Studies on Analogues of L-Cysteine and L-Cystine

III. The Effect of Selenium Cystine on Leukemia

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L-CYSTEINE and related compounds appear to have an important role in the metabolism of leukocytes.1-6 A decrease in the availability of L-cysteine or L-cystine* may therefore have important effects on leukocytes. The leukocytes of acute leukemia and chronic myeloid leukemia exhibit a more rapid turnover of radioactive L-cystine than do normal leukocytes.7,8 Leukemic leukocytes may therefore be more susceptible to depletion of this amino acid than normal leukocytes.

It is possible to decrease the influx of radioactive L-cystine into leukemic leukocytes in vitro by exposing these leukocytes to certain analogues of cysteine or cystine.9 A high degree of molecular specificity is required for this inhibitory effect. It is not known whether these analogues of cystine have any effects on leukemic leukocytes in vivo. However, experiments with Murphy lymphosarcoma tumors of rats indicate that compounds which decrease the influx of radioactive L-cystine into lymphosarcoma cells in vitro also decrease the growth of the tumor in the intact animal.10 Compounds decreasing the incorporation of radioactive L-cystine into leukemic leukocytes in vitro may therefore modify the leukemic process in vivo.

Selenium cystine (diseleno-dialanine) is structurally closely related to cystine and differs only in that selenium replaces sulfur in the molecule.9 This compound is effective in low concentrations in decreasing the incorporation of radioactive L-cystine into leukemic leukocytes in vitro and thus may be an effective blocking analogue in vivo. The effect of selenium cystine on patients with acute and chronic leukemia was therefore studied.

Material and Methods

Selenium cystine was administered orally to 4 patients. Two of the patients had acute leukemia and 2 of the patients had chronic myeloid leukemia. One of the patients with acute leukemia was a 39 year old female who had received no previous therapy. The other patient with acute leukemia was a 13 year old boy who had been maintained for 12 months on cortisone and with successive courses of Aminopterin and 6-mercaptopurine. He was given selenium cystine when he no longer responded to these chemotherapeutic agents. The leukocytes in both these patients were non-granulocytic and peroxidase negative.
One of the patients with chronic myeloid leukemia was a 48 year old male in an advanced stage of the disease. This patient responded poorly to x-ray therapy and was completely refractory to Fowler's solution, urethane or myleran.* The other patient with chronic myeloid leukemia was a 70 year old male who had received no therapy.

The selenium cystine was placed in capsules and was administered in a single dose in amounts varying from 50 to 200 mg. The usual amount administered was 100 mg daily and the duration of therapy varied from 10 days to 57 days. In one patient the effect of selenium cystine was compared with that of diphenyl diselenide. The latter is an organic selenium compound structurally unrelated to cystine.

The patients were carefully observed for possible toxic manifestations. Fluid intake and urinary output were recorded and the patients were weighed daily. Complete blood counts were obtained daily and the hematocrit and platelet counts were determined at weekly intervals. The prothrombin level, bromsulfalein excretion, quantitative bilirubin, alkaline phosphatase, cephalin flocculation, thymol turbidity, plasma cholesterol and proteins were also determined at weekly intervals. Urinalyses were performed 3 times weekly and urea clearances were performed every 7 to 10 days. Serial electrocardiograms, chest x-rays and basal metabolism determinations were obtained on all patients.

The effect of orally administered selenium cystine on the ability of leukemic leukocytes to incorporate radioactive L-cystine in vitro was determined twice weekly in one of the patients with acute leukemia (Patient 1). The serial values obtained were compared with the amounts incorporated by the leukemic leukocytes when the patient was not receiving selenium cystine.

**Results**

There was a rapid and striking drop in the total leukocyte count in all patients receiving selenium cystine (table 1). In the adult patient with acute leukemia (Patient 1), the leukocyte count dropped from a maximum of 505,000 cells per cu. mm. to 24,000 cells per cu. mm. before the patient expired because of a cerebral hemorrhage. In the other patient with acute leukemia (Patient 2), the leukocyte count dropped from 110,000 cells per cu. mm. to 13,500 cells per cu. mm. In the patient with advanced chronic myeloid leukemia (Patient 4), the leukocyte count dropped from 144,000 cells per cu. mm. to 44,000 cells per cu. mm. but subsequently rose to the initial level. In the other patient with chronic myeloid leukemia (Patient 3), the leukocyte count fell from 222,000 cells per cu. mm. to 121,250 cells per cu. mm. in 10 days, at which point selenium cystine was discontinued because of complications associated with acute myocardial infarction.

In all patients the rate of fall was extremely rapid (figs. 1, 2, 3). During the period of maximum decrease in the adult patient with acute leukemia, the leukocyte count fell 200,000 cells per cu. mm. in one week and decreased as much as 75,000 cells per cu. mm. in 24 hours. A drop of more than 40,000 cells per cu. mm. occurred in 24 hours in the other patient with acute leukemia. In both patients with chronic myeloid leukemia the maximum decrease in the leukocyte count exceeded 90,000 cells per cu. mm. in one week. In these patients the immature granulocytes disappeared much more rapidly than the mature granulocytes.

The leukocyte count decreased as rapidly in patients who had been resistant to therapy as it did in patients who had received no previous therapy. Thus the patient with acute leukemia who had become refractory to cortisone, Aminop-
The Effect of Selenium Cystine on the Total Leukocyte Count in Acute and Chronic Leukemia

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Maximum Leukocyte Count (Cells per mm$^3$)</th>
<th>Lowest Leukocyte Count (Cells per mm$^3$)</th>
<th>Duration Of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Acute Leukemia (Stem Cell)</td>
<td>505,000</td>
<td>24,000</td>
<td>57 days</td>
</tr>
<tr>
<td>2. Acute Leukemia (Childhood)</td>
<td>110,000</td>
<td>13,500</td>
<td>21 days</td>
</tr>
<tr>
<td>3. Chronic Myeloid Leukemia</td>
<td>222,000</td>
<td>121,250</td>
<td>10 days</td>
</tr>
<tr>
<td>4. Chronic Myeloid Leukemia</td>
<td>147,000</td>
<td>44,000</td>
<td>21 days</td>
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Terin and 6-mercaptopurine therapy exhibited a rapid drop in the leukocyte count. Similarly, the patient with advanced chronic myeloid leukemia also responded with an initial fall in the leukocyte count even though he had previously responded poorly to x-ray therapy and had failed to respond to Fowler's solution, urethane and myleran. However, the fall in the leukocyte count in this patient was not maintained and the leukocyte count subsequently rose to the original level.

Following the administration of selenium cystine, one of the patients with acute leukemia appeared to reacquire sensitivity to 6-mercaptopurine (Patient 2,

**Fig. 1.**—The effect of selenium cystine on acute stem cell leukemia in an adult. During the initial period of observation the leukocyte count rose from 214,000 to 390,000 cells per cu. mm. On selenium cystine therapy the count then fell to 140,000 cells per cu. mm. When another selenium preparation, diphenyl diselenide, was substituted for the selenium cystine, the count rose rapidly to 505,000 cells per cu. mm. When selenium cystine therapy was re-instituted, the leukocyte count fell rapidly to 25,000 cells per cu. mm. Note the rapid rate of fall associated with the administration of selenium cystine.
The effect of selenium cystine on acute leukemia, childhood type. The patient had been maintained on successive therapy with cortisone, Aminopterin and 6-mercaptopurine for a period of 12 months. Despite large doses of 6-mercaptopurine and Aminopterin, the leukocyte count increased and the spleen and lymph nodes became enlarged. Selenium cystine was then administered with a subsequent rapid fall in the leukocyte count and a rapid decrease in the size of the spleen and lymph nodes.

This patient had become refractory to 6-mercaptopurine (150 mg. per day) with a resultant rise in the leukocyte count, increase in the size of the spleen and lymph nodes and the development of anemia. Following a course of selenium cystine the patient responded to the same amount of 6-mercaptopurine with a fall in leukocyte count and a decrease in the size of the spleen so that it was no longer palpable. He is at present in an excellent remission and is being maintained on 6-mercaptopurine.

In all patients the spleen decreased in size during the administration of selenium cystine. In 2 of the patients the spleen became no longer palpable. In the patient with advanced chronic myeloid leukemia the spleen decreased in size even though it had failed to do so with x-ray therapy. The spleen did not increase in size in this patient when the leukocyte count rose to the initial value.

The in vitro turnover of S\textsuperscript{35} L-cystine by leukemic leukocytes was decreased during the administration of selenium cystine. In the adult patient with acute leukemia the amount of S\textsuperscript{35} incorporated before the administration of selenium
cystine was 25,000 counts per minute per ml. packed leukocytes. After receiving selenium cystine for 50 days the amount of $^{38}$Se incorporated ranged from 3,000 to 5,000 counts per minute per ml. packed leukocytes.

Diphenyl diselenide was ineffective in decreasing the leukocyte count. This selenium compound was administered orally for 7 days to one of the patients with acute leukemia. During this period the leukocyte count rose from 147,000 cells per cu. mm. to 505,000 cells per cu. mm.

Toxic manifestations associated with the administration of selenium cystine included persistent and severe nausea, vomiting and anorexia. Severe alopecia developed in both patients with acute leukemia and the hair fell out rapidly in the other patients. One patient exhibited marked destruction of the fingernail beds. Normal growth of hair and fingernails resumed when selenium cystine was discontinued. Moderate drowsiness and occasional diarrhea were associated with prolonged administration of this compound.

Hepatic and renal function tests were normal despite prolonged administration of selenium cystine. Postmortem examination in 2 patients who had received selenium cystine for periods of 57 and 10 days respectively revealed no

**FIG. 3.—**The effect of selenium cystine on chronic myeloid leukemia. The total leukocyte count falls rapidly and the immature leukocytes disappear more rapidly than the more mature granulocytes.
ANALOGUES OF L-CYSTEINE AND L-CYSTINE

changes in the organs attributable to selenium cystine toxicity. No delayed toxic manifestations have developed in the 2 patients who continue to survive.

Case Reports

Case 1. Acute Stem Cell Leukemia J. K. (No. 668-184), a 39 year old female with known diabetes mellitus, entered the hospital because of poor vision. On physical examination she was found to have extensive retinal hemorrhages, diffuse cervical, axillary and inguinal adenopathy and splenomegaly, the spleen extending 5 cm. beneath the costal margin.

Laboratory Findings: Erythrocytes 3,280,000 per cu. mm.; hemoglobin 9.4 Gm. per 100 cc.; hematocrit 27 per cent; leukocytes 214,250 per cu. mm.; platelets 88,480 per cu. mm. Differential: blasts 99 per cent, segmented neutrophils 1 per cent. The blasts were large cells with abundant basophilic vacuolated cytoplasm. The nuclear chromatin was finely granular and the nucleus contained 1 to 2 nucleoli. The cells were peroxidase negative and contained no granules.

Hospital Course: During a 7 day period of observation the leukocyte count rose spontaneously from 214,250 cells per cu. mm. to 390,000 cells per cu. mm. (fig. 1). On the 8th hospital day 100 mg. of selenium cystine was administered orally and was continued daily in amounts ranging from 50 to 200 mg. for a period of 20 days. During this period the leukocyte count dropped to 143,000 cells per cu. mm. Selenium cystine was then discontinued and equivalent amounts of diphenyl diselenide were administered. With this selenium compound (structurally unrelated to cystine) the leukocyte count rose rapidly to 505,000 cells per cu. mm. within 7 days. Diphenyl diselenide was then discontinued and selenium cystine was again administered. The leukocyte count again fell rapidly, the maximum rate of fall being over 400,000 cells per cu. mm. in a 12 day period. The lowest leukocyte count obtained was 24,000 cells per cu. mm. On the 64th hospital day the patient expired due to a cerebral vascular hemorrhage.

During the period of selenium cystine administration the spleen decreased in size so that it was no longer palpable. The erythrocyte count and hemoglobin were remarkably well maintained considering the severity of the leukemic process. The patient received transfusions electively on only 3 occasions during her entire hospital course. The platelets varied between 88,000 and 20,500 during this period and, despite the final episode of cerebral vascular hemorrhage, ecchymoses and petechiae were not unusually severe. The patient was afebrile except for one episode associated with gingival infection and regional adenitis which was successfully treated with aureomycin.

Nausea and vomiting persisted throughout the hospital course and the alopecia which developed was very extensive. Diarrhea also developed during the last 2 weeks of therapy but was readily controlled with paregoric. Tests of hepatic and renal function were within normal limits.

Postmortem examination revealed no changes in the organs attributable to selenium cystine toxicity even though the patient had received a total of 5.2 Gm. of selenium cystine over a period of 50 days. The liver, spleen, bone marrow and kidneys were extensively infiltrated with leukemic cells.

Case 2. Acute Leukemia, Childhood Type H. K. (No. 659-616), a 13 year old boy, developed acute leukemia 1 year prior to admission. During this 12 month
period he had been maintained in good remission with successive courses of cortisone, Aminopterin and 6-mercaptopurine but had become resistant to these chemotherapeutic agents (figure 2). He entered the hospital because of a rapidly increasing leukocyte count, progressive enlargement of the spleen and lymph nodes and severe anemia.

Laboratory Findings: Erythrocytes 1,940,000 per cu. mm.; hemoglobin 6.2 Gm. per 100 cc.; leukocytes 82,250 per cu. mm.; platelet count 113,650 per cu. mm. Differential: 87 per cent blasts, 2.5 per cent segmented neutrophils, 3 per cent unsegmented neutrophils, 0.5 per cent lymphocytes, 7 per cent atypical mononuclears. The blasts were about 20 microns in diameter with scanty, deeply basophilic cytoplasm. The nuclei contained 0 to 2 nucleoli and the nuclear chromatin was finely condensed. The cells were peroxidase negative and contained no granules.

Hospital Course: He was given 3 units of blood on admission and 100 mg. of selenium cystine orally. 100 mg. of cortisone were administered daily throughout his hospital stay. He was unable to retain the selenium cystine because of severe nausea and vomiting and the leukocyte count rose to 110,000 cells per cu. mm. The capsules were then coated with salol, following which he was better able to retain the selenium cystine. The leukocyte count then dropped sharply to 13,500 cells per cu. mm. during the next 9 days, and the number of blasts decreased from 87 per cent to 30.5 per cent. The spleen decreased in size from 8 cms. beneath the costal margin to 2 cms. beneath the costal margin and the lymph nodes likewise diminished in size. Intermittent nausea and vomiting persisted and he developed a very marked alopecia and a moderate diarrhea. Because of the discomfort, selenium cystine was discontinued. Within 3 days the leukocyte count rose to 47,500 cells per cu. mm. and he was then given 150 mg. of 6-mercaptopurine daily.

Following the institution of 6-mercaptopurine therapy the leukocyte count fell to 2,750 cells per cu. mm. within 14 days and the spleen continued to regress until it was no longer palpable. The lymph nodes also became barely palpable and the erythrocyte count and platelet count gradually increased. At the present time he appears to be in an excellent state of remission, despite the fact that he had previously failed to respond to the same amount of 6-mercaptopurine.

Case 3. Chronic Myeloid Leukemia T. W. (No. 502-242), a 70 year old white male, entered the hospital because of anorexia and weight loss of 6 months duration. On physical examination he appeared emaciated and chronically ill. Both the liver and the spleen extended 4 cm. beneath the costal margin. The remainder of the examination was essentially negative.

Laboratory Findings: Erythrocytes 3,540,000 per cu. mm.; hemoglobin 10.2 Gm.; leukocytes 222,000 per cu. mm. Differential: 35 per cent segmented neutrophils, 16 per cent unsegmented neutrophils, 20 per cent metamyelocytes, 25 per cent myelocytes, 1 per cent myeloblasts, 1 per cent eosinophils, 1 per cent basophils and 1 per cent lymphocytes. The platelets were increased in number. Bone marrow aspiration was consistent with the diagnosis of chronic myeloid leukemia. Liver function tests were within normal limits and liver biopsy revealed cellular infiltration consistent with the diagnosis of chronic myeloid leukemia.
**Hospital Course:** He was given 100 mg. of selenium cystine by mouth daily for 12 days. The leukocyte count fell from 222,000 cells per cu. mm. to 121,250 cells per cu. mm. during this period and the spleen decreased in size so that it was no longer palpable. The fall in leukocyte count was due almost entirely to the disappearance of immature granulocytes. Thus the absolute count of immature granulocytes (myeloblasts, myelocytes and metamyelocytes) fell from 100,000 to 8,000 cells per cu. mm. whereas the mature leukocytes remained essentially unchanged. However, nausea, vomiting, anorexia and weakness became so severe that selenium cystine was discontinued. Despite supportive therapy these symptoms continued. He expired suddenly 10 days after selenium cystine was discontinued. During this 10 day period the leukocyte count returned to the original level. Postmortem examination revealed severe stenosing coronary arteriosclerosis with calcification and a remote infarction of the posterior wall of the left ventricle. Leukemic infiltration was present in the bone marrow, liver, spleen and meninges. There were no changes in any of the organs attributable to selenium cystine toxicity.

**Case 4. Chronic Myeloid Leukemia, Advanced Stage C. D. (No. 655-891),** a 48 year old male with known chronic myeloid leukemia of 5 years duration, entered the hospital complaining of fever, weakness, fatigue, dyspnea and pain in the left upper abdominal region. Previous treatment had consisted of several courses of X-ray therapy to the spleen as well as therapy with Fowler's solution, urethane and myleran on several occasions. One month prior to admission he had received 2850 roentgens to the spleen without decrease in spleen size but with a fall in the leukocyte count from 320,000 cells per cu. mm. to 39,000 cells per cu. mm. He was then given 6 mg. of myleran daily but in spite of this therapy the leukocyte count rose to 147,000 cells per cu. mm. in 30 days.

On physical examination the temperature was 38.1 C. Small discrete cervical, axillary and inguinal nodes were palpable. The liver extended 9 cm. beneath the costal margin and the spleen extended inferiorly to the iliac crest and medially to the midclavicular line.

**Laboratory Findings:** Erythrocytes 2,630,000 cells per cu. mm.; hemoglobin 6.2 Gms. per 100 cc.; hematocrit 26 per cent; leukocytes 147,000 cells per cu. mm. Differential: 34 per cent segmented neutrophils, 9 per cent unsegmented neutrophils, 16.5 per cent metamyelocytes, 26.5 per cent myelocytes, 6 per cent myeloblasts, 1.5 per cent eosinophils, 1.5 per cent basophils, 4.5 per cent lymphocytes, and 1.5 per cent monocytes. There were 12 nucleated erythrocytes per 100 leukocytes and the platelets were normal in number.

**Hospital Course:** Approximately 100 mg. of selenium cystine were administered by mouth daily. The total leukocyte count fell from 147,000 cells per cu. mm. to 44,000 cells per cu. mm. in 8 days. The immature granulocytes disappeared more rapidly than the mature granulocytes (fig. 3) and the temperature returned to normal. The spleen decreased in size, the medial edge receding from the midclavicular line to the flank. However, tolerance to the drug appeared to develop and the total leukocyte count subsequently rose to the initial level despite the continued administration of selenium cystine.

Toxic manifestations associated with the administration of selenium cystine included nausea, vomiting, anorexia, loss of hair and damage to the fingernail
matrix. There were no changes in hepatic or renal function. Fingernail and hair growth have resumed normally. The patient's leukocyte count has risen to 455,000 cells per cu. mm. but the spleen has not enlarged during the past 3 months. He has had an excellent initial response to therapy with radioactive phosphorus.

**Discussion**

It is apparent that small amounts of selenium cystine have a rapid and striking effect on the leukocytes of both acute leukemia and chronic myeloid leukemia. Selenium cystine appears to have a greater effect on immature leukocytes than on mature leukocytes. Thus immature granulocytes disappear more rapidly than mature granulocytes when this compound is administered to patients with chronic myeloid leukemia. The effect of selenium cystine on immature leukocytes is most apparent in acute leukemia where the most rapid disappearance of leukocytes was observed.

Selenium cystine also appears to affect leukocytes at sites of formation as well as those circulating in the peripheral blood. This assumption is based on the decrease in spleen size observed during the administration of selenium cystine. Bone marrow changes were not observed, possibly because selenium cystine was administered for relatively brief intervals.

Selenium cystine also had an effect in patients refractory to other chemotherapeutic agents. Thus this compound caused a fall in the leukocyte count and a decrease in spleen size in acute leukemia no longer responding to cortisone, aminopterin or 6-mercaptopurine. Similarly, a decrease in the leukocyte count and in spleen size was observed in chronic myeloid leukemia resistant to irradiation, Fowler’s solution, urethane and myleran. This patient in turn became refractory to selenium cystine in the amounts employed. It is important to note that one patient who had become refractory to 6-mercaptopurine appeared to reacquire sensitivity to this compound after receiving selenium cystine for 21 days (Patient 2). The possibility of altering the sensitivity of leukemic leukocytes to other chemotherapeutic agents requires further investigation.

The toxic manifestations of nausea and vomiting associated with the administration of selenium cystine were so severe that it was difficult to continue administration of the compound. Consequently, none of the patients received sufficient selenium cystine for a long enough period of time to determine whether this compound can produce a remission of appreciable duration in leukemia. Preliminary trials indicate that intravenously administered selenium cystine may be better tolerated than that administered orally. Coating the capsules with salol as well as the use of chlorpromazine decreased the severity of the nausea and vomiting. Although these side effects were disagreeable, there were no discernible changes in any organs which could be attributed to selenium cystine toxicity. Thus selenium cystine appears to have a highly selective toxic effect on immature leukocytes.

Any subjective clinical improvement associated with the administration of selenium cystine was obscured by the toxic manifestations. However, in spite of the toxicity, the patients did appear to receive significant clinical benefit. In addition to the rapid fall in leukocyte count and decrease in size of lymph
nodes and spleen, the requirements for blood transfusion appeared to be decreased and platelets remained at pretreatment levels. Temperature elevations were uncommon. Transfusions and antibiotics were used so sparingly that they contributed little if anything to the changes observed.

A rapid rise in the leukocyte count ensued in 3 of the patients when selenium cystine was discontinued. However, “blast” cells had not been completely eradicated from the peripheral blood in the 2 patients with acute leukemia. The third patient received selenium cystine for only 12 days. More prolonged administration of selenium cystine might prevent such rapid relapse in the leukocyte count. Further experience with the effects of selenium cystine in leukemia, especially those resistant or refractory to therapy, is desirable.

The mechanism of action of selenium cystine is not known. L-cysteine appears to have an important role in the metabolism of leukocytes and selenium cystine may block the incorporation or utilization of L-cystine or L-cysteine. Such biologic inhibition by structurally related analogues has been demonstrated for several compounds. The rapid fall in the number of immature leukocytes may reflect the increased requirement of these cells for cysteine. Indeed, selenium cystine appears to have its greatest effects on the “blast” cells of acute leukemia.

Selenium cystine may exert its effect by inhibiting certain enzymes necessary for cell growth and function. Cysteine activates certain sulfhydryl enzymes and selenium cystine may interfere with this activation. Selenium cystine is known to inactivate the sulfhydryl enzyme, succinic dehydrogenase, and may inactivate several other sulfhydryl enzymes. Other selenium compounds are known to inactivate a number of enzymes. It is of interest that such compounds as arsenicals and nitrogen mustard, as well as irradiation, all of which produce leukopenia, also inactivate sulfhydryl compounds.

It is possible that the effects observed are non-specific and that they are due solely to the presence of selenium within the molecule. However, studies on the effect of chronic selenium poisoning in a variety of animals reveal no characteristic blood changes except for anemia. Since other selenium compounds are ineffective in producing a fall in the leukocyte count, the effect of selenium cystine appears to be dependent upon its close structural relationship to cystine.

The toxic manifestations of nausea, vomiting, diarrhea and alopecia are similar to those obtained with Aminopterin. Stekol has stated that one of the effects of Aminopterin is a decreased formation of cysteine from formate. The toxic manifestations and the mechanism of action of both Aminopterin and selenium cystine may therefore be closely related. The profound alopecia and damage to the fingernails occurring in patients receiving selenium cystine is of particular interest because of the high cysteine content of these appendages. The changes observed may, however, also be due to injury to the rapidly proliferating cells of the hair follicles and nail matrix.

The decrease in leukocyte count occurring following the oral administration of selenium cystine correlates with the ability of this compound to decrease the influx of S\(^{135}\) L-cystine into leukemic leukocytes in vitro. In contrast, diphenyl diselenide had no effect on the leukemic process in vivo and was ineffective in
blocking the incorporation of $^{35}$S L-cystine in vitro. These observations emphasize the molecular requirements for decreasing the incorporation of radioactive L-cystine both in vitro and in vivo. The ability of a compound to decrease the incorporation of $^{35}$S L-cystine by leukemic leukocytes in vitro may therefore be a useful technique in selecting other compounds which may affect the leukemic process.

These studies were initiated because of observations suggesting that L-cysteine and related compounds played an important role in the metabolism of leukocytes. The effect of an analogue of cysteine in producing such rapid and striking changes in the leukocyte count in leukemia is further suggestive of the importance of cysteine (cystine) in leukocyte metabolism.

**Summary and Conclusions**

Selenium cystine was administered orally to 2 patients with acute leukemia and to 2 patients with chronic myeloid leukemia. In all patients there was a rapid decrease in the total leukocyte count as well as a decrease in spleen size. This effect was observed in patients refractory to other chemotherapeutic agents as well as in the usually resistant types of leukemia. In patients with chronic myeloid leukemia the immature granulocytes disappeared much more rapidly than the mature granulocytes. The most striking and consistent effects were observed in acute leukemia. One patient who had become resistant to 6-mercapto purine appeared to reacquire sensitivity to this compound after receiving selenium cystine.

These effects of selenium cystine on leukocytes correlate with the ability of selenium cystine to decrease the influx of $^{35}$S L-cystine by leukemic leukocytes in vitro. Other potentially effective analogues of cystine (or cysteine) may therefore be selected by this technic.

No changes were detected in any of the organs attributable to selenium cystine toxicity. The nausea and vomiting associated with the oral administration of selenium cystine was so severe that it was not possible to administer selenium cystine for a sufficient period of time to determine whether an appreciable remission can be obtained in leukemia. Further study is necessary to determine whether selenium cystine has any practical applicability in the chemotherapy of leukemia.

Although the mechanism of action of selenium cystine is not known, these striking effects of an analogue of cystine on leukemia are further suggestive of the importance of cystine (cysteine) in the metabolism of leukocytes.
efectos esas observados en casos de acute leucemia. Un paciente, qui habeva devenite resistente a 6-mercaptopurina, pareva re-acquierer su previe sensibility a iste composito post reciper selenio-cystina.

Iste efectos de selenio-cystina super leucocytos es in correlación con le capacitate de selenio-cystina de reduce le influxo de L-cystina a S39 in leucocytos leucemic in vitro. Iste technica permite consequentemente le selection de altere potentialmente efficace analogos de cystina o cysteina.

Esseva notate nulle alterationes organice attribuibile a toxicitate de selenio-cystina. Le nause Cec vomito associate con le administration oral de selenio-cystina eseva si sever que il eseva impossible administrar selenio-cystina satis prolongatamente per determinar si per medio di illo un significative remission de leucemia es obtenibile. Studios additional es requisite pro determinar si selenio-cystina es de applicabilitate practic in le chimotherapia de leucemia.

Ben que le mechanismos del effecto de selenio-cystina es incognoscit, le hici-reportate frappante efectos de un analogo di cystina super leucemia representa un indication additional del importantia di cystina (cysteina) in le metabolismo del leucocytos.

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Studies on Analogues of L-Cysteine and L-Cystine: III. The Effect of Selenium Cystine on Leukemia

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