in neoplasic conditions and virus infections[11]. We consider it therefore unlikely that they represent some kind of expression of the vaccinal virus, but a relationship to virus replication cannot be dismissed on the basis of available data.

The presence of TRS in bursal lymphocytes is interesting in view of the observations of L. Pothier et al.[6] which found a correlation of their occurrence with the synthesis of IgG in a series of transplantable tumours of human lymphoid origin. Also, the induction of TRS by 5-bromo-2'-deoxyuridine[13] seems to succeed primarily in Epstein Barr virus-positive B-cell lines[14]. These observations point to an association of TRS with B-lymphocytes.

1 We are grateful to Dr J.L.F. Cristina Afonso for material support, to Mrs M. Lapão and J.P. Cristina Afonso for their technical help, and to the Freixial Poultry Industry for providing the chickens.

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## In vitro cytostatic effect of adenine-arabinoside (Ara-A) and cytosine-arabinoside (Ara-C)[1]

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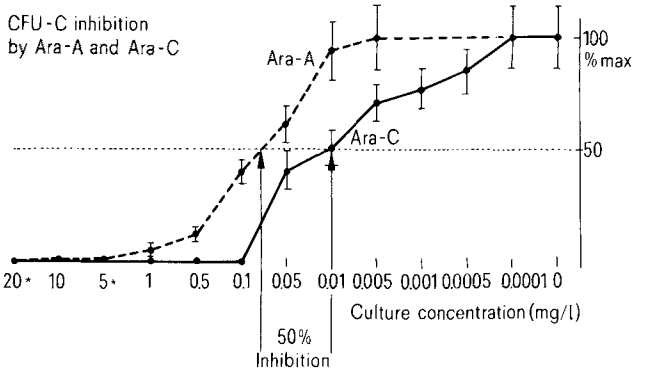
*Summary.* Adenine-arabinoside, a new antiviral drug with questionable bone marrow toxicity, inhibits colony formation by myeloid precursor cells in vitro. Compared to cytosine-arabinoside this cytotoxicity is roughly one third.

Adenine-arabinoside (Ara-A) is a new and promising antiviral agent that is particularly active against DNA-viruses of the Herpes group[3-10]. It is generally assumed that its antiviral activity greatly outweighs its myelotoxicity in contrast to other antiviral drugs[3]. Marrow depression by Ara-A, however, has been described[11]. The myelotoxicity of Ara-A is difficult to evaluate in clinical situations. Wide use of the drug is hampered by teratogenic side effects, reported in rodents[12]. Its application in man is therefore restricted to life-threatening Herpes virus infections. As these occur in diseases which themselves are likely to interfere with bone marrow function, possible myelotoxic side effects of Ara-A are difficult to document objectively. We therefore chose an in vitro technique to test the myelotoxicity of Ara-A.

Human myeloid precursor cells (CFU-C = colony forming units in culture) form granulocyte and macrophage colonies in culture. This in vitro growth is extremely sensitive to cytostatic agents and is thus an appropriate target for the investigation of drugs with questionable cytotoxicity, such as Ara-A. Cytosine-arabinoside (Ara-C), a chemically related compound of known cytotoxicity, served as reference substance.

$10^5$ nucleated human bone marrow cells from 10 normals and 6 patients with non-haematological diseases were cultured in methylcellulose as described by Iscove[13]. Ara-A or Ara-C were added in increasing amounts, the highest final culture concentrations corresponding to therapeutic doses. Benzyl alcohol, the solvent used for clinical application of Ara-A was avoided, and culture medium was used instead. After 14 days in culture, granulocyte/macrophage colonies containing more than 20 cells were scored in an inverted microscope.

Mean colony counts of 44 colonies per $10^5$ cells were decreased by both Ara-A and Ara-C. The dose-related effect on colony growth is depicted in the figure. It was totally abolished by therapeutic concentrations (indicated by asterisks) of both drugs, 50% inhibition occurred at a concentration which was 8 times higher for Ara-A than for Ara-C. Therapeutic doses, however, are 3 times higher for Ara-A, its actual cytotoxicity is thus roughly one-third compared to Ara-C. We conclude that the cytostatic effect of Ara-A has to be taken into account, particularly if the drug is administered to patients with depressed marrow function.




Dose related inhibition of colony formation by myeloid precursor cells by adenine-arabinoside (Ara-A) and cytosine-arabinoside (Ara-C). Mean values±SEM of 16 experiments on hematologically normal human bone marrow.

1 Supported by grants of the Swiss Cancer League (FOR 101.AK.77.2) and the Swiss Science Foundation (3.3320.74).
2 Acknowledgments. We wish to thank Prof. A. Lévy for support in providing normal bone marrow samples and Miss Beatrice Rubin for skilled technical assistance.
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## Iron malabsorption and hypochromic anemia in a case of Turner's syndrome

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*Summary.* Refractory hypochromic anemia was investigated in an adult with Turner's syndrome. Reduced iron absorption, serum iron, and iron incorporation were found in association with increased iron binding capacity and plasma iron turnover. 14 of 57 additional XO subjects were found anemic.

A 30-year-old woman with a karyotype demonstrating X monosomy and various clinical stigmata of Turner's syndrome had been followed for intestinal malabsorption for several years without anemia. In 1977, she developed a mild hypochromic anemia (hemoglobin nadir 11.0 g/dl), which was unresponsive to oral iron treatment. Further evaluation revealed defective iron ($^{59}$Fe) absorption on 3 serial determinations (range: 0.2–0.3%, low serum iron, (range: 9.8–13 µmole/l; normal 14–31 µmole/l), elevated total iron binding capacity (36 µmole/l; normal = 18–30 µmole/l), and normal reticulocyte counts. Ferrokinetic studies demonstrated a markedly shortened plasma iron turnover (140 mg/day/100 ml of whole blood) and borderline low iron incorporation (62.2%). The latter finding was found in association with an abnormal Shilling tests (3.9% $B_{12}$-$^{59}$Co; 6.1% $B_{12}$-$^{57}$Co with intrinsic factor). A radiographic examination of the gastrointestinal tract demonstrated abnormal mucosal contours of jejunum and distal ileum, but was otherwise normal.

Normally iron balance is precarious in female subjects, but relatively few clinical entities are commonly associated with iron malabsorption[1]. The most important of these malabsorptive states is gluten-sensitive enteropathy (GSE), although abnormalities in gastric, pancreatic, and biliary secretion have been proposed as additional causes, none has been found clinically important[1]. The late and insidious onset of anemia in the propositus might be explained on the basis of a longstanding generalized state of intestinal malabsorption. It is apparent that iron absorption studies may be the most sensitive indicator of GSE and other generalized states of intestinal malabsorption and anemia often occurs only at an end stage in such conditions[1].

Although ferrokinetic studies have fallen somewhat out of fashion, because the half-time disappearance curve of plasma iron, plasma iron turnover, and percentage utilization provide only an approximation of the state of erythropoiesis; such studies remain a valuable and rational approach to the assessment of anemic subjects[2]. Despite the inherent limitations of the methodology, it is likely that the increased plasma iron turnover and marginal iron incorporation in the propositus may be a response to her chronic iron and vitamin $B^{12}$ malabsorption. Usually the bone marrow in $B_{12}$ deficiency responds dramatically to the anemic stimulus, but because of the inability of the erythroid precursors to produce nucleic acids normally, the erythropoietic effort is largely ineffective; resulting in an increased PIT but a reduced iron incorporation and ultimately, anemia. However, the relationship of these findings to the underlying chromosomal abnormality remains to be elucidated in Turner's syndrome.

Consultation with colleagues and a thorough review of the medical literature, assisted by a computerized system of medical data retrieval (Medlars), yielded no previous reports of abnormal ferrokinetic data in Turner's syndrome. In reviewing our patient records, we found 14/57 (24.6%) anemic subjects with XO karyotypes. In 10 cases, the anemia was mild (hemoglobin $> 10 < 12$ g/dl) and moderately severe in the remainder (hemoglobin $> 8 \leq 10$ g/dl). 2 cases in the latter category were iron responsive. One of these was associated with gastrointestinal telangectasia. Although the frequency of anemia in this series of Turner's syndrome patients does not exceed that expected in a general population of individuals of this age and sex distribution[3], it should be emphasized that iron deficiency anemia is much less common among young women in Sweden, where iron supplementation of foodstuffs is governmental policy[4]. Further investigation of ferrokinetics in Turner's syndrome may be fruitful, particularly in subjects with microcytosis, anemia or malabsorption.

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