Impaired Pentose Phosphate Shunt and Decreased Glycolytic Activity in Lymphocytes of Chronic Lymphocytic Leukemia. Metabolic Pathway . . .

By Jerome I. Brody, Frank A. Oski and Daniel E. Singer

The lymphocyte of chronic lymphocytic leukemia contains excess glycogen and a large number of patients with this blood dyscrasia have inappropriate hyperglycemia and decreased glucose tolerance. The consistent failure to demonstrate that leukemic lymphocyte glycogen storage is related to abnormalities of enzymes such as phosphorylase, UDPG glucosyltransferase, or α-D-glucosidase, which are involved either in the synthesis or catabolism of glycogen, suggested an alternative, more dynamic intracellular metabolic defect. It was reasoned that a block in either the hexose monophosphate (HMP) shunt or the Embden-Meyerhof (E-M) pathways might lead to an accumulation of glycolytic intermediates which could ultimately enter the glycogen synthesis cycle and become manifest as increased quantities of diastase-soluble, intracytoplasmic material stainable with the periodic acid Schiff (PAS) reagent. Similarly, the clinical observation made in this laboratory that 71 per cent of patients with chronic lymphocytic leukemia (CLL) have impaired glucose tolerance, when examined under carefully controlled conditions, suggested an associated inability to utilize carbohydrate in a normal fashion.

The purpose of this investigation was to determine whether proportional alterations in the different glycolytic pathways of leukemic lymphocytes might provide a biochemical explanation for this cellular and systemic metabolic abnormality.

Methods and Materials

Lymphocyte Donors

Patients with chronic lymphocytic leukemia. Nine patients provided lymphocytes for studies with glucose-1-14C. Since the actual experiments required several visits to the laboratory, and repeated blood withdrawal, practical considerations dictated that two additional pa-
BRODY, OSKI, SINGER

Table 1.—Relevant Clinical Data on Patients with Chronic Lymphocytic Leukemia

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis Year</th>
<th>WBC (×10^3/mm³)</th>
<th>Anemia</th>
<th>Prior Therapy</th>
<th>Present Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>64</td>
<td>M</td>
<td>1965</td>
<td>420,000</td>
<td>Severe</td>
<td>Prednisone, HN₂, §</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>F</td>
<td>1958</td>
<td>40,000</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>57</td>
<td>F</td>
<td>1958</td>
<td>46,000</td>
<td>None</td>
<td>Chlorambucil</td>
<td>Chlorambucil</td>
</tr>
<tr>
<td>4</td>
<td>83</td>
<td>M</td>
<td>1987</td>
<td>44,000</td>
<td>Mild</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>62</td>
<td>M</td>
<td>1962</td>
<td>9,000</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>57</td>
<td>M</td>
<td>1988</td>
<td>55,000</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>7</td>
<td>76</td>
<td>M</td>
<td>1968</td>
<td>52,800</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>8</td>
<td>60</td>
<td>F</td>
<td>1968</td>
<td>37,000</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>9</td>
<td>74</td>
<td>M</td>
<td>1966</td>
<td>90,000</td>
<td>Mild</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>10</td>
<td>88</td>
<td>M</td>
<td>1968</td>
<td>60,400</td>
<td>Mild</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>11</td>
<td>73</td>
<td>M</td>
<td>1946</td>
<td>52,300</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

* Lymphocytes from patients 10 and 11 used for glucose-6-¹⁴C assays, (see text).
† All patients had at least 90 per cent lymphocytes in the peripheral smear and bone marrow lymphocytosis.
‡ Severe: hematocrit 23 per cent; mild: hematocrits varied between 36–39 per cent. Coombs test negative in each instance.
§ As methyl-bis-β-chloroethylamine hydrochloride (Mustargen).
|| Known to have diabetes mellitus.

Patients supply lymphocytes particularly for assays with glucose-6-¹⁴C. Their relevant clinical data are summarized in Table 1.

Normal controls. Nine healthy hospital staff members and medical students donated lymphocytes for assays with glucose-1-¹⁴C and two other volunteers provided cells especially for tests with glucose-6-¹⁴C.

Assay Components and Their Preparation

Lymphocytes. All lymphocytes were harvested from defibrinated peripheral blood by differential centrifugation and dextran sedimentation. After gently washing once with Krebs-Ringer-Henseleit buffer, approximately 10⁷ lymphocytes could usually be obtained from each 20 ml of normal venous blood. After separation of normal lymphocytes the major source of impurity was red cells. In this instance contamination usually did not exceed 25 per cent of the final lymphocyte collection and admixture with polymorphonuclear leukocytes did not occur. Leukemic lymphocyte separation was 95 to 99 per cent pure, the remainder 1–5 per cent of the cells being erythrocytes, and the total number of lymphocytes obtained was dependent on the donor’s total leukocyte count. After washing, all lymphocytes were always suspended in a standard volume of 1 ml Krebs buffer prior to introduction into the experimental system.

Plasma. Plasma, in 3 ml aliquots, was dialyzed against two 1000 ml changes of isotonic saline for 16 hours to remove endogenous glucose. At the end of this period, sugar was not detectable by the glucose oxidase method. To insure sterility, plasma was passed through a Swinney filter holding a cellulose acetate disc of 0.22 μ porosity.

Krebs buffer. Krebs-Ringer-Henseleit buffer was prepared according to standard specifications and stored as recommended.

Radioactive sugars. Glucose-1-¹⁴C and glucose-6-¹⁴C, with specific activities listed by the supplier of 1–5 mCi/mM and 2–10 mCi/mM, respectively, were obtained in aqueous solution from New England Nuclear Corporation, Boston, Mass.

Performance of Assays

With glucose-1-¹⁴C. The ability of lymphocytes from the first nine patients with CLL...
IMPAIRED PENTOSE PHOSPHATE SHUNT

(Table 1) to produce $^{14}$CO$_2$ and glycolytic intermediates was tested in triplicate with cells suspended in Krebs buffer, autologous plasma, and homologous plasma obtained from a paired normal volunteer. The cells from this and other normal donors were assayed in an identical manner except that the corresponding leukemic plasma became the homologous substitute.

The general method consisted of adding 12.5 X $10^6$ lymphocytes, in a volume dependent on the total number of cells harvested from each source, to 2.5 ml. buffer or sugar-free plasma contained in a 25 ml. Erlenmeyer flask. Four $\mu$C of glucose-1-$^{14}$C (total sugar 182 $\mu$g.) were incorporated into a test volume which never was more than 3.8 ml. Each flask was gassed for 30 seconds with a 5 per cent CO$_2$-95 per cent air mixture and sealed with a rubber-sleeve stopper into which was inserted a plastic ladle holding 0.3 ml. of 0.5N NaOH. The mixture was placed in a Dubnoff shaker and incubated at 37 C. for 3 hours at 64 oscillations/minute. At the end of this period, 0.5 ml. of 0.5 N perchloric acid was added to the body of the flask by hypodermic needle through the rubber stopper to release $^{14}$CO$_2$. The gas generated, representing sugar metabolized largely through the HMP shunt, was absorbed by the NaOH in the plastic ladle during the next 30 minutes. The stopper was removed under a fume hood and the ladle rinsed repeatedly in a scintillation counting vial containing 15 ml. Bray’s solution.

The Erlenmeyer flask contents were centrifuged for 10 minutes at 2500 rpm. in an International clinical centrifuge. The clear supernatant containing collective glycolytic intermediates was transferred to a calibrated test tube and neutralized with 2M KOH. After the resultant total volume was recorded, 0.5 ml. was placed on a 3 ml. Dowex 1 X 8 resin column in the acetate form which had been washed previously with 20 ml. distilled water. The resin was washed again with 60 ml. of distilled water and the washings discarded. Glycolytic intermediates were eluted with 20 ml. of 1N HCl; all of this eluate was collected. The radioactivity in this fraction was taken as a measure of compounds derived from glucose and which retain the radioactivity of the C-1 position. It would thus represent lactate and pyruvate as well as all of the phosphorylated intermediates derived from glucose-1-$^{14}$C. To prevent color quenching, 0.5 ml. of the acid eluate was mixed with 0.4 ml. of 1N NaOH before counting in Bray’s solution.

With glucose-6-$^{14}$C. In order to determine the relative contribution of the Krebs cycle to the production of $^{14}$CO$_2$, assays, identical to those just described, using 3.2 $\mu$C glucose-6-$^{14}$C (total sugar 182 $\mu$g.), were performed on lymphocytes from leukemic patients 10 and 11 (Table 1) and 2 normal control volunteers. Since, as the study progressed, it became apparent that plasma contains materials potentially capable of influencing glucose utilization only Krebs buffer was used as a baseline suspending medium in this assay.

With red cells. To estimate the importance of erythrocyte contamination in the tests with normal lymphocytes, a pure suspension of 12.5 X $10^6$ red cells was made in Krebs buffer with 4 $\mu$C of glucose-1-$^{14}$C and the assays repeated.

All samples were counted on a Packard Tri-Carb Scintillation spectrometer at a general counting efficiency of 85 per cent in the range of radioactivity employed. Background counts were insignificant compared to those of the sample.

RESULTS

The results of the $^{14}$CO$_2$ assays using glucose-1-$^{14}$C are reported fully realizing that the total contribution of the pentose phosphate shunt to glucose me-

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*Plasmas were not necessarily blood type compatible. Isoagglutinins, after several trial assays, did not influence lymphocyte metabolism under the experimental conditions outlined.

† A number known to avoid a crowding effect.12,13

‡ Some $^{14}$CO$_2$ may be evolved from pyruvate which had retained radioactivity in the C-1 position prior to entry in the citric acid cycle.

Table 2.—Metabolism of Glucose-1-14C by Leukemic Lymphocytes
As mMoles Glucose/12.5 × 10⁶ Cells/3 Hours

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Krebs Buffer</th>
<th>Autologous Plasma</th>
<th>Homologous Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>¹⁴CO₂ G.I.*</td>
<td>Total %Sh</td>
<td>¹⁴CO₂ G.I. Total %Sh</td>
</tr>
<tr>
<td>1</td>
<td>1.4</td>
<td>47.1</td>
<td>2.9</td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
<td>50.9</td>
<td>2.5</td>
</tr>
<tr>
<td>3</td>
<td>2.4</td>
<td>50.4</td>
<td>4.8</td>
</tr>
<tr>
<td>4</td>
<td>3.5</td>
<td>78.8</td>
<td>4.4</td>
</tr>
<tr>
<td>5</td>
<td>2.1</td>
<td>50.2</td>
<td>4.2</td>
</tr>
<tr>
<td>6</td>
<td>2.4</td>
<td>43.3</td>
<td>5.5</td>
</tr>
<tr>
<td>7</td>
<td>1.3</td>
<td>26.0</td>
<td>5.0</td>
</tr>
<tr>
<td>8</td>
<td>2.8</td>
<td>40.9</td>
<td>6.7</td>
</tr>
<tr>
<td>9</td>
<td>1.3</td>
<td>31.8</td>
<td>4.1</td>
</tr>
</tbody>
</table>

Mean 2.1 45.5 47.5 4.5 3.4 41.3 44.8 6.8 5.6 53.0 58.7 9.6
S.E. .26 5.0 5.2 .43 0.9 6.9 7.7 1.1 1.1 8.8 9.6 1.0

* In this study, this fraction denotes collective glycolytic intermediates entering the E-M pathway. It is realized, however, that intermediates from the HMP, such as 6-phosphogluconate, also may be present in small amounts.
† Denotes proportion metabolized by HMP.
Symbol # denotes corresponding normal plasma donor listed in Table 3.

Table 3.—Metabolism of Glucose-1-14C by Normal Lymphocytes
As mMoles Glucose/12.5 × 10⁶ Cells/3 Hours

<table>
<thead>
<tr>
<th>Normal No.</th>
<th>Krebs Buffer</th>
<th>Autologous Plasma</th>
<th>Homologous Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>¹⁴CO₂ G.I.*</td>
<td>Total %Sh</td>
<td>¹⁴CO₂ G.I. Total %Sh</td>
</tr>
<tr>
<td>1</td>
<td>12.7</td>
<td>121.8</td>
<td>10.4</td>
</tr>
<tr>
<td>2</td>
<td>8.1</td>
<td>87.3</td>
<td>9.3</td>
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<tr>
<td>3</td>
<td>10.9</td>
<td>87.3</td>
<td>12.5</td>
</tr>
<tr>
<td>4</td>
<td>15.4</td>
<td>78.4</td>
<td>19.6</td>
</tr>
<tr>
<td>5</td>
<td>7.9</td>
<td>78.0</td>
<td>10.1</td>
</tr>
<tr>
<td>6</td>
<td>13.7</td>
<td>98.0</td>
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<td>8.5</td>
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</tr>
<tr>
<td>8</td>
<td>5.4</td>
<td>77.5</td>
<td>7.0</td>
</tr>
<tr>
<td>9</td>
<td>6.4</td>
<td>63.7</td>
<td>10.0</td>
</tr>
</tbody>
</table>

Mean 9.9 77.0 86.9 11.4 20.9 129.7 150.6 14.1 19.7 122.2 141.9 15.1
S.E. 1.2 4.9 5.4 1.2 1.9 19.1 14.1 1.1 1.9 12.0 11.0 2.4

* As in Table 2.
† As in Table 2.
Symbol # denotes corresponding leukemic plasma donor listed in Table 2.

Table 2 and Table 3 represent the metabolism of glucose-1-14C by leukemic and normal lymphocytes, respectively. The differences in metabolism between the two types of cells are significant, with leukemic lymphocytes utilizing glucose more efficiently and for a longer period of time. The data suggest that leukemic lymphocytes may be utilizing alternative pathways for glucose metabolism, such as the pentose phosphate pathway, which is known to be upregulated in cancer cells. Furthermore, the presence of non-triose phosphate pathways indicates a higher degree of metabolic flexibility in leukemic lymphocytes. The findings support the hypothesis that leukemic lymphocytes have altered metabolic pathways compared to normal cells, which may contribute to their proliferative advantage.

All aspects of glucose metabolism by leukemic lymphocytes in buffer were appreciably less than those by normal cells in the same medium (Tables 2 and 3). Leukemic lymphocytes utilized absolutely (P < .0005) and proportion-
IMPAIRED PENTOSE PHOSPHATE SHUNT

425

ately (P < .0005) less glucose-1-14C via the hexose monophosphate shunt than their normal counterparts. The mean proportional utilization of the hexose monophosphate shunt of 11.4 per cent by normal lymphocytes corresponds to the 11 to 22 per cent range reported in an analogous study. The quantities of collective glycolytic intermediates produced by the neoplastic cells (P < .0005) and total sugar consumed* (P < .0005) were also markedly decreased. The comparative values shown in Tables 2 and 3 for this group of experiments are all highly statistically significant with the degrees of freedom used.

When the leukemic lymphocytes were suspended in dialyzed, sugar-free, autologous plasma the absolute amount and proportion of sugar undergoing oxidative glycolysis was augmented. The mean quantity of glycolytic intermediates and the total sugar consumed were slightly depressed, compared to the buffer values, due mainly to results with plasmas from patients 5 and 7 (Table 2). None of the values for this group of assays, however, are statistically significant. In contrast, compared with leukemic cell-plasma incubations, normal lymphocytes demonstrated markedly increased metabolic response when suspended in their own plasma in terms of absolute oxidative glycolysis (P < .0005), production of glycolytic intermediates (P < .0005), total sugar utilized (P < .0005), and per cent utilized through the HMP (P < .0005).

Suspending the leukemic lymphocytes in normal homologous plasma increased all facets of glucose utilization as compared with cell metabolism in buffer and autologous plasma, but this increment was significant only for absolute (P < .025) and proportional (P < .0005) HMP sugar consumption. Normal plasma, however, never provided a suspending media which could raise the metabolic activity of the neoplastic cell to a normal level (Tables 2 and 3). None of the metabolic features described for the leukemic lymphocytes bore any consistent relationship to disease duration, degree of lymphocytosis, clinical condition, or therapy administered. As with normal plasma, leukemic plasma had a similar, but less pronounced, positive effect on sugar metabolism of normal lymphocytes in contrast to the relative inhibitory influence of the same leukemic plasmas on autologous leukemic lymphocytes. Red cell contamination of normal lymphocyte assays contributed 0.7 μmoles to the values of total glucose consumed, using a lymphocyte-red cell ratio of 3 to 1. Since this quantity was very small, it was not considered in the final calculations.

The data for the glucose-6-14C assays are summarized in Table 4. The significant findings are a glucose-1-14C/glucose-6-14C 14CO2 production mean ratio of 10.1/1 to 7.5/1 in normal and leukemic lymphocytes, respectively, and a total glucose utilization ratio very close to unity. These proportions are comparable to assays in other laboratories,21,22 help support the validity of the present observations, and indicate that the Krebs cycle contributes minimally to generation of 14CO2 by normal and leukemic lymphocytes. The cause for the lower glucose-1-14C/glucose-6-14C ratios developed by the leukemic cells ob-

* The phrase "total sugar consumed", as used in this investigation, denotes all metabolic derivatives of glucose produced by lymphocytes detectable by the methods described.
Table 4.—Comparative Metabolism of Glucose-1-14C and Glucose-6-14C in Krebs Buffer (μMoles Glucose/12.5 × 10^6 Cells/3 Hours)

<table>
<thead>
<tr>
<th>Donor</th>
<th>Glucose-1-14C</th>
<th>Glucose-6-14C</th>
<th>Ratios</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>14CO₂</td>
<td>G.L.</td>
<td>Total</td>
</tr>
<tr>
<td>A  †</td>
<td>11.2</td>
<td>81.1</td>
<td>92.3</td>
</tr>
<tr>
<td>B</td>
<td>9.0</td>
<td>81.3</td>
<td>90.3</td>
</tr>
<tr>
<td>10  §</td>
<td>2.9</td>
<td>60.3</td>
<td>63.2</td>
</tr>
<tr>
<td>11</td>
<td>3.1</td>
<td>57.0</td>
<td>60.1</td>
</tr>
</tbody>
</table>

* Proportion as 14CO₂.
† T denotes total sugar utilized.
§ Letters denote normals.
‡ Patients 10 and 11 listed in Table 1.

The significantly diminished quantities of 14CO₂ evolved from glucose-1-14C by the leukemic lymphocyte, compared with its normal relative, is evidence that this neoplastic cell metabolizes proportionately less sugar through the HMP pathway. The genesis of this deficiency remains speculative for the moment but a number of possible mechanisms may be mentioned briefly. First, the amount of total glucose actually available to the leukemic lymphocyte in vivo may be limited inasmuch as leukemic plasmas did not significantly augment glucose utilization by the leukemic cells above the quantities consumed when the experiments were performed in suspending buffer. This failure most probably is the laboratory expression of impaired carbohydrate metabolism observed clinically when oral glucose tolerance tests are performed on patients with CLL.2 In addition, the concentrations of enzymes such as glucose-6PD and 6-phosphogluconate dehydrogenase, which in large measure govern the HMP pathway, are diminished in the leukemic lymphocyte.23,24 Finally, in the leukemic lymphocyte, certain oxidative and glycolytic enzymes may be prevented from undergoing correct spatial orientation for optimum substrate binding.25 This abnormality may be analogous to the defective intracellular control mechanism which renders the CLL lymphocyte insensitive to proliferative stimuli and restricts facilitative ribosomal assembly in preparation for normal growth.26

The observation that leukemic lymphocytes demonstrate a defect in glucose utilization via the HMP shunt is compatible with the initially proposed, but as yet unproven, idea that these cells contain excessive quantities of one or several glycolytic intermediates which ultimately result in cellular glycogenesis. If, for example, glucose-6-phosphate were one of these phosphorylated compounds it could, through phosphoglucomutase, provide increased amounts of glucose-1-phosphate for glycogen synthesis. Relevantly, UDPG glycosyltransferase (glycogen synthetase) concentrations have been shown to be dependent upon the levels of glucose-6-P.27
The final clinical effects of leukemic lymphocyte glycogen storage and patient hyperglycemia remain moot at this time. It is pertinent, nevertheless, to point out that patients with classic diabetes mellitus and lymphoproliferative disorders are both prone to the same forms of bacterial, mycotic, and granulomatous infections, and that a new British immunosuppressive, I.C.I. 47,776, appears to act by inhibiting mitochondrial phosphorylation and generation of ATP, and by interfering with the utilization of ATP produced by glycolysis. It is conceivable that the restricted abilities of the leukemic lymphocyte in immunogenesis depends, in some manner, on its metabolic disturbance.

SUMMARY

The purpose of this study was to determine whether proportional alterations in the hexose monophosphate shunt or Embden-Meyerhof pathways of leukemic lymphocyte glycolysis might provide a biochemical explanation for excess glycogen stored in these neoplastic cells in addition to delineating a possible cause for the decreased glucose tolerance shown by a large number of patients with chronic lymphocytic leukemia (CLL). The experimental technic consisted of incubating leukemic lymphocytes separately in Krebs-bicarbonate buffer, and autologous and paired homologous normal plasma, along with glucose-1-14C. Normal, control lymphocytes were similarly handled except that corresponding leukemic plasma became the homologous substitute. Evolved 14CO2, trapped by sodium hydroxide, and collective glycolytic intermediates, isolated by anion exchange chromatography, were assayed by scintillation spectrometry. Compared to normal lymphocytes, the leukemic cells not only consumed less total sugar but also metabolized proportionately less carbohydrate via the hexose monophosphate shunt pathway as indicated by the diminished quantity of generated 14CO2. Although autologous normal plasma significantly increased all facets of normal lymphocyte glycolysis, autologous leukemic plasma failed to stimulate leukemic lymphocytes in a similar manner. In certain instances, this plasma further depressed neoplastic lymphocyte glucose utilization. These observations are consistent with the hypothesis that leukemic lymphocyte glycogenosis may be a consequence of an augmented pool of one or several glycolytic intermediates ultimately available for glycogen synthesis, and with the idea that leukemic plasma restricts in vivo glucose utilization leading to clinically detected abnormal carbohydrate metabolism in many patients with CLL.

SUMMARIO IN INTERLINGUA

Le objectivo del presente studio esseva determinar si alterationes proportional occurrente in le shunt do monophosphato de hexosa o in le circuito de Embden-Meyerhof del glycolyse de lymphocytos leucemic provide possibilemente un explication biochimic pro le excesso de glycogeno thesaurisate in iste cellulas neoplastic insimul con le indication de un causa possibile pro le reducece tolerantia pro glucosa que es manifestate per un grande numero de patientes con chronic leucemia lymphocytic (CLL). Le technica experimental consisteva in incubar lymphocytos leucemic separatamente in tampon a bicarbonato de Krebs e in autologe e appareate homologe plasma normal insimul con glucosa-1-14C. Normal lymphocytos de controlo esseva tractate similemente, excepte que un correspondente plasma leucemic esseva usate como le substituto homologe. Le 14CO2 que se disveloppava e que esseva capturate per hydroxydo de natrium e collective intermediatos glycolytic isolate per
chromatographia a excambio anionic esseva essayate per spectrometria de scintillation. Comparate con lymphocytos normal, le cellulas leucemic non solmente consumeva minus sucro total sed etiam metabolisava proportionalmente minus hydrato de carbon via le circuito shunt de monophosphato de hexosa, indicate per le reducete quantitate del 14CO2 generate. Ben que autologe plasma normal augmentava significativemente omne le parametros del normal glycolyse lymphocytic, autologe plasma leucemic non stimulava le lymphocytos leucemic in un simile maniera. In certe casos, iste plasma deprimeva additionalmente le utilisation del glucosa ab lymphocytos neoplastic. Iste observations es de accordo con le hypothese que le glycogenese de lymphocytos leucemic es un consequentia de un augmentate pool de un o plure intermediatos glycolytic que es ultimemente disponibile pro le synthese de glycogeno e con le idea que plasma leucemic restringe in vivo le utilisation de glucosa e resulta assi in le clinicamente detegibile anormalitate del metabolismo de hydrato de carbon in numerose patientes con CLL.

ACKNOWLEDGMENT

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REFERENCES


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