

# Doctor's Notes for Benjamin Stokman

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## Dr. Ettl – 9/27/03

CT shows a new 4mm lesion on the apex of the right lung. Need to follow closely.  
Culture was negative for bacteria  
Blood counts were good.

Spoke with Dr. Arceci. Still trading options.

1. Break from port and take 1 month of oral 6MP and oral MTX (20mg/m<sup>2</sup>). Some studies have shown this can be effective even with brain lesions for LCH??
2. 5g/m<sup>2</sup> IV Methotrexate w/ Lukivoran rescue'
3. New lesions are on non-dominant side of his brain, Focused radiation??
4. High Dose Cytosar – probably not an option because of the bone marrow hit is extreme
5. Oral Etoposide (VP-16) in low dose – Secondary cancer is associated only with larger calmative dose.

## Dr. Ettl – 5/20/03

- Pet scan was review with the PCH hemoc team yesterday. Also talked with Dr. Arceci.
- 2-Cda could be working for 2 months after last administration
- Vinblastine, Methotrexate and Prednisone did not work, 2-Cda did but we have to worry about cumulative bone marrow toxicity
- Options:
  1. 2-Cda – can no longer use
  2. 6MP and oral Methotrexate – Not good for CNS (Brain)
  3. Just wait and watch – Risk of being forced to do something (surgery, radiation) if lesions grow
  4. Citozar – has been shown to be effective on CNS. Is bone marrow suppressive.
  5. Etoposide (VP-16) – Risk of secondary cancer, bone marrow suppressive. Risk may be too high for benefit. Good for CNS.
  6. Decadron – Oral. Short pulses. High dosage. Not bone marrow suppressive. Traditionally not accompanied by the weight gain seen with Prednisone. May cause moodiness.

Decadron is probably the best risk reward combination right now – balances the risk of bone marrow suppression with the risk of taking no action and running into trouble.

## Dr. Arceci - 5/20/03

Would like to see PET scan results to make a decision.

## Parent Note: Bill Stokman – 5/19/03

Reviewed PET scan results from printout. Can see all the brain lesions with both C-Met and FDG. Concerned because we see another possible lesion in the right side of the brain. Review of MRI shows a potential lesion in hindsight.

## Dr. ML on PET Scan 5/14/03

Multiple foci of C-Met and FDG uptake were observed corresponding in location to lesions identified on the patient's recent MRI examination. The PET labeling sites measured approximately 1 cm in diameter each with two sites appearing along the inferior surface in the right occipitotemporal region, with a focus near the medial aspect of the right temporal lobe, a focus at the lateral surface of the right temporal lobe and a solitary focus in a left paramidline location observed just medial and posterior to the left caudate head. The latter focus might correspond in location to a lesion described in the vicinity of the corpus callosum on the MRI examination. Except for this latter focus the PET abnormalities were better delineated on the FDG than on C-Met studies.

Multifocal sites of metabolically active neoplasm are suggested at locations corresponding to contrast enhancing lesion on the patient's recent MRI scan of 4/21/03 consistent with recurrent xanthoastrocytoma.

## Dr. Ettl – 5/16/03

Pet scan shows activity. Going to consult with team on Monday.

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## Dr. Ettl – 2/7/03

Good scan results. Lung nodules no longer showing. Kidney not showing any disease. Brain lesions all the same size (no growth) except for largest one which has gotten smaller. May be able to come off of chemo.

## Dr. Ettl – 12/20/02

Review of scan results from 12/17/02:

- Liver and spleen OK.
- Kidney shows the same 'shadow' - cannot tell if it is the structure of the kidney or disease. No need to biopsy.
- Lungs look the same except for the one region where he had collapse of the lungs (Atelectasis) before a lesion is not prominent or brighter than before

Brain scans – contrast issue in the scans. In other brain tumors they do see the ability of the tumors to absorb contrast decrease. Could be a good sign.

Go forward:

- Do at least two more courses of 2-CdA and reassess.
- May examine trying to remove Phenobarbital after that and see if seizures come back (Bill's request)

## Dr. Schimel – PCH – Pediatric Radiologists – 12/17/02

We called with concern that almost none of the lesions are showing up under contrast. Had this issue with the last one (only on 1 series of shots) and was told that they did not wait long enough for scans. Dr. Schimel and I had a discussion – with out contrast, how can we tell if we are getting better or worse if you cannot see the lesions. We basically concluded that there are two responses – one where we measure the size of the lesions, the other is how well they take up contrast. The lesions are NOT taking up contrast as well, therefore they may be getting better. She also said that in her measurements some of the lesions are the same size or smaller.

## Dr. Jubran - Children's Hospital Los Angeles – 9/12/02

*Basic question is does GMCSF = GCSF? Do they both equal Neupogen? GCSF is neupogen and it is not the same as GMCSF and better to give GCSF.*

## Dr. Jubran - Children's Hospital Los Angeles – 9/5/02

- Is myelosuppression equivalent to neutropenia? Is neutropenia just a subset of myelosuppression? Myelosuppression is low neutrophils and monocytes vs. neutropenia that usually refers to neutrophils only.
- For Ben in particular, how do we decide when to give him Neupogen? Neupogen is usually given for approx 7-10 days 24 hours after the completion of therapy until the ANC is greater than 1000-5000 after the drop (which usually occurs in 4-7 days after chemo). Once neupogen is stopped the ANC will drop slightly but should still be good enough for the patient to receive chemotherapy. I think that if he needs the neupogen to keep his counts up so he can get his therapy then he should get the full benefit of it.
- Should we be asking our doctor to try to minimize the amount of neupogen in order to hedge against 'reactivating' the disease?  
I would not restrict it; we don't know if it affects histiocytes and if it does at what amounts.
- What is the main point of Neupogen, I hear to protect against infection and to up the counts for the next chemo, but I am not really sure that it really works for upping the counts for the next chemo because I also hear that the value drops to pre-neupogen levels after 48 hours (is this true?). Does it really prop up counts for chemo?  
The point of neupogen is to bring the ANC up faster so the period of neutropenia is shorter and hence less risk for infection and able to give chemo in a timely manner.
- How do you know when you have crossed the line from short-term suppression to 'permanent' suppression? And once you are over that line, isn't it too late?

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If a patient has low counts for longer than expected then a bone marrow evaluation should be performed to examine what is going on.

## Dr. Jubran - Children's Hospital Los Angeles – 9/4/02

**Primary questions** (Concerned about permanent bone marrow suppression):

- Is this the typical progression you see in patients (slowly dropping Neutrophil counts that do not recover)?  
It is common to have delays in chemotherapy because of a low ANC and 1-2 weeks is ok, if it is longer than that I would recommend a bone marrow test to evaluate for bone marrow involvement or signs of suppression from the chemotherapy.
- Our doctor mentioned permanent suppression; the Cladribine package insert also mentions this (along with death from the suppression). What is meant by 'permanent' myelosuppression? Is the marrow suppressed forever? If not, for how long?  
There is a risk of prolonged bone marrow suppression primarily of the platelet precursors (which doesn't seem to be the case for Ben), and in some cases it lasts for more than 2 years (Also in higher doses of 2cda than used for histiocytosis).
- Does 'permanent' suppression equate to death?  
If the white count does not recover the patient is at risk for infections and that is what is dangerous, patients don't die of low counts but as a consequence. Should he develop a permanent problem, he may need prolonged neupogen shots or a bone marrow transplant (but we are nowhere near that at all!!!!)
- Is there a way we can more closely monitor to prevent permanent myelosuppression?  
Checking counts 2X/week is the way we monitor for problems.
- How do you decide how many courses of Cladribine to give a patient if it appears to be working?  
If the 2cda is working the current thinking is to give a total of 6 courses, there are pts however who have received more.
- What criteria do you use to decide to continue or not?  
The criteria are how he is responding- if there is stable disease after 6 or worsening at anytime I would not recommend continuing with 2cda
- Should we be doing anything differently?  
So far everything seems appropriate.

**Secondary questions** (Concerned that Neupogen could actually speed up the disease, thus artificially counteracting the chemotherapy):

- We are giving Ben Neupogen, which I understand is just actually a recombinantly generated Granulocyte-Macrophage Colony Stimulating Factor. This factor, as I understand it, is partially responsible for the production on monocytes and antigen presenting cells. By giving Neupogen, are we actually 'feeding the flame'? Are we unintentionally supporting production of the lesions?  
As for the neupogen, it is controversial whether "it feeds the flame" we certainly would not recommend GMCSF (granulocyte-macrophage colony stimulating factor (not the same as GCSF), however in patients who have myelosuppression we are using GCSF (= Neupogen) to try to keep the chemotherapy on time and decrease the risk for infection
- Does blood sample monocyte level somehow correlate or relate to lesion activity? Why or why not?  
There are no studies that I am aware of regarding levels of monocytes in the blood and disease activity, also GCSF will increase the monocyte levels in the blood hope this helps

## Dr. Ettl (via Nurse Anne) - 9/3/02

- Parents called with concern about permanent myelosuppression:
  - Dr. Ettl did not think he has permanent myelosuppression
  - Permanent suppression can happen with any chemotherapy if too much is given (Duration or Dosage? – we are not sure)
  - Cannot really live with permanent bone marrow suppression
  - Is there any way to treat it?

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## Dr. Manwaring – Neurosurgeon for Barrows & PCH – 9/4/02

- Lesions from 8/27 scan are more pronounced / more visible (metastatic) – cannot tell us what this means – does not indicate better or worse.
- Compared side by side, but did not do detailed measurements.
- Very pleased that the main lesion (yellow lesion) did not cause hydrocephalus, can still see a clear path for fluid
- Near term concern is his ability to look upward – sunset vision (due to the lesion on his brain stem (red lesion)), suggested that we observe his ability to look upward daily and notify if any change.
- Pleased with the kidney response – hopefully that indicates the chemo is working.

## Dr. Ettl – 9/3/02

- ANC too low for chemo, start Neupogen and push back to next week
- Need to wait 48 hrs between Neupogen and Chemo to make sure blood counts will not drop again
- Some risk of long term or permanent bone marrow suppression with 2-CdA
- Four doses of 2-CdA is usually the maximum

## Dr. Schimel – 8/30 – MR review / Radiologist Report Findings

(Comments in parentheses are added to for consistency with our color scheme for identifying the lesions)

The previously described multiple enhancing intracranial masses are again seen. There has been slight interval decreases in size of the two cerebellar masses on the right and the left (blue and purple). The right temporal mass is stable (pink). The mass adjacent to the right tentorium has slightly decreased in size (mint green?). The right thalamic mass also is slightly smaller now, measuring 14 mm in greatest diameter (bright green?). The two cerebellar lesions now measure no greater than 11 mm in diameter (blue and purple). The midline septal lesion now measures 13 mm in diameter (Yellow??? Seems too small, maybe only the width (ear to ear) measurement). The small frontal lesion is unchanged (orange). The ventricle size is unchanged. No new mass effect is seen. No new enhancing nodules are present.

## Dr. Ettl – 8/29/02

Quickly reviewed scans with the pediatric neuro-radiologists. Their conclusion with side-by-side visual comparison is that the lesions have not gotten any bigger – they have stayed the same (this matches my initial conclusions on the 27<sup>th</sup>). So bottom line is that we are going to stay on our current course because the lesions have 'stabilized' and administer two more courses of 2-CdA to Ben and scan in six weeks.

## Dr. Ettl - 8/28/02

- Counts are back up – discontinue Neupogen.
- Was unable to meet with the neuro-radiologists – will review scans and comparisons tomorrow
- Lung lesions look the same – but there was some fluid on the bottom of the lungs probably from collapse of the lungs (Atelectasis), but this was probably caused by the anesthesia from the scan itself.
- The kidneys look good – no lesions seem to be visible – Does this mean the chemo is working? We cannot tell, perhaps those lesions were not really there and were really contrast artifacts on the past scans.
- If Brain scans show no growth or reduction in size then the plan is to start a third course of 2-CdA next week. If they are larger or more numerous then we have to re-evaluate.

## Dr. Ettl - 8/23/02

Have to start giving Ben Neupogen (G-CSF) to kick start production of Neutrophils as his are at zero.

- Neupogen is not a blood product but instead is recombinantly generated.
- Nurse comes to your house to teach you how to do it.
- Side effects are low-grade fever, can use Tylenol – need to call if above 101F.
- May cause fussiness.
- Stimulates the bone marrow production so he may experience bone pain.

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- Neupogen is actually a cytokine, specifically a Gametocyte Colony Stimulating Factor

## Dr. Jubran - Children's Hospital Los Angeles - 8/18/02

### Arguments Against Preschool

- Since Marie has not had a lot of illness, chances are when she goes to school she will be prone to a lot and bring them home.
- Easy to keep her out of preschool – she has not started and not as critical as kindergarten
- Ben may complete his therapy in as little as four months and then you could put Marie in after that
- Chickenpox: If Marie has not been vaccinated (she has) or had the chicken pox, is to make sure that the school lets you know if another child has broken out

### Arguments For Preschool

- In general my advice would be to send her anyway since I believe families should have as normal a life as possible
- Another point to consider is Marie's social interaction with other children which is very important given the fact that she has a sick brother who demands so much of his parents attention and energy

## Notes from HAA Regional Meeting in Minneapolis, Minnesota – 8/17/02

I asked Dr. Neglia for a copy of his presentation, hopefully he would send a copy via the association.

- There is a wall of pictures in the home office (send Ben's picture)
- Discussed JXG Brochure
- The many (old) names of Histiocytosis (were grouped by symptoms, not by the underlying process before they realized they were the same disease):
  - **Hashimoto-Pritzker** - sometimes called congenital self-healing – Rash in infants – usually went away
  - **Eosinophilic Granuloma** – mainly bone lesions
  - **Hand-Schuller-Christian Syndrome** – mainly pituitary and eye
  - **Letterer-Siwe** – Mainly liver and systemic involvement – low survival rate
  - **Histiocytosis X** – Called this after they figured out above were the same, but before they figured out the Langerhans cell was intimately involved.
- Positive diagnosis requires Birbeck granules or CD1a
- Gave example on how rare the disease is:
  - 5 million people in the state of Minnesota
  - 180 children will get cancer
  - 50-60 will get ALL (Leukemia)
  - 4-5 will get LCH
  - Note: Very likely that none will get JXG
  - For each child with cancer there are 100 adults with cancer
  - But most childhood illnesses are rare, so the doctors are used to dealing with rare diseases.
- Cancer or Not?
  - Three big causes of cancer – virus, genetic and environment
  - Is clonal – same Histiocyte precursor cells
  - Disease is not life threatening in many patients – this is not like cancer
  - Does not think it is cancer
- Caused by virus or Not?
  - No regional, seasonal or family association / correlation that would indicate a virus
  - Does not think it is caused by a virus
  - Bill's note: (could be a rare vector born virus that only produces a problem under very specific conditions – or virus could cause the immune system to dysfunction and subsequently cause histiocytosis)
- Some treatment options I thought were different enough from the typical to note:
  - Thalidomide – still being studied by Dr. McClain??
  - Indomethacin – British – Anti-inflammation
  - Anti-TNF-alpha – Embrel – some individual cases reported

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- Biphosphanates -- ??
- Discussed the possibility of developing antibodies that attack CD1a receptor specifically or some other receptor
- Gene plate analysis (Gleevec for AML example)
- Pituitary involvement is very difficult to identify – if suspected involvement can request a specific MRI of the Pituitary with fine cuts
- Asked who are the top doctors:
  - **Kenneth McClain** – Baylor and Texas Children's Hospital
  - **Bob Arceci** – John Hopkins
  - **Stacy Nicholson** - Oregon Health and Science University
  - **Sharon Murphy**- Children's Memorial Hospital in Chicago
  - **Sheila Weitzman** - The Hospital for Sick Children, Toronto, Ontario, Canada
  - **James Whitlock** - Vanderbilt University in Nashville Tennessee
  - **Rob Vasalo** - Mayo Clinic in Rochester Minnesota ???
  - **Joseph Neglia** - University of Minnesota
  - **Mark Nesbit** – Retired
  - **Others...**
- Other Areas:
  - **Whitlock** - specializes in studying twins with Histiocytosis.
  - **Alexandra Flipovich** - is the HLH expert. Children's Hospital Medical Center, Cincinnati, Ohio
- Had a little discussion on Stem Cells and Bone Marrow Transplants. For HLH BMT is almost the main line of defense. Two types of BMT 1) Full body radiation & 2) Non-myeloid ablative (a little radiation, a little chemotherapy and stem cells)
- Discussion on how we are going to solve this problem:
  - Chemotherapy is effective, but does not only target the 'bad' cells.
  - Need to solve this question: What is making the LCH cell proliferate???? Answering that question will allow for designed or target solution that zero in on the cell or flaw causing the problem. This might be done someday by replacing a gene or targeting a protein.
- More discussion on causes
  - May happen early and accumulate
  - May be 'exposed' but not get it
- Growth hormone – Some good results for patients well-being – increased muscle mass, increased bone density and increased feeling of well being
- Seizures: Removal of brain tumors may not always stop seizures

## My write-up for the HAA:

The second Histiocytosis Association of America Regional Meeting of the year was held in Minneapolis, four months after the LA meeting. Families attended from Minnesota, Wisconsin, Nebraska and the Dakotas. The guest speaker was Dr. Joe Neglia, associate professor of pediatrics and University of Minnesota Cancer Center member. Close to fifty people attended; about 25 families total.

The meeting started off with a review of the HAA and introduction to the HAA staff. There was some excellent discussion of fundraising for Histiocytosis. The rounds for United Way and for the government CFC programs are starting (mid August). Now would be the time to notify your co-workers and family members that they can donate through United Way and CFC to the HAA. Please contact the HAA if you wish to learn more. The HAA has also started a program with the Entertainment® books program. You can order these coupon books for your area and sell them to family and friends. Order forms are available on the web site. Some great advice was given on how to start fund raising with your company: Start small, perhaps pick a small project and ask them to fund it and then show them the results. The families are the key connection for fundraising; direct approaches of the HAA to foundations have not been overly successful because of the lack of personal connection. Also, do not forget matching gift programs.

After the association presentation, introductions of the families were held. Many stories had common themes:

- About five families were adults with LCH, two families had HLH and one family had JXG.
- Three families had experienced BMT, and two of those lost children from complications with the disease and/or the transplant.
- Several families had LCH (as children or adults) for a long period and were noticing some long-term effects of the disease and treatment.
- Many of the families pointed out that they had a very difficult time getting diagnosed.

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Dr. Neglia presented after lunch. He gave a comprehensive presentation of LCH and touched on HLH. Dr. Neglia is planning to make his presentation available to the association. He also held about an hour-long question and answer period.

Dr. Neglia expressed the importance of finding the root reason that these cells were misbehaving, perhaps then we could design therapies or medications to target the flaw. Chemotherapies (current treatments) do not know good cells from bad; a target therapy would be much better.

## Dr. Arceci – Johns Hopkins – 8/15/02

### Quick Discussion about Scalp Lesions

- Quickly mentioned that Ben's scalp lesions were looking better. Dr. Arceci said he does not want to give any false hopes, but he has seen some correlation between peripheral lesions and the main (internal) lesions. The scalp lesion reduction may be a good sign and might indicate the 2-CdA is working.

### Discussion about Neurosurgery and Radiotherapy

- Can resect the temporal lesion (pink), not the 'orange' lesion like we were thinking earlier. Can resect the ventricular lesion (yellow). Would only want to do surgery (resection) unless there was an emergency situation. Dr. Ben Carson, Dr. Tony Avellino and Dr. Jon Weingart reviewed Ben's scans.
- Gamma knife – Gamma knife people were 'less than enthusiastic'. Too many lesions on too young of a child.

### Discussion about Marie and Preschool

- No right or wrong answer.
- Big danger is chicken pox (colds and other things may not be such a big issue). Need to be made aware early if anybody has been exposed to chickenpox. If Marie is exposed, but we know about it early, we can get Ben Gamma Globulin (Vzig) and Antiviral medication in the hospital.
- Need to be in discussion with the school (we are).
- He would recommend that we continue with our life and put Marie in preschool – but this is a personal decision.

### Discussion about Monocytes

- My question: If 2-CdA kills monocytes, and Ben's monocytes are down, does that mean the 2-CdA is working? Conversely, if his monocytes in the blood are up, does that mean it is not working?
  - Simple answer: No.
  - Complex answer. No, we cannot clearly make that correlation for the following reasons:
    - Peripheral monocytes may not be affected in the same way as the blood monocytes
    - Active monocytes may not be affected in the same way as the blood monocytes are affected.

## Dr. Ettl - 8/12/02

### Further Rash Discussion

- Many patients experience rashes from 2-CdA.
- We have no way of knowing if the rash was really from the 2-CdA.
- Ben has not had any hives, fever or wheezing so no serious concern.

### Counts Discussion

- Ben's counts are good except for ANC.
- His absolute Neutrophil counts should be above 1000 to continue, but we would go forward at 750. Ben is at 891.
- His counts are probably rising and will be higher in a couple of days.
- Can give GCFS Neupogen if his counts continue to fall.

### Monocytes Discussion

- Asked if Monocytes levels are an indication of how well the 2-CdA is working (2-CdA is suppose to attack monocytes hard and dermal dendrocytes and Langerhans cells are closely related to monocytes).
- Answer: Monocytes level is an indication of the non-specific bone marrow suppression.
- Segmented Neutrophils trail monocytes levels.

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## Next Step Discussion

- Recommend talking with Nancy Tarbell about radiation
- Discussed conformal beam radiation, stereotactic radiation (linac)
- Talked with Dr. Arceci – there is an expert at Johns Hopkins we should talk to.
- The outside (orange) lesion near the motor strip and the main (yellow) lesion that could cause hydrocephalus are both resectable (accessible by surgery).
- Could travel to JH via airplane.
- Many different chemo options, no good data to make a decision

## School for Marie Discussion (Marie is suppose to start ½ day pre-school next Monday)

- No right answer.
- Easier to keep Marie out at this age than pull her out later.
- If it was kindergarten (and not preschool) he would recommend her going.
- 80% of the indogenous (from the patients body), 20% exogenous (from others)
- Viral – not what we are worried about – same risk level with her going to school.
- Fungal & Bacterial – these are what we are worried about and what is dangerous.
- Asked if we could pull Marie out of school when counts are low – would not make much of a difference.
- Enforced that it is a very difficult decision.

## Dr. Etzl – 8/6/02

Rash on Ben chest. Probably not from food. May be caused by 2-CdA.

## Dr. McClain & Oncotech ([www.oncotech.com](http://www.oncotech.com)) -- 8/5/02

Wanted to know if we could use Oncotech's extreme drug resistance program to see if we could help target Ben's disease. Oncotech was open to trying, but Dr. McClain gave the following advice:

*Unfortunately Ben's JXG cells do not grow well in culture (no histiocytes do) so it is not possible to do those tests. We are often faced with this dilemma in childhood diseases. We have to go with the best ideas from personal experience*

From Oncotech's Web Page FAQ:

### What is the Oncotech EDR Assay?

The Extreme Drug Resistance Assay (EDR) Assay is a laboratory test performed on a patient's tumor cells. This lab test can determine the probability of a tumor's resistance to a specific chemotherapy drug. If the tumor cells grow in the presence of very high concentrations of chemotherapy drug, then the cancer cells are considered resistant to that drug.

### How does the EDR Assay help the cancer patient?

Once the EDR testing is completed on a patient's tumor cells, a lab report is created which shows the probability of resistance for each chemotherapy drug tested. The patient's physician evaluates drugs that are shown to be in the Extreme Drug Resistance range in order to determine the best course of treatment. Often, this means preventing unnecessary patient exposure to toxic, ineffective chemotherapy drugs.

## Dr. Arceci – Johns Hopkins - 7/26/02

- Reviewed scans and could see growth.
- Will put the scans in from of the review board on Tuesday for review by neuro-oncologists and neuro-radio therapists. I explained to Dr. Arceci that I understood no one would probably readily do radiation or surgery on all the lesions, but that perhaps in an emergent condition we could get to one with gamma radiation and another easily with surgery or some other similar scenario. Dr. Arceci agreed and is going to request scenarios with the review board.
- Radiation is devastating on a young child's brain.

## Chemo Discussion

- Standard dose of 2CdA is 5-6 mg / m<sup>2</sup> per day, but if no response is noted could up the dosage, but currently there is no obvious dose – improved response correlation.
- What are the possibilities for go forward:

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- If Ben stays ok, stay on 2CdA.
- If Ben's condition changes or if after two courses the lesions are still growing, we could do the following:
  - VP-16 (Etoposide)
  - VP-16 & 2CdA
  - VP-16 & Single High Dose Decadron
  - VP-16, Vinblastine and Decadron
  - Ara-C (Cytarabine)
  - Ara-C plus 2CdA
- Dr. Arceci would like to talk with Dr. Etzl about the possibility of using a single high dose Decadron.
- 2CdA can get across the blood brain barrier.
- Intrathecal delivery of chemo is good for cancers that involve the CNS fluid. Ben's lesions may not be near the CNS fluid, but may be in the parenchymal or the brain tissue itself near blood vessels, therefore his solid mass tumors or lesions would be better served by chemo delivered through the blood. Intrathecal chemo may not be the best choice for solid mass brain tumors.
- 2CdA has been found to produce a response about 34-38% of the time with LCH patients. We have no idea how well it works for JXG.

## Experience Discussion:

- Natural regression of this disease does not always happen
- Very few data point, so very little understanding of the disease
- Several cases have not responded well
- One child (from China) used VP-16 with success

## Dr. McClain – Texas Children's Hospital - 7/26/02

- *What about the possibility of giving chemo intrathecally?*  
Answer: The brain tumor specialists do not give intrathecal chemotherapy for mass lesions, only small amounts of disease on the surface of the brain. So, I would not recommend intrathecal chemotherapy.
- *What about increasing the dosage of the chemo? How are the levels set?*  
Answer: The doses of methotrexate could be increased, but since there was growth of the tumors, I would not go back and do this. 2-CdA is given in a variety of doses (your doctors can check Sheila Weitzman's article: Med Ped Oncol 33:476, 1999 for the ranges. Otherwise, the safe doses are relatively "set" since the dangers of prolonged neutropenia or thrombocytopenia are another concern.
- *What is your opinion on gamma knife and neutron radiation for histiocytosis? I remember at the April 27th family HAA conference, you said standard ionizing radiation was not a good option, at the time I could not take everything in - was this your opinion, and if it was, is this because of the sequela or because of a general efficacy issue?*  
Answer: The gamma knife can be used for tumors less than 3-4mm in select parts of the brain. If this were used in many parts it could damage too much normal tissue. I would consult the radiotherapist to learn the exact details of risk and benefit. It could be useful, but in general, I stick by what I said at the conference.
- *When should we start to learn about bone marrow transplant? Would it be a viable option? Would it allow us to hit Ben with chemo harder and then recover with a BMT?*  
Answer: Yes, higher dose chemotherapy could be used. I am not aware of any cases like Ben receiving a BMT. You can discuss this with your doctors, but in general when a patient has a lot of disease not responding to conventional doses of chemotherapy, it is less likely that higher doses will be effective.
- *Are there any other cutting edge or experimental options we should evaluate?*  
Answer: I am still in favor of VP-16 and or Ara-C for use in xanthogranuloma. I am sure Dr. Arceci told you that VP-16 has worked in some cases. Ara-C is a good drug because it gets into the CSF. (So does 2-CdA). If 2CdA doesn't help. I would be glad to help formulate a plan using VP-16 and Ara-C.

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## Dr. Grois – Austria (LCH Study Reference Center and CNS Expert) - 7/26/02

'Experience with JXG is very limited, in particular concerning CNS involvement, as this disorder is even rarer than LCH. From the limited reported experience, however, it seems that the disease is closely related to LCH and usually responds to LCH-therapies. I think that the decision to treat Ben with 2-CDA is appropriate. As far as I know this drug is active for LCH brain lesions, as such lesions are usually 'perivascular' (around blood vessels), the drug will reach the lesional cells. There have been heterogeneous anecdotal LCH CNS cases in our registry who had received intrathecal therapy with variable response, in case of nonresponse to 2-CDA dose escalation might be an option but is limited by toxicity and the young age of your son. Other systemic therapy approaches possibly including like the Vcr/AraC or with MTX intrathecally might be discussed. Irradiation in small children is not indicated due to the hazardous long term sequelae, moreover Ben has multisystem disease, so an approach limited to the CNS only seems warranted as an emergency procedure.'

## Dr. Manwaring – Neurosurgeon for Barrows & PCH - 7/24/02

- Reviewed lesions
- Expressed serious concern about progression of disease
- There are probably other lesions we cannot see
- Need chemo to work – other solutions (surgery and radiation) are too harmful (due to the size, location and number of lesions we cannot easily target or remove them all – some are nearly impossible to get at).
- Has no tool to offer
- Need to examine what we would do if Ben started showing symptoms – would we go forward and put him through surgery if the impact would be so negative.
- Though they would be purely experimental, and may be too harmful, we should learn about neutron therapy radiation (vs. the typical whole brain ionizing radiation) and about gamma knife radiation (a focused experimental type of ionizing radiation).
- Ben may be experiencing some symptoms but may not be able to tell us.
- Reviewed the potential impact of each symptom (using my naming and color scheme):
  - **A) Yellow** – Hydrocephalus – still a small clear path, but will not be clear for much longer.
  - **B1 & B2) Green** – Close to visual pathway - loss of left field of vision
  - **B3) Red** - Sunset vision (eyes look down only), Ataxia (loss of coordination and motor skills)
  - **C) Pink** - Seizure
  - **D) Orange** - Cortical lesion near motor strip - loss of motor skill on right side
  - **E & F) Blue & Purple** - Developmental Lag, Trunk Ataxia, Nystagmus, impaired fine motor reflex, poorly articulated speech

## Dr. Ettl 7/22/02

### Scan Review

- Did not get a chance to review scans himself
- Listened to the radiology report
- 7 lesions in the brain
- Another lesion in the right upper lobe of the lung
- Kidney lesions still there

### Go Forward

- Recommend starting 2CdA
- PCH has 2CdA, but will need until tomorrow to get ready
- Stop Prednisone

### Administration of 2CdA

- 2CdA will be administered using LCH dosage.
- Medication is a two hour infusion in the out-patient clinic
- To administer, want ANC about 1000 and platelets about 100K
- Need to monitor blood counts closely – weekly at a minimum

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- Will do two courses and then re-evaluate (Between 5 and 6<sup>th</sup> week)
- A course consists of a week of daily 2 hr infusions, 2 weeks of recover and monitoring

## Potential Side Effects of 2CdA

- Neutropenia and Low platelet count
- Fever
- Abdomen cramping
- Vomit
- Nausea (can give zofran)
- Decreased Appetite
- Diarrhea
- Overly sleepy
- Might not sleep through the night

## Dr. Jubran - Children's Hospital Los Angeles - 7/22/02

### About 2CdA and her experience

- Some trouble with patients experiencing prolonged neutropenia and low platelet count (knows of one patient with prolonged neutropenia, most have trouble with platelets).
- If Ben is doing well on chemo now, will probably do well on 2CdA (noted that Ben had not needed any blood transfusions yet).
- 2CdA can work very well for some (example, child with HLH & LCH was cured, child with LCH tolerated well, but did not impact disease)
- Kids are tolerating the lower doses used for LCH (as apposed to other cancers).
- Given Ben's current situation (lesions still growing, new lesions appearing), **need to try something else**; 2CdA would be a good choice.
- Can generally tell if 2CdA is working after two courses (5 days of medication, 3 or 4 weeks in between) - this is about two months.

### About Etoposide

- Etoposide would not be her first choice, but she said she has never treated a JXG patient (shown to make no difference in LCH).
- 5% secondary cancer rate would not be true for LCH patients because the dosages are lower, but would still try to avoid.

## Dr. Etzl 7/10/02

Asked about Phenobarbital (anti-seizure) dosage and scheduling. Can we reduce it or change it?

- Did not want to introduce more variation currently.
- Ben was not showing any symptoms from Phenobarbital (lethargy or irritability)
- Ben is on the top dosage of 6 mg / kg (range from 3-6 mg/kg), but he is growing and his weight will increase, effectively slowly reducing the dosage.
- Kid regularly stay on Phenobarbital for much longer periods (6 months to years).
- Should not impact his development.
- Dr. Etzl will refer to Dr. Kaplan

## Dr. Etzl 6/24/02

- Scheduling scans for the week of the 15<sup>th</sup>.
- Slight ear infection, going to put Ben on IV Rosethen at the same time he is getting chemo.
- Do not want to give chemo too close together (risk of neuro-toxicity with subsequent delay of the rest of chemo), need to stay with schedule on Monday.
- Need to get stool sample
- Skull X-ray still shows orbital lesion, detailed comparison not made nor is it important relative to brain lesions.
- Blood counts are good. ANC is high.

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## Dr. Etzl 6/21/02

### Immediate Health Concerns

- *Ben has a rash on his body, and legs, Fever and fussy yesterday* – looks like a non specific popular / macular rash, could be anything, may be a reaction to a small infection.
- *Johns Hopkins ER visit with 102.2 fever on 6/16/02*
- *Blood count results* – ANC only 510, close to neutropenic

### MRI Scans

- *Who has reviewed the scans?* Radiologist
- *What did they see?* Lesions are possibly the same size. Still not a hydrocephalus issue – no dilatation of ventricle. Cerebellum lesion is there, but same size.
- *Was a comparison made?* Compared to old scans.
- *For the orbit bone issue, is the MR sufficient or do we need a CT?* Did not review. Orbit bone lesion is not as important as brain lesions.
- *Did Dr. Manwaring see MR's? Have you talked with Dr. Manwaring?* No, not yet.

### CT Scans

- *Who has reviewed the scans?* Dr. Schaffer
- *What did they see?* Right lung has one small lesion that was not there before, or if it was, it was not visible on the scan. Right kidney has 2 lesions, in hindsight one may have been there before. These kidney lesions are less than 1 cm in size. There was some thickening of the caecum – wall of the large bowel – we do not know if this is related or an issue at all. Need to monitor. All other organs normal.
- *Was a comparison made?* Compared to old scans.
- *What specifically do you see in the lungs? How many nodules? How are they compared to the previous CT?* Again, the right lung has one small lesion that was not there before, or if it was, it was not visible on the scan.
- *What about Thymus?* Normal
- *Is there anything new in the scans? Pancreas, spleen, liver, kidney, adrenal glands?* No, all normal.

### X-Ray Survey

- *Any issues or changes?* Not yet reviewed.
- *Can you see the orbit lesions on these images?* Not yet reviewed.

### Radiology Reports

- *We would like a copy, any reports?* No reports yet.

### Treatment

- *What treatment would you recommend?* Continue 3 weeks of same treatment and then reevaluate. Then perhaps Etoposide (VP-16) or 2CdA. Big risk for Etoposide is secondary cancers, for 2CdA it is the large hit bone marrow takes, really drops your infection fighting abilities.
- *Have you talked with Dr. Arceci?* Yes, and Dr. McClain.

### Gamma Knife & Radiation

- Only for an emergent condition, surgery would be better, but we are planning ahead.
- There is also stereotactic radio therapy.
- With normal or conformal radiation doses would be much lower. Gamma knife is much 'hotter' 1200 to 1400 vs 600 to 800 on conformal.
- Difficult with young children to target the right area and hold them still – skull moves and is not as solid as adults. Makes frames to hold the head less accurate.

### Will ask at a later time:

#### Questions about 2-CdA and VP-16

##### Administration of 2-CdA & VP-16

- How is it **administered**? Continuous Drip, Push, Oral?
- **Where** is it given, in the clinic or the hospital?
- **How often** is it given?

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- What are the **dosages**?
- What are the hairy cell leukemia dosages?
- What experience do you have with 2CdA? How often have you, the other doctors and the nurses administered? In what doses?
- What would the schedule be?
- When would the start date be?
- Cross the blood-brain barrier?

## Risks and Side Effects of 2-CdA & VP-16

- What are the **side effects**?
- What are the **risks**?
- Are there any **extra precautions**?
- Is there a higher risk of neutropenia? Fungal infections?
- Nephrotoxicity (kidney)?
- Neurotoxicity (paraparesis, quadriparesis)?
- Hospital isolation? We have some serious concerns here.

## Dr. Arceci & Dr. Zambidis – Hem/Onc's @ Johns Hopkins - 6/17/02

Additional questions or areas for clarification in red.

### Diagnosis / Pathology

- *Does Ben have JXG?* Yes, they had no doubt that Ben has JXG and only JXG at this time. Johns Hopkins pathologist, Terry Barrett, also looked at the slides we provided and concurred. A copy of the Johns Hopkins pathology report was provided.
- *Do we need additional diagnosis / pathology?* They would like to get some of the paraffin block if available and do Fascin and Factor XIIIa, which stain positive for JXG. These are relatively new and experimental stains.

### Symptoms / Lesions Review / Staging Discussion

- Dr. Arceci reviewed the presentation of all of Ben's lesions, the history of the case and all the testing done with us.
- *Do you see the lesions on the lung?* Yes, they are in the parenchyma part of the lung (parenchymal/parenchyma: These are cells in a tissue or tissues in an organ that are concerned with function.). Several 'nodules' not voids. Both left and right lung. 1 cm is the largest in the right lung.
- *What do you think of the eye swelling and the orbit bone lesion?* The orbit bone is what is called a lytic lesion or a lesion that erodes the bone and causes soft tissue mass. The eye swelling was most likely caused by this lesion. The swelling may have been caused by a secondary infection but the lesion was probably the reason the infection started in the first place.
- *What about the brain lesions?* From the 4/20 to 5/22 scans we can see a growth from somewhere between 10% and 25%.
- *Do you see symptoms elsewhere?* No, pancreas, spleen, kidney, liver & adrenal glands were clear.
- *Should we do any additional testing now?* No, the scans (MR, CT & X-ray) will be sufficient. MR of the head should be sufficient for the skull lesion; a CT of the head is probably not needed.

### Personal Experience

- *Do you have experience with patients with JXG?* Yes, he has had about 12 patients with JXG.
- *Have you seen others like Ben?* Yes. *Could you expand on this?*
- *What was the outcome of the others like Ben?* Good outcomes. *Could you describe some of these cases? Which treatments they were on, how they responded.*
- *Have you had successful treatment of JXG?* Yes. *Could you expand on this? How many? Which treatments? Which symptoms?*
- *Do lesions from JXG go away or stay the same?* They may involute but this is a very slow process. They tend not to come back. Emphasized SLOW retreat of the disease.
- *How do we attribute a shrink in the size of lesions to chemo or to natural spontaneous regression?* We can attribute to chemo if it happens quickly and while we are giving chemo. If is

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happens several months after a given chemo, then we cannot safely attribute the shrinkage to the chemo.

## Treatment Options

- *Is JXG different from LCH?* It does not respond as well to chemotherapy. The drugs we use are also different. **How do you know the treatment should be different? Trial & error? Some fundamental difference in the disease? I would like to know more about how you would treat LCH vs. how you would treat JXG.**
- *Because JXG lesions are known to spontaneously regress or stop growing, and chemotherapy has side effects, is "do nothing" an option?* For Ben 'do nothing' is not an option. The risks are too high and the lesions are known to be growing in areas that could cause major problems
- *What about surgery?* Surgery may be needed in an emergent condition – if Ben's condition deteriorates quickly.
- *What about radiation?* We should look into gamma knife or focused radio surgery. Conventional radiation is too destructive. Gamma knife is available at JH.
- *What about BMT (Bone Marrow Transplant)?* Still VERY experimental and there are a ton of issues. Related donors may be better than non-related. (There are several types of BMT and we need to look into and understand, but there are many better options available first)
- *Are there any new experimental drugs or treatments?* Yes, but they are a way off. We would try other things first. Metronomic (low consistent doses of chemotherapy), antibody therapy, Cytosan (good for brain tumors), Temozolomide (good for brain tumors). **Could you expand on this? Which things are near term? What would we try first? 2CdA then VP16 then???**
- **What drugs cross the blood brain barrier? Which drugs are good for brain lesions/tumors?**
- **What are the dangers & risks of 2CdA?**

## Next Steps

- *What are the next steps given the results from the 6/19 scans?*
  - **Full response** (100% reductions) or **Partial response** (50 to 99% reduction in tumor size) – continue with Vinblastine, Prednisone, Methotrexate every 3 weeks
  - **No change or stable** – weekly Vinblastine, Prednisone, Methotrexate for 6 weeks. Note: 0 to 49% reduction would be considered no change or stable because it is hard to determine exact tumor size from 2 dimensional scan images. Consider this the gray area. Determining partial response can get tricky. What if some tumors regress and some grow? Is that a response? Also, exact tumor size is hard to determine from scans – that is why we try to use 50% minimum response. The response has to be obvious, no splitting straws.
  - **Progressive growth** – 2-CdA 5 days per month – choice now (other option is VP16 but would try 2-CdA first because VP16 is risky – 2-5% end up with secondary leukemia)
- Overall tone of discussion was hopeful that disease could regress. Must cast LCH treatments aside. JXG is a different disease and will use different treatment, though similar.
- **What would be the dosage of the 2CdA?**

## Our Case

- *Will you consult on treatment?* Yes. He will work with Dr. Ettl and Dr. McClain.
- *How will that work?* He will contact Dr. Ettl
- *Actively or reference?* **As needed.**
- *How often?* **As needed.**
- *Will it help if we move there?* No, all the treatments can be given in Phoenix currently. **What about experience issues with 2CdA or VP16?**

## About JXG and the Lesions in General

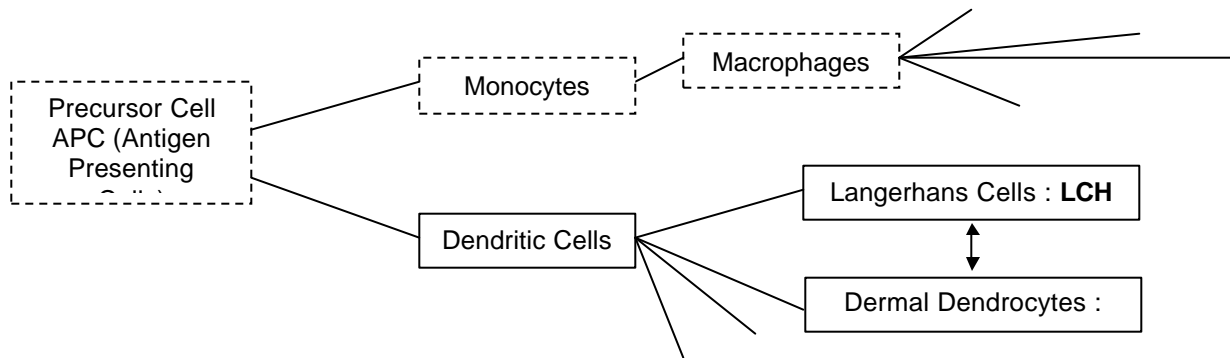
- *What do you think the mechanism is for JXG?* Explained that JXG probably arises from a dendritic cell called a dermal dendrocyte & LCH arises from another type of dendritic cell, the Langerhans cell. These cells are not macrophages like I thought, but dendrocytes or dendritic cells – but the macrophage and the dendritic cell have a common precursor cell. **How do dendritic cells act differently than macrophages? What different function do they perform?**
- *Are JXG & LCH related?* Yes, but how is unknown. There are several cases where a patient has both at one time, or where the disease changes from one to the other. Langerhans cells and dermal dendrocytes probably come from the same precursor cell. If something were to go wrong with the precursor cell, this might lead to having both of the diseases. Also, some chemical

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signals may be able to change Langerhans cells into dermal dendrocytes or vice versa. These changes have been accomplished in the laboratory??

- *Are the lesions cancer? LCH & JXG are currently not considered cancers.* But whether these histiocytic disorders are 'cancerous' or not is still hotly debated. Researchers are still not sure if one cell is going crazy (like cancer) or if the body is telling the immune system to deploy these specialized cells. Some recent evidence suggests that the disease may be cancerous, they have found that the cells in the lesions are the same cell or clonal, meaning one cell is reproducing incorrectly - this is like cancer.
- *What do the lesions look like? Did not get a description of how they look. What kind of cells are involved? Why are different kinds of cells there? From inflammation? Chemical signals? Requested by the Dendrocytes?*
- *What harm are they causing?* Lesions tend to push other material out of the way. Pressure, invasion of good connections.
- *Recent or current research? Basic research? New Drugs? Genetics? Targeted therapies? Antigens? Vaccines?*



## ER Trip at Johns Hopkins 6/16/02

- Ben had a 102.2 F fever, very fussy.
- Went to ER, got blood counts, blood cultures and urine cultures.
- Band Neutrophils were high on manual count, indicates a high generation of new Neutrophils. Could be the result of infection.
- No positive returns on the cultures.

## Dr. Singer 6/10/02

Ben has a rash on his chest. If rash does not get better by tomorrow morning, do not give the sulfameth trimeth. Could be a reaction to Phenobarbital, but not likely, should have happened earlier. Could be reaction to laundry detergent. If rash does not go away by tomorrow, call to set up an exam.

## Nurse Annie 6/10/02

Sent form to radiology request staging scans (Head MRI, Chest CT & skeletal x-ray) on 6/5/02, should hear back today. MRI scheduled for 7/3, need to get it moved forward!

## Dr. Boklan 6/9/02

Methotrexate levels are back to normal. Blood counts are good.

## Dr. Etzl 6/6/02

- Can start tapering off on Prednisone over the next two weeks – gave us a schedule. Need to taper to make sure the bodies endocrine system restarts correctly – maintain the proper feedback loop.
- Got chest X-ray for cold, it looked fine

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## Dr. Etzl 6/4/02

- Call Dr. Etzl with concern about Ben's cough & runny nose. Said we should monitor it closely and watch for fever. Could do a chest X-ray on Thursday. Was not worried about lesions causing the cough. He has other patients with large tumors of the lungs and they do not cause a cough.
- We can see Dr. Arceci on the 17<sup>th</sup> of June, we can schedule Ben's appointments for the end of that week.

## Dr. Arceci 5/31/02

Requested that we send him slides, films and medical records. Done, should arrive Monday.

## Dr. Wood 5/31/02

Clinic – Ben's ANC counts are increasing.

## Annette – Nurse Practitioner - 5/29/02

Ben's WBC Absolute Neutrophil Count is low.

## Dr. Manwaring 5/28/02

- Discussed the potential for another tumor in Ben's cerebellum (all the others appear to be in the cerebrum), in the left side, lower right corner. It appears in all three views.
- Dr. Manwaring believes it could be another lesion, but we cannot be sure. Have to wait and see if it develops next MRI. Radiologist did not believe it was one.
- He believes there are probably other lesions we cannot see.
- Counting on the chemotherapy response to make a difference. If chemo does not work, we are in trouble.
- Clinically the appearance of other lesions would not change our path.

## Dr. Wood 5/27/02

Ben tested positive for rota virus.  
Discussed blood counts.

## Dr. Wood 5/25/02 (PM)

- Blood in Ben's stools – noticed by red diaper.
- Urine tests negative.
- Stools themselves test negative, but the surrounding fluid & mucous test positive.
- Could be a fissure in the lower end of his colon, and it could be agitated by all the diarrhea.
- Could be a polyp or colitis higher up in the colon. These are usually due to bacteria (like clostridium Difisil – CDIF). But Ben was on antibiotics. Running CDIF anyway. Virus (like rota) tend not to penetrate the lining.
- Did not think it was due to the disease.

## Dr. Wood 5/25/02 (AM) - Hematology / Oncology

- Do not remove the stitches.
- **WBC – ANC** – Low (Normal Infant - 750 / Normal Adult - 1500 – 1000) – WBC is sensitive to Vinblastine. Could do nupegen replacement if there is a problem. NEED TO FIGURE OUT HOW TO CALCULATE.
- **Platelets** – Normal @ 650K (150K – 400K normal) - may increase from steroids and decrease because of Vinblastine, so we could see it bounce.
- **Red Blood – Hemoglobin** – Slightly Low @ 10.3 (Normal Infant – 10.5 to 11.5 / Normal Adult – 11-13) – Not as big an issue as WBC, will make tired at lower levels. Could do a transfusion. Discourage from direct donor because of BMT transplant possibility (blood donation would remove the possibility of HLA matching for BMT).

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- How do the steroids work? Burst & swell the cells. Called cell mediated immunity.

## Parents – 5/23/02

Ben has not been acting normally, and we cannot figure out if it is due to chemotherapy, antibiotics, rota virus or the brain lesions...

Symptoms:

- Trouble nursing
- Crying in pain
- Not sleeping / waking up when he typically would not
- Arch in back
- Gagging / Vomiting
- Diarrhea – sever for several days
- No tears
- Pulling on his ears
- Note: no fever, urinating 3 times a day, 7 stools a day, mouth still moist

What could be causing it:

- Rota Virus – stomach pain
- Jaw Pain from vinblastine – cannot eat enough
- Stomach hurting from medicine & chemotherapy
- Headache & irritable from tumors
- Esophagus pain from meds

## Dr. Manwaring – 5/22/02

- Reviewed the results of MRI #4 – measured main lesion.
- Main lesion has not grown (I am not sure if he was also implying the others were not growing as well).
- They did not shrink.
- Now have a clear path for the ventricles.
- Safe to put off next MRI for 6 weeks.
- He is going to talk with Dr. Ettl and discuss results.

## Dr. Ettl with Dr. Jaffe's results – 5/21/02

- Dr. Jaffe completely concurs with Dr. Dehner that Ben's Brain lesions are JXG. Dr. Jaffe apologizes for the delay, but was out of the country.
- He would treat him the same as LCH (epically since he has disseminated disease), so we will continue doing what we are doing and evaluate at the end of the 6 weeks.
- Surgery (except for the main lesion) and radiation therapy remain poor (or bad) options.
- We discussed the possibility of there still being some non-JXG aspect to this. There are other cases where the patient has JXG in one place and LCH in another. There is also the possibility that the disease is transforming from one disease to another. Dr. McClain even mentioned that the eye might present with LCH if biopsied.
- Reviewed the comments of a Doctor with JXG background:
  - ...What I have found ... is that JXG is capable of presenting in just about any unique way possible. It is true that the clinical course for the vast majority of children with systemic JXG (that is, beyond the skin) is benign, meaning that the lesions will remain stable, perhaps shrink, but often simply remain the same size as the child grows "around" them. However, it is also true... that some children, especially infants, can have very serious medical problems up-front, requiring major supportive care while they outgrow their initial problems due to JXG.
  - In regard to treatment...(those) who have treated patients with JXG have been underwhelmed by the effectiveness of chemotherapy. Historically, surgical removal of the mass(es) has been the most reliable approach. But the problem is that for some infants, this just isn't feasible, due to the number and/or location of the masses. If their medical condition is stable, most people have found the best approach is supportive care, as indicated above. If their condition is not stable, most physicians would feel compelled to try treatment. One option is radiation therapy, but for infants this is not very appealing and, frankly, is of uncertain benefit, too. A more attractive theoretical option is chemotherapy. The problem here is that there haven't been any medications that have been clearly effective in shrinking these JXG masses. Most physicians...have utilized chemotherapy medicines known to be effective in Langerhans cell histiocytosis, a different but somewhat related disorder. ... the responses to chemotherapy have been marginal at best, overall disappointing. Does

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treatment keep new lesions from growing? That is unknown; most observers note that patients with JXG seem to have all the lesions they will have when they are diagnosed, and do not typically grow new ones, although the existing ones can be difficult to treat in their own right.

Despite the overall good prognosis of JXG, there clearly are some patients who do die of complications of the disorder. From the medical literature, a large proportion of patients who die have lesions in their brains, which can be difficult to remove. ...

- Methotrexate is known to cross into the Brain – some chemotherapies do not.

## Dr. McClain 5/21/02

Was able to talk with both Dr. Jaffe and Dr. Arceci while they were all in Greece. Need to update Dr. McClain.

## Dr. Groise 5/21/02

- Dr. Nicole Groise from the LCH study center in Austria (who wrote the LCH article on central nervous system involvement), responded back. She concurs with Ben's current treatment and believes Ben's lesions look like other LCH lesions she has seen.

"Thank you for the comprehensive information which I read on your website. I looked at the MR images of Ben together with Dr. Prayer, our neuroradiologist. The brain infiltrates are indeed compatible with active LCH, there is no evidence of neurodegenerative lesions. What kind of treatment has Ben received so far. I would recommend systemic chemotherapy according the LCH III protocol (including MTX) or 2-CDA according to the LCH-S 98 protocol."

## Dr. Ettl 5/17/02

- First Clinic – Moved into new PCH
- There are several methods to try for the Prednisone – liquid, low concentration liquid – Prelow, crushed pills. Any of these can be put in flavored syrup, preserves, applesauce or other sweet food. If he throws up within a half hour, give medication again.
- Giving IV push of Cephtriaxone (Rosehin 650mg) in case Ben has an infection (slight fever, swollen eye).
- Lungs will be monitored by X-ray and CT at the end of 6 weeks.
- Diaper rash is probably due to secondary fungus (because body chemistry is messed up and does not fight off as well). Apply Nystatin.

## Dr. Krahl 5/16/02

Dr. Jaffe has received all samples, but analysis is not complete.

## Dr. Ettl 5/15/02

- Talked with Dr. Edelstein and Dr. Edelstein does not believe it is infection or bacterial (Father agrees). Looks like more of an infiltrative process. This agrees with first time (antibiotics did not cause a change within 24 to 48 hrs). Based on this we will not start antibiotics.
- Currently we should just wait and see. Hopefully the eyelid will not continue to swell or will go down in size. Risk of surgery is higher than the payback (diagnosis, maybe some disfigurement and other listed risks are too high)
- If the swelling goes up, we may need to re-evaluate.
- What should we watch out for? High fever, warm and tender, marked redness, eye does not move.
- Dr. Manwaring is still holding to his strict criteria before going in for surgery – invasion on the thalamus or closing of the lateral ventricle. Safer for Dr. Edelstein to go in when Manwaring is doing surgery.

## Dr. Manwaring 5/15/02

Ordering MRI w/ contrast to save time (canceled without contrast). Wants us to call him directly when the scan is done – maybe he can come over to see the results. Has a flight to Europe that day for about 8 days. Decided with Dr. Edelstein to hold off on Ben's eye if possible until a craniotomy is needed (hopefully it will not be). Need to stay in contact if the swelling gets worse.

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## Dr. Edelstein 5/15/02

- **REASON:** We are seeing noticeable swelling in Ben's eyelid again. His eyelid is about half closed, puffy and red. Looks exactly the same as the last time it swelled shut. Ben is fussy and has a slight fever – also the same as last time. It does not appear to be an emergency condition at this point.
- **CAUSE:** Dr. Edelstein was not quite sure of the mechanism that was causing this. Here are some of the ideas that were discussed:
  - 1) **Infection** – chemo should not have weakened his immune system yet, but could still be infection.
  - 2) **Chemo** causing swelling – probably not, Prednisone should reduce swelling. Maybe Vinblastine??
  - 3) Could be **surgery** acting up??
  - 4) A burst **cyst** or enlarged cyst caused by the irritation of bone lesion - not likely
  - 5) **Most likely:** The bone and the eye blood system are closely tied in that region, the body & **immune system** could be reacting to and fighting the eosinophilic granuloma (LCH in the bone, specifically) in the orbit bone and we are seeing normal swelling due to this battle.
  - 6) Is this area more prone to swelling just because he had the first surgery?
- **LOCATION:** We have asked Dr. Edelstein to review the 4/21 head and eye CT. The suspected lesion seems to be above the eye in the lateral side (outside). The original surgery would not have gone this high or that far back. Need to review CT to confirm.
- **OPTIONS:** Dr. Edelstein examined his eye and came up with several options:
  - 1) **Do nothing** – not the best solution. We do not want to have a scenario where Ben has an eye that is swelled SHUT for a prolonged period - this would affect development.
  - 2) **Take antibiotics & wait** – Since this could be an infection, antibiotics could be a good choice.
  - 3) **Surgery (Lateral Orbitotomy)** – extend existing surgery in eyelid to get out to the zygomatic bone. This bone would have to be sectioned out to gain access to the area he needs. Would remove as much affected tissue & bone as possible. Some difficulty would be faced in how to reattach the bone:
    - A. Titanium plate would interfere with scans, but would be the most stable – but could be too rigid for his age and not allow proper growth.
    - B. Self absorbing screws – problem is that they cause swelling, and would not know if swelling was due to the screws or the lesion
    - C. Polymer attachments (did not catch the exact type) –would allow for some movement, somewhat stable, would not interfere with scans probably best choice)The **benefits** of this surgery are that we may be able to get enough active samples to diagnose Ben's condition definitively. Just doing the surgery may also reduce the swelling. There are several **risks** we need to consider (Some are due to the surgery activity, some are due to the removed bone on the lateral wall):
    - A. **Scar** – will extend out further than his existing scar
    - B. Could damage the lacrimal gland which could hurt **tear production** – but he would not be in that area
    - C. Could damage tear glands in eyelid and cause **dry eye**
    - D. Removal of the bone may cause **eye to sink** slightly and make eye appear more closed – but usually takes much greater removal of bone
    - E. Could damage the lateral rectus muscle with would **restrict eye movement** (either via surgery or the removed bone)
    - F. Could damage some nerves in the area the bone would be removed, which could cause some **numbness** in that area
  - 4) **Surgery during craniotomy** – Do surgery on the orbit in concert with the brain surgery that Dr. Manwaring would be doing. If we are inevitably going to do the brain surgery (at this point we are not sure, but a consult with Dr. Manwaring would be beneficial), than this method would be less intrusive and would still allow us to get the sample.
  - 5) **Radiation** – Not a great option, typically do not like to do radiation on things when we do not know what they are. Also not good for young kids.
- **GO FORWARD:** Dr. Edelstein is going to talk with Dr. Etzl and Dr. Manwaring and they are going to try to come to the best solution.

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## • OTHER THOUGHTS

- Swelling is a normal part of this disease, could we be reacting to something 'normal'?
- Might give us a diagnosis, but would it change our action?
- Could the surgery kick the immune system in high gear and give the disease an opportunity to take off in brain? Or could the surgery slow the disease down?
- Could cause eye problems
- Could reduce eye swelling just by having the surgery.
- Swelling could be due to chemo – as cells die they cause cellular change

## Dr. Ettl 5/14/02

After return from hospital, Ben's eye began to get red and swell and slightly closed. Called Dr. Ettl with concern. Suggested we call Dr. Edelstein. Could be due to large amounts of IV fluid and surgery. Could be normal drooping, do not lay down when examining. Should not be red. Vinblastine may cause some swelling of the eyes.

## Dr. Krahl 5/13/02 - PCH Pathology

- Note: Jaffe, 12 days after Dehner is done, still does not have the samples for review. PCH received samples today. Will arrive at Dr. Jaffe by 11:00 AM tomorrow.
- Was S100 done on all the biopsies, which ones?
  - **Scalp 1:** S100 negative at PCH, not sent to Dehner
  - **Lymph Node:** No indication of abnormality. **No** tests done.
  - **Scalp 2:** S100 negative at PCH, uncertain of what Dehner wants
  - **CNS:** S100 positive at PCH, **S100 negative at Dehner???**
- Was CD1a done on all biopsies, if not, which ones? (Scalp 1, Lymph Node, Scalp 2, Brain). For bone marrow biopsy and aspiration has CD1A been done? If so, when are results expected?
  - **Scalp 1:** CD1a - Not done at PCH, Not sent to Dehner
  - **Lymph Node:** No indication of abnormality. No tests done.
  - **Scalp 2:** CD1a – not done at PCH, **Dehner CD1a negative????**
  - **CNS:** CD1a – not done at PCH, **Dehner CD1a negative????**
  - **Bone Marrow:** Negative for CD1a @ PCH 5/9
- Who is the LCH3 reference pathologist? Dr. Jaffe
- Why was EM not done for Birbeck granules on all Biopsies? Can we do it now? (Research suggests you can still do it on sub-optimal specimens)
  - Did put some tissue in special media (gluteraldehyde) for EM. Sent to Dr. Dehner. He did not do EM. Nor did he mail that piece back. They did get it. "fresh tissue". Dr. Crowl will call first thing in the morning to make sure they send it to Dehner.
  - **Still not sure if we can do EM on the scalp samples.**
- Is final CNS pathology report from Good Sam done? What are the results? We need a copy. No, will wait on results from Jaffe.
- How are samples prepared?
  - Samples are prepared for stains by taking the tissue, preparing it by dehydration, hydration and some chemical processing, then samples are put into a paraffin block. Pieces of the block are then sliced off (very thin) as needed. S100 and CD1a are both stains.
  - Samples are prepared for EM by placing in a special liquid (gluteraldehyde). To transport, they are placed in a non-toxic fluid. They often call it "fresh" tissue
- **Can we get a clean copy of Dr. Dehners pathology report?**
- **Can we do MAC 387 and Fascin?**

## Singer 5/11/02

- Reviewed case history, will send us a copy
- Ben will be getting three different chemotherapies for the next six weeks, Vinblastine, Prednisone & Methotrexate.
  - Vinblastine: Once a week by IV push. Amount and units?
  - Prednisone: Three times a day by oral liquid after food. Amount and units?

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- Methotrexate: Once every two weeks by IV starting every other Friday. (10% in first hour, remainder in remaining 23 hours). Three-day hospital stay required. Leukovorán given at 48 hrs & 54 hrs to rescue good cells. Amount and units? Bone tumors get 24 times more, but Ben will get more than leukemia patients. Anti-metabolite, blocks folic acid. Give leukovorán or folic acid to rescue.
- Anti-nausea medication given as needed and as allowed (Zofran or ondansyman, hydroxyzine – antihistamine, lorizapan at ½ dose)
- Note, hydration and PH are done consistently at PCH to reduce errors, protocol does not dictate.
- Note: No child goes through a full does of everything, kids end up not tolerating all of the drugs.
- Reviewed most common effects of chemotherapies they see in kids like Ben:
  - Vinblastine: May get tingling of fingers, watch for reduced grab strength. Jaw pain, watch for loss of chewing. Will reduce white count. All temporary.
  - Prednisone: Increased appetite, weight gain, fat cheeks, stomach upset, infection, and long healing time.
  - Methotrexate: Can impact kidney function in the short term.

## Etzli 5/10/02

- Needs to check reduced dosage for infants, protocol is tied up in move, needs to check with Dr. Bockland.
- Pushing for 11:00 AM hospital admittance. Dr Singer to admit.

## Manwaring 5/10/02

- Reviewed MRI and compared to past MRI.
- Definite tumor growth.
- The main tumor has changed shape. The other tumor that looks like two separate tumors is actually barbell shaped (green on animations).
- No current sign of hydrocephalus, we will continue looking for signs, may have a couple of weeks??? Look for swelling, fussiness... I asked what the failure mode of hydrocephalus is – it is a pressure failure, the fluid cannot expelled and builds up. The brain is then compressed. If acted upon within several days of onset, it is what they call a recoverable problem – the brain has some sponge or compression survi vability, but if not acted upon early enough, it can be very harmful (NOTE: Bill's father's brother died as an infant from hydrocephalus – possibly some relation???).
- Worried about main lesions growth into the thalamus and impacting strength and motion on right side of body (growing into left side of thalamus). Should monitor and develop some games & tests for motion and hand movement on that side. Suggested filming Ben now so we could compare later.
- Compared and contrasted surgery now then chemo with chemo first with the possibility of surgery later when and if we run into trouble:
  - Option 1: Move ahead with Chemo – this is a good choice because it is less invasive. There is NO question that he needs chemo based on the tumor growth rate and the inevitable problems.
  - Option 2: Operate on largest lesion (3-4 days in hospital, 3-4 hour surgery) – Would reduce mass effect, would reduce hydrocephalus, would give us more sample tissue for diagnosis, would reduce impact to the thalamus, would be able to go after the orbit lesion with Dr Edelstein to get more material. Some risk involved, but not high risk. 19 out of 20 chance of no major complications. More invasive than biopsy surgery, would require a large incision.
  - The effects of chemo on surgery: Note if chemo is given and then we have to do the surgery, there is a slightly higher risk to the operation, but acceptable.
  - Conclusion: Go with chemo first, while monitoring for complications carefully. Least invasive, unable to operate on all sights.
- Going to schedule next MRI for 5/23/02 (2 weeks).

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## Dr X 5/10/02 (Discussed Ben's Case With Another Doctor) – Hematology / Oncology

- *What is the difference between Neoplastic (neoplasia) and Reactive (LCH & JXG are classified as reactive and not neoplastic)?* Neoplastic is essentially equivalent to the term cancer. In cancer, something goes wrong at the genetic level. The cell acquires a gene and this gene tells the cell to produce abnormally – the cell reproduces in a crazy fashion. For Reactive processes, something tells the immune system and its histiocytes to reproduce. The body somehow sends the signal to the cells to perform their functions, but for some reason, they go crazy and produce too many cells too fast. So the means are different, but the ends are the same – you have cells reproducing abnormally, and these cells can cause all kinds of problems. They are both treated with chemotherapy, but the way the chemotherapy works to try to remove the problem may be different, for a cancerous or neoplastic process, the chemotherapy typically works at a genetic level and its goal is to kill cells, for a reactive process, the chemotherapy is really attacking the immune system, trying to slow it down and in turn bring the immune process (with the histiocytes) back into place. For reactive processes, chemotherapy should really be called immune modularity.
- Can we have chemotherapy before the brain surgery, and if we do start chemotherapy and have to have surgery, what will be the impact? It is prophylactic (preventive measure or medication), for drops in blood counts, plasmas and other additions can be given for the surgery. White cell count will be lower, and cannot be mitigated quickly and brings a slightly higher risk of infection and slow healing.
- Concluded we should start chemotherapy. No matter what, we are not going to fit into any known boxes 100%. Need to go forward on imperfect information.
- Should not try the 'do nothing' path – we need to assume that this is bad and will result in death and go forward accordingly. We should assume he is going to do worse on his own.
- Explained how common the drugs we were going to be using were, and in general, there are few concerns.
- If we do chemo and we see a change, we are not sure if it was due to the drug or to spontaneous regression. Chemo is confounded with spontaneous regression.
- Pointed out some slightly abnormal findings on the lumbar puncture (spinal tap) results – a change from the first one to the second. (white counts at 9 when it was 3)
- Who is the official LCH III pathologist? ???????
- What are the results of the full body CT and can we get a copy? ???????

## Etzl 5/9/02

- **DECISION POINT:** Decision Point Friday with Manwaring: Brain Surgery (Date?) or start Chemo (on Monday or Tuesday). Decision based on 'safety' of surgery, size, growth, location and impacted structures (thalamus, ventricles) of main tumor. May be better to do surgery first. Would keep material for pathology. Etzl to look at scans and talk with Manwaring before we see Manwaring. Etzl to be available via phone for Manwaring appointment. Bill & Carolyn to contact Dr. McClain to confirm agreement.
- **ORBIT SAMPLE:** If we do surgery, we will get a sample from the eye, Etzl to talk with Edelstein & O'Neil today and find out how they will go into eye and determine overall surgery plan.
- **SCALP SAMPLE:** Need another scalp lesion? Etzl uncertain if McClain thinks another lesion would be useful.
- **SAMPLE PREP & HANDELING:** NEED TO MAKE SURE SAMPLES ARE PREPED FOR TESTS WE NEED. Samples to be sent to Jaffe or Dehner? Send Express back and forth – BILL US. Talk with McClain

## McClain 5/6/02

- *Have you seen Ben's pathology report? If so, what do you think?* Yes, Wants to talk with Dr. Dehner about the possibility that this is transforming or at a different stage (from LCH). Will call Dr. Dehner tomorrow and contact me afterwards if possible.
- Referred to 1996 JXG Journal of Pediatrics by Dehner. Will fax me a copy.
- *Have you had a chance to confer with your colleagues about treatment of JXG?* No. Bottom line is that we would treat the same way we would treat LCH. I asked if quest for final pathology was academic, he said that it was not. We need to finalize the diagnosis.

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- Ben is a LCH III candidate – high risk. There is an urgency to start treatment. To start the study he would need to be diagnosed with LCH. If he were not on the study, he would recommend Methotrexate with Vinblastine and Prednisone. Would bypass 2-CDa in favor of Vincristine and Ara-C. He would recommend getting as vigorous as you can with the chemo because of the CNS involvement.
- Surgery Discussion: Dr. McClain was in agreement with the possibility of brain surgery for the main ventricle-blocking lesion, if Dr. Manwaring could do it with minimal risk and impact. He was open to the possibility of starting Chemo and looking for a reaction, then having surgery if we did not get one. The next MRI should drive some of this decision.
- *Is there any special way we should be directing Dr. Jaffe?* No. But we should be investigating other sources of Biopsy – Orbit soft tissue and bone and potentially the scalp. Dr Etzl should know what procedures they follow for EM biopsy.
- *Are there any JXG specialists?* No, not as far as treatment or chemo. (Dehner – Pathology)
- *How many JXG cases have you seen / treated?* Very few cases – 3 in 15 years. No CNS involvement. 1 with liver involvement – little boy – deceased. Liver involvement would show as high bilirubin count.
- *Is it worse than LCH, is it treated differently?* Can be worse. Probably is worse.

## Etzl 5/6/02

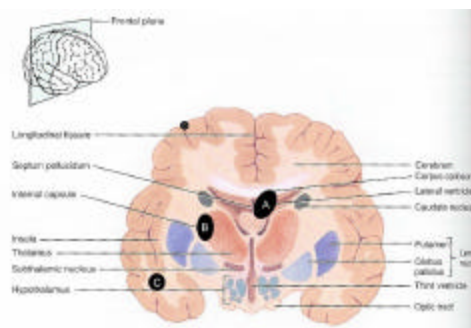
- *Did Dr. Dodge do a CD1a antigen stain on the Skin Biopsy?* Does not know, will check tonight
- *Can we get a copy of the Pathology Report from PCH on CNS biopsy (fax)?* Report was probably not completed until the return on the consult. Initial findings were negative.
- *What is the current status of the samples for Jaffe? Send back? Jaffe there to receive?* Does not know, will check tonight
- *All the reading we have been doing points to the need for Electron Microscopy to rule out LCH conclusively, is there anyway we can do this?* Prepare for this in the future? Again, it is dependent on the size of the sample, how it is prepared, the medium it is placed in. Easier in a lymph node.
- Needs to talk with Dr. McClain. Wants to draw on his experience and the experience of his colleagues. This could be an aggressive JXG, could be burning out, or could be a combination. Are we at a stage that we could treat on Dr. Dehner's pathology alone?
- Trading pros and cons of surgery for main lesion in addition to chemo.
  - May not want to start chemo, which would drop blood counts (Vinblastine) and then not be able to operate.
  - Talked several times with Dr. Manwaring
  - Radiation would need to be though over VERY carefully.

## Etzl 5/3/02

- *Would we treat LCH & JXG the same?* We are uncertain.
- *Which is more aggressive, LCH or JXG?* We do not know. JXG is usually more benign (in the skin), but in Ben's case he has lung and CNS involvement so that would be more aggressive. 'Disseminated' JXG is not well understood.
- Dr. Etzl is waiting for Dr. McClain to review pathology and talk with colleagues about how he would treat if JXG.
- Implied they would add Methotrexate with LCH, but was uncertain with JXG.
- Also discussed trading surgery, chemotherapy and radiotherapy

## Manwaring 5/3/02

- MRI:
  - Will have a third MRI next week
  - Hope to see progress before symptoms start to show.
  - We cannot get the exact same shots from MRI to MRI.
  - Will send a copy to Austria.



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- ❑ Stated that there were probably 4, not 3 tumors – the fourth being on the outside top, we could not locate on scan. See diagram at right.
- ❑ Symptoms of a problem with tumors are:
  - Tumor A (Largest in the ventricle)
    - Anterior fontanel swelling
    - Irritable, Poor Feeding - Headache symptoms
  - Tumor B (Near hypothalamus – in the internal capsule)
    - Decreased strength and motion on the left side of the body
    - Could see decreased visual ability out of left side of body, left visual field)
  - Tumor C (In right temporal lobe)
    - Could cause seizures?
  - Tumor D – no symptoms
- ❑ Surgery:
  - Surgery, instead of shunting, would accomplish three things at once:
    - Reduce Mass Pressure
    - Open Ventricles (2 locations – forward and aft)
    - Remove much of the tumor
  - Surgery would be in front of the motor strip and would entail much the same intrusion as the biopsy. You would see a 'trail' on the MRI. Impact would be minimal. Will 'push' brain out of way. A large section of skull would be removed and replaced.
  - Will only operate in a given area if there are high impact symptoms, the location is strategically accessible and the effect to quality of life is taken into account.

## Kaplen 5/3/02

- ❑ Call in 6 Weeks
- ❑ Phenobarbital usually does not cause diarrhea

## Etzl 5/1/02

### Status

- ❑ Dehner has returned his results:
  - Some S100 stains are positive for LCH
  - CD1a test is negative
  - Reminded us about the "spindly" cells
  - Diagnosed as Juvenile Xanthogranuloma (Morphologically)
- ❑ Etzl talked with McClain
- ❑ McClain was leaning toward LCH
- ❑ They were not sure if this was LCH becoming JXG for JXG becoming LCH. Looked like burnt out LCH (??? Do not know what this means – not sure they do either)
- ❑ If it was JXG this would be bad for the following reasons:
  - JXG is very rare, even more rare than LCH
  - JXG does not respond as well to chemo
  - The version Ben would have would be very aggressive because of the pulmonary (lung) involvement.
- ❑ Sending MRI films to Austria would be useful, but not to Ben. It would only be useful to their database of knowledge. They would not be able to diagnose based on the films alone.
- ❑ If they do not get a definitive diagnosis, Ben could not be on the study (LCH III), but he would be treated as if he were on the study.

### Brain Samples

- ❑ Samples to be sent to Jaffe
- ❑ They are going to be sent back to Dodge at PCH
- ❑ He has sent Dodge information to be able to send to Jaffe
- ❑ I asked him repeatedly to investigate the following with Dodge:
  - Confirm with Dodge if the samples have been sent to Phoenix yet
  - If they have, by what means (over night, 3 day...)
  - Get them re-routed if possible

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- He told me it was important that someone be at Jaffe's lab to accept the samples. They need to call to confirm this (Jaffe could be at a conference)
- Indicated that there were enough sample for Jaffe
- Samples were of size 1 x 1.5 sona-meters

## **Scalp Samples**

- Talked with Dr. Dodge to confirm if they had done CD1a on scalp samples.
- Dr. Dodge is instructed to run CD1a if it has not been run

## **Eye**

- We should not go after the eye yet. The bone lesion is small, and there is not a lot of soft tissue associated with it (small soft tissue component).

## **Brain**

- Thought shunting (or surgery) to prevent blockage of the ventricles was better than radiation because of Ben's age. Less long-term impact.
- Because brain (CNS) tumors are in an unusual place, need to trade types of chemo among each other, types of surgery among each other and radiation. Also need to trade between theses. No clear treatment path.

## **McClain 5/1/02 – Hematology / Oncology @ Texas Children's Hospital**

### **Diagnosis**

- *How can we speed up diagnosis?* Dr. McClain to make a call to Dehner & Etzl
- *Do we believe pathology is being done correctly?* Dr. McClain to talk with Dr. Etzl. Was not clear from medical records.
- *Should they be doing CD1a & EM (Electron Microscope) for all biopsies?* For EM, they would need to have been prepared a special way in a special liquid.
- *What about other organs & GI tract? How do we know they are/ are not involved? Other Tests?* Blood tests do not indicate liver and spleen are involved.
- *Skull bone biopsy, do we take orbit soft tissue and bone? Will it be enough tissue for EM?* May be able to reclaim from first surgery. Decreased chance of success.
- *Can this be something else and not LCH?* Possible but not likely. Could be JXG.

### **Brain Lesions**

- *Have you seen other cases with these types of lesions?* Yes, 2 cases (little girl – no major problems. 2 year old boy, some difficulty)
- *Have you seen other cases with lesions in this location?* A 2 year old boy.
- *Is there success issues with deep brain lesions?* Yes
- *How do we categorize these lesions?* Type III, this may point to using 2CdA
- *What do we do if we encounter a hydrocephalus problem?* Emergent radiotherapy, high dose of steroids, Decadron steroid.
- *When should we do another MRI?* 2 weeks
- *What parts of the brain are we impacting?* Functions? Don't know.

### **Chemotherapy**

- *Can we get a copy of the LCH 3 study?* No, but he drew it out for us.
- *Would Ben fit the LCH3 study?* Yes
- *6MP? Do it or not?* 6MP is a medium gun, good for cases of LCH that are responsive, not so good for cases that are not responsive.
- *For 2CDa, what does salvage mean?* Second line therapy. 2CDa is a substitute for some of the genetic code. It halts the protein production and cells die. Hard on the immune system. Can only give 4 or 5 times because it will lower lymphocytes and make susceptible to virus and fungi. Low platelets.
- *How do we choose between the either / or of Vincristine & Ara-C or L-ASP & Methotrexate?* We have more experience with the Vincristine/Ara-C combo. If that fails then you may follow it with the L-ASP/Methotrexate.
- *What is L-ASP?* Left-handed asparagines. Eats amino acids.
- *How long on each set of chemotherapies?* See TMap.
- *What are the major side-effects? Given his age (growth, sterility, mental development)?* Prednisone will inhibit growth. He may get to about 5 feet 6 or 7 inches because of the timing. Vincristine causes cramps and constipation and he will therefore only be given a quarter dose because of his age.

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Methotrexate has been associated with development issues, but this is for leukemia patients and they get higher doses. Sterility should not be a problem because of his age.

- How might this disease progress even with Chemo?* Headaches, seizures, fatal
- Who oversees treatment?* Etzl
- Where is treatment done?* PCH. Need to register Ben.
- Should we avoid immunizations?* Yes, none for Ben, no live virus for Marie.

## Etzl 4/30/02

### Tumors in brain are difficult to biopsy

- Head is different area to biopsy
- Brain tumors are dangerous. Scooping out causes neural damage. Have to take small pieces.
- Something about slides that I did not catch.
- Pieces are too small for EM.

### Pathology not complete, Jaffe a possibility

- Reviewed our pathology summary
- Talked with Dr. Dodge.
- All blocks with Dehner.
- No final status yet.
- Referred to spindle shape again,
- Doing S100 and other stains, but will also do CD1a if necessary (was not certain if they were done).
- Should send pathology to Jaffe either way (positive or negative results).
- New head of pathology worked with Jaffe at Pittsburgh, will talk with him

### Tumors are deep in the brain

- These tumors are in a strange place. We do not typically see these lesions this deep in the brain. Protocol is not designed for this.
- Lesions are more on the outside (meninges) and in the brain stem areas.
- Asked about copy of LCHIII protocol. Stated that LCH I and LCH II are inferior to German Netherlands study.
- Chemo can cross the blood-brain barrier, quoted a recent CNS tumor study.

## Etzl 4/29/02

- No return on pathology
- All blocks with Dehner
- Did not get a clear resolutions on CD1a at different sites (scalp, brain)
- Samples not big enough for EM (scalp, brain)
- Gave him pathology summary and references

## Etzl 4/27/02

Discharged from Hospital

Get another Phenobarbital fever

Red chest is not an infection

Waiting for pathology 2-3 days

Juvenile Xanthogranuloma – S100 Negative. Langerhans Cell Histiocytosis – S100 Positive

Is the inter-cranial lesion JXG?

PCH pathologist will talk to Dr. Dehner directly rather than just read report.

## Notes from 4/27/02 HAA Regional Meeting in LA

### Organization Notes

- Sign up for Histo.org bulletin board
- A lot of new research in the dendritic cells area
- Dr. Dangio?? on east coast

### Symptoms

- DI – typically shows up one year after diagnosis, 50 / 50 chance – strong indicators are orbit and multi-system involvement
- Pituitary may work as a filter.

# Doctor's Notes for Benjamin Stokman

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- Pituitary can be harmed without brain tumors.
- Collapsed vertebra
- Lung – Cystic type failures
- Failure to 'thrive'
- Cytokines – Damage nerves to possibly cause depression in cerebellum

## **Diagnosis**

- Have to have a Biopsy
- Skull bone biopsy is the most common way LCH is identified
- Difficult to identify in brain – LC not present, fat macrophage cells are present
- Electron microscope identification of Birbeck racquet shaped granules (more expensive)
- High risk identified as any lung, spleen, liver or bone marrow involvement

## **Treatments**

- For Chemo notes see Chemo TMap
- 6 week response critical!!!
- LCH III is investigating the use of Methotrexate
- 6MP also being evaluated (viewed as a maintenance course)
- 2CdA is viewed as a salvage course
- Recommend against radiation – many historic radiation issues
- No targeted radiation available
- Pituitary Radiation – Does not work
- Growth Hormones are often needed to counteract the failure of the Pituitary and the effects of Chemo
- Hematopoietic stem cell transplantation can be effective
- Surgery – get rid of offending cells, but do not remove bone. Bone will grow back in about 2 years. Bone lesions can be seen to improve via re-calcification (white sclerosis outline)

## **Etiology**

- Thyroid disease shows up as a strong link to LCH
- Inverse relationship to immunizations (immunizations good)
- Possible agriculture link
- Possibly immune system activated / other cells called to attack

## **Long Term Impact**

- Need to follow for a lifetime
- Recommend 6 month MRI's
- Collapsed vertebra
- Cytokines – Damage nerves to possibly cause depression in cerebellum
- DI
- Slow or halted growth

## **Manwaring 4/26/02 - Neurosurgeon**

- At best we have a 2-3 month window - 50/50 that we have a problem in 4 weeks.
- Scan frequency – every 2 weeks full contrasted MRI scan.
- Look for symptoms of hydrocephalus – drowsiness, nausea
- Surgery would take out a big section of bone and would tile it back in.
- Would go into corpus collusum – good recovery
- Would rather take out tumor than shunt. Shunt is difficult in given location and would only be a Band-Aid solution
- Whole brain radiation would cause learning, growth and hormone problems.
- Remove stery strip and stitches 10 days after surgery.

## **Etzl 4/26/02**

- Could be a Xanthogranuloma – should not be S100 positive
- Atypical LCH – still think it is reactive and not malignant.
- LCHIII shows that response to initial therapy is important
- Pathology not ready yet from Dr. Crawl and Dr. Dodge – wait until Tuesday.

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- ❑ How are the tumors growing? They are not attacking or consuming the brain, they are pushing it out of the way.
- ❑ Location of main tumor is near the frame of Monroe – blockage will cause hydrocephalus.

## Etzl 4/25/02

- ❑ Two lesions in the skull per CT – 1 in the orbit, the other is the brain surgery location, not a true lesion.
- ❑ Need a better chest x-ray.

## Kaplen 4/25/02

- ❑ Look for allergic reaction to Phenobarbital – a skin rash
- ❑ Optic Nurophothopy(?) – not in the brain
- ❑ Infiltrate causes blockage causes infection

## Etzl 4/25/02

- ❑ Bone marrow – preliminary – looks good
- ❑ Get full skeletal survey (skull and long bones)
- ❑ Does not look like he has diabetes insipidus yet, specific gravity of urine above 1.010
- ❑ Radiotherapy:
  - Can effect learning / behavior / neuro...
  - LCH is very radio sensitive
  - 180 to 200 cg for 3-4 days
- ❑ Dr. Ettl has had about 12 LCH patients and has 3 currently
- ❑ Vinblastine does cause shrinkage in CNS, question is how quickly and will it be fast enough.
- ❑ In the international study, intercranial is not common – may need to tailor treatment

## Etzl 4/24/02

- ❑ Spinal fluid looked clear & came out easy take 1-2 days to get results
- ❑ Bone marrow initial (aspiration) looked good but need to wait for biopsy results usually in 24 hours
- ❑ All results, answer from Dehner and surgery recovery well come together at the same time and then we decide on treatment

## O'Neil 4/24/02 – Ophthalmologist

- ❑ Looked at him, dilated eyes.
- ❑ Eyes look good. Functioning.
- ❑ Vision problems product of seizure.
- ❑ No swelling of optical nerve.
- ❑ At a bit higher risk for lazy eye or crossed eye. Secondary to the problem.
- ❑ 5-6 weeks down the road may want to have Dr. look at him again. It is treatable.

## Etzl 4/23/02

- ❑ Crowl has looked at the pathology in house. S100 in scalp is negative. S100 in brain is positive. Not typical.
- ❑ Send pathology to Louis Dehner – Foremost pediatric pathology.
- ❑ Langerhans cell histiocytes – chew up bacteria
- ❑ Whole array of issues
- ❑ Was called Histiocytosis X – now called LCH. Made up of DI and three diseases (Eosinophilic Granuloma / Hand-Schuller-Christian Disease / Letterer-Siwe Disease).
- ❑ There is an international study for LCH
- ❑ There is a US group in New Jersey
- ❑ Going to consult with Dehner, consult with eye surgeon, Kaplen on Pheno
- ❑ Assume LCH and understand chemo.
- ❑ Need to investigate diabetes insipidus – serum sodium test / water deprivation test
- ❑ Ben's age and multi-focality presentation is not good

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## □ Need to do the following baseline and prework:

- Bone marrow aspiration and biopsy
- Full skeletal survey
- Bear hearing test
- Install porta-catheter
- Examine pulmonary lesions

## Kaplan 4/23/02

- Tumors did not originate in the brain
- Histiocytic disorder – same family but not Langerhans (what did this mean???)
- Crowl – sent out for review – do not know who with
- S100 positive

## Kaplan 4/22/02 – Neurologist

- Concerned with increased seizures and loss of vision
- Prescribes Phenobarbital for seizures – will not hurt, but is addictive barbiturate.
- Ordered ophthalmologist for vision check
- CBC – Complete blood count
- BMP – Basil meta panel (blood sodium)
- CT
- Lumbar Puncture
- Revisit Infection again
- Get a group together
- Will investigate cell pathology

## Etzl 4/23/02 - Hematology / Oncology

- Talked with Dr. Matsamoto over the weekend – going to order pediatric ophthalmologist, Dr. James O'Neil
- S100 is the confirmatory stain for LCH
- Pathology takes at least 48 hours – no final reading yet
- Pathology review board in the morning – review difficult cases
- Standard process is: Fix samples -> slice -> Standard battery of stains -> other stains -> send out to specialists
- Pediatric pathology is more difficult – can look identical
- For seizures – Kaplan to try medication, no one sight strongly interfering

## Manwaring 4/21/02 – CT Review

- Surgery looks good
- Left orbit area looks enlarged
- Will check with radiologist
- Edelstein returning Monday / Manwaring back Tuesday night
- Keep head elevated

## Manwaring 4/20/02 – Before Surgery

- Risks of surgery – hemorrhage, injury, infection, anesthesiology
- Worried about hydrocephalus
- Derma cyst possible in left eye
- Eye is different, probably not related to the brain – probably a cyst

## Manwaring 4/20/02 – After surgery

- Took 10 sample
- 1/3 of tumor removed

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- Spindly cells
- Biopsy results Monday
- Looked tumorous
- Leave band-aids on for 10 days

## Hadden 4/19/02 – Neurologist

- Not seizures, than what are they?
- Not showing on EEG, can still be a seizure / but not defined as seizures
- Wait and see progress

## Singer 4/17/02

- Proteins in scalp – histiocytic
- Immunohisto Stain – Friday results from Andrew Dodge
- Does not look fungal
- Normal Lymph Nodes
- Did not see any malignancies

## Laks 4/16/02

- Six or seven areas in the brain – could be more
- Can classify cells & treat like that classification if we are uncertain or they do not meet any know issue

## Singer 4/15/02

- We have an atypical presentation of something typical
- Lymph nodes can show for infection as well as tumor (in response to ultrasound showing lymph node swelling)
- Could be nothing we are making into something
- No edema showing – both fast infection and tumors show edema
- Valley Fever & Cocci are usually 1 nodule in the lung and accompanied by a cough

## Ostdiek ??? – Infectious Disease

Possibly Histiocytosis – need biopsies to find out if tumor or infection.

## Singer ??? CT results - Hematology / Oncology

- Four nodules in the lung – finger to pencil diameter in size
- 1 subcutaneous fat layer of abdomen (possibly lymph node)
- Thymus – uncharacteristic concave
- Dr. McGill to biopsy
- Valley fever?

## Laks 4/11/02 - Pediatrician

- Dr. Matsamoto delivered MRI results
- Checked into Good Sam PCH under Dr. Ettl
- What could it be:
- Hameratoma??
- Pseudotumor – false tumor - very rare, but lights the same way as MRI – with contrast only.
- Lesions are very uniform – 2 x 1 cm is the largest in the midline – others 1x1 cm
- Not what you normally see for brain tumors (no edema)

## Edelstein 4/10/02 – Ophthalmology Oculoplastic Surgeon

- Preceptal cellulitis orbitus