

**In the Matter of
Mark R. Geier, M.D.**

* **Before the Maryland State
Board of Physicians**

*

License No. D24250

Case Nos:

* 2007-0083; 2008-0454; 2009-0308

**Respondent Mark R. Geier, M.D.
Summary Suspension Presentation
May 11, 2011**

- Tab 1 Redacted Affidavit of Parent of Patient B
- Tab 2 Redacted Affidavit of Parent of Patient E
- Tab 3 Redacted Affidavit of Parent of Patient F
- Tab 4 Redacted Affidavit of Parent of Patient G
- Tab 5 Redacted Affidavit of Parent of Patient H
- Tab 6 Redacted Affidavit of Physician Parent of Dr. Geier Patient
- Tab 7 Affidavit of James B. Adams, Ph.D.
- Tab 8 Long Term Study of Lupron, Journal of Clinical Endocrinology and Metabolism, 90(3): 1371-1376
- Tab 9 "Case Study Suggests New Therapy for Autism," Johns Hopkins University Newsletter, Feb. 26, 2009.

Tab 1

IN THE MATTER OF
MARK R. GEIER, M.D.

RESPONDENT

License No. D24250

* BEFORE THE
* MARYLAND STATE
* BOARD OF PHYSICIANS

* Case Nos: 2007-0083, 2008-0454
* & 2009-0308
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* * * * *

AFFIDAVIT

I [REDACTED] am at least 18 years of age and competent to testify. If called as a witness in the above referenced proceeding, I would testify as follows:

1. My son is identified as patient [REDACTED] in the Order For Summary Suspension Of License To Practice Medicine by the Maryland State Board of Physicians.
2. No member or representative of the Maryland State Board of Physicians has ever contacted me regarding this matter.
3. I never consented to the Board releasing my son's medical information to the general public.
4. I have read the entire Order For Summary Suspension Of License To Practice Medicine. I find many of the accusations against Dr. Geier as it relates to my son to be incomplete, inaccurate and highly misleading. The most offensive example is line 2 of paragraph 66, which states, "The Respondent documented that patient [REDACTED] had no genital development without further explanation or description". The fact is that the genitals of a six year old child were not yet showing signs of puberty. For

the Board to take a shorthand statement out of the child's medical records and twist it out of context in order to infer anything else is shocking and highly irresponsible.

5. Paragraph 67 contradicts paragraph 65 of the Order of the Board.
6. Paragraph 67 contradicts paragraph 72 of the Order of the Board.
7. Paragraph 71 contradicts paragraph 70 of the Order of the Board.
8. Paragraph 73 contradicts paragraph 76 of the Order of the Board.
9. My wife and I have discussed in detail the results of our son's periodic laboratory results with Dr. Geier during numerous telephone conferences. In addition to the phone consults and extensive laboratory tests, my son has been physically examined by Dr. Geier.
10. During one of the initial phone consultations during the assessment phase and prior to ordering lab work, Dr. Geier questioned my wife and I extensively including but not limited to the history of our son's development, behaviors, growth spurts, past and current condition, signs of puberty, the reasons we were seeking treatment, our heights and medical histories and our family members' heights and medical histories.
11. Dr. Geier has clearly explained his treatment rationale for prescribing hormonal therapy and chelation therapy to my wife and I.
12. Other physicians have also advised me that my son's conditions are the result of vaccine injuries. Other physicians have prescribed chelation therapy. The

chelation therapy, which Dr. Geier prescribed worked best in combination with Lupron.

13. Prior to the decision for my son to undergo Lupron and Chelation therapy, I was advised of the risks and benefits to my child. I gave informed consent to the treatment of my child.
14. The Board's assertion that Dr. Geier failed to secure written medical authorization forms is incorrect. Attached hereto is a copy of the written medical authorization form which I received and executed in [REDACTED] of 200[REDACTED].
15. My child has significantly benefited from treatment with Lupron and chelation. As an example, shortly after my son began treatment with Lupron, he calmly sat still for the first time in five years.
16. My son's language is extremely limited. If possible he will communicate in one word commands and requests. At one point, he had no language at all. The longest sentence he has ever stated was six words. "Santa Clause is coming to town". He made this statement a few months after we began Lupron. One of the most meaningful conversations I have ever had with my son involved him stating, "shot", "I want shot please". I asked him, "does the shot make you feel better?". He answered, "yes". I don't have any doubt whatsoever that he was accurately expressing his meaning.
17. When we began lupron therapy my son was wild and uncontrollable. It took several adults to hold him down in order to administer a shot. Now he will ask for

the shot. He will pull his pants down and calmly receive the shot with no resistance.

18. When he first had blood samples drawn, it would take several adults to restrain him. Now he will calmly sit in the chair and hold out his arm to have his blood drawn with no restraints.

19. Behavior, eye contact and cognition all improved after we began Lupron and chelation treatment.

20. Other than severe brain damage, aggression is one of the primary concerns I have for my son. Without Lupron, I fear he may have to be heavily sedated in order to prevent him from harming himself or others.

21. I have no complaints what so ever against Dr. Geier

I solemnly affirm under the penalties of perjury and upon personal knowledge that the contents of the foregoing paper are true.


Print Name Underneath


GEIER CLINICAL STUDY PROTOCOL

TREATMENT PROTOCOL –

1. The child is to be injected with the non-depot form of Lupron, (Pediatric, leuprolide acetate) 0.2 mL given by subcutaneous injection.
2. The child is carefully observed for three days for any adverse events.
3. If no adverse reactions are observed the child is given the depot form of pediatric Lupron depot (28 Days – 15 mg) will be administered on what will be called day one. Additionally, the non-depot Lupron will be administered subcutaneously on a daily basis (0.4 mL / Day) also starting on day one. The patient's parents should begin a daily log to record daily behaviors (positive and negative).
4. Absent any significant adverse reactions the child will continue to receive Lupron depot shots (28 Days – 15 mg) every 28 days and daily non-depot Lupron injections. The child will be assessed to determine if the dosage is sufficient to control androgen activity. If needed, additional doses of daily non-depot Lupron or Lupron Depot injections will added.
5. Patients on the protocol are to be monitored for androgen (including: DHEA, DHEA-S, Androstenedione, and Testosterone), glutathione levels, liver and kidney testing, thyroid testing, and CBC with differential testing once per month.

Genetic Consultants
 14 Redgate Ct
 Silver Spring MD 20905
 001-989-0548 UAA

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HECK ONE
 Q B70016-DEIER, #
 J D19114-YOUNG, #

53595304479

HECK ONE
 ACCOUNT BI.
 PATIENT BI.
 MEDICAID
 MEDICARE
 TPL () MULTIPLAN
 BILL Insurance

STAT	CALL BACK	PHONE ()	NAME	ADDRESS	FAX No.
Patient Name (Last)	(First)	(MI)	Patient Key	Sex	Date of Birth
Patient's Relationship to Responsible Party			1-Self	2-Spouse	3-Child
Medicare # (Include Prefix/Suffix)	Medicaid #/AHCCCS#	State	Responsible Party's Address (if Different From Patient)		
Insurance Company Name	Plan	Order Code	Physician ID#		
Insurance Address	Primary Care Physician #	City	State	Zip	24 Hr. Urine
Subscriber Number#	Location	Group #	Insured SS# (if Not Patient)	Workers Comp	Yes <input type="checkbox"/> No <input type="checkbox"/>
Diagnosis / Signs / Symptoms / In ICD-9 Format (Highest Specificity) REQUIRED			LabCorp Logo		

On File 3-21-06
 MEDICARE ADVANCE BENEFICIARY NOTICE (AUN)
 Use a separate ABN when ordering tests which require an ABN. Refer to the back of this form for more information.
 @ = Subject to Medicare medical necessity guidelines
 @ = Subject to Medicare frequency guidelines
 @ = Medicare deems Investigational

@ 017500 First Trimester Serum Screen
 022098 Apolipoprotein E (APOE)

959002 Reduced Glutathione

standing order: Tests to be collected once per month!

- 095688 Amino Acid Profile, Qn, Plasma
- 140442 Androstane Diol Glucuronide
- 004705 Androstenedione, Serum
- 706960 Anemia, Megaloblastic, Serum
- 511150 Angelman/PWS Methylation Assay
- 005009 CBC with Differential/Platelet
- 165128 Celiac Disease Comprehensive
- 052019 Chromosome, Blood, Routine
- 071806 Cobalt, Plasma
- 734004 Common Alloy Exposure, Urine
- 322000 Comp. Metabolic Panel (14)
- 001586 Copper, Serum
- 004697 Dehydroepiandrosterone Sulfate
- 004101 Dehydroepiandrosterone (DHEA)
- 500142 Dihydrotestosterone
- 010552 FISH-Multiprobe-Subtelomere
- 510461 Frag X Cytog/DNA Rfx Subtelo
- 070813 Heavy Metals Profile II, Urine
- 06200 Heavy Metals Profile II, Blood
- 1321 Iron and TIBC
- 03756 Lipid Panel
- 001537 Magnesium, Serum
- 071589 Manganese, Plasma
- 724195 Manganese, Blood
- 511238 MTHFR
- 716720 Organic Acid Analysis, Urine
- 084624 PCB + Pesticide Exp. P.
- 120980 Porphyrins, Qn, Random U

- 511180 Rett Syndrome, DNA Analysis
- @ 081034 Selenium, Blood
- 095113 Testicular Function Profile II
- 027011 Thyroid Profile II
- 017509 Vitamin A, Serum
- @ 000810 Vitamin B12 and Folate
- @ 004656 Vitamin B6
- 001800 Zinc, Plasma or Serum

Please Note
 must Fast

Genetic Centers of America
Consent for Enrolment in the Geier Experimental Protocol
For the Treatment of Autism

Patient: _____

Date: _____

1. I request that my child be enrolled in the Geier Experimental Protocol for the treatment of autism. The Institutional Review Board (IRB) of the Institute for Chronic Illnesses (Office for Human Research Protections, US Department of Health and Human Services IRB number: IRB00005375) has approved this study protocol.

2. This protocol utilizes Lupron to lower testosterone (the male hormone) levels. Lupron is an FDA approved drug for lowering testosterone levels in cases of precocious puberty by inhibiting the release of FSH and LH from the pituitary in the brain. Lupron is also approved for use in lowering testosterone in cases of benign prostatic hypertrophy, prostate cancer, and in other conditions where it is helpful to lower testosterone levels. The package insert for Lupron lists the following as potential adverse events: In two studies of children with central precocious puberty, in 2% or more of the patients receiving the drug, the following adverse reactions were reported to have a possible or probable relationship to drug as ascribed by the treating physician. Reactions which are not considered drug-related are excluded. Body as a Whole - General Pain, Acne/Seborrhea, Abscess, Rash, Erythema Multiforme, and Vaginitis/Bleeding/Discharge. In those same studies, the following adverse reactions were reported in less than 2% of the patients. Body Odor, Fever, Headache, Infection, Syncope, Vasodilation, Dysphagia, Gingivitis, Nausea/Vomiting, Accelerated Sexual Maturity, Peripheral Edema, Weight Gain, Emotional Lability, Nervousness, Personality Disorder, Somnolence, Epistaxis; Alopecia, Skin Striae, Cervix Disorder, Gynecomastia/Breast Disorders, and Urinary Incontinence. FSH and LH stimulate the production of testosterone in the body. Thus by inhibiting FSH and LH, Lupron temporarily halts the production of testosterone.

3. At some point on the protocol heavy metals may be removed by means of chelation. Chelation is a process by which patients are given medicines which bind mercury and help to eliminate it from the body. The chelation agents utilized in this protocol would be DMSA. DMSA is an FDA approved chelating agent. The package insert lists the following as potential adverse events: nausea, vomiting, diarrhea, appetite loss, hemorrhoidal symptoms, loose stools, metallic taste in mouth, back pain, abdominal cramps, stomach pains, head pain, rib pain, chills, flank pain, fever, flu-like symptoms, heav head/tired, head cold, headache, moniliasis, elevated SGPT, SGOT, alkaline phosphatase, elevated serum cholesterol, drowsiness, dizziness, sensorimotor neuropathy, sleepiness, paresthesia, papular rash, herpetic rash, rash, mucocutaneous eruptions, pruritus, cloudy film in eye, ear plugged, otitis media, eyes watery, throat sore, rhinorrhea, nasal congestion, cough, decreased urination, voiding difficulty, proteinuria increased, arrhythmia, mild to moderate neutropenia, increased platelet count, intermittent eosinophilia, kneecap pain, and leg pain. In order to attempt to ensure maximum safety of chelation, if employed, essential mineral levels are monitored and kept within normal levels by supplementation to assure that the chelation process does not interfere with normal minerals in the body.

4. Children on the protocol will have kidney, liver, and thyroid function tests routinely monitored. When the protocol is complete the chelation, if employed, and anti-testosterone medications are discontinued.
5. I understand that this protocol is experimental. I further understand that although some initial success has been observed in children undergoing this protocol, there is no assurance that it will help my child.
6. I understand that although the medicines and procedures used in this protocol are believed to be relatively safe, since the protocol is experimental and the drugs are being used in a new way, there may be some yet to be determined risks associated with it.
7. I have had all of my questioned about this protocol answered and I full understand the potential risks and benefits of this protocol. I have made an informed consent decision to have my child undergo treatment under this protocol and I agree to follow the protocol. I agree to allow the publication of results obtained from my child's participation in this study with identifying information removed. I fully understand that I may withdraw my child from the protocol at any time that I so desire. I also understand that the medical personnel may ask me to withdraw my child from the protocol if they determine in their minds that it is not working well for my child.
8. No warranty, guarantee, or assurance has been given to me by anyone as to the results that may be obtained from the protocol described above.

**DO NOT SIGN THIS FORM UNLESS YOU HAVE READ IT
AND AGREE WITH IT**

Parent or Guardian

Counselor/Physician

Tab 2

IN THE MATTER OF
MARK R. GEIER, M.D.

RESPONDENT
PHYSICIANS

License No. D24250
2008-0454

* BEFORE THE
* MARYLAND STATE
* BOARD OF

* Case Nos: 2007-0083,
* & 2009-0308
*

* * * * *

AFFIDAVIT

I, [REDACTED] am at least 18 years of age and competent to testify. If called as a witness in the above referenced proceeding, I would testify as follows:

- 1. I provide this affidavit in support of Dr. Geier and his treatment of my daughter.
- 2. I initially went to Dr. Geier to discuss treatment options for my daughter's autism.

I have been to several DAN doctors over the years for various treatments to alleviate the negatives of autism and to enhance the positives. Some treatments were positive and were used and others did not seem to have any affect and were discontinued.

- 3. My experience with Dr. Geier and his protocols have been nothing but positive and very professional. My initial visit and all subsequent communications have been extremely detailed. A very thorough set of labs and exams were required before we could even be considered for the Lupron Protocol. Once the results

were in, a long and detailed conversation took place where every aspect of the results was covered.

4. I was fully informed about the Lupron treatment and I did considerable research on my own prior to proceeding. Dr. Geier was extremely responsive to all my questions and concerns. All my phone calls were promptly returned and the information I requested was provided.
5. Most importantly, my daughter responded beautifully to the Lupron therapy once the correct dosage was attained. She was finally able to regulate her emotions, she was much more cognitively aware, she was better able to control her anger, she was less anxious, she was less hyperactive, she was less hyper-focused, she was better able to communicate in a back and forth exchange, she was able to better participate in activities, she slept better, and she was happier.
6. Our lives as a family improved significantly as a result of her improvements. This is also the experience of many other patients of Dr. Geier. Finally, a doctor that understands the hormonal, metabolic and toxic issues associated with autism and has developed a treatment with a product that has been used in children for decades.
7. This is an important treatment that should be allowed to continue. It has made a tremendous difference in the lives of my daughter, and many others just like her.
8. I do want to express concerns on a recent conversation I had with a "medical investigator" for the state of Maryland. After playing phone tag several times, we were able to schedule a time to talk about Dr. Geier. He introduced himself and that the reason for the call was, and I paraphrase, *that he was a medical*

investigator for the state of Maryland and as such they periodically and randomly choose doctor's in the state to investigate as part of quality control.

- a. He initially had questions that pertained to Dr. Geier and his practice and my experience with the practice. However, the conversation quickly shifted to details about my daughter and her treatment. From the type of questions he was asking I realized that he must have a copy of her records in front of him and confronted him. He admitted that he did have her file. I then asked him why he was asking me questions for information that he already had and he stated that he wanted to make sure it was correct.
 - b. This was a very uncomfortable conversation. He was insincere, his intent obvious in hindsight, and was not forthright in his reasons in speaking with me. Suspicious, I immediately called the Geiers office to inquire as to why this person had a copy of my daughter's information. I subsequently learned that he has been actively investigating Dr. Geier.
9. Lastly, I am extremely concerned of an invasion of privacy and a violation of HIPPA laws in the Official Order for Summary Suspension of License To Practice Medicine that I was able to pull off the internet after being informed by a friend who had read it that my daughter must be "patient [REDACTED]" because there cannot be two girls with that description.
- a. To my horror, I read the description and knew instantly (as did everyone who knows my daughter in our very large autism network/community) that it was in fact her.

b. There were three very distinct traits my daughter had that were well known to all that knew her –

- i. [REDACTED]
- ii. [REDACTED]
- iii. [REDACTED]

c. Three very distinct traits that are unique to her as an individual and a person with autism. I have never met another child with these distinct traits. This information was shared with Dr. Geier when he was asking me to tell him about [REDACTED] life and personality. They had nothing to do with the reasons we were in his office. They were personality traits unique and wonderful to her.

d. Why they would be divulged in a public document such as this for the entire world to see is an egregious violation of the HIPPA act. I have received numerous inquiries as to her treatment and involvement in this case. This is information that should have never been released. You may as well have just listed her name and address.

10. At the heart of both medical and legal proceedings relative to health and human service is a respect for the individual and a guarantee of their anonymity. What has been done here is duplicitous and invasive with a total disregard of our family and their well being.

11. My experience with the Dr. Geier has been exemplary of what medicine should be. He has contributed to my daughter's betterment. His care has been compassionate and selfless.

I solemnly affirm under the penalties of perjury and upon personal knowledge
that the contents of the foregoing paper are true.

Tab 3
Material Not Received in Time

Tab 4

IN THE MATTER OF
MARK R. GEIER, M.D.

RESPONDENT

License No. D24250

* BEFORE THE
MARYLAND STATE
*
BOARD OF PHYSICIANS

*
Case Nos: 2007-0083, 2008-0454
& 2009-0308
*

* * * * *

AFFIDAVIT

We, the parents of "Patient [REDACTED]", are at least 18 years of age and competent to testify. If called as a witness in the above referenced proceeding, we would testify as follows:

1. We sought out Dr. Mark Geier for medical care of our child after coming to personally know another child who had benefitted from Dr. Geier's medical care.
2. During the time our child was a patient of Dr. Mark Geier's, our child was at no time treated in a manner that was not medically indicated.
3. At no time was treatment for our child undertaken, that was not expressly understood and consented to by us, the parents. If we had any complaint about the care our child received from Dr. Geier, we would have initiated an appropriate proceeding.
4. Dr. Geier provided competent and compassionate care for our child. Through extensive conversations with Dr. Geier at the onset of treatment, we were informed of the risks and potential benefits to our child, just like one would expect

to have with any doctor regarding any form of treatment for any medical problem.

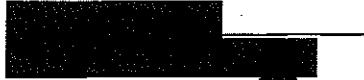

We also did our own research and were well informed of our choices.

5. We as private citizens of this country and as beneficiaries of its' Federal HIPAA laws pertaining to the privacy and security of our child's medical records, between ourselves and any medical practitioner or entity we engage to treat our child, are outraged and appalled at the appearance of our child's private medical treatment being outlined in a document of public record and posted to the Internet. We were not given any notice of such act taking place, and we were certainly never contacted for permission of any kind to do so. It is a flagrant and unconscionable violation of our right to medical privacy on the part of the Maryland Board of Physicians, and we request in no uncertain terms that any identifying specifics of the Patients listed therein, such as age and state of residence, be redacted; that the Complaint against Dr. Geier be removed from its' website; and that the Board be censured for having violated our right of privacy, and the rights of the families of the other Patients outlined in the Complaint.

6. If harm was done to our child or our family, as the current Complaint against Dr. Geier states, it was not done by any medical treatment provided to our child by Dr. Geier, but rather by the blatant unauthorized use of our child's private medical records in a public forum by the Maryland Board of Physicians. It is because of the actions of this Board that we will not at this time, without legal assurances and guarantees of our child's and our own privacy going forward, further jeopardize our family's privacy by signing our names to this document. We nonetheless wish

to convey our outrage and indignation at the disrespectful treatment of Dr. Mark Geier, and the reprehensible and cavalier disregard of our family's medical privacy by the Maryland Board of Physicians.

I solemnly affirm under the penalties of perjury and upon personal knowledge that the contents of the foregoing paper are true.


Parents of "Patient 

Tab 5



IN THE MATTER OF
MARK R. GEIER, M.D.

RESPONDENT

License No. D24250

* BEFORE THE
* MARYLAND STATE
* BOARD OF PHYSICIANS

* Case Nos: 2007-0083, 2008-0454
* & 2009-0308
*

* * * * *

AFFIDAVIT

I [REDACTED] am at least 18 years of age and competent to testify. If called as a witness in the above referenced proceeding, I would testify as follows:

1. Dr. Mark Geier saw and treated my daughter [REDACTED] as a private matter between Dr. Geier [REDACTED] and myself. Dr. Geier treated [REDACTED] using evidence-based medicine, full disclosure, and the highest professional standards.
2. Dr. Geier accurately and truthfully represented himself and his clinical expertise, as well as treatment advise as part of our daughter's health care team. Dr. Geier is among my highest regarded clinicians and researchers not only as a parent but as a Registered Nurse in the health care field.
3. [REDACTED] benefited significantly from Dr. Geier's care.

I solemnly affirm under the penalties of perjury and upon personal knowledge that the contents of the foregoing paper are true.

Tab 6

IN THE MATTER OF
MARK R. GEIER, M.D.

* BEFORE THE
* MARYLAND STATE
* BOARD OF PHYSICIANS

RESPONDENT

License No. D24250

* Case Nos: 2007-0083, 2008-0454
* & 2009-0308

* * * * *

AFFIDAVIT

I, [REDACTED] am at least 18 years of age and competent to testify. I am

[REDACTED] board certified and have a full time
Emergency Medicine practice. If called as a witness in the above referenced proceeding,
I would testify as follows:

[I would like to take this opportunity to request utmost privacy and discretion with
regards to my family's medical information. I have concerns about the origins of this
complaint, and have reason to believe that the originating person(s) have, in the past,
spread personal information about Autism Spectrum Disorder (ASD) families on the web
with the goal of defamation and embarrassment.]

1. My daughter with ASD developed breast buds at about 7 years, 5 months. I was
concerned because this was way out of the norm for our family history. She had
already been masturbating very publicly, and these behaviors were very difficult to

control because of our severe difficulty with communication with her. Although she has never been aggressive, she had shown self-injurious behavior for a long time (hitting herself, primarily) and also had exhibited severe OCD type behaviors.

2. At 7 years, 7 months she had her first seizure and was hospitalized at [REDACTED] Hospital. By this time, I was also aware that puberty often precedes the onset of seizures in children with Autism.
3. At the time of her first seizure I had already looked at options for precocious puberty and was interested in Lupron. Staff at [REDACTED] hospital agreed that she had signs of precocious puberty. We were in a precarious position with our insurance (about to switch), and the pediatric neurology service agreed to begin the depot Lupron (the long-acting form of the drug), giving her her first shot in the hospital. They also agreed to facilitate the precocious puberty workup with a pituitary protocol MRI, although a head CT had been done as part of her seizure workup.
4. I had approached local MDs, including her endocrinologist (who was treating her for growth hormone deficiency and hypothyroidism) about treating her for precocious puberty, but was told since she was [REDACTED] and older than 7, that it was normal puberty. When I objected (very incompatible with family history, evidence of other endocrine disruption, severe behaviors that precluded any hope of mainstreaming in the schools), I did not find any help. Through local friends, I was aware that [REDACTED] Pediatric Endocrinology was not receptive to treatment of precocious puberty, based on strict age criteria. One of my good friends with a

girl slightly older than mine who was far more advanced with her development got a very cold reception. Today, that girl has reached her adult height of 4'10", and while she had not stopped growing at the time I was looking for help, I predicted that she would likely have this outcome. I was also aware of similar experiences of others outside the area.

5. I was thrilled to meet Dr. Geier, who unlike the local doctors, did not avoid embarrassing questions about her behavior, and initiated a thorough medical workup, which included labs, ultrasound, and reviewed her previous workup, including imaging. He was very generous with his time at the office visit, and was very forthcoming about the pros and cons of the treatment. He also certainly wasn't making much money treating us, as he accepted our insurance, including Medicaid (which our daughter later qualified for).
6. Of all the things we have tried to help our daughter with autism, treatment with Lupron has been the only clearcut thing that has helped. It has slowed down her development (now she is [REDACTED] and still slowly developing, and is what I would consider age-appropriate.) I consider Dr. Geier extremely knowledgeable about the treatment of precocious puberty in autism.
7. Our daughter has seen many specialists, including GI, neuro, and endocrine. I have always shared our puberty treatment with the other doctors, and no one has ever made any negative comments. Interestingly, one of the [REDACTED] Peds Neurologists at one of our clinic visits talked about how effective Lupron was for hypersexual young adults, and shared a case with me how he started one of his

patients on it (who had a neuro-developmental disorder, it may have been autism) and it "stopped him cold" and clearly he was pleased at how effective this was.

8. Our family is so grateful to Dr. Geier for his help. I have long been aware of how he has been targeted by those who pretend to know what autism is. There is nobody local to us with his level of expertise in the problem of precocious puberty in autism. We continue to hope that our daughter can be mainstreamed in school someday, but there is no way we would be able to do this if she exhibited inappropriate sexual behavior. If Dr. Geier is not allowed to continue to practice, I believe our daughter would regress in her behavior and not ever be able to be with her peers. It would be difficult for her siblings to have friends over if her behavior deteriorated, and would dramatically increase the stress in our lives. As it is, our home life is already complicated and difficult, thanks to autism.

I solemnly affirm under the penalties of perjury and upon personal knowledge that the contents of the foregoing paper are true.

[REDACTED]

[REDACTED]

Tab 7

IN THE MATTER OF
MARK R. GEIER, M.D.

RESPONDENT

License No. D24250

* BEFORE THE
MARYLAND STATE
*
BOARD OF PHYSICIANS

*
Case Nos: 2007-0083, 2008-0454
& 2009-0308
*

* * * * *

AFFIDAVIT

I, James B. Adams am at least 18 years of age and competent to testify. If called as a witness in the above referenced proceeding, I would testify as follows:

1. I am a Professor and the Program Chair in Materials Science and Engineering at Arizona State University, and a member of the graduate faculty in Chemistry and a member of the graduate faculty in Biochemistry. I also direct the ASU Autism/Asperger's Research Program, which is focused on medical and nutritional problems in autism and how to treat them, including investigations of heavy metal toxicity in autism. I have over 120 scientific publications in peer-reviewed journals, including over 20 publications on autism.
2. I serve as the co-leader of the Science Advisory Panel of the Autism Research Institute, founded in 1967, which is the oldest and one of the largest autism research foundations in the US. In that capacity I help plan our research agenda, review scientific proposals, plan an annual scientific think tank, and plan scientific conferences.

3. I am also the president of the Autism Society of Greater Phoenix, and have served in that capacity for the last 10 years. I have recently served on the Board of Directors of the Autism Society of America, the largest autism society in the US, with over 150 chapters across the US.

4. Heavy Metal Toxicity

5. I have twice taught a course on Heavy Metal and Chemical Toxicity at Arizona State University.

6. I have published many scientific articles investigating possible heavy metal toxicity in children with autism, and those articles include a review of the scientific literature, which I will summarize in the next several paragraphs. In general, it appears that most children with autism have a decreased ability to excrete toxic metals, resulting in an increased body burden of toxic metals.

7. Several published research studies, have demonstrated that children with autism (James et al 2004, 2006, 2009, Geier et al 2009, Adams et al 2011) and their mothers (James et al 2008) have decreased levels of glutathione. Glutathione conjugation is the primary pathway for removal of several toxic metals, so decreased levels of glutathione would result in a decreased ability to excrete toxic metals. One of these papers (Geier et al 2009) involved a study by the Respondent, myself, and others, and the results were consistent with those of the other studies.

8. Another factor which decreases the ability of children with autism to decrease excretion of toxic metals is that several studies (Konstantareas 1987, Adams et al

2003, 2007, 2008) have reported that they had a higher usage of oral antibiotics than do typical children. Oral antibiotics almost completely inhibit the ability to excrete mercury in rats (Rowland et al 1980, 1984), and the effect is likely to be similar in humans.

9. Determination of toxic metal exposure in classic lead poisoning, such as due to ingestion of lead paint, is relatively easy and involves measuring blood levels of lead. However, in autism, the problem is not high exposure, but rather decreased excretion. The half-life of lead, mercury and other toxic metals in the blood is weeks to months, so those metals rapidly leave the blood and accumulate in tissue and/or bone. This makes assessment of toxic metal exposure in autism difficult, but several studies have been conducted which demonstrate increased body burden of toxic metals, and those studies will be discussed in the following paragraphs.
10. One study by our group (Adams et al 2007) found that children with autism had 2x higher levels of mercury in their baby teeth than did neurotypical children. Baby teeth are formed in utero and during early infancy, so they are a measure of cumulative exposure during that time.
11. One study (Desoto et al 2007) found an abnormal ratio of mercury levels in blood and hair of children with autism vs. controls, consistent with an excretion problem.
12. One large study by the Respondent and others (Geier et al. 2010) found 1.9x higher levels of mercury in the red blood cells of children with autism compared to neurotypical children.

13. One study investigated the administration of dimercaptosuccinic acid (DMSA), a medication which is FDA-approved for treating lead poisoning in children. DMSA binds to toxic metals and is excreted with them in the urine. One study (Bradstreet et al 2003) found that administration of DMSA to children with autism and neurotypical children resulted in the children with autism excreting 3-6x as much mercury as the typical children. The Respondent and I were co-authors of that paper.
14. One study by my group (Adams et al 2009a) found that 22-45% of the variation in autism severity was significantly associated with the level of toxic metals pre and post administration of DMSA. In other words, children with higher levels of toxic metals tended to have more severe autism.
15. I led a 3-month clinical trial of the safety and efficacy of DMSA therapy in 63 children with autism (Adams et al 2009b, 2009c). We found that DMSA therapy was very safe, and effective in removing toxic metals, improving glutathione levels, and partially effective in improving platelet status (a marker of inflammation). It also resulted in improvements in autism severity, with the degree of improvement being associated with the baseline level of toxic metals and glutathione (Adams et al 2009c).
16. Three epidemiology studies (Windham et al 2006, Palmer et al 2006, 2009) have linked autism incidence with increased level of airborne mercury and other toxins.
17. Another way to estimate body burden of toxic metals is to measure urinary porphyrins. Porphyrins are formed in the kidney, in a complex series of reaction

steps. Elevations in certain porphyrins are associated with mercury, lead, and other toxic metals that are known to inhibit certain pathways. Overall, porphyrins appear to be a simple, non-invasive method to estimate body burden of some toxic metals. Several studies (Nataf et al 2006, Geier et al 2006, Geier et al 2007, Woods et al 2010) found elevated porphyrins in children with autism compared to controls. One of those studies (Geier et al 2009) found that increased porphyrin levels were associated with more severe autism. It is relevant to point out that the results of the studies by the Respondent were generally similar to those by other researchers.

18. In 2005 a group of 25 researchers and physicians wrote a consensus report on Treatment Options for Mercury/Metal Toxicity in Autism and Related Developmental Disabilities. The consensus report was released as a publication of the Autism Research Institute, and recommends the use of DMSA and DMPS for treating elevated levels of toxic metals. I was the lead author of the report, and the Respondent was one of many co-authors.

19. Based on the above information, it appears that many children with autism have a decreased ability to excrete mercury and other toxic metals, resulting in an increased body burden. Chelation with DMSA appears to be a safe and effective method to remove many toxic metals, when following the guidelines set in the 2005 Consensus Paper.

20. Thus, I believe that the Respondent's use of porphyrin testing is one sensible method to initially screen for heavy metals in children with autism, and that

treatment with DMSA and/or DMPS is appropriate if the test results indicate that increased heavy metals are present. DMSA and DMPS have different affinities for different toxic metals, with DMSA binding more strongly to lead, and DMPS binding more strongly to mercury. DMSA is FDA-approved for treating lead toxicity, and its use in autism is “off-label.” DMPS is not FDA approved, but it is legal for a physician to have it compounded for an individual.

21. Testosterone and Lupron in Autism

22. There has been speculation for many years that some children and adults with autism and their parents have increased levels of testosterone, and that the increased testosterone is a significant factor in the development of autistic symptoms.
23. One study found that adults with autism spectrum disorders had significantly higher levels of serum androstenedione compared to age and gender-matched controls (Ruta et al 2011). Another study found increased levels of testosterone in women with autism compared to controls (Schwarz et al 2010).
24. One study (Takagishi et al 2010) found that testosterone levels correlated with autism severity in adults with autism.
25. Three studies found that foetal testosterone correlated with the development of autistic traits in typical children (Knickmeyer et al. 2005, Auyeng et al 2009, 2010).
26. The ratio of the length of the 2nd finger to the 4th finger is associated with the level of foetal testosterone (Lutchmaya 2004). Several studies have reported

abnormal 2nd digit:4th digit ratios in children with autism (Manning et al 2001, de Bruin 2006, Noipayak 2009) and in their relatives (Manning et al 2001).

27. In summary, there does appear to be evidence that, on average, children and adults with autism have increased testosterone, and the increased testosterone is associated with severity of autistic symptoms.

28. Based on the above studies, I believe it is reasonable to investigate treatments which are able to normalize elevated testosterone levels in children with autism. Lupron appears to be one reasonable candidate medication, since it is already FDA-approved for children for other conditions. As with any medication, it is important to weigh the potential benefits vs. the potential side-effects. Autism is a severe developmental disorder, and studies have shown that 90% of adults with autism are unable to work and unable to live independently; the Autism Society of America estimates that the cost of life-long care for autism is \$3-\$5 million. If a medication may be helpful in partially reducing the symptoms of autism, then the potential gain in quality of life may be worth the risk of the medication.

29. Regarding off-label use of medications for autism, it is important to point out that only two medications have been FDA-approved for treating symptoms related to autism. Based on the hundreds of medical histories I have collected as part of my research studies, it appears that most of the medications given to children with autism are "off-label", including Lupron. The challenge for any physician in treating children with autism is that we still have a lot to learn about the best treatments for autism, and a lot more research is needed. Therefore, most medical

treatments for autism will continue to be "off-label" use of FDA-approved medications, which is reasonable provided that families are informed of the potential risks and benefits.

30. Research Experience with the Respondent

31. The respondent and I have been co-authors on several peer-reviewed scientific publications together. I believe that the studies we have published together have been well-done, and have contributed to the scientific literature, and that is borne out by the peer-review process. My interactions with the Respondent have led me to believe that he is very knowledgeable about heavy metal toxicity (testing and treatment) and very knowledgeable about testosterone in autism (testing and treatment), including a strong knowledge of the scientific and medical literature on those topics.

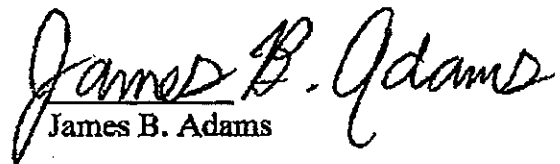
32. Personal Experience with the Respondent

33. I have a 19-year-old daughter with autism. Today she functions academically at about the 3rd grade level, and her language ability is roughly that of a 3 or 4 year old. She has or had many co-occurring medical conditions that are common in autism, including mental retardation, gastrointestinal problems, low muscle tone, and hypothyroidism.

34. Based on the research about elevated levels of testosterone in individuals with autism, I decided to have her levels tested. I have contacts with dozens of excellent physicians across the US, and I chose to ask the Respondent to serve as her physician because in my opinion he was the most experienced physician in the

US in investigations of testosterone in autism. Her test results with LabCorp revealed a significant increase in her serum testosterone, compared to the laboratory reference range for girls of her age. Therefore, we discussed several treatment options to lower her testosterone to a normal level. We chose the use of YAZ, a hormonal therapy which is normally used for contraceptive purposes, because it is an FDA-approved medication for women, and appeared to have a reasonable safety record. After several months of treatment, her symptoms did not significantly change, so we decided to discontinue treatment. Overall, I felt that the Respondent provided a high quality of medical care for my daughter.

I solemnly affirm under the penalties of perjury and upon personal knowledge that the contents of the foregoing paper are true.


James B. Adams

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Tab 8

Results of Long-Term Follow-Up after Treatment of Central Precocious Puberty with Leuporelin Acetate: Evaluation of Effectiveness of Treatment and Recovery of Gonadal Function. The TAP-144-SR Japanese Study Group on Central Precocious Puberty

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We evaluated the effect of leuporelin treatment on adult height (AH) and followed recovery of reproductive function in 63 girls and 13 boys with central precocious puberty (CPP). Mean treatment durations were 3.8 ± 2.0 and 4.1 ± 2.5 yr, and posttreatment follow-up durations were 3.5 ± 1.3 and 2.6 ± 1.1 yr for girls and boys, respectively. AH was 154.5 ± 5.7 cm for girls, and 89.5% of girls reached AH within their target height range. For boys, AH was 163.2 ± 13.0 cm, and 90.9% reached target height range. It appeared that the Bayley-Pinneau method, modified for Japanese children, using a table for advanced bone age (BA), overestimated AH in CPP; and this

method, using a table for average BA and projected height for BA, was suitable for prediction of AH in CPP.

Menarche or remenarche occurred in 96.8% of girls at the age of 13.1 ± 1.5 yr. Of 11 girls who contributed urine samples, all seven idiopathic and two organic cases were considered to have ovulation. Serum testosterone levels reached normal adult level in all boys.

In conclusion, long-term leuporelin treatment for children with CPP improved AH and had no adverse effects on recovery of reproductive function. (*J Clin Endocrinol Metab* 90: 1371-1376, 2005)

THE OBJECTIVES OF treatment for children with central precocious puberty (CPP) are to avoid psychosocial problems caused by early pubertal development and to normalize adult height (AH). Long-term GnRH analog administration induces persistent suppression of the hypothalamic-pituitary-gonadal axis and reduction of sexual hormones to prepubertal levels (1-2). GnRH analog administration effectively arrests further development of secondary sex characteristics, slows bone age (BA) maturation, increases pubertal height gain, and is believed to eventually improve AH prognosis (3-4). Recently, several investigators have reported that improvement in AH above pretreatment predicted AH (PAH) was obtained after long-term GnRH analog treatment (5-8). However, the accuracy of PAH methods remains con-

troversial, because they are based on the auxological data from normally growing children.

Although it has been reported that gonadal function almost fully recovers after the cessation of GnRH analog administration, little information is available regarding ovulation in girls (7, 9, 10).

Since 1989, we have followed children with CPP who enrolled in two prospective clinical trials (phase II and phase III) that investigate the effects of leuporelin acetate depot on CPP (4, 11-13) and have now obtained AH measurements for 76 children (63 girls and 13 boys). In this report, we present AH results of long-term follow-up after leuporelin acetate treatment, evaluate the effectiveness of treatment using target height (TH) and PAH methods, and demonstrate good recovery of reproductive function, particularly of ovulation in girls.

Subjects and Methods

Subjects

Children with CPP were enrolled in this prospective clinical trial at 35 study sites of the TAP-144-SR Study Group. The diagnosis of CPP was based on the early occurrence of secondary pubertal signs, advanced BA, accelerated growth rate, pubertal LH and FSH responses in the GnRH test and pubertal sex steroid levels. Peak LH greater than 6 mIU/ml in both boys and girls and ratio of peak LH/peak FSH greater than 0.8 in

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Abbreviations: AH, Adult height; BA, bone age; CA, chronological age; CPP, central precocious puberty; PAH, predicted AH; PAH-BPad, PAH based on the Bayley-Pinneau method for advanced BA; PAH-BPav, PAH based on the Bayley-Pinneau method for average BA; PAH-phSD, PAH based on projected height SDS for BA; SDS, sd score; TH, target height; TW-2, Tanner-Whitehouse 2.

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boys and 0.5 in girls were judged as showing pubertal responses (14, 15). The study protocol was approved by the Institutional Review Board of each study site, and the study was conducted in accordance with the guidelines of the Declaration of Helsinki. Written consent was obtained from the patients and their parents before enrollment of patients.

Of 106 enrolled patients, 76 (63 girls and 13 boys) for whom AH was determined were included in analysis. Patient characteristics are summarized in Table 1. Forty-eight patients had idiopathic CPP (mean age, 8.2 ± 2.2 yr), and 24 had organic CPP (mean age, 7.8 ± 2.3 yr). Hypothalamic hamartoma was observed in 10 patients (mean age, 7.4 ± 2.0 yr); hydrocephalus in four; astrocytoma in three; and microcephalia, suprasellar germinoma, pineal cyst, pineal hamartoma, cerebral infarction, arachnoid cyst, and nuclear jaundice in one patient each. The other patients had sex hormone-induced CPP with congenital adrenal hyperplasia ($n = 2$), testicular cancer ($n = 1$), or nonclassical 3β -hydroxysteroid dehydrogenase deficiency ($n = 1$).

Clinical data for the patients at the start of treatment, during treatment, and at the end of treatment are summarized in Table 1.

Patients were treated with a depot formulation of leuporelin acetate [D-Leu (6)-[des-Gly (10)-NH₂]-GnRH ethylamide acetate, Takeda Pharmaceutical Co. Ltd., Osaka, Japan] given sc every 4 wk at an initial dose of 10, 30, or 90 μ g/kg (5, 63, and 8 children, respectively). Initial dose varied because 21 children were initially enrolled in phase II trial (dose-finding study), which compared effect on secondary sex characteristics between three doses (11). Fifty-five children initially enrolled in the phase III trial received an initial dose of 30 μ g/kg. The dosage was adjusted in the case of inadequate gonadal suppression. Treatment was discontinued at the age of pubertal onset in normal Japanese children or at the wish of a patient's family. Concurrent treatment with GH was not allowed.

Methods

Height was measured with a stadiometer at each study site. Height D score (SDS) was calculated according to the standard height table for Japanese children. One experienced physician estimated all of BA in this study using the modified Tanner-Whitehouse 2 (TW-2) method (radius-ulna-short bone) standardized for Japanese children (16). She was informed of the sex and chronological age (CA) of each individual patient at the time of estimation of BA. PAH at the start of treatment was determined by three different methods: PAH based on the Bayley-Pinneau method (17) modified for Japanese children (18) using a table for advanced BA (PAH-BPav) or using a table for average BA (PAH-BPav), and that based on the projected height SDS for BA (PAH-phSD) (19). The Bayley-Pinneau method modified for Japanese children is standardized for the use of the modified TW-2 method for Japanese children (16, 18). TH was calculated as midparent height minus 6.5 cm for girls and midparent height plus 6.5 cm for boys. TH ranges ($TH \pm 8$ cm for girls and $TH \pm 9$ cm for boys) were calculated using parental height adjusted for Japanese data. AH was defined as height velocity less than 1 cm/yr and/or BA surpassing 14 yr for girls and 15 yr for boys

as determined by the modified TW-2 method for Japanese children. AH was determined after a mean posttreatment follow-up period of 3.5 ± 1.3 yr for girls and 2.6 ± 1.1 yr for boys.

Plasma levels of estradiol and testosterone were measured by RIA. In girls who underwent daily urine sample collection during a menstrual cycle, urine levels of LH, FSH (determined by time-resolved fluorescence immunoassay or chemiluminescent enzyme immunoassay), estradiol (by RIA), and pregnanediol (by gas chromatography) were measured. When peak pregnanediol level was more than 1 mg/g Cr, a patient was considered to have an ovulatory menstrual cycle. Biphasic basic body temperature, LH surge greater than 5 IU/g Cr, and estradiol level greater than 10 μ g/g Cr provided ancillary evidence of the occurrence of an ovulation. In two girls, basic body temperature was measured every morning during one menstrual cycle.

Statistics

Values are expressed as mean \pm SD. Student's *t* test for paired samples with Bonferroni adjustment for multiple comparisons or repeated-measures ANOVA were performed when appropriate. Correlations between two parameters were determined by Pearson's correlation coefficient analysis. Stepwise multiple regression analysis was performed to determine correlations between AH or height gain and clinical factors. Findings of $P < 0.05$ were considered significant.

Results

AH, TH, and PAH

AH, TH, and PAH, determined by the three methods at the start and end of treatment, are shown in Table 2. Of 57 girls and 11 boys for whom TH was available, 51 girls (89.5%) and 10 boys (90.9%) reached AH within their TH range. AH was higher than TH in 34 girls (59.6%) and three boys (27.3%). No significant difference was observed between AH and TH either for girls or boys.

AH was significantly higher than PAH-phSD for girls but not for boys. PAH-BPav did not differ from AH either for girls or boys. AH was significantly higher than PAH-BPav for girls but not for boys.

AH was positively correlated with height SDS for CA at the start of treatment (girls, $r = 0.66$, $P < 0.01$; boys, $r = 0.69$, $P < 0.01$), height SDS for BA at the start of treatment (girls, $r = 0.35$, $P < 0.01$; boys, $r = 0.83$, $P < 0.01$) and mean growth velocity during treatment (girls, $r = 0.32$, $P < 0.05$; boys, $r = 0.57$, $P < 0.05$). Stepwise regression analysis revealed that height SDS for CA, height SDS for BA at start of treatment,

TABLE 1. Clinical and auxological characteristics of CPP patients at the start, during, and at the end of treatment

	Girls (n = 63)	Boys (n = 13)
At the start of treatment		
CA (yr)	7.7 ± 2.2	9.8 ± 1.8
BA (yr)	10.2 ± 1.5	12.9 ± 0.7
Height (cm)	129.1 ± 12.4	143.7 ± 12.9
Height SDS for CA (SD)	1.4 ± 1.5	1.6 ± 2.0
Height SDS for BA (SD)	-1.5 ± 1.1	-1.4 ± 1.8
Treatment period		
Duration of treatment (yr)	3.8 ± 1.9	4.1 ± 2.5
Δ BA/ Δ CA	0.4 ± 0.2	0.2 ± 0.1
Mean growth velocity (cm/yr)	4.3 ± 1.3	3.5 ± 1.5
At the end of treatment		
CA (yr)	11.6 ± 1.4	13.9 ± 1.5
BA (yr)	12.0 ± 0.8	13.9 ± 0.8
Height (cm)	146.7 ± 6.8	157.5 ± 11.7
Height SDS for BA (SD)	-0.4 ± 1.0	-0.1 ± 0.8

Data are expressed as mean \pm SD.

TABLE 2. AH, TH, and PAH

	Girls (n = 63)	Boys (n = 13)
At AH		
CA (yr)	15.1 ± 1.2	16.5 ± 1.2
AH (cm)	154.5 ± 5.7	163.2 ± 13.0
Height SDS	-0.67 ± 1.13	-1.29 ± 2.32
TH		
TH (cm)	154.9 ± 4.6	167.6 ± 4.2
Height SDS	-0.61 ± 0.91	-0.50 ± 0.75
PAH at the start of treatment		
Projected height SDS method (cm)	150.5 ± 5.4	162.5 ± 10.3
Modified BP by advanced BA (cm)	154.5 ± 7.1	167.5 ± 15.7
Modified BP by average BA (cm)	151.1 ± 7.3	162.1 ± 15.3
PAH at the end of treatment		
Projected height SDS method (cm)	156.1 ± 4.8	170.0 ± 4.7
Modified BP by advanced BA (cm)	158.5 ± 6.7	172.6 ± 7.2
Modified BP by average BA (cm)	157.9 ± 6.3	172.0 ± 6.1

BP, Bayley-Pinneau method.

and mean growth velocity during treatment influenced AH for girls ($r = 0.83$, $R^2 = 0.69$).

When height gain was defined as the difference between AH and PAH-phSD at the start of treatment, height gain was positively correlated with mean growth velocity during treatment (girls, $r = 0.59$, $P < 0.01$; boys, $r = 0.81$, $P < 0.01$), treatment period (girls, $r = 0.58$, $P < 0.01$; boys, $r = 0.28$, $P = 0.35$), and change in BA during treatment (girls, $r = 0.41$, $P < 0.01$; boys, $r = 0.58$, $P = 0.05$) and negatively correlated with CA at the start of treatment (girls, $r = -0.73$, $P < 0.01$; boys, $r = -0.47$, $P = 0.11$) and BA at the start of treatment (girls, $r = -0.40$, $P < 0.01$; boys, $r = -0.45$, $P = 0.12$) for both girls and boys. Stepwise multiple regression analysis revealed that both CA and BA at the start of treatment, treatment period, and mean growth velocity during treatment influenced height gain for girls ($r = 0.82$, $R^2 = 0.66$). Stepwise multiple regression analysis was not performed for boys because of the small number of subjects.

Reproductive function

Menarche, including remenarche, was observed after the end of treatment in 61 girls (96.8%). Age at menarche was 13.1 ± 1.5 yr (range ~ 10.4–16.8 yr). For 13 girls in whom menarche already had occurred before the start of treatment, mean age at remenarche was 12.7 ± 1.3 yr (range ~ 11.0–15.3 yr). Duration between last injection of leuprorelin and menarche was 17.5 ± 11.2 months (median, 14.7; range ~ 3.6–62.8 months). Among these patients, a regular menstrual cycle was observed in 53 girls. For two girls for whom menarche was not observed after the end of treatment, ages at last observation were 14.6 and 14.9 yr, and posttreatment follow-up durations were 36.6 and 50.1 months, respectively. One of these girls (age, 14.6 yr) had hypothalamic hamartoma, and the other (age, 14.9 yr) had a diencephalohypophysial disorder due to brain tumor.

When the girls were divided into a menarche group and a remenarche group, the duration from the last injection was significantly shorter in the remenarche group than in the menarche group, as shown in Fig. 1.

Patterns of urinary hormone levels were evaluated in 11 girls who contributed urinary samples for one menstrual cycle. Figure 2 shows a typical ovulatory pattern of urinary

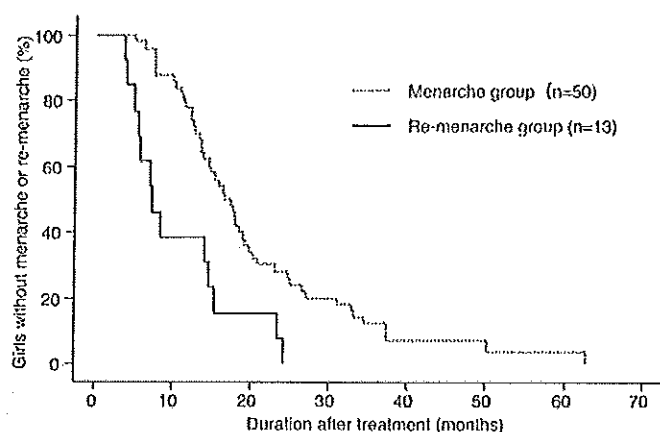


FIG. 1. Occurrence of menarche or remenarche after cessation of GnRH analog treatment.

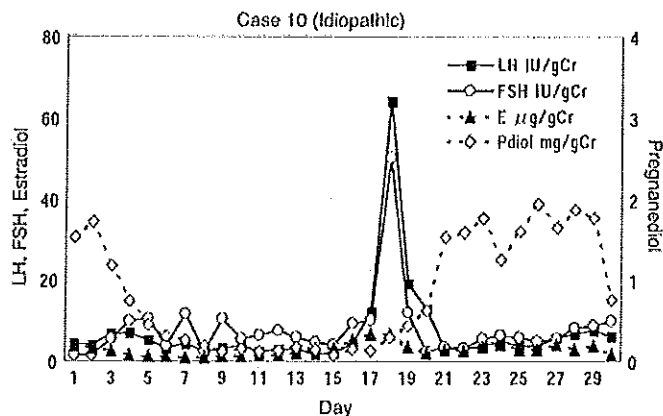


FIG. 2. A typical pattern of urinary hormone levels in a girl with ovulation.

hormones in case 10. Case 10 experienced menarche at 13.2 yr, 14 months after cessation of GnRH analog and collected morning urine samples at 16.8 yr. Menstruation was observed from d 4–8 of urine collection. Estrogen surge was observed on d 17, and gonadotropin surges on d 18, followed by elevation of pregnenediol. Figure 3 shows an anovulatory pattern. Neither an estrogen surge nor a LH surge greater than 5 IU/ml was observed, and pregnenediol level did not increase. Table 3 shows peak values of urinary LH, FSH, estradiol, and pregnenediol in 11 girls (seven idiopathic and four organic cases) who contributed one menstrual cycle of urine samples. All idiopathic cases and two organic cases were judged to have an ovulatory menstrual cycle. Although pregnenediol level was not greater than 1 mg/g Cr in case 4, she was considered to have an ovulation because of the finding of LH and estrogen surges and biphasic basic body temperature. Two organic cases (pineal cyst and suprasellar germinoma) were considered to have anovulatory menstruation because of low pregnenediol level and low gonadotropin and estradiol peaks. In all boys, serum testosterone levels were elevated to normal adult level after the end of treatment. The duration between the last injection of leuprorelin and elevation of testosterone to adult level was 11.0 ± 10.9 months (median, 6.1; range ~ 3.0–40.6 months).

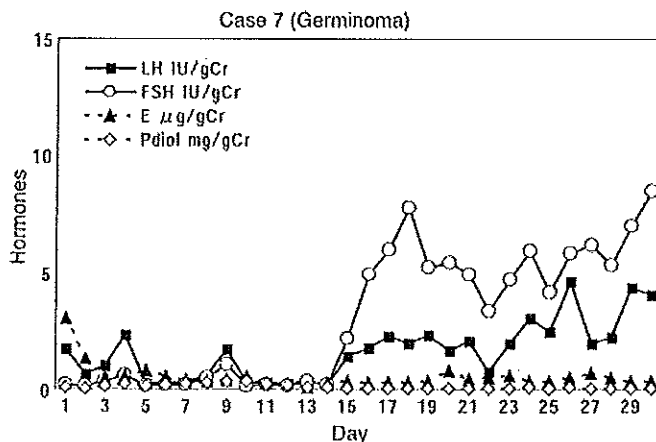


FIG. 3. Urinary hormone levels in a girl with anovulatory menstruation.

TABLE 3. Urinary hormone levels, basic body temperature (BBT), and ovulation

Case no.	Diagnosis	Age at menarche or remenarche (yr)	Age at test (yr)	LH (IU/g Cr)	Pregnenediol (mg/g Cr)	Estradiol (μ g/g Cr)	Biphasic BBT	Ovulation
1	Idiopathic	13.4	18.2	80.84	3.36	12.54		+
2	Idiopathic	13.4	13.9	23.53	2.55	7.96		+
3	Hamartoma	12.1	14.7	17.1	2.1	5		+
4	Idiopathic	10.9	17.0	40.86	0.41	5.88	+	+
5	Idiopathic	12.3	16.8	2.61	3.08	15.76		+
6	Idiopathic	12.8	16.7	7.51	2.33	13.14		+
7	Germinoma	15.3	16.7	4.62	3.06	0.35		-
8	Pineal cyst	11.3	16.5	12.5	0.42	4.89		-
9	Pineal cyst	14.0	16.1	6.6	3.44	10.07	+	+
10	Idiopathic	13.2	16.8	64.06	1.93	6.78		+
11	Idiopathic	12.5	15.0	119.75	2.06	11.18		+

Cr, Creatinine; +, present; -, absent.

Discussion

AH, TH, and PAH

Because it is well known that AH in untreated patients with CPP is significantly shorter than TH, by approximately 3.5–10 cm (3, 20, 22–24), improvement of AH within TH range is one of the major objectives of treatment for CPP. In our study, 90% of girls and of boys reached AH within TH range, and AH did not significantly differ from TH. Treatment with leuporelin appears to be effective for improvement of AH.

One of the indicators of therapeutic effects is the difference between AH after treatment and PAH at the start of treatment. The Bayley-Pinneau method has been used to determine PAH for patients with CPP in various studies (5–7). However, the accuracy of PAH methods should be evaluated carefully using clinical data, because the Bayley-Pinneau method is based on auxological data from normally growing children. We therefore evaluated the usefulness of PAH-BPav, PAH-BPav, and PAH-phSD in our study. If treatment for CPP is judged to be effective, PAH at the start of treatment should be significantly shorter than AH after treatment.

Because the number of boys in our study was small and some boys had started GnRH analog treatment at a very late BA, when efficacy of treatment had not been expected, we evaluated the effectiveness of PAH methods only for girls. There was no significant difference between PAH-BPav and AH after treatment, suggesting that treatment was not effective in improving AH. On the other hand, PAH-BPav was significantly shorter than AH. Because long-term treatment with leuporelin was judged to be effective, the Bayley-Pinneau method using a table for advanced BA might be thought to overestimate PAH.

Recent studies demonstrated that determination of PAH by the Bayley-Pinneau method, using a table for advanced BA, overestimated AH in untreated patients with CPP (24, 25). Kauli *et al.* (24) reported that PAH-BP in untreated CPP patients was significantly higher than actual AH (difference, 5.6 cm) when the Bayley-Pinneau table for accelerated BA was used. They concluded that the table for average BA was more appropriate for AH prediction of children with CPP because PAH-BPav did not differ from actual AH in patients without any treatment. In patients treated with GnRH analog, they reported that no significant difference was found

between AH and PAH-BPav but that AH was significantly higher than PAH-BPav. Mul *et al.* (26) reported similar results. Our results are similar to those by Kauli *et al.* (24).

The Bayley-Pinneau method that we used was the modified method for Japanese children (18). Our results demonstrate that this modified method is as useful as the original Bayley-Pinneau method used in Western countries.

In addition, we demonstrated the usefulness of PAH-phSDS, which is based on the hypothesis that height SDS for BA in childhood is preserved in AH. Because BA advance is progressive in untreated CPP patients, PAH-phSDS will progressively decrease if patients do not receive any treatment for CPP. Therefore, when AH after treatment is equal to or greater than PAH-phSDS at the start of treatment, improvement of AH can be considered to have been obtained by treatment. In the present study, AH was significantly greater than pretreatment PAH-phSDS for girls, and PAH-phSDS was comparable with PAH-BPav, indicating the usefulness of PAH-phSDS as well as PAH-BPav in patients with CPP.

Determination of factors that influence the therapeutic effect of GnRH analog administration is very important for identifying groups of patients who will benefit from treatment. Klein *et al.* (5) reported that height gain was positively correlated with duration of treatment and height SDS for CA at the start of treatment, and negatively correlated with age at onset of puberty and age at the start of treatment. Mul *et al.* (26) reported that a model including BA at the start and end of treatment, CA at the start of treatment, and BA advance at the end of treatment could explain 48.9% of variance in the results of multiple regression analysis. Arrigo *et al.* (27) reported that BA/CA at the start of treatment was the only significant variable in the results of stepwise regression analysis. In the present study, stepwise multiple regression analysis for girls showed that CA and BA at the start of treatment, treatment duration, and average growth rate during treatment mainly affected height gain. This finding suggests that patients who were younger and had advanced BA at the start of treatment had greater gain in height. Our results also suggested that longer treatment and higher growth velocity during treatment contributed to greater height gain, as Klein *et al.* (5) reported. Because it has been reported that continuing treatment beyond BA of 12–12.5 yr (13, 27) or beyond CA of 11 yr does not improve AH (28), an earlier start of GnRH analog treatment might be important in obtaining longer

treatment duration in accelerated progressive forms of precocious puberty.

Reproductive function

It has been reported that the hormonal suppression induced by GnRH analog is reversible (7, 21). We observed menarche, including remenarche, after the end of treatment in 61 of 63 girls (96.8%). Jay et al. (9) found that, of a total of 46 subjects, 44 (96%) had attained menarche by completion of their study. Feuillan et al. (10) reported that all idiopathic CPP and CPP with hypothalamic hamartoma began spontaneous menses 17.6 ± 11.0 months and 20.5 ± 16.3 months after the cessation of GnRH analog, respectively. In the present study, the mean time interval between cessation of GnRH analog treatment and the start of spontaneous menarche was 17.5 ± 11.2 months, an interval compatible with that reported by Feuillan et al. The age at menarche of 13.1 ± 1.5 yr was significantly higher than that of normal Japanese girls, 12.24 ± 0.92 yr ($n = 226$).

When the patients were divided into remenarche and menarche groups, the remenarche group was found to have started menstruation with a shorter duration after the last injection of leuporelin than the menarche group. In the remenarche group, uteri appeared to be more mature than in the menarche group. This finding might be useful for predicting the time of occurrence of menarche after the treatment.

We established a method of evaluation of ovulation by measuring urinary gonadotropins, estradiol, and pregnanediol. As shown in Fig. 2, patterns of urinary hormone levels were identical with those of daily serum sampling: estrogen surge, gonadotropin surge, and elevation of pregnanediol as an index of progesterone secretion and corpus luteal function. Our results demonstrated the usefulness of urinary hormone sampling for assessment of ovulation. Of 11 girls for whom investigation of ovulation using urine samples was performed, all idiopathic cases appeared to have ovulatory menstrual cycles, but two of four organic cases were considered to have anovulatory menstruation. It is possible that their organic disorders (pineal cyst and suprasellar germinoma) affected ovulation.

In all boys, serum testosterone levels were elevated to normal adult level after the end of treatment.

No severe adverse drug reaction was observed during leuporelin treatment. Long-term leuporelin treatment appeared to be well tolerated in terms of safety and reversibility of reproductive function.

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Tab 9

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Case study suggests new therapy for autism

By: DEANNA CHIECO

Posted: 2/26/09

In recent years autism has been the focus of much attention. Parents worry about identifying the disorder in their children at a young age.

Scientists puzzle over the combination of biological and environmental factors that lead to autism, as well as how best to treat this enigmatic condition.

A new case report suggests an intriguing new approach for correcting some of the most severe behavioral problems associated with autism.

Autism is a developmental disorder that is characterized by deficits in language, social and behavioral skills. Autism represents a broad spectrum of disorders that range from mild to severe. A particularly severe symptom includes self-injury, or the act of hitting oneself so that it leads to tissue damage.

Many symptoms of autism are treated through medications or behavioral approaches. Both approaches often work well for individuals and have even proven effective in preventing self-injury.

Lee Wachtel of the Kennedy Krieger Institute presented a case report of an eight-year-old autistic boy with severe self-injury behaviors that were not responsive to treatment in a recent journal article.

Wachtel collaborated with colleagues at Hopkins Hospital and the University of Mississippi Medical Center, and they proposed the controversial treatment of electroconvulsive therapy (ECT) in this case.

They report that this boy, known as D., maintained self-injurious behaviors despite many different medical and behavioral interventions. This boy often was restrained with padded equipment to prevent serious injury from occurring. However, he still

attempted to make hitting movements while restrained.

When observed without restraints over a 24-hour period, D. was reported to have hit himself in the head an average of 109 times per hour. Because of the high frequency of self-injury incidents, D. was unable to participate in structured school programs or family activities.

D.'s physicians felt that this damaging behavior might be ameliorated through ECT. ECT maintains a link with the shock therapy of early psychiatry, which was used on patients with a variety of mental illnesses.

ECT is still widely used as a treatment for severe depression. Wachtel and colleagues report that ECT has been successful in improving self-injurious behaviors in patients with mental illnesses, yet it is not often used in young children.

Wachtel and colleagues were able to successfully treat D. with ECT, resulting in a large decrease in the amount of self-injurious incidents per hour. He dropped from 109 hits per hour to 19. This drastic decrease allows D. the possibility of an improved quality of life. He is able to attend educational programs, behavioral therapies and family activities.

A main cause of concern for children exhibiting this behavior is the risk of a head or brain injury, which could possibly be life-threatening. Without ECT treatment, D.'s only options were to remain confined by padded restraints or to risk severe injury.

ECT was administered three times a week for a period of five weeks. In each administration, D. was given an anesthetic and muscle relaxant before the therapy commenced.

D. received bilateral treatment, which means that one electrode was placed on either side of the head. Electrical impulses flow through the electrodes and into the brain.

While the exact mechanism of how ECT works is not known, the authors postulate that several neurotransmitter systems may be affected. These systems may help reverse some of the characteristic behaviors of autism.

Wachtel notes that this is the first documented case of a young autistic child who successfully improved self-injury behaviors after receiving ECT.

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