TREATMENT OF CHILDREN WITH ACUTE LEUKEMIA BY PASSIVE CYCLIC IMMUNIZATION WITH AUTOPLASMA AND AUTOLEUKOCYTES OPERATED DURING THE REMISSION PERIOD

By S. V. SKURKOVICH, L. A. MAKHONOVA, F. M. REZNICHENKO, G. I. CHERVONSKIY

PRESENT THERAPEUTIC METHODS in acute leukemia (antimetabolites, hormones, others) can induce complete clinical and hematologic remissions. The mechanism of the onset of these remissions still remains obscure. The possibility is not excluded that the onset of remission occurs with participation of humoral and cellular immunologic mechanisms. However, without the application of therapeutic agents, such a reformation probably takes place rarely.

It can be assumed that the leukemic patient is immunologically tolerant to leukemogenic agents of his own tissue. This may be associated with the vertical transmission during fetal life of leukemogenic profactor (provirus) with its subsequent transformation into active leukemogenic agent. It is also possible that there occurs a specific inhibition of certain mature clones of lymphocytes which under usual conditions are capable of being stimulated to antileukemic production. The immunologic system of the patient “considers” this factor to be “its own” and is thus not capable of immunologic reformation just as in the case of its own antigens. In such a situation, immunologic reformation to the leukemogenic agent could probably be brought about by at least 5 methods:

1. Administration of immunocompetent tissue “unfamiliar” with the leukemogenic agent to the leukemic patient against background leading to a temporary inhibition of his own immunologic system and active antigenic stimulation with his “own” previously prepared leukemogenic factor (leukemic cells).

2. Administration (immunization) of a leukemogenic agent (leukemic cells, untracentrifugalized deposit of plasma) to another individual (under conditions of homosystem) with subsequent passive immunization of the patient. This is preferably done during remission using plasma adsorbed by normal tissue and leukocytes (lymphocytes) obtained from an immunized person by systematic plasmaleukopheresis. Also perhaps desirable would be exchange immunization of two leukemic patients in the acute phase with leukemogenic...
agents followed by exchange of passive immunization plasma and leukocytes (lymphocytes) of both. The active immunization with living leukemic cells during the remission period is justified as well.\textsuperscript{1,3,5}

3. Extraction of the leukemic cells from the patient, change of his antigenic specificity by creating new antigenic determinants and subsequent active immunization of the patient with his own leukemogenic factors that have been altered in the antigenic sense.

4. The infusion in the patient of mixed hemacytoplastic vaccine (from whole leukemic cells and their filtrates) in the period of remission.

5. Change of antigenic specificity of the leukemic cells in the patient by therapy.

The present study is based on the assumption that in acute leukemia the antigenic specificity of leukemic cell becomes modified under the influence of therapy, (i.e., 6-mercaptopurine) and is followed by immunologic reformation and formation of protective antibodies.

In special experiments we showed that by combining 6-mercaptopurine with albumin (through the amino acid valine) a complex antigen is formed, which stimulates the formation of antibodies to the determinant group (6-mercaptopurine) as well as to the albumin carrier.\textsuperscript{*} Fatal anaphylactoid shock occurred with guinea pigs after sensitization and administration of their own serum albumin with 6-mercaptopurine.

The results of skin tests made during remission after the administration of the leukemic cell extracts indicate the possibility of the development of immunologic reformation to antigens contained in the leukemic cells.\textsuperscript{6,7} Data from the literature data are available indicating the possibility of changes in the antigenic specificity of leukocytes (chronic myelogenous leukemia) under the influence of alkylating agents.\textsuperscript{9}

If immunologic mechanisms participate in the onset of remission in acute leukemia, it cannot be excluded that plasma and lymphocytes extracted during this period will possess preventive, and under certain conditions, possibly remedial properties, particularly in an auto-system. By analogy with experimental leukemia\textsuperscript{10,11} it can be assumed that humoral and cellular mechanisms also participate in the development of immunologic reformation in human leukemia. Proceeding from these premises, studies of the influence of plasma and leukocytes (lymphocytes) obtained from children in remission on the course of the leukemic process have been made.

We had assumed that in the remission of acute leukemia, the intensity of antileukemic immunity is unstable and gradually decreases until its complete disappearance, indicating the onset of repeated intensification of the disease. Our task has been to keep leukemic patients in a hypothetical condition of immunologic reactivity at its original level during remission, or, in other words, to maintain permanent immunologic homeostasis and in this way to prolong remission.

For this purpose it seemed expedient in the remission period to administer periodically "remission" plasma and leukocytes taken at earlier stages of re-

\*Performed by Prof. E. D. Kaverzneva at our request.
mission. In several cases we also decided to study the effect of plasma and leukocytes obtained during remission on the relapse of the disease. Thus, the investigation was based on the immunologic concept described above, and our measures have been confined to the scheme of the immunologic effect. In this connection, periodic administration of plasma and leukocytes obtained during remission was conditionally estimated as passive cyclic autoimmunization. This term will be used further in this paper.

In addition to the studies of the above mentioned influences on the leukemic process, studies of immunologic reactivity of children with acute leukemia (in its various stages) have also been carried out in respect to antigens contained in the leukemic cell.

**Materials and Methods**

For investigations concerning the influence of "remission" plasma and leukocytes on the leukemic process, it became necessary to prepare considerable amounts of the above mentioned ingredients from children with acute leukemia during remission without danger of inducing anemia.

Plasmaleukophoresis with return of erythrocytes to the patient was used. 10 per cent gelatine suitable for intravenous injection and centrifugation were used to separate the erythrocytes from the blood. It should be pointed out that the use of gelatine is preferable to centrifugation alone since with this method up to 80 per cent of leukocytes can be extracted from plasma, and in addition, small numbers of platelets can be extracted as well.

The apparatus used was described in the previous paper with the difference that a triangular plastic bag (suggested by R. A. Rutberg) was used instead of the glass reservoir. In addition, the gelatine was sterilized together with the preservative solution contained in the plastic bag connected to the veni puncture system. (R. A. Rutberg) The apparatus described is given in Figure 1.
PASSIVE CYCLIC IMMUNIZATION

The principal scheme of cyclic passive immunization with autoplasma and autoleukocytes obtained during remission consisted of the following:

With the onset of remission (not earlier than 1–1.5 months after the onset) the child was subjected to plasmaleukophoresis 4–5 times at intervals of 10–14 days and sometimes as little as 7 days for accumulation of plasma and leukocytes.

As pointed out above, on each occasion the erythrocytes were returned to the bloodstream. The amount of blood taken varied from 60 to 200 ml. depending on the child’s age. Plasma and leukocytes (together with thrombocytes) were kept separately at −30°C. Then, passive cyclic immunization combined with plasmaleukophoresis was begun at the same time intervals, that is, plasma and leukocytes obtained during regular plasmaleukophoresis was stored, and the patient was given plasma (intravenously) and leukocytes (intramuscularly) obtained at the first plasmaleukophoresis. During the next plasmaleukophoresis the patient received plasma and leukocytes from the second plasmaleukophoresis, and the extracted ingredients (plasma and leukocytes) were consigned to storage and so on. Thus, during every subsequent plasmaleukophoresis, the patient was given plasma and leukocytes of the earliest separation on hand.

In periodic plasmaleukophoresis combined with passive immunization with remission plasma and leukocytes, 4–5 units of plasma and leukocytes were always on hand in case of a relapse. Sometimes plasma and leukocytes were accumulated by plasmaleukophoresis without their subsequent periodic administration. The accumulated plasma was used during the onset of a relapse.

RESULTS

Twenty children with acute leukemia ranging from 3 to 12 years of age were observed. Two children were excluded from the observation because of their removal to another city.

Ten children were in their first complete remission, 5 in their first partial remission, and 3 children were in one of 2 or more remissions. Out of the 10 children in their first complete remission, 9 were subjected to plasmaleukophoresis and cyclic autoimmunization with plasma and leukocytes. One patient of this group was subjected to plasmaleukophoresis without cyclic injections of autoplasma and autoleukocytes. Of 5 children with partial remission, one child was subjected to plasmaleukophoresis and cyclic autoimmunization with plasma and leukocytes. Four patients from this group and the three patients in repeated remission were subjected to plasmaleukophoresis only.

All the children were given 2–3 mg. of 6-mercaptopurine per Kg. of body weight, and 1–2 mg. of Prednisone per Kg. in the acute period. During remission, the patients were given 6-mercaptopurine in doses of 2–3 mg. per Kg. body weight with plasmaleukophoresis. Prednisone was given occasionally for short periods of time (2–4 weeks) in small doses (5–20 mg.)

Complete remission was understood as normalization of the clinical situation, and of peripheral blood, and the development of marrow puncture specimens with normal content and cytology of cells; the content of blast cells in the puncture specimens not exceeding 5 per cent.

All the children were observed regularly. Clinical examinations and peripheral blood analysis were performed at least once every 2 weeks; sternal punctures were made every 3–4 months. Protein and blood serum aluminum fractions were studied regularly.

According to our data, systematic plasma leukophoresis did not change the patients’ status for the worse, the content of protein and protein fractions
in blood sera did not change, and no detectable reduction of thrombocytes, leukocytes and erythrocytes was observed.

The best results were obtained with plasmaleukophoresis and passive cyclic immunization in a group of patients during the first complete remission (9 children).

By July 1966 the onset of relapse was noted in 3 of 9 patients; the duration of remission in these patients ranged from 8.5 to 10.5 months which was minimal for this group. It is interesting to note that decompensation of the leukemic process in these 3 patients was manifested usually, being of extramedullary nature with normal indices of blood and marrow punctate: one patient showed a leukemic lesion of the meninges, the other the appearance of tumor-like growths on the cranium, the third, an enlargement of the testicles.

The other 6 patients continue in a state of complete hematologic remission, its duration varying from 11 months to nearly 4 years by the 1st of July of 1966.

At the same time, a group of 9 children with acute leukemia in their first complete remission, served as control. These children were not subjected to cyclic passive immunization with autoplasm and autoleukocytes during remission. In terms of their clinical and morphologic nature and drug treatment in the acute and remission periods, the patients of this group corresponded to the group of patients receiving cyclic passive autoimmunization. It should be emphasized that no children with so-called tumorous form of acute leukemia were in either the first or the second group.

Despite the fact that there is sufficient information on the average duration of remission in children treated with 6-mercaptopurine and steroid hormones (5.5 months), we still attached great importance to the control group which was observed under conditions similar to those in which the children subjected to cyclic passive autoimmunization were observed.

By July 1, 1966 the onset of relapse was observed in 8 of our 9 children in the control group and the duration of remission ranged from 2.5 to 8.5 months. One girl in this group continues to remain in remission which has lasted more than 10 months.

In order to establish the degree of difference in the duration of remission between the group of patients receiving cyclic passive autoimmunization, and the control group not receiving cyclic passive autoimmunization, it was conditionally assumed that in patients who were still in remission, a relapse had taken place by the time of writing of this material, and from this, the average duration of remission was estimated for each group. (Table 1, Fig. 2).

Comparison of the conditional indices of the duration of remission in both groups by Wilcoxon's criteria showed that the difference between them was statistically significant (p < 0.01).

Thus, in children treated with the usual antileukemic drugs, the average duration of remission was 173 days, whereas in children receiving cyclic passive immunization, the average duration of remission was 491 days, that is 2.5 times greater. However, it is suggested that a true indication of the average duration of remission in children will probably differ to a still greater
Table 1.—Average Duration of Remission in Children with Acute Leukemia Under the Influence of Different Treatments

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Average duration of remission (in days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclic passive immunization with autoplasma</td>
<td>491</td>
</tr>
<tr>
<td>and autoleukocytes</td>
<td></td>
</tr>
<tr>
<td>Drug treatment only</td>
<td>173</td>
</tr>
</tbody>
</table>

AVERAGE DURATION OF REMISSION INDUCED BY DIFFERENT TREATMENTS IN CHILDREN WITH ACUTE LEUKAEMIA

Fig. 2.—Average duration of remission induced by different treatments in children with acute leukemia.

extent if it is taken into consideration that the majority of patients receiving cyclic passive autoimmunization were still in remission at the time of writing this report. Apparently, cyclic passive autoimmunization with plasma and leukocytes obtained from patients with acute leukemia during remission, combined with medicinal antileukemic therapy, resulted in a well-defined prolongation of the duration of remission.

According to our observations cyclic passive immunization with autoplasma and autoleukocytes in the patients with partial remission and also plasma-leukopheresis (for accumulation of plasma and leukocytes) in patients with acute leukemia in the period of complete, partial and repeated remissions without passive cyclic autoimmunization with plasma and leukocytes, do not significantly affect the duration of remission.

Attention was paid to the study of the medicinal action of plasma and leukocytes obtained in the period of remission on the course of relapse. Twelve patients were studied. The stored remission plasma and leukocytes were injected for the duration of 1–2 days. Upon the onset of relapse in 5 patients, administration of plasma and leukocytes obtained in the period of complete or partial remission has produced some positive effect.

Transfusion of plasma and leukocytes upon the onset of relapse carried out with the treatment applied during remission produced an improvement of well-being in 2 children, decreased pain in joints and bones and reduced
the sizes of lymph nodes, liver and spleen. In the case of 2 patients in relapse, administration of plasma and leukocytes obtained during remission produced a definite effect 3-7 days later, characterized by a marked reduction of blast cell content in the marrow punctate as compared to that seen in the previous myelograph obtained the day before the administration of plasma and leukocytes and indicating a relapse of the leukemic process.

One patient with beginning decompensation of the leukemic process responded by normalization of cell content of the bone marrow after administration of "remission" autoplasma and autoleukocytes.

2.* As has already been pointed out, we also studied immunologic reactivity of children with acute leukemia (at different stages of the disease) in respect to antigens contained in leukemic cells. The phenomenon of delayed hypersensitivity was used. The results of these investigations should have shed some light on the development of immunologic reformation according to cell type in children with acute leukemia, mainly during remission. Studies were carried out with children both in the acute stage and during remission.

Aqueous-saline extracts (1:5, 1:10) of the bone marrow and peripheral

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*This part of the report was delivered at our request by our recently deceased friend, Prof. L. A. Zilber at the International symposium on Specific Antigens in Sukhumi in 1965.
blood leukocytes obtained at the height of the disease and destroyed by repeated freezing and thawing were used as antigens after being passed through a Seitz filter. In most cases, the children were given an antigen prepared from autologous leukemic material. In some cases the material used was obtained from other patients with acute leukemia. A corresponding extract of marrow and leukocytes obtained from healthy donors served as control. Group compatibility was taken into account in this reaction.

Protein content (according to Lowry) in the extract varied from 0.2 to 3.2 mg. (ml.) Protein concentration was not found to affect the intensity of the reaction. Tests were made in the forearm by means of intracutaneous injection of 0.1 ml. of the extract. Skin reaction was noted directly after the antigen administration (during 30 minutes) and 24, 48 and 72 hours later. The extent of skin lesions, their nature and time of disappearance were noted. The test was considered positive if the degree of reaction induced by the leukemic material exceeded the reaction induced by the injection of control material by at least a factor of 2. The minimal value of skin reaction when the sample is considered positive was taken as 5 mm.

The reaction usually reached its maximum intensity after 24 hours, and decreased on following days. Immediate reaction was observed in only one patient.

Thirteen children were studied. In the acute stage, skin tests were made in 11 children. All the tests with either autologous antigens or with antigens obtained from other patients with acute leukemia were considered negative.

In remission, the skin tests were made on 10 children. The tests were considered positive in 8 children. In most cases, positive skin reaction had the character of hyperemia; in some cases the formation of papules was observed at the site of antigen injection. It should be stressed that the reaction to “foreign leukemic antigen” introduction is less marked as compared to that induced by autologous antigen.

Sequential Studies

Dynamic tests were made in 8 children—both in the acute stage and during remission. In 6 of them, a transition of negative reaction in the acute stage to a positive one was noted upon the onset of remission. Of great interest, was the following: Children who responded positively during remission, failed to respond to antigen introduction in the period of relapse. In one child, the skin reaction had already subsided in the remission period. The fact should be noted that in two children in remission, no skin reaction was seen following the introduction of the material obtained from the same children in remission (Table 2).

Discussion

The investigations that were carried out suggest that during remission cyclic introduction of plasma and leukocytes obtained during remission prolonged the duration of remission. The introduction of these ingredients at the beginning of acute phase produced a temporary antileukemic effect in a number of cases.
Table 2.—Delayed Hypersensitivity in Children During Different Periods of Acute Leukemia

<table>
<thead>
<tr>
<th>Antigens</th>
<th>Acute period</th>
<th>Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of</td>
<td>Reaction</td>
</tr>
<tr>
<td></td>
<td>Children</td>
<td>positive</td>
</tr>
<tr>
<td></td>
<td>negative</td>
<td></td>
</tr>
<tr>
<td>Extract of marrow and leukocytes obtained in</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>the period of relapse</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Extract of marrow and leukocytes obtained</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>during remission</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Despite the fact that the obtained clinical results were quite encouraging, at present we cannot definitely speak about the mechanism of positive action of "remission" plasma and leukocytes on the leukemic process.

As pointed out, our investigations were based on the immunologic concept. Undoubtedly, objective serologic and immunologic criteria are necessary to support this conception. At present, a search for humoral and cellular antibodies in patients with acute leukemia during remission is in progress using serologic and biologic methods for this purpose. In addition to native leukemic cells and ultracentrifuged plasma obtained at the height of the disease, similar materials obtained at earlier stages of treatment with antimetabolites are also used as antigens, particularly in search of humoral antibodies. Investigations were carried out mainly in an autologous system.

Data were obtained showing that in the period of remission, an immunologic reformation occurred; this was of the cellular variety, corresponding with the antigenic factors contained in the leukemic cells of the bone marrow and peripheral blood. The onset of remission led to the disappearance of this antigenic factor. The absence of reaction of delayed hypersensitivity in response to the material injected during remission and obtained at the same period attests to this.

At the present we are carefully evaluating the reaction of delayed hypersensitivity as a manifestation of specific antileukemic immunologic defense. However, together with positive data found in the study of humoral antibody and results of clinical examinations, skin tests may serve as definite additional criteria characterizing antileukemic immunologic defense in patients with acute leukemia in remission.

However, it may be suggested with a certain degree of confidence that the state of remission in acute leukemia is not a passive process caused only by deletion of the etiologic factor (leukemic cell, virus) as some investigators suppose, or by disturbance of leukemic cell metabolism. There is no doubt
that remission in acute leukemia is an active condition associated with the appearance of some defense elements in the organism of the leukemic patient. These protective elements can apparently be transmitted passively and produce some preventive effect.

It should be also taken into consideration that systemic plasmaleukophoresis in itself can be an additional positive factor for extended stabilization of immunologic (antileukemic) reactivity at a high level. However, some other biologic mechanisms which may play an additional role in the positive action of plasmaleukophoresis and cyclic autoimmunization of the leukemic process should not be ignored. As is known, systemic leuko—and thrombophoresis are factors contributing to stimulation of normal leuko—thrombocytopoiesis.

It is necessary to carry out comprehensive investigations aimed at discovering the active principles of “remission” plasma and leukocytes. In other words plasma and leukocytes obtained in the remission period of acute leukemia must be studied in detail, especially immunologically. The immunologic concept, which was assumed as the basis of the present study, has stimulated us in the search for immunologic mechanisms of antileukemic activity of “remission” plasma and leukocytes. At the same time, these investigations present us with the task of further perfecting the procedure of passive cyclic immunization with autoplasma and autoleukocytes obtained in the remission period.

At present, our efforts are directed toward elaborating the most effective methods of preparation of plasma and leukocytes in the remission period in large amounts, and at working out effective means of cyclic autoimmunization. It seems to us that solution of this problem will make it possible to stabilize leukemic remission. For passive immunization in the future, it is planned to use the “remission” leukocytes (lymphocytes) which retain their viability for a long time. Although, according to available data, frozen and thawed leukocytes retain their immunologic ability, it seems to us that during every passive immunization the administration of suspensions of living “remission” autoleukocytes (lymphocytes) simultaneously with “remission” plasma in the blood stream will make autoleukemic treatment more effective. It is also probably expedient to carry out cyclic administrations of previously prepared viable “remission” autologous bone marrow cells simultaneously with the administration of “remission” plasma and leukocytes during remission. In the near future we intend to conduct cyclic injections of “remission” plasma and autoleukocytes (lymphocytes) in the period of remission not only in blood but in spinal fluid as well at monthly intervals.

It has already been stated above that in children subjected to cyclic autoimmunization, the relapse proceeds extramedullarly. As is known, antibodies do not penetrate the blood-brain barrier and therefore, injection of “remission” autoplasma (serum) and living autoleukocytes (lymphocytes) directly into the cerebrospinal fluid can create the possibility of preventing leukemic infiltrates of meninges.

As far as the use of “remission” plasma and leukocytes in the period of acute leukemia is concerned, this problem need special study. Probably, the administration of “remission” plasma and leukocytes can be effective at the very start of the relapse which cannot always be detected. What is more, a
great quantity of the above-mentioned ingredients is needed to achieve a satisfactory effect.

In conclusion it should be pointed out that studies directed at increasing medicinal (immunologic) activity of “remission” plasma and leukocytes are required. In this respect, simultaneously with passive immunization with “remission” plasma and leukocytes during remission, it appears expedient to carry out active immunization of patients with leukemic cells and plasma ultracentrifugate obtained at the height of the disease and at earlier stages after application of therapy.

It should be emphasized too, that our positive results were obtained with 6-mercaptopurine at the height of the disease. It is necessary to verify the preventive capability of “remission” plasma and leukocytes after treatment with other medicinal antileukemic medications administered at the height of the disease.

It also seems to us that the preservation of permanent immunologic homeostasis by cyclic passive immunization with “remission” autoplasma and autoleukocytes may be utilized in other states, where the remission is episodic during the illness, and perhaps conditioned by immunologic mechanisms.

**Summary**

The original premise of the recent study is the assumption that under usual conditions, the patient with acute leukemia is immunologically tolerant to his own leukemogenic agent. The antigenic specificity of the leukemogenic factor may change under the influence of drugs (6-mercaptopurine), thus bringing about the possibility of antigenic stimulation. In connection with this it is suggested that the onset of remission in acute leukemia occurs with the participation of humoral and cellular immunologic mechanisms.

We have demonstrated that during remission of acute leukemia, the use of cyclic passive immunization with autoplasma and autoleukocytes obtained at earlier stages of the first complete remission leads to a considerable prolongation of the remission periods.

Administration of plasma and leukocytes (obtained in the remission period) upon the onset of the acute phase is accompanied in some cases by a short-term effect which manifests itself in the improvement of subjective well-being, decreased pain, reduced size of lymph nodes, liver and spleen, and in reduction of the “blast” content of the bone marrow. Intracutaneous injection in the remission period of the extract from bone marrow and leukocytes obtained from patients in the acute phase of leukemia produces a positive skin reaction.

**SUMMARIO IN INTERLINGUA**

Esseva assumite como premissa del presente studio que sub conditiones usual le patiente con leucemia acute es immunologicamente tolerante pro su propre agente leucemiogenic. Le specificitate antigenic del factor leucemiogenic pote cambiar sub le influentia de pharmacos (6-mercaptopurina), con le resultato del possibilitate de stimulation antigenic. In connection con isto iles suggestionate que le declaration del remission in leucemia acute occurre con le participation de humoral e cellular mechanismos immunologic.

Nos ha demonstrate que durante le remission de leucemia acute le uso de immunisation
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passive cyclic con autoplasm e autoleucocytes obtenite a previe stadios del prime complete remission resulta in un prolongation considérable del periodos de remission.

Le administration de plasma e leucocytes (obtenite in le periodo de remission) post le declaration del phase acute es accompagne in certe casos per un effecto de breve duration le qual se manifesta in le melioration del subjective sensation de ben-esser, reducite dolores, reducite dimensiones del nodos lymphatic, del hepate, e del splen, e reduction del contenu "blastic" del medulla ossee. Durante le remission le injection intracutanee de extracto ab medulla ossee e ab leucocytes obtenite ab patientes in le phase acute de leucemia produce un positive reaction cutanee.

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