ERTHROCYTES


Six children who presented with what appeared to be acquired aplastic anemia demonstrated a very rapid and complete response to corticosteroid therapy. All subsequently developed acute lymphoblastic leukemia, usually within 2–6 mo. From this experience the authors conclude that the prognosis in acquired aplastic anemia is very bad if response to steroids is very good.—J.C.


In a boy moderately affected with a non-spherocytic hemolytic anemia, the content of adenylate kinase (AK) found in the hemolysates was 1–13% of normal while after electrophoresis on starch gel, no AK was found on specific staining. Both parents were AK i−i type and had 45–65% of the normal average of AK. The role of the deficiency of AK in hemolysis is not certain and the genetic mechanism is unknown. —J.C.


In 52 patients followed for 6 mo to 9 yr, there was no correlation between degree of hemolysis, immunochemical class of the autoantibody and the site of red cell se-
questration. On the contrary, there was a good correlation between the splenic site of sequestration of the labeled red cells and the effect of splenectomy. —J.C.


The ALA-synthetase activity of erythroblasts was markedly decreased in five of eight patients with iron deficiency anemia and was at the lower limits of normal in two of them. Erythrocytes of iron deficiency anemia showed only an increase of 50% of normal in porphyrin synthesis when ALA was added in vitro. The ALA-dehydrase (ALA-D) activity of erythrocytes was increased to twice the normal in 14 to 22 cases, whereas the prophobilinogenase (PBCase) activity was markedly decreased in all 14 cases. These disturbances of heme synthesis were improved with iron therapy. In order to clarify the disturbance of heme synthetic enzymes, the effect of protoporphyrin IX, Fe++ and hemin on the ALA-D activity and the PBCase activity of human erythrocytes was studied in vitro. Protoporphyrin IX showed no effect on the PBCase activity in concentrations of from $10^{-6}$ to $10^{-4}$ M, but inhibited ALA-D in concentrations of $5 \times 10^{-4}$ M. Fe++ had no effect on ALA-D in concentrations of $2 \times 10^{-6}$ to $2 \times 10^{-5}$ M and promoted ALA-D activity in concentrations of $2 \times 10^{-4}$ M, but ALA-D activity was markedly inhibited with concentrations of $2 \times 10^{-3}$ M and inhibited completely in concentrations of $2 \times 10^{-2}$ M of Fe++. The activity of PBCase was not changed by Fe++ in concentrations of $10^{-5}$ to $10^{-4}$ M, but was markedly decreased in concentrations of $10^{-3}$ M. Although hemin inhibited ALA-D in concentrations of $10^{-5}$ M and of $10^{-3}$ M, PBCase was slightly activated at the concentration range of $10^{-4}$ to $10^{-3}$ M. —K.F.


The ATP level of the red cell has been known to be increased in uremia. The authors have examined the red cell ATP level in various renal diseases (32 cases) and found a high incidence of increased red cell ATP (53.1%). This level correlated well with the severity of the anemia, then with the BUN level, and the plasma inorganic phosphate. It did not correlate, however, with the reticulocyte count. It is considered that the severity of renal disease might have a profound effect upon the red cell ATP level. Four out of six patients under peritoneal dialysis showed a decrease of the red cell ATP level. Some dialyzable factor might be responsible for the high ATP level of the red cell. —K.F.


In a series of complicated experiments serum and various protein fractions obtained from placental and abortion blood were injected into rats and the hematologic response observed in blood and bone marrow during the following 24 hr. It appears that serum from placenta blood possesses erythropoietic activity equivalent to that of dog serum following a single massive venesection. —J.V.


In 94 patients with hypoplastic or aplastic anemia comprehensive tests for hemolysis, including studies of bilirubin metabolism, red cell morphology and regeneration, os-
motic fragility, acid hemolysis, and sequestration of radiochromium-labeled red cells demonstrated an accelerated red cell destruction in 93.2%, this occurring largely in the spleen. Intravascular hemolysis was also noted in 17.4%, such cases being classified as mixed hemolysis. Splenectomy of 30 patients failed to arrest the hemolytic process.—J.V.

LEUKOCYTES


The electrophoretic mobility of lymphocytes obtained from axillary lymph nodes of young rats was determined and compared with cells obtained following immunization with a variety of antigens. The results indicated a heterogeneous population amongst the normal cells which could be resolved into two independent components with Gaussian distribution profiles. The response of these two types of cells to antigenic stimulation was different; for one type neither the relative concentrations nor the mean electrophoretic mobility varied but in the other group the relative concentration decreased and there was a new cell type detectable with a much lower electrophoretic mobility.—J.M.B.


The intracellular pH of leukocytes separated from normal blood by dextran sedimentation technique was measured under conditions in which the extracellular pH was kept constant, but the extracellular pCO2 and bicarbonate concentration were varied. At pCO2 40 mm Hg the intracellular pH was 7.104 ± 0.115 (mean ± SD), at pCO2 15 mm Hg the pH was 7.567 ± 0.084, and at pCO2 72 mm Hg it was 7.098 ± 0.063.—J.M.B.


Two groups of patients with Burkitt’s lymphoma, comparable as regards staging of the disease, were studied. In one group the patients received oral cyclophosphamide alone and in the other this drug plus oral potassium iodide. Irrespective of the stage of the disease, those patients getting potassium iodide had a longer mean survival and a higher incidence of remission. It would appear that potassium iodide potentiates the effect of oral cyclophosphamide in this condition but the mechanism is not known.—J.M.B.


Leukocytes from five normal patients, eight patients with chronic lymphatic leukemia (CLL) and three with acute leukemia (AL) were incubated with varying amounts of L-glutaminase for 7 days. Cell viability was then assessed by phase microscopy. Cells from normal individuals were resistant to incubation with 1700 mIU/ml of the enzyme whereas, cells from 7/8 patients with CLL and 3/3 with AL were sensitive with concentrations down to 5–0.5 mIU/ml. Addition of NH4Cl or glutamic acid did not kill leukemic cells, suggesting that the lethal effect of L-glutaminase was due to depletion of glutamine in the medium.—A.A.M.
ABSTRACTS

The effect of various proteolytic enzymes on marrow colony-stimulating factor from human urine was investigated. Inactivation was produced by α-chymotrypsin, subtilisin, and ficin but not by a variety of other enzymes. The authors conclude that colony-stimulating factor has a peptide component and suggest that, in view of its relative resistance to most proteolytic enzymes, controlled enzymatic digestion may be of value in further purification of colony-stimulating factor.—A.A.M.


Cytosine arabinoside was evaluated in pilot studies in 44 children with acute leukemia and/or lymphosarcoma. All patients received at least one other antileukemic drug and three regimens of cytosine arabinoside were used—one weekly, twice weekly, and 4-day courses of 8-hourly injections. Best results were obtained with the latter in which seven of nine children with acute lymphoblastic leukemia obtained a complete or partial remission. The drug was given intrathecally as treatment for meningeal leukemia in five patients. Two of the five had myeloid leukemia and two were resistant to intrathecal methotrexate. Good results were obtained.—A.A.M.


By observing the effect upon cultures of leukocytes, a study was made of the toxicity of blood serum and blister fluid taken from burned patients, samples being taken during the first few hours and then at 24, 48, and 72 hr. Blister fluid taken in the early stages showed a marked toxicity for leukocytes, much greater than did serum removed at the same time. The difference became less marked during the first 24 hr and had all but disappeared at the third day. The authors consider that toxin from the blister fluid enters the blood stream and thus recommend early removal of burn blisters and fluid to eliminate one source of intoxication.—J.V.


Two of five siblings, both noted at birth to be small for gestational age, developed lymphosarcoma. The first died at age 3½ yr and had thymic aplasia at autopsy. Her brother had a history of chronic diarrhea during infancy and of repeated respiratory infections. At the age of 12 he developed lymphosarcoma. Lab studies demonstrated depressed levels of IgG, IgA, and IgM, absent skin sensitivity to a variety of antigens, and apparently normal lymphocyte response to PHA. Despite absence of evidence of bone marrow involvement with LSA he had a normocytic anemia and a bone marrow in which there was abnormal erythropoiesis with multinucleated cells, Howell-Jolly bodies, giant reticulocytes, and erythrophagocytosis. Karyotyping revealed bimodal distribution with one in four cells having 47 chromosomes. In these cells a group A chromosome was replaced by two large fragments one of which was “D group-like”. The authors believe these patients represent a new syndrome of short stature, ineffective dyserythropoiesis, cytogenic and immunologic abnormalities, and a predisposition to lymphosarcoma.—J.B.S.


In vitro RNA synthesis of leukemic leukocytes (six cases of acute myelogenous leukemia, each case of lymphocytic and monocytic leukemia, and one case of acute exacerbation of chronic myelogenous leukemia) was apparently inhibited by the
addition of 100 μg per ml of hydrocortisone to the incubation medium. This inhibition of RNA synthesis was demonstrated to be caused by a decrease of chromatin RNA-polymerase activity in the cells preincubated with hydrocortisone. Although the RNA synthesis of normal peripheral granulocytes, lymphocytes, normal bone marrow cells, and chronic myelogenous leukemia cells was also inhibited by the addition of hydrocortisone, the degree of inhibition was far less than that observed in acute leukemia cells. It is suggested that this difference in the sensitivity to hydrocortisone in vitro is caused by a difference in the turnover rate of these cells. A relationship between the in vitro inhibitory effect and the clinical effect of the hydrocortisone treatment is not clear.—K.F.


The aim of this study was to analyze clinical and hematological characteristics of six adult patients with acute leukemia (L.A.) who survived more than 1 yr in order to see whether there was any factor that could explain such long survival. Three of these patients were under 20 yr of age and clinical manifestations in them were not particularly marked. Five patients had acute lymphoblastic leukemia and one had acute myeloblastic leukemia. The initial treatment in all patients consisted of 6-mercaptopurine alone or in combination with prednisone. Two patients were on maintenance therapy throughout the entire course of the disease. Three patients were given intensive therapy consisting of prednisone, 6-mercaptopurine, endoxan, and vincristine. By comparing these patients with others, it was concluded that the longer survival could not be ascribed to any single factor. It is postulated that hitherto unknown characteristics of leukemic cells and immunological defense mechanisms may play a role in determining the survival time in acute leukemia.—Z.R.


Vascular invasion was detected in the pretreatment lymph node biopsy sections in nine (5.9%) of 153 patients with Stage I or II Hodgkin’s disease. This finding was associated with a greater than twofold increase in extension of disease to nonadjacent areas and with a life-table survival
at 18 mo, almost one-half that of cases without evidence of vascular invasion. Of the nine cases of vascular invasion, four occurred in Hodgkin's disease of the nodular sclerosing type and four in Hodgkin's disease with mixed cellularity. The finding of vascular invasion in lymph node biopsy sections from patients with Hodgkin's disease, regardless of histologic type, appears to be a feature indicating an increased risk of the occurrence of nonadjacent or extranodal disease, or both.—J.E.U.


Hodgkin's disease developed in a girl 8 yr, 9 mo of age with the physical and hematologic stigmata of Chediak-Higashi syndrome. The association of malignant lymphoma with Chediak-Higashi syndrome has been reported previously, but to our knowledge, no case of Hodgkin's disease has been described to date.—J.E.U.


The pathologic findings in 117 untreated patients subjected to laparotomy for the staging of Hodgkin's disease, at Stanford University Medical Center, were correlated with the preoperative clinical evaluation. The validity and applicability of the modified classification of Lukes, Butler, and Hicks were confirmed, and the consistency of the histologic pattern in multiple lesions was verified. Nodular sclerosis was the most frequent histologic type encountered and showed a predilection for the mediastinum (81%), with a high incidence of abdominal involvement (39%). The recognition of a cellular phase within the spectrum of nodular sclerosing Hodgkin's disease by virtue of the presence of characteristic "lacunar cell," with minimal or absent sclerosis, appeared to be justified by the observation of typical sclerosis in other lesions from the same patient. Occult abdominal disease was most often located in the spleen and the splenic hilar lymph nodes. Focal and microscopic involvement of abdominal lymph nodes was frequently observed with partial preservation of the nodal architecture. Preoperative evaluation of the spleen was inaccurate in one third of the cases. Liver function tests were unreliable indicators of hepatic disease, whereas interpretation of the lymphangiogram was generally accurate below the level of the second lumbar vertebra. Abdominal involvement was encountered only once in the absence of left cervical lymph node disease. The observation of isolated granulomas in 14% of cases was not considered evidence of Hodgkin's disease or Broeck's sarcoidosis.—J.E.U.


Total nodal irradiation (TNI) of all major lymph node areas was evaluated in 163 consecutive previously untreated patients with Hodgkin's disease and compared to extended-field therapy in Stages I and II. The decreased relapse rate following TNI is reflected in improved survival rates. TNI has also been effective for Stage III-A, less satisfactory for Stage III-B. Extension of disease to extranodal sites has correlated with clinical staging and histopathology, defining certain groups as especially suitable for adjuvant chemotherapy.—J.E.U.


The histologic classification of Hodgkin's disease was applied to lesions in children in the Manchester region of England and to those in East Africa. It showed statistically significant differences in the distribution of types of lesions, with African children having
many more lesions of the lymphocytic depletion type which has a less favorable prognosis. African children also differed significantly in this respect from French and Texan children. The reasons for this finding are obscure but may represent a less favorable reaction to the disease among African children.—J.E.U.


Six cases of Hodgkin’s disease in which lymph node biopsy sections demonstrated only minute foci of Hodgkin’s disease are presented. The lymph node sections showed an essentially preserved nodal architecture and a cellular composition that in most areas was not suggestive of Hodgkin’s disease. It is our intention to emphasize the need for careful examination of lymph node sections in which clues suggesting early involvement of a lymph node by Hodgkin’s disease can be found. This is of great importance in both diagnosis and staging of the disease. The focal obliteration of subcapsular sinuses, the finding of foci of inflammatory cells, the discovery of atypical, malignant-appearing histiocytes, and an increase in the deposition of collagen, occasionally in a band-like fashion, should alert the pathologist to search for conclusive evidence of focal involvement of a lymph node by Hodgkin’s disease.—J.E.U.


Blood vessel invasion in Hodgkin’s disease has rarely been reported in lymph node biopsies. Although this phenomenon may occasionally be noted in hematoxylin and eosin-stained sections, it is more readily demonstrable when elastica stains are employed. In all biopsy sections, the involved vessels were veins. Blood vessel invasion was most frequent in Hodgkin’s disease with lymphocytic depletion, according to the Rye modification of the classification of Lukes and Butler; it occurred in approximately 50% of these cases. This high incidence in the reticular type of Hodgkin’s disease was accordingly associated with the presence of extensive disease (80% of the patients with vascular invasion were stage III or IV) and with a relatively short survival. The phenomenon of blood vessel invasion in Hodgkin’s disease tends to support the concept of Hodgkin’s disease as a malignant neoplasm. It is essential to explain bone marrow and visceral involvements other than those occurring by contiguity.—J.E.U.


The mean nadir white blood cell and platelet counts occurring during radiotherapy were consistently higher in splenectomized (Group A) than in nonsplenectomized (Group B) patients. The Group A patients recovered toward pretreatment levels faster and more completely than the Group B. Treatment was better tolerated, elapsed time was less, and interruptions fewer in Group A, compared to Group B.—J.E.U.


Four patients are described in whom an acute nephrotic syndrome was associated with clinical relapse of Hodgkin’s disease. In three there were multiple episodes of increased proteinuria, hypoalbuminemia, and edema; each of these periods was associated with evidence of recurrent growth of Hodgkin’s tumor. The proteinuria was promptly relieved by effective treatment of the Hodgkin’s disease with either chemotherapy or local radiation therapy delivered.
to areas distant from the renal bed. The data in ten similar cases of Hodgkin's disease associated with single episodes of an idiopathic nephrotic syndrome, previously reported, are summarized. In these unusual patients, the nephrotic syndrome appears to be etiologically related to the presence of the Hodgkin's tumor; removal or destruction of the tumor relieves the proteinuria. It is suggested that a substance originating in tumor damages the renal glomerular basement membrane, perhaps after combining in an antigen-antibody complex.—T.E.U.


We have selected patients under the age of 52 who received chemotherapy for Hodgkin's disease and died at this hospital during the periods from 1950 to 1961 (Group 1) and 1964 to 1970 (Group 2). A comparison of the ages, sexes, histologic variants, and stages of the patients in the two groups suggests that the two populations are similar. We have observed that the median duration of survival from diagnosis increased considerably from 34 mo. (Group 1) to 56 mo (Group 2); likewise, the median duration of survival after initiation of chemotherapy lengthened from 18 mo in the earlier group to 42 mo in the later group. Both groups of patients received alkylating agents and radiation therapy but only the later group received the benefit of vinblastine and, in most cases, procarbazine. We believe our observations reflect a true prolongation of survival in the more recent group of patients and we attribute this principally to more vigorous therapy, particularly the introduction of these two effective new chemotherapeutic agents. Although this is a retrospective study, the data indicating prolongation of survival by vinblastine and procarbazine appear convincing.—T.E.U.

HEMOSTASIS


The authors examined the sera of 46 patients with persistent glomerulonephritis for the presence of immunologically detectable degradation products of fibrinogen and fibrin, using the tanned red cell hemagglutination inhibition assay. As a group, these products were present in significantly higher concentrations in the patients than in normal subjects. There was a high degree of correlation between increased amounts of these products and the extent of the glomerular lesion. Demonstration of fibrin by immunofluorescent methods and electron microscopy appeared to correlate with the increased amounts of degradation products found in the serum. These findings suggest that coagulation may play a role in the pathogenesis of persistent glomerulonephritis.—H.J.W.


The authors used a hemagglutination-inhibition test to detect factor VIII immunologically. Immunologic activity was detected in 14 normal subjects and 14 patients with hemophilia. No factor VIII activity was detected in eight patients with von Willebrand's disease.—H.J.W.


During storage of platelets at 22°C, glycogen and ADP-induced aggregation decreased, but there were no changes in platelet ATP, ADP, or potassium. After storage, the platelet's capacity for glucose utilization through glycolysis, the hexose monophosphate shunt, and the tricarboxylic
IMMUNOHEMATOLOGY


Adult rabbits are known to have I antigen on their red cells; the intravenous injection of anti-I cold agglutinins obtained from the serum of patients with chronic cold hemagglutinin disease caused acute intravascular hemolysis and usually transient thrombocytopenia and neutropenia. These reactions could be prevented by injection of massive doses of heparin, possibly by interference with complement binding by the cold agglutinin. It is suggested that this rabbit model could be of value for in vivo studies of complement binding and removal of complement-coated cells.—J.M.B.


The application of immunofluorescence techniques to the buffy coats of 15 normal subjects and 43 with eosinophilia revealed intracellular immunoglobulin in five patients with eosinophilia; intraleukocytic immunofluorescence was blocked by specific unconjugated antisera. It is suggested that phagocytosis of antigen-antibody complexes is the most likely explanation of this phenomenon.—J.M.B.


The antimitotic effect in vitro of thioguanine on the division of PHA-stimulated human lymphocytes can be abolished by the addition of adenine but not guanine or hypoxanthine; it is suggested that in this test system the main inhibitory action of 6-thioguanine is on phosphoribosylpyrophosphate amidotransferase.—J.M.B.


The administration of L-asparaginase to mice produced immunological deficit as measured by a variety of techniques. The animals developed lymphocytopenia with atrophy of thymus, spleen, and lymph nodes and the capacity to reject skin grafts and to form antibodies against sheep red cells was impaired. The migration to lymphoid organs of lymph node lymphocytes from enzyme-treated mice was abnormal and splenic lymphocytes from these animals caused less graft-vs.-host reaction on injection into F, hybrids. Adrenalectomized mice manifest the immunosuppressive effects of asparaginase therapy. It is suggested that asparagine depletion underlines the effect of the enzyme on lymphocytes.—J.M.B.

Similarly to what was previously found in sera from human adults and newborns, an inhibitor of anti-i antibody was found in the serum of almost all monkeys. The relationship of this substance with the genetic model of the I/i blood system is still not clear.—J.C.


It has recently been shown that it is possible to anesthetize porpoises for major surgery. During studies in the training of porpoises, it was deemed necessary to do ear surgery and, in one case, a hysterectomy, on some of the animals. Considerable blood loss was associated with these operations. The problem of blood transfusion was therefore faced. It was apparent that it would be best if compatible blood were available for transfusion. Initial studies showed that when the animals' sera were mixed with their own red cells and then cooled to 4°C, autoagglutination occurred in about 75% of the tests. Autoagglutination was usually not present if the reaction was carried out at 12°C. To remove the autoagglutinin, the sera were repeatedly absorbed overnight at 4°C with their own packed, saline-washed red cells, until no subsequent autoagglutination occurred. The remainder of the studies were carried out using porpoise cells and autoabsorbed porpoise sera. The results showed the presence of "naturally-occurring" agglutinins in the serum which demonstrate three blood groups. These blood groups influence the survival of transfused cells and thus have clinical significance. To date, 39 animals have been studied and four have been found that fit the category of Type O. The other two types are Type 1 and Type 2. Type O red cells did not react with any of the sera studied. To determine if in vitro incompatible cells would survive, autologous blood group-compatible and blood group-incompatible red cells were labeled with 51Cr and infused into recipients. The survival half life of the autologous cells was 16.5 days and of the compatible cells was 13.5 days, while the half-life of the incompatible cells was 7.4 days. It therefore appears that interspecies in vitro incompatibility signifies a short in vivo half-life. During the course of the work, it became necessary to transfuse four different animals due to blood loss during surgery. Compatibility was determined by cross-matching using the red cells in saline suspension as previously experimented in vitro. In each case, 500 ml of blood was drawn from a Type O donor into a sterile bottle containing ACD solution and the transfusion was then performed with no apparent change in the animals' vital signs. No hematuria was observed nor was there any evidence of hemoglobinemia. It is clear therefore that these blood groups influence the survival of transfused cells and thus have clinical significance in surgery of the porpoise.—M.G.B.


Folate deficiency has been implicated as an etiological factor in a number of complications of pregnancy other than anemia. A double-blind trial involving 692 patients was carried out comparing 5 mg of folic acid to a placebo. There was no significant difference between the folic acid group and the placebo group with respect to birth weight, duration of pregnancy, or in the frequency of obstetrical complications. If anything, results with the placebo were slightly better.—A.A.M.

A variety of tests of pulmonary function were performed in 23 young patients with chronic severe anemia and repeated after correction of the anemia. There was a mild respiratory alkalosis in anemic subjects with lowering of the arterial oxygen saturation because of marked widening of the alveolar — arterial oxygen tension gradient. The transfer factor (pulmonary diffusing capacity) was very much reduced but oxygen consumption and carbon dioxide production were normal in the anemic subjects.—J.M.B.

To the Editor,

Last year on April 1st, the FDA published in the Federal Register a proposal to require the fortification of flour and bread with iron. The intent is to correct and prevent mild iron deficiency anemia that can be found in some menstruating women. At that time, proponents of the program had given little or no consideration to the probability that increasing the dose of iron in the American diet would also accelerate the accumulation of iron by men with clinical and preclinical hemochromatosis and by patients with other sorts of iron storage disease such as thalassemia and some forms of hemolytic anemia. There is also a possibility that increasing the dose of iron would serve to mask chronic low grade blood loss and this would sometimes delay the diagnosis of otherwise silent malignancies.

You and I wrote letters to the FDA, pointing out the dangers implicit in such an uncontrolled experiment involving the entire American population. Proponents of the program have taken comfort that these two letters together with one from Dr. Margaret Krikker of Albany comprised the total opposition to the program, but few physicians read the Federal Register.

Nevertheless, the FDA has taken some cognizance of the possibility of adverse effects of iron fortification. They have contracted with the Federation of American Societies for Experimental Biology (FASEB) to prepare experimental protocols to determine the efficacy as well as the toxicity of the proposed enrichment. The problem of efficacy is important because no one has yet demonstrated that the fortification of bread with iron will actually change the incidence or intensity of anemia in young women. Women do not eat much bread and do not absorb much iron from the bread they do eat. On the other hand, patients with hemochromatosis absorb 80% of the ferrous sulfate added to bread in the dose required by the FDA.

The FDA has not waited for the results of the investigations they intend to sponsor. Even while the protocols are being drafted by an expert panel assembled by FASEB, the FDA has published a second proposal to fortify bread and flour in the United States (Federal Register, Dec. 3, 1971.) The FDA requests that any comments on this proposal be sent before February 1 to The Hearing Clerk, Department of Health, Education and Welfare, Room 6-88, 5600 Fishers Lane, Rockville, Md. 20852. Because the FDA is sensitive to numbers of responses to their proposals, it is hoped that the hematologists of America will respond to the request for opinions.

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Editor’s Note: A formal request has been made to the FDA to delay the hearing until April in order to permit interested persons an opportunity to respond.