CASE 1 (Children Centre #557-373): This seven-year-old girl was admitted to the hospital with a small intermittently bleeding polypoid mass approximately 1 cm. in diameter filling and protruding from the left external ear canal. This had been curedtted some weeks previously at another institution where it had been reported histologically as granulation tissue. She had had no preceding history suggestive of otitis media.

CASE 2 (Misericordia Hospital #7613-64): This 41-year-old man was admitted in December, 1964 for right hip pain of three months duration following a fall. The pain gradually increased in severity and roentgenograms revealed an endosteal cystic lesion of the upper right femur, thought to be a non-ossifying fibroma. The lesion was curedtted and slides sent to various authorities for consultation. The patient underwent deep x-ray therapy to the right hip region.

In September, 1965, a pathological fracture occurred at the primary tumor site, but a biopsy failed to reveal residual neoplasm.

In January, 1966, there was clinical and radiological evidence of recurrent neoplasm in the right femoral head. A biopsy showed histologically similar characteristics. Shortly thereafter, a transiliac hind quarter amputation of the right leg was performed, and the resection margins were judged to be free from neoplastic involvement.

Three weeks prior to death in August 1966, the patient experienced respiratory distress, numbness and paraesthesias of the left shoulder region. Postmortem examination revealed no locally residual neoplasm, but there was metastatic tumour in the left lung, left adrenal, and right parietal cerebrum. Bronchopneumonitis was the terminal event.

CASE 3 (General Centre #6019-2/76): This 27-year-old female has a history of repeated respiratory infections and skin abscesses related to injury since childhood. Two or three years ago, typical condyloma accuminata were removed from her perineal region. She is now described as having warty lesions scattered over her body. One removed in January looked the same as the present lesion removed from the left upper thigh. Three other lesions removed at the same time as the present lesion proved to be two verrucae vulgares and one molluscum contagiosum.

Immunological investigations which have been done show that she has a low absolute T cell count in her peripheral blood and lymphocytes are not stimulated by candida in spite of previous infections by the organism. Her lymphocytes have also failed to be sensitized to DNCB. In January, she had an injection of typhoid vaccine into her thigh and the draining lymph nodes were examined a few days later. They showed follicle hyperplasia with numerous plasma cells, but the immunologists claim that although gamma globulins were produced, they did not function normally with only poor antibody titres to H&O antigens.

CASE 4 (Concordia Hospital #755-1655): This 56-year-old woman noted a lump about the size of a pea in the right upper arm. It had apparently been present for about 4-5 years but in July, 1975, it became painful, with movement of the arm and the lump increased to the size of an egg. An excisional biopsy was performed on July 30, 1975.

Case 5 (General Centre #1885/76): The patient is a 37-year-old male and the specimen is a fatty tumor removed from the left posterior triangle of the neck deep to trapezius muscle. It had been present for 5 years, but the patient believes it had been
growing more rapidly for the last 8 months. The tumor was apparently removed without difficulty except for the anterior inferior part where the surgeon felt a thickening which he felt might represent some residual tumor. He removed this, but unfortunately, it was lost and did not reach the laboratory.

The tumor measured 12.5 x 8.5 x 5.7 cms. and weighed 230 gms. There were fibrous and occasional muscle tags attached to the outer surface. The cut section showed obvious fatty tissue intermingled with greyish, gelatinous appearing areas.

CASE 6 (General Centre #2374/76 and #4410/76): This lady, born in April 1919, has disseminated lupus erythematosus, the chief manifestations of which have been arthritis with episodes of pleural involvement. She has been on relatively low dose steroid which appears to control this disease quite well.

About the first of this year, she noticed a painless, reddish, small raised skin nodule situated over the manubrium sterni, which gradually grew to approximately 1.5 cm. in diameter. It was not fixed to underlying structures. The biopsy raised concern about the possibility of a lymphoma, but no definite diagnosis could be made. Marrow aspirate showed one group of lymphocytes, which were somewhat abnormal, but again not diagnostic. Bone biopsy from iliac crest was negative. There was a 1 cm. axillary node thought to be unchanged for 4 years. A supraclavicular node was also palpable. A lymphangiogram showed enlarged pelvic and para-aortic nodes and was considered to be typical of lymphoma. A lymph node biopsy was then done.

Repeat immune electrophoresis examination since October 1975 showed an increasing M band. No Bence Jones protein was found.

CASE 7 (General Centre #21635/75): Parotid mass in 77-year-old woman. Pinkish-tan lobulated mass within the parotid gland measuring 1.7 x 1.4 cms. in size.

CASE 8 (St. Boniface Hospital #1269-74, #2740-75 and #83-76). This patient is an 83-year-old male. In 1971, he was found to have polycythemia vera complicated by thrombophlebitis. He claimed to have anemia 10 years prior to 1971 and had been receiving monthly injections (? Vitamin B12) until 1967. Schilling test confirmed the absence of intrinsic factor. Total protein was 8.8 gms. with 5.3 gms. globulin. Immunelectrophoresis showed a myeloma band. Bone marrow showed slight plasmacytosis.

In 1974 an inguinal lymph node was biopsied which revealed poorly differentiated lymphocytic lymphoma. Bone marrow aspiration showed infiltration with lymphosarcoma cells and mild megaloblastic change. Hgb. - 14.9 gms.; Hct. - 49.3%; WBC - 8,500. He was started on Chlorambucil. Subsequently he had developed persistent pseudomonas infection of the urinary tract. Gradual enlargement of the abdominal and peripheral nodes was noted. Four mos. prior to his demise he also developed persistent cough and fever with very little improvement with antibiotics. On Feb. 6, 1976 he was transferred from Dauphin Hospital to St. Boniface General Hospital in a moribund condition with bilateral pneumonia and massive lymphadenopathy. Hgb. - 13.3 gm.; Hct. - 40.7%; WBC - 3,100/cu. mm. with 85% polys, 11% lymphs, 2% monos and 1% atypical lymphs. Total protein 6.7 gms. with 2.8 gms. albumin. The patient expired 24 hours after admission.

CASE 9 (St. Boniface Hospital #3975-74): This 76-year-old woman was admitted to St. Boniface General Hospital in May, 1974 for polyarthritis but at the same time she was found to have ulcers, one on each supraclavicular region with the larger one measuring up to 3 cms. These ulcers had been present for 2 years and had been healing and breaking down again. There were no enlarged nodes noted. One of the skin ulcers was biopsied. Rheumatoid factor was negative. Hgb. - 9.5 gms.; Hct. - 37.9%; WBC - 10,900/ cu. mm. Bone marrow aspiration was within normal limits. She was given analgesics, vitamins and physiotherapy.
**DIAGNOSES**

**CASE 1 - MIDDLE EAR - EMBRYONAL RHABDOMYOSARCOMA**


**CASE 2 - BONE, FEMUR - MALIGNANT FIBROUS HISTIOCYTOMA**


**CASE 3 - SKIN - BOWEN'S DISEASE, POSSIBLY ARISING ON A VIRAL LESION. (not presented)**


**CASE 4 - SOFT TISSUE, ARM - MALIGNANT MELANOMA**


**CASE 5 - SOFT TISSUE, NECK - HIBERNOMA**


CASE 6 - SKIN AND LYMPH NODE - IMMUNOBLASTIC PROLIFERATION, PROBABLY MALIGNANT


CASE 7 - PAROTID - ADENOID CYSTIC CARCINOMA, ANAPLASTIC VARIANT.


CASE 8 - LYMPH NODE AND BONE MARROW - PLASMA CELL MYELOMA


CASE 9 - SKIN - ATYPICAL LYMPHOID INFILTRATE.


SEMINAR 243 - COMMENTS

Well attended and well received, judging from the comments. Good representation from academic and private pathologists. Somebody told me that almost all the Winnipeg pathologists (which means almost all of the Manitoba pathologists) were there.

CASE 1: Everybody agreed with the Dx of embryonal rhabdomyosarcoma. The chief of Pathology at Children Hospital, who contributed the case, showed some impressive clinical pictures. The tumor grew at an appalling speed and killed the patient. He also made the comments that (1) not infrequently the metastases of rhabdomyosarcoma are better differentiated than the primary; (2) Cross striations in these tumors are often found not in the solid tumor nodules but rather in tumor cells embedded in connective tissue stroma.

CASE 2: Contributor agreed with the Dx of malignant fibrous histiocytoma. He showed additional photomicrographs which showed some abnormal bone between the tumor cells. He said that he showed it to Unni of the Mayo Clinic, who agreed with the Dx and apparently made the comment that it is ok for malignant fibrous histiocytoma of bone to make a little bit of malignant osteoid.

CASE 3: Not presented. It did not really belong in this Seminar.

CASE 4: No reaction to my presumptive Dx of malignant melanoma. The contributor called it liposarcoma and an amputation was done. Apparently the lymph nodes were not involved. Maybe it is another epithelioid sarcoma.

CASE 5: General agreement with my Dx of hibernoma. Dr. Penner had diagnosed it as myxoid liposarcoma but sent it to the AFIP and Enzinger called it hibernoma. Apparently the tumor was not brown on gross inspection.

CASE 6: General acceptance of my diagnosis of immunoblastic proliferation, but not much discussion.

CASE 7: Buntine, who contributed the case, agreed with Dx of adenoid cystic carcinoma and wondered whether it might have arisen from a mixed tumor. He added that he has seen several of these malignant lymphoepithelial lesions in the parotid of Eskimos and that they don't look like the present one. This particular patient was an Indian.

CASE 8: The clinician who took care of this patient was there and showed clinical pictures exhibiting a very impressive cervical and axillary lymphadenopathy. He added that the patient had Bence-Jones protein. Clinically, it sounded more like lymphoma than myeloma. The monoclonal peak in the serum was an IgG.

CASE 9: Following this lymph node biopsy, the patient developed lymphadenopathy. An inguinal LN was biopsied and Lu showed photomicrographs of it. He diagnosed it as Hodgkin's disease and gave me a slide which I incorporated to the Seminar.
John Hope, M.D.
Family Practice Center
Roblin, Manitoba R0L1PO
CANADA

Re: Bella Titanich
NIH# 11-91-14-7

Dear Dr. Hope:

As you know from my recent letter, Mrs. Titanich was a patient in the National Institutes of Health Clinical Center from January 11th, 1977, until February 11th, 1977. She had been referred by Dr. K. S. Tse of Winnipeg for evaluation and treatment of cellular immunodeficiency.

Her rosette-forming T-cells were 15% after one hour of incubation and 60% after 24 hours. These values are somewhat lower than the controls and at the lower side of our normal range. The absolute lymphocyte counts were about 1500-2000 per mm³.

The other studies of T-cell function were more abnormal, as shown below:

<table>
<thead>
<tr>
<th>Mitogen</th>
<th>DPM</th>
<th>Stim.</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1776</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>PHA - 1ng</td>
<td>102979</td>
<td>60</td>
<td>100-700</td>
</tr>
<tr>
<td>0.5ng</td>
<td>77596</td>
<td>44</td>
<td>60-200</td>
</tr>
<tr>
<td>Con A 40ng</td>
<td>47764</td>
<td>27</td>
<td>60-150</td>
</tr>
<tr>
<td>PWM</td>
<td>68183</td>
<td>38</td>
<td>60-150</td>
</tr>
</tbody>
</table>

There were no responses when her lymphocytes were stimulated in vitro with candida, PPD or tetanus toxoid. The response to streptokinase-streptodornase (SK-SD) was 8.5x the instimulated control, which is in the normal range for our lab. It is of interest that we were able to normalize her in vitro responses to mitogens by adding levamisole (50ng/ml) to the cultures.

In other experiments we have attempted to look for suppressor cells in her blood. These experiments require prolonged tissue culture and the results are not yet available.
Her delayed skin test studies were similar to yours. She developed 2.2 cm of induration to SK-SK and no responses to PPD, candida, trichophytin or tetanus toxoid.

Therapeutically, we may not have taken a very heroic course. I decided not to give her thymosin (or thymus) until I had a plasma thymosin level. This is in the works. Secondly, the supply of thymosin is somewhat in doubt right now and I did not want to start something that we could not complete. Thirdly, I have a feeling that her defect is not due to a defective differentiative function of the thymus. Instead, I think the problem is more at the level of regulation of helper-suppressor functions.

In any case, I have started her on a trial of transfer factor. Some of our candidiasis patients also have recurrent acute pulmonary infections and have benefited from an apparent non-specific effect of transfer factor. It could help her. We plan a four month trial and then plan to re-evaluate her.

Shortly after admission, Mrs. Titanich became acutely ill with bronchitis and pneumonia due to H. influenzae. This responded to antibiotics, but it made it impossible to do bronchograms which may be useful in her overall management. She was also given an aggressive program of hydration and pulmonary drainage physical therapy. Her ventilatory functions were rather good (copy enclosed).

I appreciate your giving the transfer factor for me. Please contact me if any problems or questions arise.

Sincerely yours,

Charles H. Kirkpatrick, M.D.
Head, Clinical Allergy and
Hypersensitivity Section
National Institute of Allergy
and Infectious Diseases
Laboratory of Clinical Investigation

NIH/NIAID/LCI
CH/Kirkpatrick/dra

Enclosure
Dear Dr. Hope:

Please excuse the delay in providing information on Miss Titanich. She had several biopsies done and there was some indecision about the final diagnosis. After the slides were reviewed by various consultants the consensus diagnosis was Bowen's disease, which I understand is a low grade squamous carcinoma, but one that does metastasize. A copy of the pathologists report is enclosed.

Next we reviewed the case with a GYN-oncologist who recommended a rather aggressive approach to the problem that included multiple surgical procedures including hysterectomy, vaginectomy, total vulvectomy and possible colonic resection. Plastic surgical procedures would be required to preserve residual tissues. Obviously, this is major surgery and no one should enter into it without some deliberation. It would necessitate a long hospitalization, and, if done, it probably would be preferable to have it done closer to home than Bethesda.
Transfer factor has obviously not provided must benefit to her overall problem. We decided to continue treatment a little longer to see if benefits did occur.

Sincerely yours,

Charles H. Kirkpatrick, M.D.
Head, Clinical Allergy and Hypersensitivity Section, LCI National Institute of Allergy and Infectious Diseases

Enclosure

cc:
Medical Records
Patient's File

NIAID/LCI:CHKirkpatrick:kd
March 21, 1978

Dr. John Hope
Family Practice Center
Roblin, Manitoba ROL 1PO
Canada

RE: Bella Titanich
11-91-14-7

Dear Dr. Hope:

Mrs. Titanich was admitted to the NIH Clinical Center on January 10, 1978 and discharged on March 20, 1978. Although it was prolonged, this was a particularly informative hospitalization.

First, her pulmonary status. On January 24, 1978, Mrs. Titanich became acutely ill with fever and left diaphragmatic pain. The x-ray showed consolidation of a basal segment. This responded to IPPB, hydration and antibiotics.

We continued an active chest P.T. program during the remainder of her hospitalization and she did rather well. On one weekend in February, she had some chest pain and low grade fever. She received a few days of antibiotics and never became ill. In retrospect, there is some doubt that she was developing pneumonia at that time.

Mrs. Titanich continues to be a moderately heavy smoker and to deny that she smokes. This is a bad combination and makes it more difficult to care for her. In spite of this, we recommend that she have an IPPB machine at home and use bronchosol inhalations. I understand that the local lung association can help her rent or borrow the machine if it is recommended by her physician. This should be used in conjunction with chest P.T. and postural drainage.

Our pulmonary consultants reviewed her case and felt that she had diffuse airways disease and that a bronchogram would be of no value. Her ventilatory function studies showed mild airways obstruction.

We may have discovered the underlying cause of her susceptibility to respiratory infections. She has a severe defect in leukocyte chemotaxis. Her cells responded to chemotactic factor at about 30 per cent
of normal. There was no improvement when levamisole was added to the system, and this may explain why the trial on levamisole several years ago was not successful. The phagocytic and bactericidal activities of her PMNs were normal.

Dr. Olsen of the Dermatology Branch treated many of her warts with liquid nitrogen. Some of them regressed totally, others did not respond at all. One on her right elbow became infected and produced a moderate cellulitis of the surrounding tissues. We applied some Retin-A to the skin of her face and forehead. This produced good results.

The debate over the histology of her perineal biopsies continued. There was agreement that she had condyloma acuminata. Dr. Costa of our Pathology Department felt that some tissues were abnormal enough to suggest invasive carcinoma. The tissues were reviewed by Dr. Jason Norris of the AFIP who reportedly agreed with Dr. Costa. However, Dr. Norris has never provided a written evaluation of the tissues. On February 9 and again on February 23, additional biopsies were obtained. The final reading on all of this effort was that the biopsies showed condyloma acuminata and Bowen's disease, but no invasive cancer.

We have embarked on a form of immunotherapy of her perineal lesions. The treatment is under the direction of Dr. Max Cohen. On February 9, 1978, Dr. Cohen injected chlorodinitrobenzene in acetone into several of the verrucous areas. At this time she was not sensitive to CDN'B. By February 18 she had marked pain and edema in her left thigh. This area had been injected but I am not sure how much material was used. The reaction lasted about 7-10 days and I was quite concerned that she had a deep abscess. Anyway, it subsided without specific therapy.

On February 23, she was again taken to the operating room for a D&C and additional biopsies. Dr. Cohen again injected some lesions with a "lower dose" of CDN'B. In the meantime she had been sensitized with the chemical and a challenge test on March 10 with 100 µgm of CDN'B was positive. The test with 50 µgm was negative.

The reaction to the second set of injections was somewhat less severe. About March 7, she had edema of the vulva that became fluctuant but never drained. In spite of the fact that this treatment has considerable morbidity, it appears to be producing regression of her perineal warts. She is to return on April 16, 1978 for another round of injections.
In addition to the postural drainage and chest P.T. we hope that Mrs. Titanich can obtain an IPPB machine. She was given the following discharge medications:

a) Bronchosol, 0.5 ml in 2.0 ml of saline in IPPB machine;
b) Quibron, 2 tabs q 6 hr;
c) Retin-A cream to face daily;
d) Lidocaine, 12% oral solution, apply to perineal area Q.I.D. prn;
e) Darvon 32 mgm and darvon compound, take 1 capsule of each as needed for pain. (Mrs. Titanich has a tendency to use analgesics in excess); and
f) Valium, 5 mgm, 1 tablet b.i.d.

As you know, a hospital summary will be sent along at some future data.

Sincerely yours,

Charles H. Kirkpatrick, M.D.
Head, Clinical Allergy and Hypersensitivity Section
Laboratory of Clinical Investigation
National Institute of Allergy and Infectious Diseases
May 26, 1978

Dr. John Hope
Family Practice Center
Roblyn, Manitoba
Canada

RE: Bella Titanich
NIH # 11-91-14-7

Dear Dr. Hope:

Bella Titanich was admitted to the NIH Clinical Center on April 17, 1978 and discharged on May 18. As usual, there were a number of problems to check out.

There seems to be progressive clearing of the verrucae on her perineum. This change is occurring in areas that have not been injected with CDNB and manipulated in any way. The changes are not dramatic but there seems to be a trend toward clearing. A CDNB patch test gave a weak (1-2+) response. On April 27 CDNB in acetone was injected into several condylomatous areas on the left side of her vulva. The response was similar to the previous injections; about 7-8 days later she developed pain and edema with some ulceration at the injection site. This subsided in 5-7 days. A repeat CDNB patch test shortly before discharge showed a moderate (strong 2+) reaction.

The dermatologist advised against any more liquid nitrogen treatments for the warts that had not responded to the first attempt. The possibility of painting the warts with CDNB was discussed but never done.

The gynecologist reviewed her case again. She continues to have excessive menstrual bleeding and the evaluation so far has shown no evidence of malignancy. At his suggestion, Mrs. Titanich was given Provera, 10 mg daily for five days each month. Her bleeding decreased and in May, she had a normal menstrual period.

Mrs. Titanich had an episode of herpetic keratitis in April 1978, but she had no acute pneumonias this time. She seems to be willing to follow chest P.T., but unwilling to give up smoking.
Her discharge medications were:

1. FeSO₄, 300 mgm, 1 B.I.D.
2. Provera, 10 mgm, five days each month
3. Quibron q 3 hrs
4. Kenalog cream for eczema of ear lobes
5. Valium

She is tentatively scheduled for reevaluation on September 7, 1978.

Sincerely yours,

Charles H. Kirkpatrick, M.D.
Head, Clinical Allergy and Hypersensitivity Section
Laboratory of Clinical Investigation
National Institute of Allergy and Infectious Diseases
2740-75  **CASE 8**

- B cell lymphoma + multiple myeloma 1.5
- Lymphosarcoma with Russell bodies 1.5
- Multiple myeloma with dysproteinemic storage 1
- Multiple myeloma 2
- Histiocytic granuloma 1
- Whipple's disease 1

3975-74  **CASE 9**

- Mycosis fungoides 3
- Hodgkin's disease - vasculitis present 1.5
- "Parasitic ulcer" 1
- Lymphoma 1.5

1885-76  **CASE 5**

- Hibernoma 3
- Liposarcoma, well differentiated 2
- Lipoblastomatosis 1

4410-76  **CASE 6**

- Waldenstrom's macroglobulinaemia 3
- Immunoblastic disease 1.5
- Plasma cell dyscrasia 1
- Lymphocytic lymphoma with possible macrophages 1
- Lupus erythematosus type of node 1
<table>
<thead>
<tr>
<th>Case</th>
<th>Diagnosis</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>21635-75</td>
<td>Adenoid cystic carcinoma</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Adenoid cystic carcinoma with mixed tumor and lymphoepithelial lesion</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>With basal cell elements</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Cylindroma</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Mucoepidermoid carcinoma</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Malignant mixed tumor</td>
<td>1</td>
</tr>
<tr>
<td>57-373</td>
<td>Embryonal Rhabdomyosarcoma</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>No diagnosis</td>
<td>1</td>
</tr>
<tr>
<td>7613-64</td>
<td>Malignant giant cell tumor with fibrous inflammatory reaction</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Liposarcoma</td>
<td>1</td>
</tr>
</tbody>
</table>