1. Luteal Cell Studies. Studies to examine the possible cell death signal. There is some evidence that regressed cells are already programmed to die. First, what is a healthy functioning luteal cell must be established. Then the two types, control vs. regressed, can be compared and contrasted to what adenylate cyclase function is in each, which protein kinases and related nucleotides are activated or not and if the dual (hCG/PGF_{2a}) pathway does exist.
The progesterone secretion may be measured as a hormone response while the regions of the genome are examined for each stage. Further, the adenylate cyclase enzyme complex, nucleotides, G proteins and other components could be removed from each cell type (control vs. regressed) and tested as to their ability to function independent of their local environment (so placing hormonal control either at the membrane or other location, i.e. the genes).

2. To measure the progressive changes in dispersed luteal cells cultures to differing periods induced and the related progesterone secretion (and related adenylate cyclase, nucleotide, protein kinase responses). The plasma membrane can be examined for changes in the lipid population; is there a difference in the "(electro)static" charge of the plasma membrane (due different headgroups) and is such a static charge also seen in tumour cells? How does the static charge relate to lymphocyte chemotaxis/attraction or repulsion? Does the cholesterol content increase, and how are the enzymes, and nucleotides affected (or not)? What parts of the genome are activated? What phospholipids are present or lost with regression and are the eicosanoid precursors? Are these part of the negative adenylate cyclase pathway, cyclooxygenase enzyme and the cell death signal? Is this genome missing (or masked) in transformed cells? Could the genome be reactivated to terminate "immortal" cancer cells? Do cells have the phospholipid precursors for eicosanoid synthesis? Hormones and eicosanoids seem to be in a balance and eicosanoids may be part of intercellular communication.

Part of the phospholipid population change can be examined by s-adenosylmethionine (Aldomet) augmentation. Control and regressed luteal cells would be studied to see if the hormone response is due to a fluidity change, a phospholipid change due carbon chain methylation or whether the genome was methylated. Related questions would concern the effect of adenylate cyclase, G-proteins, etc. The Aldomet experiments could then be applied to transformed cells to determine a response (phospholipid? gene change? or none?).

1. Plasma membrane/Phospholipid Population Change

To design monoclonal antibodies to the regressed luteal plasma membranes. A ligand or tracer could be attached to the antibody so that the regressed cells could be tagged and identified from control cells. The tag could be a number of methods, immunofluorescent, a metallic (NMR) or radio isotope (not preferred). The method could be applied to an ovary in vitro and then ultimately in situ. The method then could be developed for tumours and the unintrusive detection in the whole body (specifically for applications in human medicine).

4. Lymphocyte/cyclooxygenase/Regression Taxis Experiments

Essentially a "barrier" culture experiment where control cells are separated by a barrier from lymphocytes by another barrier from regressed cells:

i.e. control I lymphocytes I regressed cells

↑porous barrier↑

Variations would include control/lymphocytes/control; control/lymphocytes/medium plus PGF_{2a}, and/or other agents. The theory is based on arthritis and infection studies wherein lymphocytes are guided to inflammation sites.

The agents to be tested may be:

1. To inhibit the lymphocytes: leukotrienes, interferon, NSAIDS, antioxidants and other drugs which may be under pharmaceutical consideration.

2. To promote or direct the lymphocytes: such as oxidants, essential fatty acids (components of blood, serum/plasma from cancer/AIDS victims could be considered). The study would examine various media for secreted products, and measure these products (and/or the media) on various sections of the brain.

Alternately, or inclusive, the experiment could also consist of: cells tested, barrier, brain section, to study the concept of the feedback loop (and remission). Since the hippocampus involves the emotions, remission is a valid question to study. In the brain sections, prostaglandin receptors could be studied along with related biochemical reactions and other changes.

Future consideration would involve in vivo studies on whole specimens, but these would be further along at a later date.

5. The Zygote-Ova Fusion Experiment

This model, as noted in my earlier letter, interests me and has implications for genetic engineering, cancer research, plus other areas. However, I only mention the work now as a future consideration dependent on how all the other research goes. Perhaps, these studies would be the springboard to a later research period.

RESEARCH PROPOSAL TO EXPLORE THE OVERLAP OF THE ENDOCRINE, LYMPHATIC AND NEURAL SYSTEMS TO DEVELOP DIRECT CLINICAL METHODS FROM THESE STUDIES USING THE RAT MODEL AND THE OVARY, DISPERSED LUTEAL CELLS AND UTERUS.

1. The luteal cell dispersion would study the responses of various toxins, chemicals and drugs:

I chemicals and drugs:

a. In vivo injection of pseudopregnant females. A preliminary study with selenium gave measurable results. Perhaps new drugs could be compared to established and known safe products to extrapolate levels for clinical testing, plus potential problems and pitfalls. Effects on the neural system (hypothalamus) could be measured. An early suggestion involves the treatment with NSAIDS/antioxidants to help pregnant women, with difficulty, carry to term.

b. In vitro treatment of the dispersion to study drugs/toxins and their effects on the cell's: membranes, cytoplasmic functioning and DNA.

To note how (a) and (b) may (or not) invoke the proposed cell death signal, the plasma membrane's "static charge/energy barrier" theories and the relationship to eicosanoids, intercellular communication/homeostasis (health). To examine how these studies may show an interrelationship of eicosanoids, interferons (others) and the lymphatic system to the hypothalamus/pituitary. The above may indicate how cancer/AIDS circumvent the immune system, so that intercellular communication may have important consequences to stress and remission.

2.To study tumours in the ovary and uterus and examine feedback to the 3 systems. Tumour and luteal cell membrane changes could constitute the basis for a non-intrusive early detection technique. The uterus is especially interesting because prostaglandins (PGs) formed post partum may guide lymphocytes to clean up debris (and reduce tissue mass: part of the cell death signal theory). Cancer/AIDS may circumvent such, hence a broad area of study and implication.

3.A fusion/cloning experiment using ova from the same female and via centrifugation/PEG techniques produce a zygote. The zygote could be bi-, tri- and tetra-nucleate. The result would further explain DNA and other cellular functioning. The direct clinical application would use the binucleate zygote implanted in a primed surrogate uterus. By studying the difficulties to achieve implantation of this "trophoblast", the clinical applications could lead to:

a. "sterile" fathers may be missing a chemical (sufficient quantity) to facilitate sperm penetration of the ova membrane. By forcing the cloning experiment, the treatment could uncover the required substance to augment the semen so a zygote (child) would result under more natural conditions (i.e. artificial insemination of the mother and not more complicated procedures). A direct clinical application.

b. Humans have a low success rate (plus the risk of uterine cancer) with present techniques, so solving the cloning-implantation experiment could lead to definitive fertilization treatments with less risk and higher success. Also gained would be increased knowledge on the interrelationship of the three (neural, endocrine, lymphatic) systems.

4. Using the fusion experiment, there is the possibility of fusing cancer/HIV virus within the zygote to study oncogenes and the incorporation of viral DNA (viral RNA? function) into the genome (a new species: a theory states that viruses control our evolution). The zygote through morula-gastrula-germinal layer stages could be examined for (new) chemical signals, and the effects of drugs and chemicals (Dr. Duesberg's. lifestyle theory).

HCCI

HCCI Management Services Inc.

September 11, 1992

Edward A. Greenhalgh
265-7 Regina Street North
WATERLOO, Ontario
N2J 3B9

Dear Mr. Greenhalgh:

Upon reading the documentation you forwarded to me Aug. 31st, which illustrates your impressive educational background, I can understand your sentiments on receiving notice of a job at our Resco Plant for general labourer positions. I would however, like to clarify that it is the responsibility of Resources representatives to advise all our employees after the recent business changes of any job openings available in our organization. This gesture on our part is in no way to lessen the importance of our employees' qualifications, but forwarded to all the Cambridge employees concerned.

It is a fact that our North American business oriented towards the marketing of our product line and not in the scientific research. Therefore, we cannot sponsor the research project you have presented.

I have asked Mr. Jean—Pierre Kolo to contact you in future to assess with you if there are any other avenues you could explore.

I am confident that your experience and perseverance you to a successful career and I wish you the best of luck in future endeavours.

Yours truly,

Alban W. Schuele

Edward A. Greenhalgh
265-7 Regina St. N.
Waterloo, Ontario
N2J 3B9
(519) 884-3318

25 August 1992

President A. W. Schuele
Hoechst Canada Inc.
P.O.B. 6160, Station A
Montreal, Quebec
H3C 3K8

Dear President Schuele:

I am writing an update to my 31 July 1992 letter. Your response can be considered no worse than other pharmaceutical firms. Those whose main goals are not exactly as my proposal wrote back saying so and wishing me well. The few firms where my proposal was exactly what their industry is based upon have simply avoided the issue. Although you are no worse than the industry standard; however, according to Quality Assurance, and Road Map to Problem Solving, shouldn't you want to be better?

Please note the kind reply to my request for scientific papers from Dr. Ohno (21 July 1992 - The Ben Horowitz Chair of Distinguished Scientist…). On a strictly scientific basis I receive considerable worldwide courtesy still. On a strictly scientific basis I wish to update my proposal and its benefit. Please contact Dr. Kott as I have explained the theoretical details to him; and if my theory (of evolution) is correct the benefits are immense. If I am correct, I may be able (within a year) to produce a protein responsible for remission. The protein could then be mass produced by genetic engineering. Is Hoechst going to turn such a project down? Again we can "brainstorm" the possibilities.

On a sadder note, a poor individual (24 Aug. 1992) has settled a foolish dispute with Concordia by murdering people. A tragedy. I asked you to read a Time magazine article concerning academic problems; further many people in the USA have settled dispute similarly. I, too, have been involved in an academic dispute; however, like Ms. O'Toole (and any proper pharmaceutical firm) I have retained legal counsel. McMillan and Binch is proceeding with my plagiarism charge: such a responsible firm would not do so unless they were very convinced of the validity of the case. I have watched positions in England and the US disappear while driving a forklift for Hoechst. Nevertheless, I kept a good work record, a positive attitude and paid my bills (the Province has announced it is going after students who have defaulted their loans as far back as 1965). Do I not fit your Quality Values as the type of individual your QA program states you should support.

Why not meet with me and discuss the project? Taxol will soon be on the market, so why not have an equally valid alternative? I honestly do not see you risking very much capital on the project, while the returns are potentially incredible.

…2

RESEARCH PROPOSAL

This research proposal has two parts:

One: A practical short term (one year) project to establish a work base.

Two: A longer term (to run concurrent to One) basic research project.

Both projects are eligible for government assistance and cost sharing with a private firm under existing NSERC, NRC and MRC programs. This should meet the spirit of Bill C-22.

Part One: Development of a New AIDS Test

The Federal government has set aside funding for AIDS research and should be interested in this project. Only a preliminary outline follows. On conditional approval actual cost estimate and logistics will be provided.

Broad Spectrum Analysis

Blood samples would be acquired from the Red Cross, hospitals and other clinics who would associate themselves with the project. Such involvement represents a positive and practical image to the public through a working relationship between a pharmaceutical firm, government and medical centres for medical research. The blood samples would be collected as required by law for safety and anonymously (ethical and privacy concerns) with a code designation, i.e., for collection source, disease condition, sex and age.

The first expense will be the fee applied to the participating agencies for collection and labeling of the blood samples. The samples will be transported to the testing facility. The second expense will be the fee applied to the use of the facility, equipment and any required personnel for necessary technical skills.

Blood Testing would be:

A Healthy control (uninfected)
B. AIDS
C. HERPES
D. SYPHILIS
E. CANCER – i.e. leukemia,
i.e. lupus
F. Influenza
G. Meningitis

(Concept of a spectrum because HIV may "piggyback" with other diseases.)

The chosen diseases could cover the following categories:

i. Attacks the immune system
ii. Not affect the immune system
iii. Viral vs. bacterial
iv. Affect or not the nervous system

Testing to Develop Profiles (a cataloguing)

1. Microscopic examination (L.M. & E.M.) associated with video recording and computer scanning and counting to produce a rapid comparison and contrast.

2. Blood Segmentation

   a. Fractional centrifugation methods to give:
   -plasma
   -solid segments – r.b.c.
   - other cells
   - viral, viroid, etc.
   - other (proteins, hormones, ions)

   b. Examination of Segments

i. spectrophotometric profiles (i.e., light, flame)
ii. chromatographic profiles
iii. the solid segments can be examined for their physical components, i.e., membrane lipids can be compared
iv. viroid, viral, etc., segments can be studied for known and unknown particles using accepted culture methods.

The results of (2) may be used in a dagnostic computerized spectrophotometer scanner that could use a very small blood sample (not centrifuged) to clearly and quickly diagnose a patient. The result would denote the total state - - i.e., HIV present, helper virus present, associated protein present, etc. Normal vs. abnormal health states and how advanced any disease present would also be determined.

Further, once "catalogued" and all the components (HIV, satellite virus, etc.) detected then:

i. A simple, i.e., anti-body test could be developed for a reliable "over
-the-counter" AIDS test. There may be several levels of the disease and each could be identified. The potential is significant.

ii. If each state can be recognized, then different drug regimen may be used to "break the chain" and interrupt the disease with a less drastic therapy. Similarly, cancer treatments could be examined on this experimental theme.

Part Two: The Basic Research

To explore the theoretical work demonstrating the possibility that viruses are the basis of life representing a "living crystal" concept controlled by the laws of thermodynamics. One experiment would make energy measurements based on the theoretical paper's mathematical predictions (work presently in progress). Then, an experimental model would be designed: i.e., the original prototype cell (a protocyte, to coin a phrase), from a virus, a protein and a micelle/vesicle. Another area would examine viral induced lysis in cells — the actual genes activated plus the formed products from a variety of infected bacteria. These would then be compared to an evolved cell model. One such model is the luteal cell and regression lysis. By

comparing the gene sequences, lysis as evolutionary conservation may be explored. Part of the evolutionary study is the central theorem of the conservation of genes (a vivid example is the use of coral in bone surgery). Coral is quickly accepted by the body. Similar genes from two dissimilar organisms: the genes were conserved to be utilized by higher organisms.

The lysis mechanism (see my papers *v125(3)* J. Endo 1990 and the mention of a possible cell death signal), related parts and functions, should prove, on a wide scale, to be of medical importance.

Lvsis and cell death (for a variety of cells). There may be a common (conserved) gene sequence with related (i.e., enzyme) components that are activated.

The Important Occurrences: red blood cells and aging; muscle atrophy which may be healthy (i.e., the decrease in uterium size post partum) or dangerous (i.e., heart damage as in ischemia and heart disease).

Why cancer cells do not lvze. Either because the gene sequence is absent or blocked. Therefore, can the proper gene sequence be specified and the cancer cells then be given a specific signal and told to "die", i.e., with a cell specific signal drug.

Basic Research Goals

a. To discover how viruses were developed to seek and attach to the cell, etc.: all of which have significant consequences to viral control and drug delivery.

b. How self and identity of self (of the cell and the environment) were developed.

c. How control of lysis was developed with consequences to reproduction, arthritis and feedback to the brain.

d. How the colony (higher organism) was developed: healthy coexistence and its implications.

e. How the nucleus and genome evolved: how energy was stored in the nucleus and passed along.

f. Development of membranes and how the proteins (enzymes) came to be placed in same. This has implications for disease control and drug delivery.