LAMBDA KAPPA SIGMA
International Pharmacy Fraternity

# Blue & Gold Triangle

March 1982

## PLANS ARE SET FOR A GREAT CONVENTION

### Schedule of Activities for LKS 1982 Convention

Monday, July 19, Grand Council Meetings.
Tuesday, July 20, Grand Council Meetings.
Wednesday, July 21,
Delegates Arrive (12:00 on)
Registration
Independant cruises of Pittsburgh on Gateway Clipper on Pittsburgh's 3 rivers
General Reception- at hotel, scrapbook exchange, munchies, ethnic entertainment, D.J.
Thursday, July 22,
Opening Breakfast- 8:00 am
General Meetings- 9:00-12:00
Lunch
Officer Information
General Meetings- till 5:00
Bimbo's Good Time Emporium- all the pizza and beer you can eat and drink
Friday, July 23,
General Meetings- 9:00-12:00
Professional Fraternity Assn. Luncheon-12:00
General Meetings- 2:00-5:00
Pittsburgh at Night- Individual Tours of Pittsburgh's Night Life: includes discos, skyline, shopping, lounges and entertainment, possibly a Pirates game if schedule permits.)
Saturday, July 24
Breakfast- 8:00
General Closing Meeting 9:00-12:00
Drug Fair- 12:30-3:00
Continuing Education- 2:00-4:00
Pictures
Cash Bar- 7:00
Final Banquet-installation of Officers, awards, presentations
Sunday, July 25- Departure

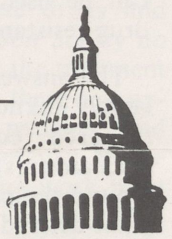
Finalize your schedule now to attend the 27th Lambda Kappa Sigma biennial convention to be held in Pittsburg, Pennsylvania, July 21-24, 1982.

Travel arrangements will be handled by

**FUGAZY INTERNATIONAL TRAVEL**

**67 Whitney Avenue**
**New Haven, CT. 06510**

## PITTSBURGH — SOMEPLACE SPECIAL!



Join us at the 1982 Biennial Convention this summer, and see just what it is that makes Pittsburgh a special place. The 1982 Convention is being hosted by Delta and Tau Collegiate chapters, along with Tau Alumnae chapter. The Sheraton Inn, located at Station Square, will accommodate our guests and prove to be a delight to even the most wearisome traveler. Station Square offers everything from old world antiques to modern clothing boutiques to cozy restaurants, promising every personality a thoroughly enjoyable time. Pittsburgh is a city as active by night as by day, making our convention a good time whether your tastes in entertainment lie in sing-a-long taverns, discotheques, or Shakespearean theatres.

Along with the fun and excitement, let's not forget the important tasks at hand. Continuing Education sessions, workshops, and informative meetings will also be listed on the agenda.

Make plans now to attend the 1982 Convention — and help to make Pittsburgh an even more special place!

## Lambda Kappa Sigma Educational Trust

Our thanks to the contributors to the Lambda Kappa Sigma Educational Trust. We are most grateful for your continuing gifts to the Trust.

What great satisfaction it is knowing that your donation is helping to finance the Cora E. Craven Educational grants for undergraduates in pharmacy, and the Olive B. Cole grants for graduate students!

The first LAMBDA KAPPA SIGMA EDUCATIONAL TRUST fund raising drive is underway. In order to maintain our triple exempt status this TRUST must receive donations from what are termed the general public. Our goal is to match the $3,800 annual income of the interest from the TRUST.

Available are envelopes which list these suggestions: Memorial, Initiation, Graduation, Birthday, Wedding, Anniversary, Get Well, or any other occasion.

Remember that your contribution is tax deductable to you, the TRUST pays no taxes on its income, and the grant recipient is not taxed on their gift.

Join the hundreds of Loyal Lambs who are mailing their contributions to:
LKS EDUCATIONAL TRUST
6181 North Parker Avenue
Indianapolis, Indiana 46220

# CURRENT APPROACHES TO TREATMENT OF DRUG-RESISTANT LEUKEMIA

### *Author's Comments*

*Dear Sisters:*

*After talking with Judy Riffee about including a research section in the Blue and Gold Triangle, I have given the matter much thought; and I must admit that I have some misgivings about submitting a manuscript. Here at St. Jude Children's Research Hospital, many of the drugs and drug protocols used are experimental. The "facts" that I am able to share with you about the research going on here at St. Jude are, therefore, not facts at all. While I'm afraid that this may be disappointing at first, I also feel that it is exciting to hope that some day this work may be applicable to the treatment of catastrophic diseases in children for which this hospital was founded.*

*I thank you most sincerely for the opportunity to share our work with you.*

*Fraternally,*
*Mary K. Danks Whipple*
*Division of Biochemical and*
*Clinical Pharmacology*

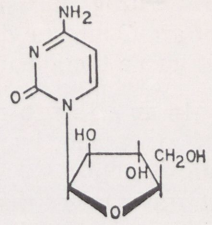
Much progress has been made in past years in the treatment of childhood leukemias. With chemotherapy and radiation, it is now possible to induce an apparent leukemia-free status in over 90 percent of newly diagnosed patients. The disease is often not permanently suppressed, however, and more than 50 percent of patients achieving remission will ultimately relapse. The leukemic cells which are present at relapse in many cases do not respond to the first drug protocol with which the patient was successfully treated at diagnosis. When this occurs, there are only a few alternatives to which pediatric oncologists can turn in treating patients in relapse. Since St. Jude Children's Research Hospital is a research institution, problems of this type can be considered simultaneously from a clinical as well as a basic science point of view. The next few paragraphs will briefly summarize several approaches that are currently being used to try to find ways to treat refractory patients.

From the pharmacological standpoint, we can view the population of drug-resistant leukemic cells which are present in refractory patients from several angles, with the primary goals being to determine why a cell is drug-sensitive or drug-resistant, and how drug resistance can be overcome. Using a chemotherapeutic approach, drug-resistant cells can be challenged either with new cytotoxic agents, or with improved methods of administration of drugs now available. Both of these approaches are being pursued and have recently resulted in two new chemotherapeutic agents for the treatment of childhood leukemia, as well as a promising new method of administering a known drug.

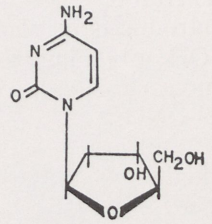
The first of the new drugs is a podophyllum derivative. It belongs to the same family of podophyllotoxins from the May apple which are familiar to many of us from pharmacognosy lectures. Two semisynthetic products have been made from the rhizomes of the plant; these derivatives are known as VM-26 and VP-16. When used in combination with cytosine arabinoside (ara-C, Cytarabine), VM-26 or VP-16 has induced remissions in some acute lymphocytic leukemic (ALL) patients in relapse. By what mechanism, then, were some cells sensitive and some cells still resistant to the oncolytic effect of these drugs? What approaches can be used to circumvent the new drug resistance which develops?

The answers to these questions are largely unknown. The original line of research concerning the drugs' mechanism(s) of action was centered around the possibility that, like other plant-derived cytotoxic agents, e.g. vincristine and vinblastine, they would arrest the cell in metaphase (M phase) by binding to the protein, tubulin, which makes up the spindly apparatus which is present during mitosis. It now appears, however, that even though some drug-tubulin binding occurs, this is not the primary mechanism by which VP-16 and VM-26 induce cell death because the *in vitro* concentration at which this binding phenomenon occurs is too high to be attainable in patients. It appears more likely that the drug acts by causing breaks in the DNA strands themselves. It is known that the drug can block incorporation of thymidine (one of the four nucleotides that make up DNA) into DNA, but it is unknown whether the cytotoxicity is a result of the effect on thymidine incorporation or whether the drugs cause DNA strand breaks by another mechanism. It is also possible that a combination of these mechanisms is what finally results in cell death. The mechanisms of drug action and drug resistance are still under investigation.

A second new drug in the chemotherapeutic regimen is a derivative of a drug with which we are already familiar. The parent drug is cytosine arabinoside (ara-C) (Figure 1) which is an analog of the endogenous compound deoxycytidine (Figure 2). The difference between the drug and the naturally-occurring compound is in the sugar portion of the molecule:



*ara-C*
*Figure 1*



*deoxycytidine*
*Figure 2*

Deoxycytidine has a deoxyribose sugar, and ara-C has an arabinose sugar. In order to exert its oncolytic effect, many investigators believe that the parent drug, ara-C, must be metabolized to its triphosphate form, i.e., cytosine arabinoside triphosphate (araCTP). This transformation takes place via an enzyme reaction. A second enzyme, DNA polymerase, then incorporates either the drug (araCTP) or the naturally-occurring deoxycytidine triphosphate (dCTP) into DNA. The araCTP acts as a competitive inhibitor with dDTP for DNA polymerase. Investigators now believe that the intracellular event which is finally lethal to the cell is either inhibition of the DNA polymerase itself or incorporation of araCTP into DNA. In susceptible cells, this sequence of events takes place unimpeded. In some resistant cells, however, an extremely rapid alternate route of metabolism has been identified. As a result of the reaction shown in (Figure 3), ara-C is converted to uracil arabinoside (ara-U). In this way the

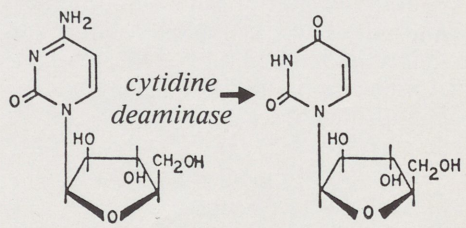



*Figure 3*

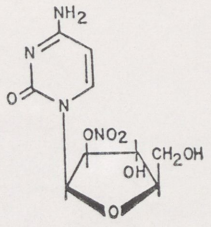
*ara-C* *ara-U*

drug is inactivated because ara-U is not cytotoxic and no oncolytic effect occurs. A high plasma titre of ara-C is needed as a 'prodrug' reservoir for the

formation of the active araCTP form of the drug. In resistant cells, the level of ara-C may be depleted too quickly to give a therapeutic effect.

In an effort to overcome this route of drug inactivation, a new drug similar to ara-C has been synthesized. It was known that by changing the substitution on the 2'-position of ara-C, susceptibility to inactivation by the deaminase enzyme was altered.

Therefore, a nitro- ($NO^2$) group was introduced in place of the hydroxyl (OH) group in the sugar portion of the molecule. The new compound, 2'-$ONO^2$ara-C or nitrara-C, (Figure 4), is not deaminated as rapidly as the parent compound, and remains in the plasma for an extended period of time. The drug is then available to be transported across cellular membranes, to be metabolized intracellularly, and to exert its antitumor activity. This drug is still being tested in cultured cells and laboratory animals, but appears to have significant antitumor activity.




*nitrara-C*
*Figure 4*

The third example of experimental approaches in treating refractory leukemia is shown by use of the high dose ara-C protocol (HDARA-C). Conventional doses for ara-C therapy are in the range of 200mg/$m_2$/day. At St. Jude, an investigational protocol has been started with leukemic patients who are refractory to other forms of treatment. These patients are given more than 10 times the conventional dose of ara-C. The rationale for this approach is that the concentration of active drug (araCTP) in the cells should be greater than the concentration of the endogenous nucleotide (dCTP) in order to effectively compete for DNA polymerase and, in this way, to exert an antitumor effect. The greatest concern when this protocol was initiated concerned toxicity to the patient; but, suprisingly, there is little difference in the toxicity seen at low vs. high doses.

Since this is a unique protocol in that the patients receive only one drug instead of the usual combination chemotherapy, parallel biochemical studies are being done to obtain data on the biochemical basis for the primary mechanism of drug action in human leukemic cells and also the mechanism of resistance. Preliminary results show that some patients who were previously thought to be resistant to ara-C will respond to some degree to the HDARA-C. While these results are encouraging, another pharmacologic dilemma has presented itself: Even when the concentration of araCTP/concentration of dCTP is very high, the patients do not always respond to therapy. In light of this preliminary data, therefore, alternate directions for this research must be considered. For example, is it possible that a metabolite other than araCTP is the determining factor in drug effectiveness? What is the basis of the drug resistance that is still present?

In summary, VM-26, VP-16 and nitrara-C show promise as new drugs for the treatment of leukemia, and the HDARA-C protocol reminds us again that we must continually reevaluate "accepted" chemotherapeutic protocols. However, these drugs and methods of administration are by no means a final answer in the treatment of leukemia. Even with these new approaches, refractory patients and drug-resistant cells continue to be identified. Clearly, more work must be done.

*Sources and references furnished upon request from the editor.*

## LAMBDA KAPPA SIGMA POST CONVENTION TOUR

ITINERARY: MONDAY, JULY 26 — Depart your Pittsburgh Convention Hotel in the morning by private motorcoach. We reach Hershey Park midday for an afternoon of fun. Late afternoon depart for Lancaster and the typically Pennsylvania Dutch Willow Valley Farms Inn for a two nights stay. This evening you will partake in a Pennsylvania Dutch Feast — all you can eat, family style!

TUESDAY, JULY 27 — In the morning we drive to the Farmers Market for shoping, followed by lunch at Miller's Smorgasbord — home of 7 sweets and 7 sours. Then we begin tour with local guide of Amish homes, farms, and schools. Stops include a working Amish Homestead and Kitchen Kettle Village, a unique collection of shops for the souvenir hunter. Following this tour we ride the Strasburg Steam Railroad to "Paradise".

WEDNESDAY, JULY 28 — This morning our private motorcoach takes us to our nation's capital, Washington, DC. On arrival check in to the Holiday Inn Capitol in the downtown area, a brand new hotel located within walking distance of the Aerospace Museum. This afternoon we'll take a driving tour, with local guide, to include major sights such as Capitol Building, Kennedy Center, Embassy Row, White House (if available), etc. Return to hotel to freshen up. Early evening departure for fine, professional Dinner Theatre at the Harlequin.

THURSDAY, JULY 29 — The morning is free for visiting the Smithsonian Buildings of your choice or other activites. We will meet for lunch at the Flagship Restaurant on the waterfront where seafood is the specialty! After the meal, our motorcoach will take us for a visit of Arlington National Cemetary. Return to the hotel and a free evening.

FRIDAY, JULY 29 — Morning departure for historic Gettysburg, Pennsylvania and a visit to the Eisenhower Farm. Lunch on own. Afternoon sights include the Battlefield Tower, Lighted Map and narrated bus tour of the battlefield. At the conclusion of the tour we will check into Howard Johnson's Gettysburg for overnight.

SATURDAY, JULY 31 — Morning departure for the return drive to Pittsburgh with rest stops en route. The tour will terminate at the Pittsburgh Airport at approximately 2:00 P.M. Travel arrangements are being made by Fugazy International Travel, 67 Whitney Ave., New Haven, Ct. 06510, (203) 772-0470, or toll free 1-800-243-1723.

The Blue and Gold Triangle is the official publication of Lambda Kappa Sigma, International Pharmacy Fraternity published quarterly by Lambda Kappa Sigma.

Ms. Sue Corkum, Grand Editor
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Lambda Kappa Sigma is a member of the College Fraternity Editors Association and the Professional Fraternity Association.

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International Pharmacy Fraternity
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**If you plan to attend the Convention, you must return both forms below by June 23, 1982.**

## 1982 Convention Registration Pittsburgh, Pa.

Name _____ Chapter _____

Street _____

City _____ St. _____ Zip _____

Grand Council _____ Office _____

Regional Representative _____ Region _____

Delegate ____ Alternate ____

Non-delegate Member ____

Chapter Advisor ____

Family of Member ____

The REGISTRATION FEE for everyone for the full convention is $65.00.

PARTIAL REGISTRATION

Wednesday night ($5.00) ____

Thursday Opening Breakfast ($7.25) ____

Thursday, excluding trip to Bimbo's ($15.00) ____

Trip to Bimbo's Thursday Evening ($15.00) ____

Shakespearean Theatre Trip, Thursday evening ($20.00) ____

Friday ($12.00) ____

PFA Luncheon, Friday ($10.00) ____

Saturday, excluding Banquet ($7.00) ____

Banquet only ($25.00) ____

No refunds will be made after Wed., June 23, 1982; registration may be transferred to another person who must complete a Registration form.

TOTAL ENCLOSED _____

## Room Registration - 1982 Convention
## Sheraton Inn at Station Square

Name _____ Chapter _____

Street _____

City _____ St. _____ Zip _____

I wish to reserve:

____SINGLE $60.00 per night (& tax)
____DOUBLE $70.00 per night (& tax)
____TRIPLE $70.00 per night (& tax)
____QUAD. $70.00 per night (& tax)

for:

____Wednesday ____ Monday (GC & Reps.)
____Thursday ____Tuesday "
____Friday
____Saturday

Enclosed is the first night's registration $ _____

I would like to have the following roommates:

_____

_____

_____

Please arrange roommates for me. _____

Send BOTH forms and REGISTRATION FEE to:
Ms. Linda Wieloch
211 Ruxton St.
Pittsburgh, Pa. 15211
by June 23, 1982.