in vitro.)—H. S. J.


These processes were studied in rabbits thymectomized and/or appendectomized within 24 hours or 3 weeks after birth and then X-irradiated. Thymectomized-irradiated rabbits showed a reduced capacity for production of humoral antibodies to sheep red cells and conalbumin, but not to Salmonella typhi. These findings indicated that thymectomy produced only a limited impairment of immunity. Antibody levels following primary stimulation were usually much lower in appendectomy-irradiated and thymectomized-appendectomy-irradiated rabbits than in irradiated controls. The cellular immune response, development of delayed tuberculin hypersensitivity and skin homograft immunity were impaired in thymectomized and thymectomized-appendectomy-irradiated rabbits than in irradiated controls. The immune response was observed more strongly in thymectomized-appendectomy-irradiated than in thymectomized rabbits. Some thymectomized-appendectomy-irradiated rabbits had very low levels of serum gammaglobulins, but the majority of thymectomized and/or appendectomy-irradiated rabbits had serum gammaglobulin levels comparable to those of irradiated controls. One or more sharp narrow bands within the gamma G region were observed in the sera of some thymectomized and/or appendectomy-irradiated rabbits.

Human monocytes and macrophages fixed as monolayers on plastic dishes bound firmly to red cells coated with IgG. Binding was specific for cells so coated and was inhibited by this immunoglobulin or its Fc-fragment in solution. Although not involving complement, this binding damaged red cells, as manifest by their spherering, increased osmotic fragility, fragmentation and deformation.


Human monocytes and macrophages fixed as monolayers on plastic dishes bound firmly to red cells coated with IgG. Binding was specific for cells so coated and was inhibited by this immunoglobulin or its Fc-fragment in solution. Although not involving complement, this binding damaged red cells, as manifest by their spherering, increased osmotic fragility, fragmentation and deformation.
HEMOTOLOGICAL AND ISOTOPIC INDICATED rabbits. These observations suggested that disturbed gammaglobulin synthesis, i.e., a- or hypo-gammaglobulinemia, and the appearance of sharp narrow bands in the gammaglobulin region were caused by removal of the rabbit's thymus and appendix. —K. F.

APPARENT PRODUCTION OF TWO TYPES OF ANTIBODIES BY A SINGLE CELL. J. G. Michael and R. Marcus. From University of Cincinnati College of Medicine, Cincinnati, Ohio. Science 159:1247, 1968.

This is the Nth paper in a series which I am sure will continue into the far distant future. The subject is the simple but important question as to the number of different antibodies which can be produced by a single cell. Mice were immunized with sheep erythrocytes, E. coli and the somatic antigen of E. coli. These antigens were given separately, together, or with sheep erythrocytes coated with the somatic antigen of E. coli. The Jerne plaque technic was used. Both sheep erythrocytes and E. coli were incorporated into the agar and the presence of both hemolytic and bactericidal plaques could be detected. In animals immunized with erythrocytes coated with E. coli antigens, some cells were found which appeared to have both hemolytic and bactericidal activity. By cross absorption studies of the serum, the authors ruled out the possibility that their double-producing cells were the result of the production of a cross-reacting antibody.—I. G.


Reduced serum concentrations of folate and an abnormally rapid plasma clearance of intravenously administered folic acid have been reported previously in polycythemias vera (Brit. J. Haemat. 31:600, 1965) and were attributed to an excessive requirement for folate. This report described the first instance of a person with polycythemia who developed overt megaloblastic anemia due to folate deficiency.—F. A. K.


Intestinal malabsorption of vitamin B₁₂, which could not be corrected by intrinsic factor, and malabsorption of other test substances was detected in 4 of 10 successive patients with pernicious anemia. Jejunal biopsy obtained in one of these 4 patients was normal. Following therapy with vitamin B₁₂ for from 1 to 10 months, all 4 patients had normal intestinal absorption of vitamin B₁₂. The authors proposed that intestinal malabsorption may have been a result of B₁₂ deficiency.—F. A. K.


The quantity of gastric juice required to enhance absorption of vitamin B₁₂ was found to be identical in patients with pernicious anemia irrespective of the presence or absence of circulating antibody to intrinsic factor. This finding suggested to the authors that the presence of serum antibody to intrinsic factor was not responsible for malabsorption of vitamin B₁₂ in pernicious anemia.—F.A.K.


Serum vitamin B₁₂ levels were determined in 188 patients with various hepato-biliary diseases. Elevated values were invariably found with hepatocellular damage. The relative usefulness of serum B₁₂, serum COT and serum iron in liver disease was discussed. The serum level of B₁₂ was a sensitive, reliable and specific index of liver cell damage.—B. R.

RESULTS OF SPLENECTOMY IN HEMOLYTIC SYNDROMES ON THE BASIS OF CLINICAL, HEMATOLOGICAL AND ISOTOPIC INDICA-
CONGENITAL HEMOLYTIC ANEMIA AND MICROSPHEROCYTE FORMATION.

The index of spleen-liver sequestration of Cr-51 labeled erythrocytes was evaluated as an indication for splenectomy in 19 patients with various types of hemolytic anemia. In 15 cases of congenital spherocytic anemia, permanent improvement was obtained after splenectomy, including 6 patients with low spleen-liver indices. Favorable results were observed in only 3 cases of acquired hemolytic anemia in which this index exceeded 3:1. The spleen-liver index was a valuable criterion in selection of patients for splenectomy in acquired hemolytic anemia, while its value was much less in congenital spherocytosis.—M. K.


Five cases were presented: 1) Congenital hemangiomata (Kasabach-Merritt syndrome) with hemolytic anemia and defibrination. 2) Hemangioma of the liver with hemolysis and a low fibrinogen level. 3) Rheumatic heart disease with perforation of the anterior mitral leaflet due to S.B.E. 4) Compensated hemolytic process with recurrent aortic insufficiency after insertion of a Magovern artificial valve. On reopening the heart, the natural aortic cusps were found to penetrate into the cage of the Magovern valve and to prevent its closure. 5) Cirrhosis of the liver. All patients had, apart from the conventional signs of hemolysis, burr cells, fragmented cells and helmet cells on stained and wet smears, slightly increased autohemolysis and ATP instability.—B. R.


In iron deficient infants, jejunal biopsy revealed histochemical evidence of depressed
cytochrome oxidase activity and/or decreased concentrations of cytochrome c. Following iron administration, return to a normal staining pattern paralleled new mucosal cell production. In iron deficient rats, similar histochemical findings pre- and post-treatment, were noted. In the animals, enzymatic studies revealed normal cytochrome oxidase activity, suggesting that cytochrome c was depressed, rather than its oxidase. Non-heme-containing enzymes were normal and no evidence of intestinal malfunction was found in the iron-deficient rats.—J. B. S.


Children who had ingested toxic amounts of iron-containing drugs were treated with supportive therapy alone, with desferoxamine by mouth, or with oral plus intravenous desferoxamine. Although serum iron levels returned to normal in all three groups within a day, mean urinary excretion was 0.38, 3.3 and 10.7 mg per hour, respectively. There were no deaths in any group, and the authors questioned the use of desferoxamine in iron intoxication of mild to moderate severity. The difficulty in the precise determination of severity at the time of hospitalization was discussed.—J. B. S.


Utilizing the precipitation of lead phosphate as a marker of phosphate generation in the ATPase reaction associated with active cation pumping, the authors conclusively demonstrated that this enzymatic reaction occurred on the inner aspect of red cell membranes only. On electron photomicrographs, lead phosphate precipitates were localized specifically on the inner part of red cell ghosts, not on the outer part. No apparent differences were found in the localization of Na-K-Mg (cation pump) ATPase and (non-pump) Mg-ATPase. (Abstracter’s note: Similar electron microscopic localization of ATPase to the inner aspect of corneal membranes (Science 150:1167, 1965) suggests a more general phenomenon. The accumulation of phosphate intracellularly, rather than extracellularly, might have the beneficial effect of stimulating glycolysis within the cell and, thereby, the regeneration of ATP needed for continued cation pumping).—H. S. J.


Approximately 20 per cent of membrane-bound protein can be solubilized and obtained free of other cell components by dialyzing guinea pig ghosts against ATP and 2-mercaptoethanol. Following extraction, the recently described filamentous material seen along the inner surface of intact membranes (J. Cell Biol. 35:385, 1967) is lost. By electron microscopy, the extracted protein forms coiled filaments of approximately 40-60 Å diameter when incubated at 37°C with Ca++ or Mg++. Rabbit antibodies to the protein extract react specifically with red blood cells or their ghosts, but not with serum, erythrocyte cytoplasm or other blood cells. In the presence of complement, red cells sensitized with such antibody hemolyze. The functional role of this protein is unknown, but to the authors it seems likely to be involved in the maintenance of the structure of the ghost membrane.—H. S. J.


The ouabain-insensitive ATPase activity in red cell membranes obtained from patients with hereditary spherocytosis was significantly reduced when compared with normal membranes. In paroxysmal nocturnal hemoglobinuria, this ATPase activity was significantly reduced in a slightly acidified medium. A hypothetical mechanism for hemolysis was discussed.—K. F.

ALPHA-TALASSEMIA WITH Hb H AND Hb Bart’s in a German Family. P. Rönsch and E. Kleihauer. From the Medical
An eight year old mentally retarded girl with a thalassemic blood picture had typical Hb H inclusion bodies in several red cells. Electrophoretically, 5.6 per cent Hb Bart’s and trace amounts of Hb H were found; Hb F was 3.3 per cent and Hb A2 was 1.3 per cent. The mother also had a thalassemic blood picture with single cells per cent. The father was hematologically normal. This case was the first of α-thalassemia in a German family. The authors argued that in this case not only α-chain synthesis was suppressed, but β-chain synthesis as well.—K. B.


Human hemoglobin treated with bis-(N-maleimido-methyl) ether (BME), but not other sulfhydryl-reactive reagents, showed impaired binding to serum haptoglobin. Since dissociation of hemoglobin into its symmetrical dimers \((α_2β_2\rightarrow2αβ)\) was suppressed in BME, but not in other treated hemoglobins, and since such dissociation was also diminished in deoxyhemoglobin which in turn was also poorly bound to haptoglobin, it was suggested that haptoglobin binds separate αβ dimers in preference to the intact tetramer. (Abstracter’s note: This conclusion has teleological merit since haptoglobin is utilized to bind hemoglobin present in low concentrations in plasma. In such dilute solutions, hemoglobin is especially liable to dissociation into dimers).—H. S. J.


Studies of the peroxidase activity of human hemoglobin A and its separated α and β subunits showed that optimal peroxidase activity required interaction between α and β chains. Isolated chains, despite normal heme activity, had poor peroxidase activity. From these data and experiments by others that showed that haptoglobin enhanced peroxidase activity through conformational effects on the globin moiety, it was concluded that, as with its binding of gaseous ligands, heme activity was greatly affected by interactions between unlike polypeptide globin chains.—H. S. J.


Endogenous production of CO has been demonstrated to be derived almost completely from the α methene bridge of heme during its catabolism. Previous studies from this laboratory have shown close correlation between CO production, as measured by a closed rebreathing technic, and destruction rates of circulating red cells in hemolytic syndromes and in normals. The present work revealed large discrepancies in CO evolution and circulating heme metabolism in patients with ineffective erythropoiesis (thalassemia and primary refractory anemias). Marked increases in C14O after administration of C14-glycine occurred as an “early labeling” peak, concomitantly with the increase in labeled fecal stercobilin under these circumstances. Production of “early labeled” C14O in patients with ineffective erythropoiesis was increased up to 14 times that in normals. The contribution of hepatic heme and porphyrin compounds to CO production was also attested to by the finding of high CO evolution in a patient with prophyria cutanea tarda.—H. S. J.


The authors examined, by electron microscopy, the elliptocytes of humans, both homozygotes and heterozygotes, and the normally elliptical red cells of the llama. A shadow-casting technic showed what the authors interpreted as bipolar massing of hemoglobin in the human cells, but not in llama cells.—C. R. M.
LEUKOCYTES


Children suffering from acute lymphoblastic leukemia fared better than those suffering from other types, except for those who presented with mediastinal lymph node enlargement who had a very poor prognosis. Patients with lymphoblastic leukemia diagnosed during the latter period of the survey fared better than earlier cases, probably due to advances in treatment. Adverse features included age less than three years at diagnosis, enlargement of liver, spleen and lymph nodes, white cell count greater than 20,000/μl, or blast cell count greater than 10,000/μl and thrombocytopenia.—A. L. B.


Ninety-five cases of leukemia were seen between January, 1960, and December, 1965. When the first reported symptom was considered, no month with an increased prevalence was found. An increase in incidence was observed between July and October with an isolated peak in February, if the time the patient sought medical care was considered. This increase was not due to changes in temperature.—M. J.


This is a very interesting paper. The authors have investigated the leukocytes of a number of species and find that there is consistently higher iron content in the granulocytes of rabbits and squirrels. Human granulocytes and their precursors are free of iron, but iron is present in “toxic” granules. The authors suggest that “toxic granulation” is an active, adaptive state, not a toxic degeneration.—C. R. M.


From the labeled-mitosis curve and the double labeling technic with H3- and C14-TdR, the length of DNA synthesis by granulocyte precursors was estimated as approximately 8 hours for myeloblasts, 10 hours for promyelocytes and 11 hours for myelocytes. Generation time, estimated as the interval between the first and second increase in labeled-mitosis curve, was 18 to 20 hours for either promyelocytes or myelocytes. Efflux from the proliferating compartment and influx to the non-proliferating compartment were estimated. These two fluxes were roughly the same, indicating that overproduction in the proliferating compartment was not remarkable in healthy dog granulocytopenia. Labeled metamyelocytes appeared about 3 hours after injection of H3-TdR. The initial rate of entry of metamyelocytes was about 3.5 per cent per hour. Transit time of metamyelocytes appeared to be about 27 hours. Labeled segmented neutrophils in bone marrow were seen about half a day later than labeled band-forms. Emergence time of labeled neutrophils in peripheral blood was found to be from 30 to 48 hours after injection of H3-TdR; a steep rise occurred between 48 and 72 hours. The maximum labeled index, 40 to 60 per cent, was attained on the 4th or 5th day. By the 10th day, almost all labeled neutrophils had disappeared from the peripheral blood. The pattern of the curve of labeled eosinophils was similar to that of neutrophils, but occurred a little earlier and was usually higher. Labeled monocytes and lymphocytes were found in peripheral blood on the first day. In monocytes, the labeled index reached the maximum value on the 2nd or 3rd day, then decreased slowly until the 14th day. In lymphocytes, the maximum labeled index was the lowest and labeled lymphocytes persisted for more than 10 days without any marked fluctuation in number. Even on the 30th day after H3-TdR administration, a few labeled lymphocytes still remained in the circulation.—K. F.

Transformation of Human Lymphocytes: Inhibition by Homologous Alpha Globulin. S. R. Cooperband. II.

The phenomenon of blast transformation of lymphocytes in vitro has become an important method for investigation of the immune response, as well as a method of studying other aspects of lymphocyte physiology in normal and pathologic states. An alpha globulin isolated from human serum lymphocytes and a delayed hypersensitivity the lymphocytes. This alpha globulin was shown to have the capacity of inhibiting blast transformation of lymphocytes in vitro after stimulation by specific antigens or after exposure of the cells to phytohemagglutinin. This inhibition was not due to any toxic effect of the alpha globulin on the lymphocytes. This alpha globulin fraction may represent a normal humoral factor important in the regulation and modulation of lymphoid cell activity.—I. G.


Patients with Hodgkin's disease have consistent lymphocytopenia. Profound lymphocytopenia was remarkable in the late stage, although it was difficult to assess to what extent this may have resulted from therapy. The lymphocytopenia assumed new significance in the light of recent investigations on the role of the lymphocyte in immunologic activity. Twelve of 25 patients were skin tested with tuberculin, all cases had cutaneous anergy in the course of the disease. One remained tuberculin negative in the presence of active tuberculosis. Parallelism between the number of circulating lymphocytes and a delayed hypersensitivity reaction was observed. Seventeen were autopsied and 7 were shown to be infected at the time of death. There were three cases of cryptococcosis, two of herpes zoster, and one of miliary tuberculosis. The greater the lymphocytopenia, the greater was the risk of complications, such as tuberculosis, viral and fungal infections. Patients with Hodgkin's disease were particularly susceptible to diseases which normally cause a granulomatous reaction. The high coexistence of tubercle bacilli and mycotic infections in Hodgkin's disease has been demonstrated. Such infectious complications led naturally to the suggestion of decreased resistance to these agents, mediated through lymphocyte depletion and an immunologic defect. The influence of treatment, especially with lymphocytolytic agents, on the development of such complications remains uncertain.—K. F.


Hematologic results obtained for 13 AKR mice in the pre-leukemic and leukemic phases were compared with data in the literature to evaluate the behavior of blood cells during development of leukemia. The purpose of the study was to make a survey of the natural history of spontaneous leukemia in AKR mice. Qualitative study of erythrocytes in the pre-leukemic phase showed the constant presence of polychromatophilia and Jolly's corpuscles which increased in the final phase of the disease. The mean survival period was 13.4 days.—M. J.

HEMOSTASIS


The defibrinating fraction of the venom was separated and was called 'Arvin'. Its defibrinating effect and toxicity varied with different species. Toxicity was increased by EACA and was reduced by giving an initial small dose, followed by later doses, or by administering it by slow intravenous infusion. When given this way, it did not significantly alter the E.C.C., systemic pressure or respiration and did not promote spontaneous bleeding or influence blood loss in rats with gastric ulcers. Arvin caused pyrexia in rabbits, but did not influence the course of certain infections in mice.—A. L. B.

ANTICOAGULANT THERAPY WITH A PURIFIED FRACTION OF MALAYAN PIT VIPER VENOM. A. A. Sharp, B. A. Warren, A. M. Paxton and M. J. Allington. From The
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Nineteen patients with thrombosis or a thrombotic tendency were treated with Arvin, a purified coagulant fraction of the Malayan pit viper venom. Complete defibrination, maintained by continuous I.V. infusion, sometimes resulted in bleeding from operation sites, but spontaneous bleeding did not occur. Less complete but adequate defibrination was safer but more difficult to maintain. Anticoagulant activity due to split products developed and plasminogen therapy. Clinical improvement occurred over the lower part of the body. Laboratory studies showed hypofibrinogenemia, thrombocytopenia, fibrinolysis and low levels of Factors V and VIII, suggesting defibrination. In addition, a hemolytic anemia with fragmented red cells was found. Heparin, EACA, blood, plasma, fibrinogen and platelet concentrates had little effect on the fulminating course. Autopsy revealed a small carcinomatous ulcer of the cardia of the stomach with widespread metastases, especially to blood and lymphatic vessels.—

A. L. B.


A child with acute leukemia and leukopenia developed a hemorrhagic diathesis associated with evidence of defibrination. Treatment with heparin, while not leading to any significant laboratory improvement until after a week, was associated with decreased bleeding and more solid clots.—

J. B. S.


A 76 year old woman had episodes of pulmonary infarction and diffuse ecchymoses over the lower part of the body. Laboratory
platelet aggregation, caused precipitation of fibrinogen which was thought to be caused by lowering of pH. Platelet aggregation may be caused by specific absorption of an acidic calcium-adenosine phosphate complex, causing lowered pH near the surface with resultant precipitation of fibrinogen and formation of bridges between platelets. —A. L. B.

MISCELLANEOUS


The authors describe the methodology and the results of standard hematologic and chemical procedures likely to be of value in biomedical research.—C. R. M.


Quantitative determinations of conjugated and unconjugated bilirubin in liver homogenates confirmed the impression, previously gained with histochemical technics, that a large amount of unconjugated bilirubin accumulates in the cholestatic liver. A constant ratio between the amount of conjugated and unconjugated bilirubin, independent of the total bile pigment present, was observed. The presence of bilirubin granules in the cholestatic liver was associated with lysosomal beta-glucuronidase activity in both hepatic and Kupffer cells. In addition, the lysosomes had been displaced from the pericanalicular region to the sinusoidal border of the hepatic cell. In extrahepatic biliary obstruction, some conjugated bilirubin may be regurgitated from bile canalculi through hepatic cells within the lysosomes to the sinusoids. During this transit, partial deconjugation may occur. This process is continued in Kupffer cells and accounts for the presence of unconjugated bilirubin in the liver and plasma of patients with biliary obstruction.—M. J.


No consistent correlation between PSP binding capacity and high serum bilirubin levels or the presence of kernicterus was noted in 93 jaundiced newborn infants.—J. B. S.


In subcellular fractions of normal rat liver, the greatest part of iron (64 per cent) was in the cytoplasmic soluble fraction, about 8 per cent in mitochondria, 8 in the microsomal fraction and about 20 in the nuclear fraction. During acute damage induced by intraperitoneal administration of CCl₄, a significant decrease in the iron content of the cytoplasmic fraction was observed 12–24 hours after injection. After 48 hours, total liver iron returned to the control value. The serum iron increased 12 to 48 hours after injection. These changes depended on the release of iron from liver and mobilization of other iron stores in the body to compensate for iron deficiency in liver.—M. K.
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