☞ **05hr_JC-Au_Misc_pt36g**

☞ Details: Audit requests, 2005

(FORM UPDATED: 08/11/2010)

WISCONSIN STATE LEGISLATURE ...
PUBLIC HEARING - COMMITTEE RECORDS

2005-06
(session year)

Joint
(Assembly, Senate or Joint)

Committee on Audit...

COMMITTEE NOTICES ...

- Committee Reports ... **CR**
- Executive Sessions ... **ES**
- Public Hearings ... **PH**

INFORMATION COLLECTED BY COMMITTEE FOR AND AGAINST PROPOSAL

- Appointments ... **Appt** (w/Record of Comm. Proceedings)
- Clearinghouse Rules ... **CRule** (w/Record of Comm. Proceedings)
- Hearing Records ... bills and resolutions (w/Record of Comm. Proceedings)
  (**ab** = Assembly Bill) (**ar** = Assembly Resolution) (**ajr** = Assembly Joint Resolution)
  (**sb** = Senate Bill) (**sr** = Senate Resolution) (**sjr** = Senate Joint Resolution)
- Miscellaneous ... **Misc**

* Contents organized for archiving by: Stefanie Rose (LRB) (July 2012)

Thexton, Arthur

From: Robert Baratz [imcsi@rcn.com]

Sent: Sunday, March 03, 2002 6:45

To: Thexton, Arthur

Subject: What a surprise/small world

Well, what a surprise to find the information you received just after Valentine's Day from an anonymous physician.

It makes you wonder what other forms of "therapy" are going on in the office. I can't wait to be the "fly on the wall" on the Ides of March.

Can you ask him to bring along any info. on IPT, and records from any patients he has treated with it? or will his lawyer have apoplexy. Perhaps an "encore appearance" will be necessary, after the proper procedures are followed. Here is his web page on the topic:
http://www.watersmedcenter.com/ComprehensiveCancerCare.htm

Of course, that page has links to: ECP, and quite a few other things. Seems like you will be a busy guy with all of this, and perhaps me too.

What a small world, of course, since the first hit on the Google search for IPT yields, http://www.iptcancer.com/ and this site is hosted by Ross Hauser and his wife. It just happend that they are the authors of a series of books on Prolotherapy, and are part of another case in NY in which I am involved.

Then again, there seem to be a series of linked therapies that are "out there". Interesting how the same people seem attracted to the ones that one never hearrd of in medical school.

Back to IPT and the handout you mailed.

I suppose you could easily find the patient with some diligent searching. You have the dates of service, the fact that the reporting MD is female, and the diagnosis of the patient.

The handout suggests that someone was "invited" to present a Best Case Series on IPT and cancer before the Cancer Advisory Panel of the National Center for Complementatry and Alternative Medicine. This is a study group that recommends where research might be done, not anything more. To feed this to patients is to suggest that it is approved and ready for "prime time". In fact, IPT is not approved, and it would appear that these patients are guinea pigs. I don't know if there is a protocol, but I didn't find one in my searching. Google had 344 sites on the topic.

here is the NCCAM meeting minutes. A little scary.

http://nccam.nih.gov/an/advisory/capcam/sept2000_minutes.htm#best

Hauser, who practices in Illinois, right in your own backyard, claims to be treating hundreds of patients.

Try this for starters....

http://www.iptcancer.com/

here is a sampling of what I found.....

Cancer Chemotherapy can be Gentle without Side Effects – ...
Cancer Chemotherapy with **Insulin Potentiation Therapy** -- Gentle. No Major Side Effects... **... Insulin Potentiation Therapy** (IPT) A New Approach for Medicine. ...
www.iptq.com/ - 26k - Cached - Similar pages

Insulin potentiation therapy, IPT treatment with no surgery ...

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03/11/2002

Berndt, Michael

From: Thexton, Arthur
Sent: Monday, December 15, 2003 1:30 PM
To: Berndt, Michael
Subject: Waters: Baratz report

-----Original Message-----
From: Robert S. Baratz, MD, PhD [mailto:imcsi@rcn.com]
Sent: Monday, December 15, 2003 10:40 AM
To: Thexton, Arthur
Subject: Summary draft

Attached hereto is my draft summary of the Waters case. It still needs some tweaking and elaboration. Your comments are invited. This should make it clear to the Board that there is a case and it is not trivial.

I expect to accompany this with several other documents, notably case summaries of each of the patients we selected to review (vide infra), and capsule summaries of the rest (the remaining 6 in Group I). I have full summaries of WM, BS, FC, NW, RA and TM from Group I. I have all of the IPT patients (ST, MB, KK) (Group II) and NM (Group II). These are largely done, but need additional comments to elaborate detail. All of these are transcribed, annotated, and typed. EAch act of deviation will be elaborated an annotated.

I can send you these in their present state, but will be finishing them off over the next several days and prefer to send them as finished pieces. I am reframing them a bit to align with my summary. If you need them now I can send them "as is".

Additional documents will discuss the nomenclature of Alternative medicine, concept of IPT and history of what is being done by Waters, and detail the deviations from the standard in Waters' research, and the use of IPT.

While this case appears simple it is not. The volume of materials is extensive. Research had to be conducted into three different forms of cancer and multiple agents. Research had to be conducted into the whole IPT issue. Each of these were a major undertaking.

Sparse record cases require extraordinary work. One has to try to determine what the patient really had, and then explain how the care was deficient. The lack of cooperation from Waters made this work all the more difficult.

Call me to discuss.

Bob

Enclosure 23

Thexton, Arthur

From: Berndt, Michael
Sent: Friday, August 17, 2001 11:02 AM
To: Thexton, Arthur; Petersen, Dennie
Subject: FW: Waters, 97 Med 101/108

Arthur and Dennie,
I confirmed with Bill Conway this morning that he approved the rate of 175/hr as set out below for Dr. Baratz in Waters.
Thanks, Mike

-----Original Message-----
From: Berndt, Michael
Sent: Monday, August 13, 2001 11:43 AM
To: Conway, William; Riedasch, Gail-DRL
Cc: Temby, Jack
Subject: FW: Waters, 97 Med 101/108

Bill,
A request for an expert is attached. The requested expert is already retained in another chelation therapy case and is being paid at $175/hr. In this other case, the higher rate was approved due to the very limited number of persons who can testify about this unusual type of therapy. This expert is knowledgeable in the area and is doing everyting possible to keep his time to a minimum.
There are obvious savings to using him in this second case and we will continue to try to use his time in an efficient manner.
A memo from Atty. Thexton on the case and the related cases is set out below.
Please let me know if you have any questions.
Thanks, Mike

-----Original Message-----
From: Thexton, Arthur
Sent: Thursday, August 02, 2001 12:06 PM
To: Berndt, Michael
Subject: Waters, 97 Med 101/108

Mike, I seek approval to hire an expert at more than $75/hr in the above cases.

These cases are chelation therapy cases, and parallel the Kadile cases (94 Med 94, 96 Med 287). Chelation is a controversial issue and while all of conventional medicine considers it quackery, it has a dedicated group of adherents who have assembled resources to defend it. As you know, the department has approved retaining Dr. Robert S. Baratz, Ph.D., MD, of Massachusetts, as our expert in the Kadile case, and he has worked well with me in preparing that case. I propose to retain Dr. Baratz for the Waters cases, as well. Dr. Baratz has agreed to do this, if you approve.

In that all of the basic research into the chelation therapy literature has been done, there will be some time (and therefore money) savings by using the same expert. Additionally, I am considering asking for a joint hearing, so that the cases may be tried together, at least insofar as the danger or fraudulent nature of chelation therapy is involved to save additional time and money.

Dr. Baratz' fee is $175 per hour, a reasonable fee for experts (and a discount from his usual fee), and of course these fees are costs under our statute and therefore recoverable from a respondent who is disciplined.

I am not aware of any suitable expert in this rather specialized area, in Wisconsin.

Arthur Thexton, Prosecuting Attorney
Department of Regulation & Licensing
Division of Enforcement
1400 E. Washington Ave
Madison, WI 53708-8935
608-266-9814

Enclosure 24

Sarah Chapman

From: Debbie Coolidge
Sent: Monday, February 24, 2003 3:36 PM
To: sarah@watersmedcenter.com
Subject: Fw: In re Kadile, 94 Med 94

—— Original Message ——
From: Thexton, Arthur
To: 'Debbie Coolidge'
Cc: Schweitzer, John
Sent: Monday, February 24, 2003 1:13 PM
Subject: In re Kadile, 94 Med 94

Although I am not willing to share my communications with my expert witness, I will tell you how I found and retained him; there is no big mystery here. After Dr. Renner died, I contacted Steve Barrett of Quackwatch and asked him for a recommendation. I knew about Quackwatch because Dr. Renner told me about it. Dr. Baratz was recommended, along with (I believe, although my recollection is a bit hazy now) others. I contacted and asked Dr. Baratz for references, and was given the names of attorneys with whom he had worked. I telephoned fellow prosecutors in two other states and asked them about Dr. Baratz. They both recommended him and said that he had done a good job, and they would retain him again. So I retained him. But I did not keep any notes on those conversations (which were now well over 2 years ago) and cannot tell you the names of who I talked to, or much about what was said. I just know that it happened, and remember a few bits and pieces.

Having said all this, and having heard the criticisms of Dr. Baratz levied by the defense and by Mr. Bolen, I am happy to say that I have no regrets at all, and would hire him again, today. And, I would recommend him to others. I regard his "bias and prejudice" in favor of science, in favor of scientific rigor, and in favor of evidence-based medicine, to be entirely appropriate and proper.

Arthur Thexton
Prosecuting Attorney
Wisconsin Department of Regulation & Licensing
1400 E. Washington Ave.
P.O. Box 8935
Madison, WI 53708-8935
608-266-9814
FAX 266-2264
arthur.thexton@drl.state.wi.us

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A. Yes.
Q. And were you compensated as such?
A. Yes.
Q. A reference was made yesterday to certain memoranda in your personnel file there which resulted in -- in your being suspended for a day and reprimanded. Did there come a time when Harvard Health informed you that there would be a change in your -- in how your position would be constituted at Harvard Health?
A. Yes.
Q. And what was that?
A. They wanted to change me over to full time clinical.
Q. Okay. And what would this have done to your other duties that you just described?
A. Some of those would be eliminated.
Q. Okay. And what you mean was they wanted to change you over to clinical duties?
A. Well, it was how my time was spent. In other words, I had some time in an administrative capacity that meant going to meetings and writing reports and doing various things and they wanted to re-arrange the way the administration was there. They do that on a regular basis. And I was offered full time clinical duties.
Q. Were there any preconditions placed upon this

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offer of a full time clinical position?
A. No.
Q. Whose decision was it to not accept that offer?
A. Mine.
Q. Was there any pressure placed upon you by anybody in or on behalf of Harvard Health to not accept a full time clinical position?
A. To not accept? No, no pressure was placed on me.
Q. Reference was made yesterday to the amount -- the method by which your -- I guess I would just call it severance pay was calculated at the rate of $61.80 per hour. Do you recall that?
A. I recall the conversation.
Q. Okay. Was in fact that your rate of pay at the time that you were negotiating your departure from Harvard Health?
A. No.
Q. Okay. What -- was your rate of pay higher or lower?
A. It was higher.
Q. What -- why does the severance agreement use a lower rate of pay for calculating the -- the rate at which you would be paid this week of transition time?
A. No, severance pay went beyond that.
Q. Ah.

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A. It was --
Q. I stand corrected.
A. It was for a flat sum actually. It was what we negotiated.
Q. In addition to your hourly rate was there other -- was compensation received by you and other physicians at Harvard Health in -- in any other form?
A. Yes.
Q. What was that?
A. Well, because of their budgetary problems I guess physicians were put on a different pay mechanism so that instead of getting pay raises they were giving us quarterly bonuses because it appeared on the books differently in terms of how they billed and several other things. And they adopted this policy about half way -- the time I was there. A couple years when no raises were given to anybody but one of the raise mechanisms for physician providers was bonusing and it was based upon a quarterly system. So they didn't want to commit to -- they didn't want to change everyone's contracts but they -- they sort of -- it allowed them not to bonus if they didn't have the money. So they -- but we did get the bonuses. Also when I did coverage in the hospital for in patients those were billed separately and I was paid separately. And that in fact was referenced in one of the documents yesterday.

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Q. So all that is in addition to the 60 or 61.80 or whatever the hourly rate was?
A. Whatever the base -- so called base pay rate.
Q. All right. Now, there was considerable testimony yesterday about the injury that resulted from the incident involving Florence Wilson. Do you recall that exchange yesterday?
A. I recall we talked about it at some length.
Q. And you recall that Dr. Wilson was here?
A. She was here.
Q. Now, this incident occurred how long ago?
A. December of '98.
Q. Four and a half years?
A. Yes.
Q. Okay. Would you describe the medical mechanism of the injury that you suffered in December of 1998?
A. Yes. I need to elaborate.
MR. RECKER: I would only object --
Q. Please describe the medical mechanism of that injury?
LAW JUDGE: There's been an objection. So --
MR. RECKER: It just goes beyond anything he was asked yesterday.
MR. THEXTON: I --
LAW JUDGE: Well, it does and as soon as the

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STATE OF WISCONSIN

DEPARTMENT OF REGULATION AND LICENSING

In the matter of the disciplinary proceedings against:

Eleazar Kadile,

Respondent.

Case Number LS-0112061-MED

Day 6 Hearing before John N. Schweitzer

July 15, 2003

1400 East Washington Avenue

Madison, Wisconsin

APPEARANCES

For the State of Wisconsin:

Department of Regulation and Licensing

Arthur K. Thexton

1400 East Washington Avenue

Madison, Wisconsin

Jim Doyle
Governor

Donsia Strong Hill
Secretary

WISCONSIN DEPARTMENT OF REGULATION & LICENSING

1400 E Washington Ave
PO Box 8935
Madison WI 53708-8935
Email: web@drl.state.wi.us
Voice: 608-266-2112
FAX: 608-267-0644
TTY: 608-267-2416

January 9, 2004

Dr. Robert Waters
P.O. Box 357
Wisconsin Dells, WI 53965

Re: 97 MED 108, 97 MED 101

Dear Dr. Waters:

As I told you on the telephone, I am a new prosecutor at the Department of Regulation and Licensing, and your cases have been reassigned from Arthur Thexton, to me. I have appreciated your cooperation and willingness to discuss theses cases.

I would also appreciate it if you would be willing to send me any information you can regarding the NIH chelation trials that you are involved in. I understand, from our conversation, that some of the material is confidential and you have been asked not to forward it without authorization. I think that we can do without that material, which relates to the mechanics of the research study. I am more interested in information about how the treatments are to be given. I would like to see the consent forms, for example, and anything else that discusses the treatment regime. I would also be willing to look at anything else that you have, that you haven't already provided to us, that shows the safety of the procedure, such as other research studies outside the U.S., or historical information.

Thank you for taking the time to speak to me today, and yesterday as well. I look forward to our meeting next week.

Sincerely,

Jeanette Lytle
Attorney
Division of Enforcement
(608) 266-9840

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WISCONSIN DEPARTMENT OF
REGULATION & LICENSING

Jim Doyle
Governor
Donsia Strong Hill
Secretary

1400 East Washington Avenue
PO Box 8935
Madison WI 53708-8935
Email: dorl@drl.state.wi.us
Voice: 608-266-2112
FAX: 608-267-0644
TTY: 608-267-2416

January 30, 2004

Hand Delivered

Dr. Robert Waters
P.O. Box 357
Wisconsin Dells, WI 53965

RE: 97 MED 101, 97 MED 108

Dear Dr. Waters:

The Wisconsin Medical Examining Board received two complaints regarding your practice of chelation therapy in 1997. This information was reviewed for the purpose of determining whether disciplinary action was warranted.

The information received by the Division of Enforcement was screened and opened for investigation. An attorney and an investigative staff person were assigned to this matter. You and other individuals were contacted during the investigation.

Upon completion of this investigation, representatives of the Division of Enforcement presented the relevant facts to the Medical Examining Board at a meeting on January 21st, 2004. After considering the facts, the Medical Board closed these cases without further action.

If you have questions concerning this matter, please call me or write to the Division of Enforcement, Room 194, P.O. Box 8935, Madison, Wisconsin 53708-8935. In the event you write, please refer to the file number of the case.

Sincerely,

Jeanette Lytle
Attorney
Division of Enforcement
608-266-9840

STATE OF WISCONSIN
BEFORE THE MEDICAL EXAMINING BOARD

IN RE THE INVESTIGATION OF ROBERT SCOTT WATERS, M.D.	Case No. 97MED101

MOTION DECISION AND ORDER

TO: Mr. Arthur Thexton
Department of Regulation & Licensing
Division of Enforcement
P.O. Box 8935
Madison, WI 53708-8935

Mr. Gregory D. Seeley
Seeley, Savidge & Ebert
800 Bank One Center
600 Superior Avenue, East
Cleveland, OH 44114-2655

PROCEDURAL HISTORY

On March 11, 2002, Respondent, by his attorney, filed a Motion to Quash the Subpoena Duces Tecum (issued February 25, 2002) with the Medical Examining Board. An oral hearing was held on the matter before the undersigned administrative law judge on March13, 2002. Attorney Arthur Thexton appeared on behalf of the Medical Examining Board. Attorneys Gregory D. Seeley and Douglas Whipple appeared on behalf of Dr. Waters.

ORDER

NOW, THEREFORE, IT IS HEREBY ORDERED that Respondent's motion is **Denied** in part and **Granted** in part.

DISCUSSION

At issue is whether the Subpoena Duces Tecum issued on behalf of the Medical Examining Board on February 25, 2002, to Dr. Robert Scott Waters ought to be quashed or, in the alternative, be modified to limit its scope. The subpoena identifies ten, separate items.

Although Dr. Waters was the subject of an investigation by the Medical Examining Board (Board) in 1991, that matter was closed in 1993, and is not the subject of the current investigation. New complaints have since been filed against Dr. Waters which has led to the current investigation and the issuance of the Subpoena Duces Tecum. Nevertheless, Dr. Waters maintains that his exoneration with respect to the 1991 complaint should exempt him from any further investigations by the Board, including any pending ones. Dr. Waters' argument is not convincing. Simply because Dr. Waters was

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the subject of an earlier complaint does not, in turn, shield him from having other complaints filed against him or prevent him in any way from becoming subject to subsequent investigations. And while Dr. Waters may find such complaints and the ensuing investigations to be distasteful, the Board is fully within its rights to investigate the complaints that come before it, including those against Dr. Waters.

Respondent further objects to the Subpoena on the grounds that the documents sought are not relevant to the investigations. There is no reason to believe that the documents sought are not relevant to the current investigation. All of the items requested appear to legitimately relate to Dr. Waters' medical practice and to his patients. As such, they are proper and not beyond the scope of the current investigation.

Finally, Respondent opposes the Subpoena because he believes that the documents sought are excessive for the purpose of the investigation. Upon reviewing each of the ten categories, it appears as some modifications are in order. Each of the items is identified below and has been modified accordingly.

I. ***Any document purporting to be a certificate of recognition from a medical specialty board***

A photocopy of any document that purports to be a certificate of recognition from a medical specialty board will suffice. The term "medical specialty board" is not limited to those recognized by the American Medical Association or any other medical organization.

II. ***Any and all brochures, pamphlets, or other written handouts created by or for your office, which you have given to a patient in the years 2001-02, and all advertising copy used by you or your office in the years 2001-02***

This is limited to those brochures, pamphlets, or other written handouts that were custom produced solely for or on behalf of Dr. Waters, including advertising copy during the years identified. This does not include items that are mass-produced by organizations such as the American Heart Association.

III. ***Any professional literature relied upon by you in formulating your opinions on the efficacy and safety of chelation therapy as administered by you, including textbooks***

Citations to professional literature or to textbooks will suffice. Actual articles and/or textbooks need not be produced.

IV. ***Any and all documentation of any courses or programs you have taken in the area of chelation therapy, including certificates, syllabi, and the like***

This shall be limited to the documentation that Dr. Waters has within his possession, *i.e.*, at his office, home, or other storage facility.

V. ***The labels and package inserts from all ingredients used by you in your chelation therapy admixture(s) (including DMSO), together with any literature (including textbooks) relied upon by you supporting the use of each such ingredient, from 1996-present***

This shall be limited to documents that demonstrate what ingredients Dr. Waters uses or has used in his chelation therapy admixtures from 1996-present, including labels and package inserts, to the extent they exist, and any other supporting literature not previously identified in Item III.

VI. ***The labels and package inserts from all supplements recommended by you in your practice, together with any literature relied upon by you supporting the use of each such supplement***

This item is limited to non-prescription supplements that Dr. Waters consistently or repeatedly recommends to patients, including labels and package inserts, to the extent they exist, and any other supporting literature not previously identified in Item III.

VII. ***Any IND, protocol, or other documentation concerning any experiments or studies you have conducted or participated in as a physician licensed in Wisconsin***

This item shall remain unchanged.

VIII. ***All consent forms used by you for patients receiving chelation therapy from 1996-present***

Providing blank consent forms that patients receive (or have received) prior to undergoing chelation therapy from 1996-present will suffice.

IX. ***All logs or other records of compounding or preparing the chelation admixtures for patients, compounding/mixing instructions, administration/delivery instructions, order sheets, post-care instructions for patients, and all other forms used in relation to chelation therapy by your practice, for the years 1996-present***

For the years 1996-present, Respondent is not required to produce the records for each, individual patient, but shall instead provide any logs or other records of compounding or preparing the chelation admixtures for patients, compounding/mixing instructions, and administration/delivery instructions, which may include standing orders. For those same years, Respondent shall also provide order sheets, which may be blank forms, post-care instructions for patients, and all other forms used in relation to chelation therapy.

X. ***All records relating to any billings sent to any insurance company or other third-party payor from 1996-present***

For the years 1996-present, Respondent shall provide the names of patients for whom any billings were sent to any insurance company or other third-party payor, along with the purpose of the billing, and the name and address of the insurance company billed.

To the extent that Dr. Waters is able to produce these items for his scheduled appearance before Mr. Thexton, he shall do so. However, Mr. Thexton has indicated that

if it is not possible for Dr. Waters to produce all the requested items by that date, he will not object to their being submitted to him within a reasonable period of time thereafter.

Dated at Madison, Wisconsin, this 14th day of March, 2002.

STATE OF WISCONSIN
DEPARTMENT OF REGULATION & LICENSING
1400 East Washington Avenue
P.O. Box 8935
Madison, Wisconsin 53708
Telephone: (608) 266-5836
FAX: (608) 267-0644

Jacquelynn B. Rothstein
Administrative Law Judge

November 19, 2003

Judge Rothstein
Department of Regulation and Licensing
1400 East Washington St
Madison WI 53716

Dear Judge Rothstein,

Enclosed you will find herewith copies of three documents I filed with Prosecutor Arthur Thexton in reference to cases 97MED101 and 97MED108. I want you to have these documents for your file as I anticipate I will be making further motions/pleadings in the above referenced cases. I would also appreciate your aiding me in acquiring the information I requested of Mr. Thexton and the Department of Regulation and Licensing in my pleadings. Thank you for your anticipated cooperation.

Sincerely,

Robert S. Waters, M.D.

Enclosures

Enclosure 29

Jim Doyle
Governor

Donsia Strong Hill
Secretary

WISCONSIN DEPARTMENT OF REGULATION & LICENSING

1400 E Washington Ave
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TTY: 608-267-2416

November 25, 2003

Robert S. Waters, M.D.
Medical Director
Waters Preventative Medical Center
P.O. Box 357
Wisconsin Dells, WI 53965

Dear Dr. Waters:

I am in receipt of your letter dated November 21, 2003. If you have concerns involving Mr. Thexton, kindly bring them to the attention of his supervisor, Mr. Michael Berndt, as I do not have the authority to address them.

Very truly yours,

Jacquelynn B. Rothstein
Attorney at Law
Office of Legal Counsel

waters
Preventive Medical Center

Robert S. Waters, MD
Medical Director

October 30, 2003

In Re: Investigation of Robert Scott Waters, MD
Respondent
#97 MED 101 and
#97 MED 108

Arthur Thexton
Prosecuting Attorney
Wisconsin Department of Regulation & Licensing
1400 East Washington Avenue
Madison WI 53708-8935

Re: Respondents Request for Pre-Administrative Hearing

Dear Mr. Thexton,

This letter is to serve as my official request and demand for a Pre-Administrative Hearing with your agency.

The purpose of this hearing is to determine whether there is a factual, reasonable and lawful basis to begin or commence an investigation and request for records of Respondent concerning patients included in cases 97MED101 and 97MED108.

Since the result of these investigations and requests for records could be that Respondent is disciplined in some manner from the suspension of license to revocation of license, fines, restrictions, etc., a property interest and substantial rights are involved on the part of the Respondent. This license is protected property interest under federal constitutional law being due process of law under the Fourteenth Amendment to the U.S. Constitution.

In addition Respondent has a liberty interest, that being the Right of Privacy under the First, Fourth, Fifth and Fourteenth Amendment to the U.S. constitution. The Respondent also has the right to be left alone. Additional property interests include the right to be secure in one's private books and records under the Fourth Amendment to the U.S. Constitution and the right to not expend and experience the expense of time, money and energy to defend oneself and furnish records.

The Respondent in this case is entitled to a Pre-Administrative Hearing before any further action is taken by the Board. Your agency must make sure that the following is adhered to:

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Race and Vine Streets • Box 357 • Wisconsin Dells • Wisconsin • 53965 • 608/254-7178 • Fax 608/253-7139

1) Furnish Respondent in writing a timely and adequate notice detailing the reasons for the investigation.
2) Give the Respondent an opportunity to defend himself regarding those reasons.
3) Respondent be able to confront and cross-examine any adverse witnesses that were relied upon in the Board's decision to initiate these investigations.
4) Respondent has opportunity to present argument and evidence orally.
5) Respondent is able to appear personally with or without counsel before the official who finally determines the issues. Written submissions do not satisfy Due Process of Law.
6) All evidence utilized by the agency to decide sanctions or another action must first be disclosed to the Respondent before an action is taken.
7) The final decision-maker's conclusions must rest solely on the legal rules and evidence required and adduced at the hearing.
8) The final decision-maker must be impartial. (This may require someone outside of the agency.)
9) The decision-maker must state reasons for determination and indicate what law, regulations and rules he or she relied upon in the final decision.

This Pre-Administrative Hearing and its characteristics are demanded by the U.S. Supreme Court in the cases of Goldberg v. Kelly, 25 L. Ed. 2d 287; Sniadach v. Family Finance Corp., 23 L.Ed. 2d 349; and others. Any and all previous final determinations are void due to lack of proper administrative legal procedures in this case.

The laws, regulations and rules you and/or the DORL relied upon to open and continue the investigations of my possible violation of such rules, etc. are required by Statue [227.20(1)] to be written and certified in the office of the Secretary of State and the office of the Revisor.

If the Board does not respond favorably or give a response to this request and demand for a Pre-Administrative hearing within (20) days from the date that this request and demand is received, then your agency will be considered to be in default and appropriate legal proceeding will be commenced against your agency.

Sincerely,

Robert S. Waters, M.D.

CC: Donsia Strong Hill
Wayne Austin
Michael Berndt

Jim Doyle
Governor

Donsia Strong Hill
Secretary

WISCONSIN DEPARTMENT OF REGULATION & LICENSING

1400 E Washington Ave
PO Box 8935
Madison WI 53708-8935
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Voice: 608-266-2112
FAX: 608-267-0644
TTY: 608-267-2416

November 4, 2003

Robert Scott Waters MD
P.O. Box 357
Wisconsin Dells, WI 53965

Re: 97 Med 101/108

Dear Dr. Waters:

With respect to your letter of October 30, 2003, there is no such thing as a "pre-administrative hearing" required by agency practice or rule, or state statute or constitutional provision, or federal constitutional law. Further, the cases you cite do not stand for the proposition you assert.

If a determination is made to proceed to disciplinary hearing in this investigation (and no such determination has yet been made), a formal complaint will be made in writing and sent to you, and you will have the opportunity to have a full hearing on the allegations made in any such complaint. All of your constitutional, statutory, and administrative rights will be respected, as they have been at all times during the investigatory process.

Sincerely yours,

Arthur Thexton
Prosecuting Attorney
608-266-9814
FAX 266-2264
arthur.thexton@drl.state.wi.us

i:\waters.ltr4.doc

October 27, 2003

In Re: Investigation of Robert Scott Waters, MD
Respondent
#97 MED 101 and
#97 MED 108

Arthur Thexton
Prosecuting Attorney
Wisconsin Department of Regulation & Licensing
1400 East Washington Avenue
Madison WI 53708-8935

Dear Mr. Thexton,

I have received no reply to my May 14, 2003 certified communication requesting certified copies of your Oath of Office, delegation of authority, evidence of professional competency as well as your license to practice law. You have not honored my requests.

I hereby resubmit these requests and also require from you and/or the appropriate employees of the DORL, copies of the Oaths of Office of all Medical Examining Board Members, officers, attorneys and administrative law judges involved in my case.

Sincerely,

Robert S. Waters, M.D.

CC: Donsia Strong Hill
Wayne Austin
Michael Berndt

Enclosure 31

January 28, 2003

Arthur Thexton
Prosecuting Attorney
Wisconsin Department of Regulation & Licensing
1400 East Washington Avenue
Madison WI 53708-8935

Dear Mr. Thexton,

You mention in your letter that you will keep the FSMB guidelines in mind as the Board determines whether my practice "comports with the minimum standards of competence and the other rules of the Board." Are these "minimum standards" written? If so, I would like a copy of them. What are the "other rules of the Board?" Are these written? Please forward a copy of these also. Were these "minimum standards" and/or "other rules of the Board" arrived at during a meeting that was open to the public as required by the law?

The Bates stamped page 00001 and page 00002 were a front and back piece of paper. I wrote "(over)" to indicate that I had wrote the next note dated 9/25/01 on the other side. I've included a typed noted for Bates stamped page 00003. I have also included the second page of the consent form from Margaret Barry's chart.

Sincerely,

Robert S. Waters, MD
Enc: 2

CC: Governor James Doyle (without enclosures)
Senator Dale Schultz (without enclosures)
Representative Sheryl Albers (without enclosures)

UNOFFICIAL TEXT
Chapter 227
227.20

227.20

227.20 Filing of rules.

227.20(1)

(1) An agency shall file a certified copy of each rule it promulgates in the office of the secretary of state and in the office of the revisor. No rule is valid until the certified copies have been filed. A certified copy shall be typed or duplicated on 8 1/2 by 11 inch paper, leaving sufficient room for the secretary of state's stamp at the top of the first page. Forms that are filed need not comply with the specifications of this subsection.

227.20(2)

(2) The secretary of state shall endorse the date and the time of filing on each certified copy filed under sub. (1). The secretary of state shall keep a file of all certified copies filed under sub. (1).

227.20(3)

(3) Filing a certified copy of a rule with the secretary of state creates a presumption of all of the following:

227.20(3)(a)

(a) That the rule was duly promulgated by the agency.

227.20(3)(b)

(b) That the rule was filed and made available for public inspection on the date and time endorsed on it.

227.20(3)(c)

(c) That all of the rule-making procedures required by this chapter were complied with.

227.20(3)(d)

(d) That the text of the certified copy of the rule is the text as promulgated by the agency.

227.20 - ANNOT.

History: *1985 a. 182; 1993 a. 214.*

227.20 - ANNOT.

Cross-reference: *See s. 902.03 for provision for judicial notice of administrative rules.*

227.21

227.21 Publication of rules; incorporation by reference.

227.21(1)

(1) All rules that agencies are directed by this chapter to file with the revisor shall be published in the code and register as required under s. 35.93.

227.21(2)

(2)

Enclosure 32

Certified mail 11/6/03

waters

Preventive Medical Center

Robert S. Waters, MD
Medical Director

November 5, 2003

In Re: Investigation of Robert Scott Waters, MD
Respondent
#97 MED 101 and
#97 MED 108

Arthur Thexton
Prosecuting Attorney
Wisconsin Department of Regulation & Licensing
1400 East Washington Avenue
Madison WI 53708-8935

Re: Request for Index and cross-Index under the Wisconsin and Federal Freedom of Information Acts and 2nd request for Rules of the Board

Dear Mr. Thexton,

This letter is to serve as my official notice of the request for Indices and cross-Indices of any and all Board rules, regulations, opinions, determinations, etc. in compliance with the Wisconsin Administrative Code and the Common Law for all the years required by the Code.

In addition, I have never received copies of the "minimum standards of competence" and "the other Rules of the Board" you wrote about in your January 7, 2003 letter to me. Since this is a second request, this communication is now a demand for this information under the Wisconsin and Federal Freedom of Information Acts.

It appears that you and your agency are refusing to obey the laws of the State of Wisconsin and the Federal Government and are thereby acting in bad faith. If you continue to pursue the complaints against me, then I will have no other choice but to consider these actions as a violation of due process of law under the First, Fourth, Fifth and Fourteenth Amendments to the U.S. Constitution and the provisions of the Wisconsin Constitution.

Sincerely,

Robert S. Waters, M.D.

CC: Donsia Strong Hill
Wayne Austin
Michael Berndt

Enclosure 33

Race and Vine Streets • Box 357 • Wisconsin Dells • Wisconsin • 53965 • 608 / 254-7178 • Fax 608 / 253-7139
Web Site: www.watersmedcenter.com

STATE OF WISCONSIN
BEFORE THE MEDICAL EXAMINING BOARD

IN RE INVESTIGATION # 97 MED 101

WIS. STATS. §§440.03(4) & 885.12
SUBPOENA DUCES TECUM

TO: Robert Scott Waters, MD, Wisconsin physician license # 20-27520

You are hereby required to appear before me in Room 194 at 1400 East Washington Avenue, Madison, Wisconsin on Friday, March 15, 2002, at 9:00 AM to answer questions regarding the above investigation, and to produce for inspection and copying the following items:

1. Any document purporting to be a certificate of recognition from a medical specialty board.

2. Any and all brochures, pamphlets, or other written handouts created by or for your office, which you have given to a patient in the years 2001-02, and all advertising copy used by you or your office in the years 2001-02.

3. Any professional literature relied upon by you in formulating your opinions on the efficacy and safety of chelation therapy as administered by you, including textbooks.

4. Any and all documentation in his possession of any courses or programs you have taken in the area of chelation therapy, including certificates, syllabi, and the like.

5. The labels and package inserts from all ingredients used by you in your chelation therapy admixture(s) (including DMSO), together with any literature (including textbooks) relied upon by you supporting the use of each such ingredient, from 1996-present.

6. The labels and package inserts from all supplements recommended by you in your practice, ~~together with any literature relied upon by you supporting the use of each such supplement.~~

7. Any IND, protocol, or other documentation concerning any experiments or studies you have conducted or participated in as a physician licensed in Wisconsin.

8. All consent forms used by you for patients receiving chelation therapy, from 1996-present.

9. All logs or other records of compounding or preparing the chelation admixtures for patients, compounding/mixing instructions, administration/delivery instructions, order sheets, post-care instructions for patients, and all other forms used in relation to chelation therapy by your practice, for the years 1996-present.

Enclosure 34

EXHIBIT
A
ALL-STATE® INTERNATIONAL

10 All records relating to any billings sent to any insurance company or other third-party payor, from 1996-present.

You should expect to be present to answer questions for the entire business day.

Dated this February 25, 2002

WISCONSIN DEPARTMENT OF REGULATION & LICENSING, by:

Arthur Thexton
Prosecuting Attorney
Department of Regulation & Licensing
Madison, WI 53708-8935
(608)266-9814
FAX 266-2264
arthur.thexton@drl.state.wi.us

cc: Gregory M. Seeley, 800 Bank One Cntr, 600 Superior Ave. E., Cleveland, OH 44114-2655

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STATE OF WISCONSIN
BEFORE THE MEDICAL EXAMINING BOARD

IN RE INVESTIGATION # 97 MED 101	WIS. STATS. §§440.03(4) & 885.12 **SUBPOENA DUCES TECUM**

TO: Robert Scott Waters, MD, Wisconsin physician license # 20-27520

You are hereby required to appear before me in Room 194 at 1400 East Washington Avenue, Madison, Wisconsin, on Friday, May 16, 2003, at 9:00 AM to answer questions regarding the above investigation, and to produce for inspection and copying the following items:

1. A true copy of any document purporting to be a certificate of recognition or status from a medical specialty board. The term "medical specialty board" includes, but is **not** limited to, those recognized by the American Board of Medical Specialties.

2. Any and all brochures, pamphlets, or other written handouts reproduced or created by or for your office, which you have given to a patient in the years 2001-03, and all advertising copy used by you or your office in the years 2001-03. This is limited to those brochures, pamphlets, or other written handouts that were custom produced for on behalf of Dr. Waters, including advertising copy during the years identified, This does not include items that are mass produced by organizations such as the American Heart Association.

3. Any and all World Wide Web (Internet) site pages used by your office, your practice, or you in any medical context pertaining to your practice of medicine in the State of Wisconsin from 1995-present, which purported to give information about your, your office, or your practice, and which were available to patients, potential patients, or others.

4. Any professional literature relied upon by you in formulating your opinions on the efficacy and safety of chelation therapy as administered by you, including textbooks. Citations to professional literature or to textbooks will suffice (but citations must be complete). Actual articles and/or textbooks need not be produced, unless the text is no longer in print or the article is not indexed in Medline, and you have them within your custody or control.

5. Any and all documentation of any courses or programs you have taken in the area of chelation therapy, including but not limited to certificates, syllabi, and the like, which are within your custody or control.

6. Any and all documentation of any courses or programs you have taken in the area of IPT (Insulin Potentiation Therapy), including but not limited to certificates, syllabi, and the like, which are within your custody or control.

7. The labels and package inserts from all ingredients used by you in your chelation therapy admixture(s) (including DMSO), together with any literature (including textbooks) relied upon by you supporting the use of each such ingredient, from 1996-present. This is limited to documents that demonstrate what ingredients you use or have used in the chelation therapy admixtures from 1996-present, including labels and package inserts to the extent that they exist, and any other supporting literature not previously identified in the professional literature citations, above (¶4).

8. The labels and package inserts from all supplements recommended by you in your practice, together with any literature relied upon by you supporting the use of each such supplement. This is limited to non-prescriptions supplements that you consistently or repeatedly

18. The names of patients for whom any billings or records were sent to any insurance company or other third-party payor, together with the purpose of the billing and the name and address of the insurance company or third party payor billed, from 1/1/1996-present.

19. Your article: "EDTA chelation effects on urinary losses of cadmium, calcium, chromium, cobalt, copper, lead, magnesium, and zinc." (Biol Trace Elem Res 2001 Dec; 83(3):207-21), if you have a copy.

You should expect to be present to answer questions for the entire business day.

Dated this April 16, 2003.

WISCONSIN DEPARTMENT OF REGULATION & LICENSING, by:

Arthur Thexton
Prosecuting Attorney
Department of Regulation & Licensing
Madison, WI 53708-8935
(608)266-9814
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10.1007/s00280-003-0716-7

Cancer Chemotherapy and Pharmacology

10.1007/s00280-003-0716-7

Original Article

Insulin-induced enhancement of antitumoral response to methotrexate in breast cancer patients

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(1) Department of Medicine, School of Medicine, University of Uruguay, Montevideo, Uruguay

(2) Interdoctors Medical Center, Montevideo, Uruguay

(3) National Cancer Institute, Montevideo, Uruguay

(4) PharmaBlood Inc, North Miami Beach, Florida, USA

(5) (Former Director of the Department of Medicine, School of Medicine, University of Uruguay, Montevideo, Uruguay and National Cancer Institute, Montevideo, Uruguay), Research & Development Department, PharmaBlood Inc, 2050 NE 163rd Street, 2nd Fl, # 202, North Miami Beach, Florida 33162, USA

Enclosure 36

10.1007/s00280-003-0716-7

✉ **Eduardo Lasalvia-Prisco**
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Abstract

Purpose It has been reported that insulin increases the cytotoxic effect in vitro of methotrexate by as much as 10,000-fold. The purpose of this study was to explore the clinical value of insulin as a potentiator of methotrexate.

Patients and methods Included in this prospective, randomized clinical trial were 30 women with metastatic breast cancer resistant to fluorouracil + Adriamycin + cyclophosphamide and also resistant to hormone therapy with measurable lesions. Three groups each of ten patients received two 21-day courses of the following treatments: insulin + methotrexate, methotrexate, and insulin, respectively. In each patient, the size of the target tumor was measured before and after treatment according to the Response Evaluation Criteria In Solid Tumors. The changes in the size of the target tumor in the three groups were compared statistically.

Results Under the trial conditions, the methotrexate-treated group and the insulin-treated group responded most frequently with progressive disease. The group treated with insulin + methotrexate responded most frequently with stable disease. The median increase in tumor size was significantly lower with insulin + methotrexate than with each drug used separately.

Discussion Our results confirmed in vivo the results of previous in vitro studies showing clinical evidence that insulin potentiates methotrexate under conditions where insulin alone does not promote an increase in

10.1007/s00280-003-0716-7

tumor growth. Therefore, the chemotherapy antitumoral activity must have been enhanced by the biochemical events elicited in tumor cells by insulin.

Conclusions In multidrug-resistant metastatic breast cancer, methotrexate + insulin produced a significant antitumoral response that was not seen with either methotrexate or insulin used separately.

Keywords Breast Cancer - Chemotherapy - Insulin - Methotrexate - Tumor growth

Introduction

It is known that slowly growing cancers have tumor cell populations with a low-growth fraction and are less sensitive to chemotherapy than rapidly growing tumors with high-growth fractions [11]. Slowly growing malignancies have relatively more cells in a noncycling status and fewer cells in a cycling status than rapidly growing malignancies. It has been demonstrated that insulin as a pharmacological agent induces the switch from a noncycling to a cycling status in tumor cells [5]. In MCF-7 human breast cancer cells, insulin has been shown to increase the cytotoxic effect of methotrexate up to 10,000-fold in vitro [1]. Ellipticine uptake is also increased by insulin [9]. It has been suggested that insulin is effective in potentiating most chemotherapy drugs. This insulin-induced potentiation has been proposed as a strategy for breast cancer treatment, but confirmatory clinical trials are still lacking [2]. This study was carried out to confirm insulin-induced clinical potentiation of the antitumoral effect of methotrexate as suggested by preclinical studies and to establish a mechanism of action for this antitumoral effect.

10.1007/s00280-003-0716-7

Patients and methods

Patients

The study was conducted in 30 patients with breast cancer admitted to medical centers that reported medical data to the Cooperative Trials Center (CTC) of PharmaBlood, R&D Department, Florida. A prospective, randomized trial was carried out. All patients met the following eligibility criteria: histologically confirmed breast carcinoma, metastatic stage (M1); Eastern Cooperative Oncology Group (ECOG) performance status (PS) $\leq$2; age $\leq$74 years; and adequate hematological function (WBC count $\geq$4000/μl, neutrophil count $\geq$2000/μl, hemoglobin level $\geq$9.0 g/dl, platelet count $\geq 10\times10^4/\mu$l), renal function (serum creatinine $\leq$1.5 mg/dl, 24-h creatinine clearance $\leq$60 ml/min), liver function (total bilirubin $\leq$2.0 mg/dl, serum transaminases not more than twice the upper limit of the normal range), and respiratory function (PaO_2 $\geq$60 Torr). The patients included had measurable lesions, as required by the Response Evaluation Criteria In Solid Tumors (RECIST) system of tumor assessment [13], and if they had a positive estrogen receptor status, they had been treated with and become resistant to hormone therapy.

All patients included in the study had progressive disease (RECIST criteria) after chemotherapy with at least four series of fluorouracil + Adriamycin + cyclophosphamide (FAC) and had not been treated with any other chemotherapy. They were randomly allocated to three groups

of ten patients each: group 1 was treated with insulin + methotrexate as described below, group 2 was treated with methotrexate without insulin, and group 3 was treated with insulin without methotrexate. Written informed consent, including detailed information about risks and benefits, was approved and signed by all the patients included in the study. Central computerized remote randomization was performed, with patients being allocated to one of the groups through random sequence generation by the permuted block method. An assessment of the results after 30 patients had completed the trial showed that this sample size was enough. The patients were recruited from two oncological medical centers in Montevideo, Uruguay (first at the National Cancer Institute and then at Interdoctors Medical Center), both of which participated with their data in the network operated and sponsored by the Cooperative Trials Center (CTC) of PharmaBlood R&D Department.

The institutional ethics committee of PharmaBlood and the institutional review boards of the participating medical centers approved the trial. The ethical reviewers considered that an 8-week delay before starting second-line chemotherapy after FAC had failed in all the patients included in the trial was acceptable. This determination was consistent with the standard of care in this clinical situation which has been recently well summarized [3]:

> Despite almost 30 years of clinical cancer research, the true impact of second and subsequent lines of chemotherapy on the outcome of metastatic breast cancer patients, especially on the duration of survival, is still unknown. In the virtually incurable metastatic setting, issues like quality of life and patients' preferences gain particular relevance.

The accepted protocol was resubmitted to the committee for review in order to obtain approval for treatment of patients with insulin alone

considering the potentially harmful effect through the activation of receptors for insulin/insulin-like growth factors. The committee confirmed the approval on the basis of reports of no harmful effect of this treatment [6, 7]. The results of the study confirmed the committee's criteria because no significant differences were found in tumor growth either between the insulin-alone group and the methotrexate-alone group or between before and after treatment in the insulin-alone group.

Treatment

All the patients included in the study received two 21-day courses of treatment separated by a 7-day interval without treatment between courses. In group 1, the treatment course was intravenous human recombinant insulin (0.3 U/kg body weight every other day) followed 20 min later by a 15-min intravenous infusion of methotrexate (2.5 mg/m^2 in 50 ml 30% glucose). If symptomatic hypoglycemia was observed, the 30% glucose solution containing methotrexate was infused immediately. An oral glucose supplement was also prescribed to prevent delayed hypoglycemic symptoms. In group 2, insulin was omitted and methotrexate was administered intravenously at the same dose and in the same solution (2.5 mg/m^2 in 50 ml 30% glucose) as in group 1. In group 3, methotrexate was omitted, insulin was administered at the same dose as in group 1, and 30% glucose solution was also administered intravenously 20 min after insulin or sooner if hypoglycemic symptoms were evident.

Tumor growth assessment

After 8 weeks (two 3-week courses plus 1 week interval after each course), the response to treatment was assessed in each patient using

RECIST criteria [13]. The sum of the longest diameter of measurable target lesions and the number of non-target lesions were recorded immediately before and after this 8-week period. Skin nodules and palpable lymph nodes were measured using calipers. Lung and liver target lesions were measured by a CAT scan. Responses were confirmed by repeating the assessment 4 weeks after status assignment. Three independent reviewers performed all image measures (Telemedical Organization, North Miami Beach, Fl.).

The distribution of RECIST status (progressive disease, stable disease, or remission) in each group was recorded. This distribution was dependent on treatments that showed statistical significance according to the Chi-squared test. The data from the RECIST measurements of the change in tumor size of the patients in each treatment group, expressed as a percentage of pretreatment measurements, were compared using Student 's *t*-test. Additionally, increases in tumor size were expressed as a proportion of the initial value and analyzed by the two-proportion test comparing pairs of groups: group 3 vs group 1, and group 2 vs group 1. The sample size was assessed after analysis of the results when the trial was finished for the 30 patients allocated to the three groups. The above pairs of groups were analyzed for the proportion of progressive disease in each. Ten patients in each group was the required sample size for an 80% chance of rejecting the hypothesis of equal proportions at the 0.05 level of significance when the true proportions were those shown by the study. Statistical analysis was performed using StatsDirect software and an independent expert was consulted.

Results

The characteristics of the patients included are shown in Table 1. The three groups were comparable in the most relevant prognostic parameters for the clinical condition studied. Previous treatments were also comparable. The similar range of sizes of target lesions measured before treatment was especially significant, allowing the change in size to be measured as a percentage of initial size.

Table 1 Clinical characteristics of the 30 women with metastatic breast cancer (M1) included in the three treatment groups

	Group 1 (insulin + methotrexate)	**Group 2 (methotrexate)**	**Group 3 (insulin)**
No. of patients	10	10	10
Age range (years)	42–64	44–68	39–69
<50 years	4	3	4
Estrogen receptor-positive	7	7	6
Progesterone receptor-positive	7	5	7
Measurable M1			
Lung	6	4	4

Liver	1	2	2
Skin	2	2	3
Lymph nodes	1	2	1
Range of initial (pretreatment) RECIST sum of target measures (mm)	57–65	59–64	56–66

Figure 1 shows the RECIST status assessed under the study conditions. Progressive disease was the most frequent response in two of the three groups: in group 2 (treated with methotrexate alone) there were seven progressive disease and three stable disease, and in group 3 (treated with insulin alone) there were eight progressive disease and two stable disease. In group 1 (treated with insulin + methotrexate), stable disease was the most frequent response (nine stable disease, one progressive disease). The distribution of RECIST type responses (stable disease and progressive disease) was dependent on the treatments tested, and was statistically significant ($P<0.01$, Chi-squared test).

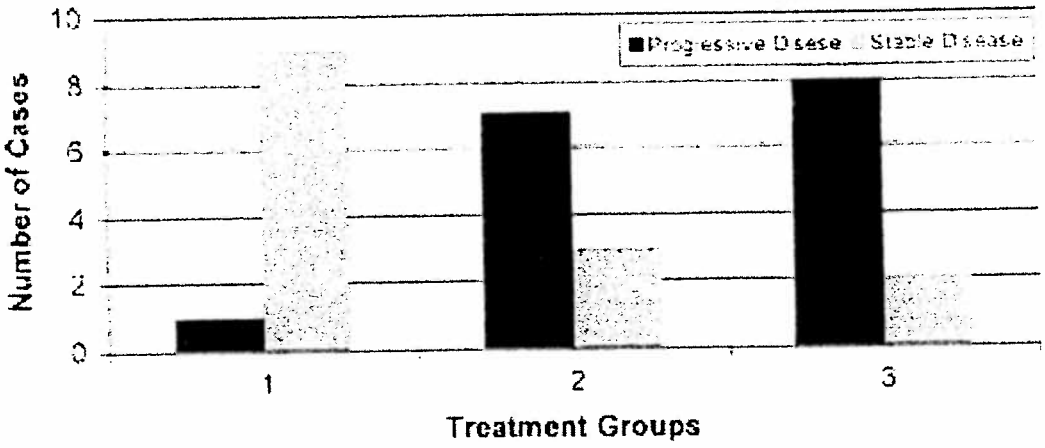

Fig. 1 Post-treatment RECIST status of measurable target lesions. After the respective treatment, the change in the measurable lesions selected as targets in each patient was evaluated and the status of therapeutic response, defined in terms of the RECIST criteria, was recorded. Under the conditions of this study, two response statuses were recorded: stable disease (less than 20% increase or less than 30% decrease in the sum of largest diameters of targets) and progressive disease (more than 20% increase in the sum of diameters). Stable disease, the best response obtained, was more frequent in the group treated with insulin + methotrexate (nine of ten) than in methotrexate-treated group (three of ten) or insulin-treated group (two of ten). The distribution of RECIST type responses (stable disease or progressive disease) was dependent on the treatments tested and statistically significant ($P<0.01$, Chi-squared test)

Figure 2 shows the means and 95% confidence intervals (CI) of the percentage increase in tumor size after treatment in the three groups. Increases in tumor size were significantly lower in patients treated with insulin + methotrexate than in those treated with insulin alone and significantly lower than in those treated with methotrexate alone.

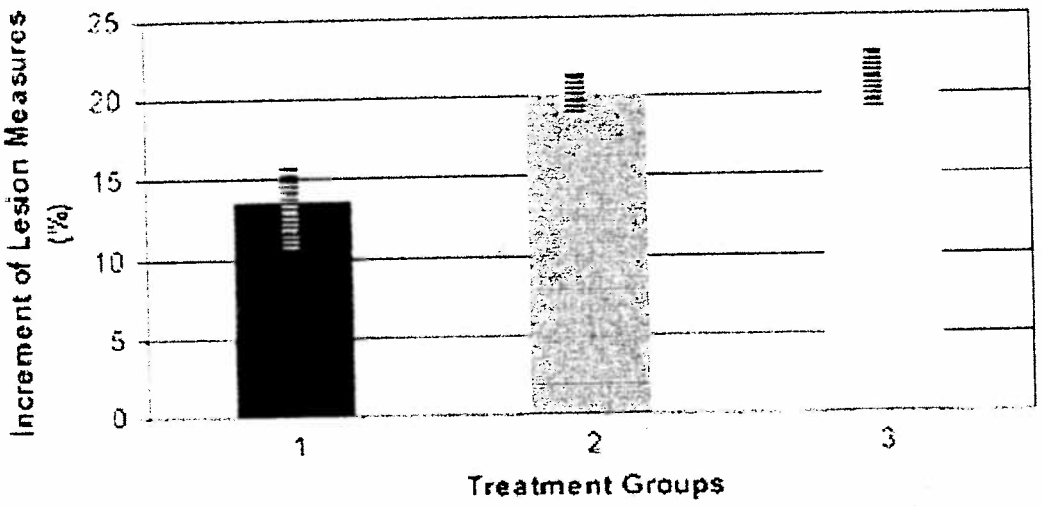

Fig. 2 Increase in size of measurable target lesions (RECIST assessment). After each treatment, the change in the measurable lesions selected as targets in each patient was evaluated in terms of the RECIST criteria and expressed as a percentage of the measured pretreatment size. For each treatment group, the mean±SD and 95% CI for the values of this response were calculated: group 1 (insulin + methotrexate) 13.51±3.01% (95% CI 11.35–15.67%); group 2 (methotrexate) 20.21±2.27% (95% CI 18.58–21.84%); group 3 (insulin) 21.04±2.17% (95% CI 19.49–22.59%). The increase in size of lesions in group 1 (insulin + methotrexate) was significantly lower (Student's *t*-test) than the increase in size in group 2 (methotrexate) ($P<0.001$) and group 3 (insulin) ($P<0.001$). Group 2 showed no significant difference from group 3 ($P=0.41$)

From the same set of measurements, Figs. 1 and 2 show the clinical and biological effects of the treatments, respectively. Figure 1 indicates that the decrease in tumor growth induced by insulin + methotrexate reached the level of a clinically confirmed antitumoral response because more patients in this group achieved stable disease. Figure 2 shows that insulin + methotrexate treatment reduced tumor growth. All patients completed the study. Hypoglycemia was induced in all patients receiving insulin as part of their protocol. Eight patients in group 1 and nine patients in group 3 showed no hypoglycemic symptoms during the 20 min after insulin

injection; they showed a mean blood glucose level of 456 mg/dl (range 376–520 mg/dl). Two patients in group 1 and one patient in group 3 showed hypoglycemic symptoms within 20 min of insulin injection (13, 16 and 19 min), but recovered immediately after starting the glucose infusion. There was no evidence of any harmful sequelae attributable to the hypoglycemia induced.

Table 2 shows the toxicities associated with antitumoral chemotherapy (according to WHO criteria) recorded in this study.

Table 2 Maximum recorded WHO toxicity grade in the patients included in the trial comparing insulin + methotrexate (group 1), methotrexate (group 2) and insulin (group 3). The numbers of patients with each toxicity grade (0 to 4) in the three groups are shown. No other toxicities referred to in the WHO criteria were recorded

Toxicity	Grade				
	0	1	2	3	4
Erythrocytes					
Group 1	10	0	0	0	0
Group 2	8	2	0	0	0
Group 3	10	0	0	0	0
Leukocytes					

Group 1	10	0	0	0	0
Group 2	6	3	1	0	0
Group 3	10	0	0	0	0
Platelets					
Group 1	10	0	0	0	0
Group 2	9	1	0	0	0
Group 3	10	0	0	0	0
Mucositis					
Group 1	8	2	0	0	0
Group 2	4	3	3	0	0
Group 3	10	0	0	0	0

Discussion

The methotrexate dose used in this study was chosen because a similar dose of methotrexate had been used previously in patients receiving low-

dose combined chemotherapy potentiated with insulin [2]. In addition, the cumulative monthly dose was no higher than the monthly dose used in the well-known standard protocol of methotrexate + fluorouracil + cyclophosphamide (CMF). Indeed, each individual methotrexate injection (2.5 mg/m^2) was less than the dose usually considered optimal in non-potentiated protocols but is within the presumed range of effective dose for a potentiation similar to the one observed in vitro. The results of this study confirmed the expected safety of the selected methotrexate dose. The toxicities in the methotrexate-alone group were not relevant (WHO grades 1/2) and they were even lower when methotrexate was associated with insulin, only producing a grade 1 mucositis. In this study, methotrexate at this safe low dose did not have an antitumoral effect when used alone (group 2), but it did produce a significant antitumoral effect when administered after insulin (group 1). The term antitumoral is used here as a description of the clinical effect of a reduction in the proportion of patients showing progressive disease.

Therefore, as reported previously, our results support the hypothesis that insulin can potentiate the antitumoral effect of methotrexate [2] and confirm in vivo previously reported in vitro results [*10*]. Our results also show insulin potentiation of methotrexate in this condition, where insulin alone did not promote an increase in tumor growth (group 3). This effect is in agreement with previous results from in vitro models where insulin enhancement of cytotoxicity was not a direct consequence of an insulin-dependent increase in the growth rate of tumor cells [*1*, *10*]. The same in vitro models do not allow an explanation of the insulin potentiation of methotrexate in terms of the known effects of insulin treatment upon the specific metabolism of methotrexate which include a decrease in intracellular pH induced by glucose metabolism and tight binding of the drug to its target, dihydrofolate reductase. Insulin potentiation of other antitumoral drugs has been reported [9].

If we discount the promotion of tumor cell growth and the interaction with the specific target as the mechanism of potentiation of methotrexate by insulin, we can hypothesize that this mechanism could involve another general insulin-dependent biochemical pathway as has been previously suggested to explain the in vitro potentiation of methotrexate by insulin [1]: protein synthesis in tumor cells is one of the biochemical pathways activated by insulin [8]. Most chemotherapy drugs that have been tested using insulin to increase cytotoxicity are known modifiers of protein structure that act at the genetic or epigenetic level [12]. High levels of mutated or epigenetically modified proteins could be responsible for the cytotoxic mechanism elicited by the insulin-dependent increase in protein synthesis associated with chemotherapy drugs. The relative selectivity of this mechanism of action for insulin + methotrexate in malignant cells is attributed to the agonism of insulin and insulin-like receptors in tumor cells. Certainly, the response to insulin is more intense in most tested cancer cells than in most normal cells. This is probably because cancer cells are richer in receptors for insulin-like growth factors that are cross-stimulated by insulin [4].

Conclusion

The in vitro potentiation of methotrexate cytotoxicity by insulin in human breast cancer cell lines was previously known. We report the results of a randomized, controlled trial that confirmed, at the clinical level, the potentiation by insulin of the antitumoral effect of methotrexate in women with advanced breast cancer. The term antitumoral is used as a description of the clinical effect of a reduction in the proportion of patients with progressive disease. Under the conditions of this study, the dose of insulin used did not increase tumor growth. Therefore, we

suggest that, as has been reported in vitro, methotrexate potentiation by insulin was not a direct consequence of the expansion of the tumor cycling cell population but a consequence of some of the biochemical events that are simultaneously activated. The enhancement of methotrexate uptake by tumor cells and/or the promotion of protein synthesis in a mutagenic intracellular environment are hypothesized to be mechanisms of potentiation. It is known that both events are promoted by insulin acting as a cross-agonist of the highly expressed receptors for insulin-like growth factors in breast cancer cells.

These mechanisms, which are shared with other primary tumor cells and with other chemotherapeutic agents suggest that it would be worthwhile to pursue further study of these phenomena in other tumors and with other chemotherapeutic agents.

References

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Chapter ER–MRS 24

CODE OF ETHICS

Note: Chapter Pers 24 was renumbered to chapter ER–Pers 24, effective March 1, 1983.Chapter ER–Pers 24 was renumbered chapter ER–MRS 24 under s. 13.93 (2m) (b) 1., Stats., Register, October, 1994, No. 466.

ER–MRS 24.01 Statutory authority and purpose. This code of ethics is promulgated under the directive of s. 19.45 (11) (a), Stats., for the guidance of employees to avoid activities which cause, or tend to cause, conflicts between their personal interests and their public responsibilities.

History: Cr. Register, March, 1974, No. 219, eff. 4–1–74; am. (intro.), renum. (1) to (3) to be ER–Pers 24.02, r. (4), Register, February, 1981, No. 302, eff. 3–1–81.

ER–MRS 24.02 Declaration of policy. (1) The observance of high moral and ethical standards by its employees is essential to the conduct of free government. The employee holds his or her position as a public trust, and any effort to realize personal gain through official conduct is a violation of that trust.

(2) It is the state's policy to recognize that:

(a) Employees have the same personal and economic interest in the decisions and policies of government as do other citizens.

(b) Employees retain their rights as citizens to interests of a personal or economic nature.

(c) Standards of ethical conduct for employees need to distinguish between those minor and inconsequential conflicts which are unavoidable in a free society, and those conflicts which are substantial and material.

(d) Employees may need to engage in employment, other than official duties, or may need to maintain investments, but no employee shall engage in any employment or maintain any investment if the employment or investment conflicts with the specific provisions of this chapter.

(3) The ethical standards set forth in this chapter for employees in the performance of their official duties are intended to avoid conflicts of interest between their personal interests and their public responsibilities, improve standards of public service, and promote and strengthen the faith and confidence of the people of this state in their state civil service.

(4) In the enforcement of this chapter the administrator shall protect to the fullest extent possible the state's best interests and the rights of individuals affected.

(5) Nothing in this chapter shall interfere with the general rulemaking powers of agencies with respect to the implementation of their programs and operations unless the interpretation of any agency rule is in contradiction of this chapter, and in that case this chapter shall control.

History: Cr. Register, March, 1974, No. 219, eff. 7–1–74; (1) renum. from Pers 24.01 (1) (intro.) and am., (2) renum. from Pers 24.01 (2) and am., (3) renum. from Pers 24.01 (1) (a) and am., cr. (4), (5) renum. from Pers 24.01 (3) and am., r. (6), Register, February, 1981, No. 302, eff. 3–1–81.

ER–MRS 24.03 Definitions. The following are definitions for terms used in this chapter:

(1) "Anything of value" means any money or property, favor, service, payment, advance, forbearance, loan, or promise of future employment, but does not include compensation and expenses paid by the state, fees, honorariums and expenses which are permitted under this chapter, political contributions which are reported under ch. 11, Stats., or hospitality extended for a purpose unrelated to state business by a person other than an organization.

(2) "Hospitality" includes, but is not limited to, meals, beverages, and lodging which a host other than an organization offers a guest on premises owned or occupied by the host or his or her immediate family as the host's principal or seasonal residence.

(3) "Associated" when used with reference to an organization, includes any organization in which an employee or a member of the employee's immediate family is a director, officer or trustee or owns or controls, directly or indirectly, and severally or in the aggregate, at least 10% of the outstanding equity.

(4) "Employee" in this chapter means any person who receives remuneration for services rendered to the state under an employer–employe relationship in the classified service or in the unclassified service of the state of Wisconsin except state public officials and employees subject to subch. III of ch. 19, Stats., officials and employees of the judicial branch, and university of Wisconsin system unclassified personnel.

(5) "Immediate family" means:

(a) An employee's spouse; and

(b) An employee's relatives by marriage, consanguinity or adoption, and any other person who directly or indirectly receives more than one–half of their support from the employee, or from whom the employee directly or indirectly receives more than one–half of his or her support.

(6) "Organization" means any corporation, partnership, proprietorship, firm, enterprise, franchise, association, self–employed individual, trust or any other legal entity other than an individual or body politic which engages either in nonprofit or profit–making activities.

(7) "State property" includes, but is not limited to, facilities, vehicles, supplies, equipment, stenographic assistance and reproduction services.

History: Renum. from Pers 1.02 (8), Register, September, 1975, No. 237, eff. 10–1–75; (4), (5), (1), (6) and (3) renum. from Pers 24.02 (1) to (5) and am., cr. (2), (7) renum. from Pers 24.02 (7) and am., Register, February, 1981, No. 302, eff. 3–1–81; cr. (intro.), Register, May, 1988, No. 389, eff. 6–1–88.

ER–MRS 24.035 Hospitality; relation to state business. Hospitality may be accepted by an employee when it could be concluded that the hospitality would be extended if the guest or a member of the guest's immediate family was not a state employee.

History: Cr. Register, February, 1981, No. 302, eff. 3–1–81; am. Register, May, 1988, No. 389, eff. 6–1–88.

ER–MRS 24.04 Standards of conduct. This chapter shall not prevent an employee from accepting outside employment or following a pursuit which in no way interferes or conflicts with the full and faithful discharge of his or her duties to this state, subject to the following:

(1) A conflict of interest on the part of a state employee exists whenever:

(a) The employee's action or failure to act propitiously could reasonably be expected to directly or indirectly produce or assist in producing a private benefit for the employee or the employee's

immediate family or an organization with which the employee is associated; or

(b) The matter is one in which the employee in his or her private capacity or a member of the employee's immediate family or an organization with which the employee is associated, as defined in s. ER–MRS 24.03 (3), has a substantial interest.

(2) The state must, by necessity, specifically prohibit those activities that will cause a conflict of interest to the employee or to the state of Wisconsin. Therefore:

(a) No employee may use or attempt to use his or her public position or state property, including property leased by this state, or use the prestige or influence of a state position to influence or gain financial or other benefits, advantages or privileges for the private benefit of the employee, the employee's immediate family or an organization with which the employee is associated.

1. Any salary or other compensation received by the employee from this state for his or her services does not constitute "financial gain" as the term is used in this rule.

2. Use of state telephones for essential personal local calls does not constitute "benefit" as the term is used in this rule.

(b) No employee may solicit or accept from any person or organization, directly or indirectly, money or anything of value if it could reasonably be expected to influence such employee's official actions or judgment, or could reasonably be considered as a reward for any official action or inaction on the part of such employee.

1. No employee who is assigned or acts as an official representative of the state in the presentation of papers, talks, demonstrations or making appearances shall solicit or accept fees, honoraria or reimbursement of expenses for personal gain. Any fees, honoraria, or reimbursement of expenses which may be offered in connection therewith shall be paid to the employee's employing agency.

2. Acceptance of fees and honoraria paid for papers, talks, demonstrations or appearances made by an employee on the employee's own time and not directly part of the employee's official duties, shall not be a violation of this rule. Employees shall notify their appointing authority prior to accepting fees and honoraria for papers, talks, demonstrations, or appearances to insure no conflict of interest exists.

3. When an employee is offered an unsolicited award or reward for an exceptional accomplishment or outstanding performance other than that specified in par. (a) 1., the administrator shall determine whether or not it may be accepted by the employee after considering whether acceptance of the award or reward would conflict with the purposes of this chapter. Employees shall notify their appointing authority prior to accepting unsolicited awards or rewards, who in turn shall request that the administrator make a determination regarding acceptance or refusal of the award or reward.

(c) No employee may intentionally use or disclose information gained in the course of or by reason of the employee's official position or activities in any way that could result in the receipt of anything of value for himself or herself, for his or her immediate family, or for any other person or organization, if the information has not been communicated to the public or is not public information. However, no reprisal may be taken against an employee for the lawful disclosure of information which the employee reasonably believes evidences:

1. A violation of any law, rule, or regulation, or

2. Mismanagement, a gross waste of funds, an abuse of authority, enforcement of unreasonable agency work rules, or a substantial and specific danger to public health or safety.

(d) No employee, member of an employee's immediate family, nor any organization with which the employee or a member of the employee's immediate family owns or controls at least 10% of the outstanding equity, voting rights, or outstanding indebtedness may enter into any contract or lease involving payment or payments of more than $3,000 within a 12–month period, in whole or in part derived from state funds unless the employee has first made written disclosure of the nature and extent of such relationship or interest to the appointing authority of the agency with which the employee is associated and obtained the appointing authority's written approval. The appointing authority shall approve an employee's interest in a lease or contract unless he or she determines that the employee's personal interest in the agreement will conflict substantially and materially with the employee's discharge of his or her public responsibilities. This paragraph does not effect the application of s. 946.13, Stats.

(e) An employee may recommend or decide to hire or promote another person for a permanent, seasonal or sessional position when the person affected is a member of the employee's immediate family, if that person has been certified from an open or competitive promotional register. No employee may recommend or make a limited term or project appointment when the person to be hired is a member of the employee's immediate family.

(f) No employee shall give preferential or favored treatment in the supervision or management of another employee who is a member of his or her immediate family.

(3) The administrator may waive this section whenever its literal application would be adverse to the state's best interest or would work an unreasonable hardship on the employee. If this section is waived, the administrator shall do so by setting forth in writing as a matter of public record an explanation of his or her finding that the waiver is in the state's interest.

(4) Nothing in this section prohibits an employee from making decisions concerning salaries, salary–related benefits or reimbursement of actual and necessary expenses when the action does not result in preferential or favored treatment of a member of the employee's immediate family.

History: Cr. Register, March, 1974, No. 219, eff. 4–1–74; renum. from 24.03, Register, December, 1976, No. 252, eff. 1–1–77; (intro.) renum. from Pers 24.03 (1) and am., r. and recr. (1), renum. (2) and (3) to be (2) (b) 1. and 2. and am., (2) (c) renum. from Pers 24.05 and am., cr. (2) (d) to (f), (3) and (4), Register, February, 1981, No. 302, eff. 3–1–81; reprinted to correct error in (2) (d), Register, April, 1982, No. 316; am. (intro.), (2) (b) 2. and (e), cr. (2) (b) 3., Register, May, 1988, No. 389, eff. 6–1–88; correction in (1) (b) made under s. 13.93 (2m) (b) 7., Stats., Register, October, 1994, No. 466.

ER–MRS 24.045 Guidelines for outside employment. Agencies shall establish guidelines regarding outside employment of employees which shall include identifying those activities which are likely to cause a conflict of interest and requiring employees to obtain prior approval before accepting outside employment. Agencies shall submit their proposed guidelines to the administrator for review and approval before implementation.

History: Cr. Register, February, 1983, No. 326, eff 3–1–83.

ER–MRS 24.05 Action to avoid possible conflict. **(1)** Any state employee who, in the discharge of his or her official duties, is involved or about to be involved in any matter that could result in a conflict of interest on his or her part, shall so notify his or her appointing authority by submitting a written statement describing the matter requiring action or decision, and the nature of the possible conflict of interest with respect to such action or decision.

(2) In those situations where a possible conflict of interest may occur, the appointing authority shall take action which may include:

(a) Relieving the employee of the assignment and assigning the matter to another qualified employee who does not have a conflict of interest.

(b) Preparing a memorandum of the particulars of the action taken under par. (a) and forwarding such memorandum, together with a copy of the employee's statement received under sub. (1) to the administrator. In all cases, the appointing authority shall furnish to the employee a copy of such memorandum.

(3) An appointing authority, an employee, or any individual may request an advisory opinion from the administrator on the application of this chapter to a given set of circumstances to which the person or agency may become a party. The administrator may keep confidential the identity of the person requesting an advisory opinion or of persons mentioned in an opinion.

(4) The administrator may consult with the ethics board on any matters relating to this chapter.

History: Cr. Register, March, 1974, No. 219, eff. 4–1–74; renum. from 24.07, Register, December, 1976, No. 252, eff. 1–1–77; (1) to (3) renum. from MRS 24.08, and am., cr. (4), (1), (3) and (4), Register, February, 1981, No. 302, eff. 3–1–81.

ER–MRS 24.06 Violations. Notice of alleged violations of this chapter shall be directed to the administrator, who may then refer the allegations to the appropriate authority.

History: Cr. Register, February, 1981, No. 302, eff. 3–1–81.

ER–MRS 24.07 Criminal penalties. For penalties for violations of this chapter, see s. 19.58, Stats.

History: Cr. Register, February, 1981, No. 302, eff. 3–1–81.