

Trip Report - Kiev, January 13 - 23, 1999
by Stuart C. Finch

Arrived in Kiev the afternoon of Wednesday, January 13, 1999. The following morning was accompanied by Dr. Tsvetkova to the new clinical center where I was met by Drs. Dyagil, Klimenko and Gudzenko and several members of their staffs. The day was spent checking out microscopes, lighting, projectors, computers, copying facilities and conference rooms. A large paper pad for recording consensus events was requested but I was told that such is not available. Substituted for this was an approximately 4 x 4 foot blackboard. All in all I was most pleased with the arrangements for the review. The microscopes and substage lighting were of excellent quality. The table on which they were placed was of ample size and the chairs were of the proper height.

Dr. Gudzenko showed me the slide folders containing the collected materials from the oblasts for the 85 cases of leukemia, myelodysplasia, multiple myeloma and related disorders. Sixty eight of the cases had slides and abstracted histories and 17 had abstracted case histories only without hematologic slides. Material also had been collected on 15 cases of non-Hodgkin's lymphoma and 15 cases of Hodgkin's disease. Three of these cases had only clinical records. The remainder had both slides and abstracted clinical records. Our discussion then turned to the nature of the material and the many problems in obtaining it. Dr. Gudzenko indicated that for the randomized cases she selected the overall return in the 6 oblasts was only about 30-40%. For this reason she selected additional cases from her lists in order to satisfy the need for enough cases to conduct an adequate review of representative surrogate cases. Dr. Gudzenko indicated that there were specific problems in some oblasts that were responsible for the low yield of her initial list of randomly selected cases. For example, in ^{SUMY} Sumiskaya a fire had destroyed virtually
or SUMSKAYA OBLAST

all slides and records prior to 1990. In contrast, the results from Dnepropetrovsk were excellent. Dr. Gudzenko has agreed to analyze the result of her efforts for each oblast by type of case disorder requested. Naturally, I discussed with Drs. Dyagil, Gudzenko and others the obvious problem of conducting good histologic verification of retrospective liquidator cases if the slide yield was as low as 30-40%. Their responses were as follows: 1) the analysis could show that some oblasts could be eliminated and others substituted on the basis of the frequency with which slides for target cases can be identified; 2) a more intensive effort to find materials could be made in certain oblasts; and 3) (and most important!) that the state of preservations of materials for liquidators is much better than that for the general population. This position also was taken by Drs. Bebeshko and Klimenko in subsequent discussions. (This was the first time that the possibility that preservation of medical records and biological materials might be better for liquidators than for the general population.)

Drs. Dyagil and Gudzenko indicated that only intervention through the highest level resulted in good cooperation by the staffs of the hospitals and polyclinics (Romanenko and/or Bebeshko directly to oblast health officials). Dr. Gudzenko stated that she generally was well received but that being accompanied with or followed by one of the hematologists from the Center greatly improved results in finding blood smears and in abstracting case histories. Hospital personnel expressed much concern about the return of their slides without damage. It also was noted by them that if oncology clinics were involved the problems were much greater than if involvement was only with hematology. They also felt that the hematology materials and records were much better for the hematology patients than for the oncology patients.

In view of the low yield of histological materials for the surrogate population which we studied and their now taking the position that the yield should be much higher for liquidators, I discussed very briefly with them the possibility of determining the frequency with which histologic slides can be identified in the same oblasts for liquidators known to have developed leukemia, lymphoma or a related disorder. They now see the importance of doing this and believe that it could be done quite rapidly and quite easily.

On Friday (January 14, 1999) the day was spent organizing slide folders for review and filling out worksheets for the reviewers as much as was possible. Worksheets were coded for the reviewer's names and then separated into groups for each reviewer. Dr. Gudzenko noted that slide labels were coded to indicate the oblast of origin and type of disease. The slide folders were placed in piles of 5 each with leukemia, myeloma and related disorder cases to precede study of the lymphomas. The agenda was reviewed and modified.

Dr. Reiss arrived on Saturday and Drs. Adam and Peterson arrived on Sunday. Dr. Brunning did not arrive as was planned on Sunday or on Monday so that Dr. Reiss was asked to substitute for him in the review process. Many attempts to determine the reason why Dr. Brunning did not arrive as scheduled proved futile (it later was learned that he did travel as far as Boston but flight cancellations due to inclement weather prevented him from continuing on in time to have meaningful participation in the review panel).

On Monday, January 18th Dr. Romanenko met with us and many of his staff members in a large conference room in the new hospital. Present were Drs. Romanenko, Bazyka, Klimenko,

Dyagil, Gudzenko, Gaikudova, Gluzman, Reiss, Peterson, Adam, Finch and others. Dr. Romanenko gave a short history of the development of the Center and its structure. Introductions of persons at the meeting were made and I then followed with a short history of the origins and development of the project to date. I then outlined the objectives of our review. Dr. Gudzenko then described how and from where the histologic materials were identified and collected. She noted that there were two phases in materials selection beginning with random cases then filling in later with other cases selected by diagnosis only.

The working and staff support groups then moved to the slide review room where I reviewed use of the worksheets for the study. I stressed that the primary purpose of the review was to determine whether the clinical diagnosis made at the oblast level could be confirmed by them with a reasonable amount of certainty. I emphasized that the precise FAB type of leukemia or NIH working classification was of secondary importance. Determination as to whether a leukemia was acute or chronic or lymphocytic or myelogenous also was important but still not as important as confirmation of the major diagnosis. They agreed on those general principals and each to look at only 5 cases before having a consensus diagnosis session for those cases. They also agreed to stay with a single microscope for the reviews rather than to move from one scope to another. They were not asked to sign their worksheets and were not told that the sheets had been coded - although I did say that we would look at the variations in estimates for certain parameters among members of the group. Agreement was reached very quickly that the disease classification systems on the worksheets were acceptable (basically this included the FAB system for acute leukemia, the NIH Working Formulation for non-Hodgkin's lymphoma and the Rye classification for Hodgkin's Disease).

The review process went very smoothly. The slide folders were excellent for the preservation and organization of slides. The clinical abstracts (bilingual) generally were quite good and assisted greatly in the confirmation of several cases of leukemia. Actually, panel members were quite certain of the diagnosis of leukemia in 5 of the 17 cases with case histories alone. All members of the panel appeared to be quite competent in leukemia diagnoses with perhaps Dr. Gaikudova being the weakest of the group.

A consensus diagnosis for each case was agreed upon by all members of the review panel after 5 cases had been reviewed. I then recorded the consensus diagnoses on summary sheets. Upon completion of 10 cases the worksheets were collected and the results for each case were recorded for each reviewer on the summary sheets by Dr. Gudzenko and me. The results on the summary sheets will be analyzed in many different ways in order to provide information regarding such things as: a) the quality of the material by oblast, type of disease, etc.; b) frequency of disease confirmation; c) value of clinical abstracts; d) variations in examiners for major diagnosis, opinions regarding slide qualities.

Case reviewers started slowly with only 20 cases reviewed on Monday, 30 on Tuesday and 35 on Wednesday. The members of the panel rotated the responsibility for leading discussion for establishment of a consensus diagnosis. This worked out very well. It would appear from preliminary analysis of comparisons between the clinical diagnosis and workshop panel members diagnoses that if slides are available that the diagnostic confirmation rate for the leukemias are high (CLL-100%, AL-96%, CML-87%). 73% of the myeloma cases were

confirmed (only 3 cases were not confirmed, there were no slides for 2 cases and they were poor for 2 others). The slides were poor for the 3 cases of MDS which were not confirmed and for the other cases of leukemia related disorders the low confirmation rates usually were due to a lack of bone marrow tissue sections (i.e. aplastic anemia, hypoplastic anemia, myelofibrosis, etc.). A few cases identified as acute leukemia were thought more likely to be advanced types of myelodysplasia but that difference was not felt to be serious as differentiation between these disorders without special stains is most difficult, even by the best of experts. There were no problems with the diagnoses of the chronic leukemias. Medical histories alone were convincing for 5 of the 15 submitted to the panel for the probable diagnoses of either acute or chronic leukemia. Dr. Gudzenko provided medical histories for 8 cases of leukemia from her original randomly selected list for which slides could not be located. Dr. Reiss, Dr. Adam and I felt that a diagnosis of leukemia could be made for only one of these cases. (The results of review of these 8 cases with histories only has not been included in the report of final results.)

A one hour meeting of the panel group was conducted the morning of Thursday, January 21 in order to discuss preliminary analysis of consensus diagnosis of leukemia, myeloma and related disorders in comparison to the previous clinical diagnosis (see table attached). Panel members agreed that if slides and an abstracted history were available that the confirmation level for the diagnosis of acute and chronic leukemia and myeloma is high.

The remainder of the morning and most of the afternoon was spent with review of the lymphoma cases by Drs. Peterson, Gaikudova and Gluzman. This was a fortunate arrangement since both Drs. Adam and Reiss did not feel competent to review the lymphomas. Dr. Peterson

was the driving force for the lymphoma diagnostic review but both Drs. Gluzman and Gaikudova usually were in agreement with her diagnosis and classification. Slides were absent from 2 of 15 cases of non-Hodgkin's lymphoma and 5 of 15 cases with Hodgkin's disease. 12 of the 13 cases of non-Hodgkin's lymphoma with slides were confirmed and 8 of 10 with slides for Hodgkin's disease (see attached). Many of the slides were of poor quality. Panel members felt that for many cases the tissue blocks should be located, recut and restained. Determination of the availability of tissue blocks at various locations would be advisable before embarking on an extensive retrospective study of the lymphomas.

At 4:00pm on Thursday Dr. Peterson gave an excellent lecture on lymphoproliferative disorders. There were about 50 persons present in the audience. Many questions were asked by the hematologists in the audience.

Dr. Romanenko sponsored a dinner on Thursday evening for members of the panel along with Drs. Bazyka, Tsvetkova, Klimenko, Bebeshko, Pyatak, Gudzenko and Finch. He expressed his thanks to the panel members for their participation at that time. Drs. Reiss and Adam departed on Friday.

It should be noted that the entire review program was enhanced through the donation of some excellent educational materials from the American Society of Hematology (ASH) and NCI. The ASH contributions consisted of two recent monographs of theirs updating hematologic diseases, a 35mm slide collection of acute leukemia blood cells and a CD-ROM on which there are over 2,500 pictures of blood cells and graphs concerning leukemia, lymphoma and many

other hematologic disorders. The NCI contribution consisted of 2 copies each of the AFIP monographs on Tumors of the Bone Marrow and Tumors of the Lymph Nodes.

The process could have been made easier if a large paper display pad had been available in order to summarize consensus opinions for the record as we progressed. The blackboard was adequate but erasing consensus information after each 5 cases opened the possibility of information loss, unless it was correctly and continuously recorded by Dr. Gudzenko and me as we went along.

It was indeed unfortunate that Dr. Brunning was unable to attend the review due to air flight cancellations. It was fortunate, however, that Dr. Reiss did attend and was able to very ably replace Dr. Brunning at the review table. Dr. Peterson was a star and Dr. Adam was excellent. Both Ukrainian participants were good morphologists and worked well with the other review panel members.

Follow up plans call for a much more detailed analysis of collected information and some recommendations regarding the next steps.

In summary, the panel review session was most successful in accomplishing its main objectives. The most reassuring result of the review is that the independent review panel was able to confirm most diagnoses of leukemia, myelodysplasia and lymphoma (including multiple myeloma) on the basis of the clinical and histologic materials obtained from persons identified on lists of cases with these diagnoses.

However, the serious problem of the low yield of medical records and histologic materials for random identified cases in the oblasts also was uncovered. This suggests that the next step is to determine in key oblasts the availability of clinical information and tissues for liquidators with histories of leukemia and lymphoma (going on the assumption that more materials are available for the liquidators than an age and sex matched general population). Perhaps the way to proceed is to identify the names of 15-20 liquidators who are known to have developed leukemia, lymphoma or multiple myeloma and then to determine the availability of their medical records and tissues in their respective oblasts. It would be ideal to concentrate on the oblasts targeted in the protocol since previous contact with authorities in these oblasts should make the process easier and would make it possible to compare the availability of liquidator materials with those of the previously selected population. If possible cases should be identified from the early, middle and late years as was done for the cases reviewed by the expert panel.

Preliminary Analyses of Results of Review of Hodgkin's Disease and Non-Hodgkin's Lymphoma

Type of Disorder	Total Number of Cases	Number With Slides	Number Confirmed	% of Total Number Confirmed	% With Slides Confirmed *
NHL	15	13	12	80	93
HD	15	10	8	53	80

* Lack of confirmation of cases with slides was due mostly to poor condition of slides (i.e. tissues too thick, coverslip artifacts, tissue fragmentation, poor stain, gel on coverslip, etc.).

Preliminary analysis of results of review of leukemia, myeloma and related disorders

Type of disorder	Total number of cases	Number with slides	Total number confirmed*	Number with slides confirmed	% total confirmed	% with slides confirmed
CLL	12	7	9	7	75	100
Acute Leuk.	31	28	27	27	87	96
CML	11	7	8	6	73	87
Myeloma	13	11	9	8	70	73
MDS	6	6	3	3	50	50
Myelofibrosis	7	4	1	1	15	25
Aplastic (hypoplastic) anemia	5	5	1	1	20	20
Total	85	68	58	53	70	78

* of 17 cases with histories 5 cases (2 CML, 2 CLL, 1 MM) were considered "probable" on the basis of the medical records.