

UNITED STATES DISTRICT COURT

EASTERN DISTRICT OF LOUISIANA

JOYCE BARROIS, ET AL) CIVIL ACTION NO:
 PLAINTIFFS,) 09-380
)
VS.) SECTION: R
)
FIREMAN'S FUND INS. CO.,) JUDGE: VANCE
ET AL)
 DEFENDANTS.) MAGISTRATE: KNOWLES

 ORAL AND VIDEOTAPED DEPOSITION
 OF
 ETHAN A. NATELSON, M.D.
 FEBRUARY 10, 2010
 Volume 1 of 1 Volume

ORAL AND VIDEOTAPED DEPOSITION OF ETHAN A. NATELSON,
M.D., produced as a witness at the instance of the
Plaintiff, and duly sworn, was taken in the above-styled
and numbered cause on the 10th of February, 2010, from
1:38 p.m. to 3:09 p.m., before Minnie Cadena, CSR, RPR,
RMR, in and for the State of Texas, reported by
stenographic method, at the Marriott Hotel, 6580 Fannin
Street, Houston, Texas, pursuant to the Federal Rules of
Civil Procedure and the provisions stated on the record
or attached hereto.

1 A P P E A R A N C E S:

2
3 FOR PLAINTIFF:

4 Mr. Eric Williams
5 Williams Law Office, LLC
6 3000 W. Esplanade Avenue, Suite 200
7 Metairie, Louisiana 70002
8 (504) 832-9898
9 Eric@amlbenzene.net

10 FOR DEFENDANT BAXTER HEALTHCARE CORPORATION:

11 Mr. Ethan E. Trull
12 Ungaretti & Harris
13 3500 Three First National Plaza
14 Chicago, Illinois 60602-4224
15 (312) 977-4400
16 Etrull@uhlaw.com

17 FOR DEFENDANT FIREMEN'S FUND INSURANCE CO:

18 Mr. Robert Scott
19 Abrams Scott & Bickley, LLP
20 700 Louisiana, Suite 4000
21 Houston, Texas 77002-2727
22 (713) 228-6607
23 Rscott@asbtexas.com

24 FOR DEFENDANT FISHER SCIENTIFIC:

25 Mr. Ross Asher
Roberts Markel
2800 Post Oak Blvd., 57th Floor
Houston, Texas 77056
(713) 840-1666
Rasher@robertsmarkel.com

ALSO PRESENT:

Jim Leonard, Videographer

INDEX

	Page
Appearances	2
Stipulations	4
Testimony of ETHAN A. NATELSON, M.D.	
By Mr. Williams	4
By Mr. Scott	36
By Mr. Asher	61
FURTHER EXAMINATION	
By Mr. Williams	65
By Mr. Scott	68
By Mr. Asher	71
By Mr. Scott	71
Witness' Signature Page	73
Reporter's Certificate Pages	74

EXHIBITS

	Page
No. A Subpoena to Testify.....	4
No. B Testimony Given by Dr. Ethan A. Natelson.....	4
No. C-1 Original Petition.....	4
No. C-2 Preliminary Trial Witness List.....	4
No. C-3 June 22, 2007, Letter to Kevin Parks from Dr. Natelson.....	4
No. D Copy of Depo of Dr. Natelson, 9/17/07.....	4
No. E Subpoena to Produce Documents.....	4
No. F E-mail from Kindy to Williams.....	25
No. G Copy of BLOOD Cover.....	42
No. H Hematopoietic Malignancies and Related Disorders.....	47
No. I Chemico-Biological Interactions.....	51
No. J Myelodysplastic/ myeloproliferative neoplasm, unclassifiable.....	56
No. K Invoice.....	67

(Exhibit A-E were marked.)

THE COURT REPORTER: Will the witness read
and sign his deposition?

THE WITNESS: Read and sign.

THE VIDEOGRAPHER: We're on the record. 01:38
The time now is 1:38, Wednesday, February 10, 2010.

ETHAN A. NATELSON, M.D.,
having been first duly sworn, testified as follows:

EXAMINATION

BY MR. WILLIAMS: 01:39

Q. Good evening, Dr. Natelson. Would you please
state your full name and address for the record?

A. Yes, Ethan A. Natelson, N-A-T-E-L-S-O-N; and my
address is 6550 Fannin Street, Suite 1001, Houston, Texas
77030. 01:39

Q. And, Doctor, I'm going to show you a subpoena;
and I want you to tell me whether or not you received a
subpoena to appear here today.

A. Yes, I did.

Q. Okay. And earlier we had an opportunity to go 01:39
over some of the documents, and I'll get to that in a
minute.

Can you briefly tell us your educational
background?

A. Yes, I went to college at Haverford College 01:39

1 which is outside Philadelphia and had a bachelor of
2 science degree; and then in 1962, came to Baylor College
3 of Medicine in Houston where I graduated in 1966 from
4 medical school, getting an M.D. degree. And then I did
5 an internship at the Methodist Hospital from '66 to '67 01:40
6 and then a residency in internal medicine in what were
7 then called Baylor affiliated hospitals, which are the
8 Ben Taub Hospital, the Veterans Hospital and the
9 Methodist Hospital, to a slight extent, St. Luke's
10 Hospital. 01:40

11 Following that, I did a fellowship in
12 hematology at Baylor College of Medicine for one year;
13 and then I was in the service and assigned under what's
14 called the Barry plan to the Wilford Hall Hospital in
15 San Antonio, which is the referral hospital for 01:40
16 hematology for the Air Force or was at that time. And
17 so, I did purely hematology for two years in the service
18 and then came back to join the faculty at Baylor College
19 of Medicine.

20 Q. And you are a hematologist? 01:41

21 A. Yes.

22 Q. Doctor, do you do expert witness work?

23 A. Yes.

24 Q. Earlier you provided me with a list --

25 MR. WILLIAMS: And we're going to have to 01:41

1 mark this as B.

2 Q. (By Mr. Williams) And if you could, tell us
3 how many cases you've identified that you've served as an
4 expert witness.

5 A. This is a record of the cases I've given 01:41
6 testimony in since 1992 to the present, and there are a
7 total of 74 cases.

8 Q. And can you tell me how many of those cases
9 involved myelodysplastic syndrome?

10 A. Yes, ten of those cases did. 01:41

11 Q. And can you tell me how many involved
12 refractory anemia with ringed sideroblast?

13 A. Five of the 10 cases that have to do with MDS.

14 Q. And can you go through the list and identify
15 the name of the case and tell us who you worked for and 01:42
16 tell us what the disease -- as far as the ten we just
17 discussed?

18 A. Yes.

19 MR. SCOTT: Have you marked this as an
20 exhibit? 01:42

21 MR. WILLIAMS: B.

22 A. The first one is No. 22 on this list, which is
23 Donald Ward v. Atlantic Richfield Company; and that was
24 an RARS case.

25 Q. (By Mr. Williams) What date was that? 01:42

1 A. That would be January 18, 2002.

2 Q. Could you tell us the next case?

3 A. The next case is No. 24, which is Howard
4 Collins v. American Petrofina; and that case was in May
5 of 2002.

01:42

6 Q. Okay. Could you tell us the next case?

7 A. The next case was No. 35, which is Federico
8 Tagle v. Citgo Refining & Marketing; and that was in
9 October of 2004.

10 Q. And, Doctor, did you work on 30 and 31? Were 01:43
11 they myelodysplastic syndrome cases, too?

12 A. Yes, I thought you were asking me about RARS in
13 particular.

14 Q. I'm asking you about all of them.

15 A. I'm sorry. Yeah, I was looking at them as just 01:43
16 RARS cases. I have them marked here in yellow if they
17 are MDS.

18 So, I mentioned the Ward case; the Collins
19 case. No. 30 is the James Cowey v. Radiator Speciality
20 Company. That was in 2003.

01:43

21 No. 31 was the Ronald Awalt, A-W-A-L-T, v.
22 Applied Energy Services & Company Incorporated; and that
23 was in December of 2003.

24 Then the Tagle case, which I mentioned; and
25 that's in October of 2004.

01:43

1 And then Guy Hamman v. American Oil
2 Company, and that was in July of 2007. That's No. 52 on
3 my list.

4 And then No. 54, Charles Wilson v.
5 Rycoline Products Incorporated. That was in 2007, 01:44
6 9-17-2007.

7 And then No. 62, Connie Lea Gibson Andrews
8 v. United States Steel Company; and that was in August of
9 2008.

10 Then the Bonnie L. Mallory case. That's 01:44
11 No. 68. Bonnie L. Mallory v. The Goodyear Tire & Rubber
12 Company. That was in June of 2009.

13 And then Mary Ellen Hall v. Radiator
14 Specialty Company, which was in January of 2010.

15 Q. And, Doctor, in all ten of those cases, did you 01:45
16 work for the defendants?

17 A. Yes.

18 Q. And in all ten of those cases, did you find
19 that the benzene exposure caused the person's
20 myelodysplastic syndrome? 01:45

21 MR. SCOTT: Object to the form of the
22 question.

23 Q. (By Mr. Williams) Did you find that the benzene
24 exposure caused anyone's myelodysplastic syndrome in
25 those ten cases? 01:45

1 A. I don't know that they all had to do with
2 benzene. There may be optional chemicals. Some may have
3 been butadiene. I don't know if they were specifically
4 noted as benzene, but I didn't find that the alleged
5 chemical exposure caused the disease. 01:45

6 Q. Okay. In the case identified as No. 22, Donald
7 Ward v. Atlantic Richfield and Howard Collins v.
8 American Petrofina, in either of those RARS, we can call
9 them, cases, did you find -- did you opine that benzene
10 does not cause RARS in either of those two cases? 01:46

11 A. I don't recall in detail, but I'm sure that
12 that was correct. I don't believe benzene causes RARS;
13 so, that's what I would have said.

14 Q. And when did you formulate that opinion?

15 A. I can't tell you exactly. Probably many years 01:46
16 ago because the original work by Dr. Wintrobe on that,
17 which I've referenced in that article you have,
18 Dr. Wintrobe considered benzene as a cause of RARS and
19 rejected it. So, I think the literature for many years
20 has not suggested RARS can be caused by benzene. 01:46

21 Q. Doctor, would you say that the majority of your
22 cases in the 74 that you have provided were blood
23 malignancy cases?

24 A. I would think the majority are. Some are
25 malpractice cases. Some have to do with residency 01:47

1 training programs and other things, but the majority
2 probably are to do with blood diseases.

3 Q. Were you paid as an expert witness in all of
4 these cases?

5 A. Not all of them because some of them, for 01:47
6 example, residency training programs, I wouldn't have
7 been paid; but if they had to do with either testifying
8 in malpractice or testifying in, let's say, a
9 benzene-related issue, yes.

10 Q. And how much do you charge an hour, Doctor? 01:47

11 A. To review records, \$250 an hour; and to testify
12 at trial or deposition, \$400 an hour.

13 Q. Have you ever opined that a plaintiff's blood
14 malignancy or blood cancer was caused by benzene?

15 A. No. 01:48

16 Q. Have you ever opined or testified that benzene
17 can cause myelodysplastic syndrome?

18 A. Yes.

19 Q. Is myelodysplastic syndrome the same thing as
20 myelodysplasia? 01:48

21 A. Yes.

22 Q. Would you say myelodysplasia, myelodysplastic
23 syndrome, myelodysplastic disorder are all the same
24 thing?

25 A. Well, they are a classification of a group of 01:48

1 illnesses.

2 Q. Okay. What level and part per million years is
3 required for benzene to cause myelodysplastic syndrome?

4 MR. SCOTT: Objection, form.

5 A. I don't know that it's known with absolute 01:48
6 certainty. It's very, very high levels. I think in one
7 article I wrote I said, I'd like to see at least higher
8 than 40-part per million years as accumulated dose
9 recognizing that in many instances the levels are not
10 accurately measured. In many other areas of literature, 01:49
11 the 200-part-per-million year accumulated dose is used;
12 but I simply say it's very, very high doses.

13 Q. You think 370-part-per-million year dose is a
14 high dose?

15 A. Yes. 01:49

16 Q. Doctor, I'm going to direct you to an article
17 which is in Exhibit A, if you would flip the pages,
18 please, entitled Benzene Exposure.

19 A. Yes, you have a copy of that.

20 Q. And it's attached to your subpoena. Benzene 01:49
21 Exposure and Refractory Sideroblastic Erythropoiesis.

22 Did you write this article?

23 A. Yes.

24 Q. And can you tell us what journal this is
25 published in? 01:49

1 A. This is in the AMERICAN JOURNAL OF THE MEDICAL
2 SCIENCES.

3 Q. And is there a citation for this article?

4 A. Yes, it was published. It's Volume 334, Year
5 2007, Page 356 to Page 360. 01:50

6 Q. And, Doctor, when did you start working on this
7 article?

8 A. Probably -- let's see. I submitted this,
9 according to the paper, in January of '07. Probably
10 several months prior to that submission date. 01:50

11 Q. Several months prior to January of '07?

12 A. Yes. In other words, it's marked -- on the
13 paper it says, submitted January 16, 2007. And so,
14 therefore, I would likely have worked on it for, perhaps,
15 three, four months or so, at least, before submitting it. 01:50

16 Q. Okay. What process did you go through in
17 submitting this article to the journal?

18 A. Well, I've been interested in sideroblastic
19 anemia for many years, actually, since my training
20 because two of my professors were heavily involved in 01:51
21 studying sideroblastic anemia; and I frequently did bone
22 marrows on those patients and saw them clinically. So,
23 I've been interested in the disease for many years.

24 As I -- as I began to give testimony in
25 benzene-related cases and actually was asked to review 01:51

1 certain allegations of causation, I realized that this
2 would be an interesting article to write because, No. 1,
3 I had a lot of background with this illness. I enjoy
4 this illness. I've always wanted to write a paper on the
5 illness, and I have access to a lot of references that 01:51
6 would bear on this question. And so, I thought it would
7 be a good paper to write.

8 Q. Were there any rules for submitting this
9 article to the journal?

10 A. I don't know of exactly what you mean by that. 01:52
11 Most journals -- and today, things have changed.
12 Everything is submitted electronically. But at this
13 point in time, you would type up a manuscript. You would
14 put a cover letter to the editor; and you would say, Dear
15 Editor, this is a manuscript. I'd like to seek 01:52
16 publication in your journal. Here it is, and you would
17 mail it in.

18 And then after some period of time, you
19 would hear something back from the Journal about whether
20 they were interested in publishing it, whether they had 01:52
21 corrections they would like you to make, whether they
22 rejected it and so on.

23 Q. Does this journal, the AMERICAN JOURNAL OF
24 MEDICAL SCIENCES, require disclosing potential conflict
25 of interest at the time you submit the article? 01:52

1 A. Yes, I think all journals would say that,
2 disclose a conflict of interest to that form.

3 Q. At the time you submitted this article, Doctor,
4 were you serving as an expert witness in any benzene
5 cases?

01:53

6 A. I don't know, probably so.

7 Q. At the time you submitted this article, were
8 you serving as an expert witness on any Benzene cases
9 that involved myelodysplastic syndrome?

10 A. I don't know; but possibly so, depending on
11 what those lists of cases are that we went through.

01:53

12 Q. And at the time that you submitted this article
13 in the journal, were you involved in any cases where your
14 opinion was that RARS was not caused by Benzene in the
15 case?

01:53

16 A. Well, I -- as we went through those cases, some
17 of those cases, I think, dated back to 2002 or earlier,
18 long before I wrote this article; and that was my opinion
19 that RARS was not a benzene-related illness.

20 Q. Doctor, I want to show you a petition -- we
21 have this marked as C-1 to a case, and I believe -- could
22 you read the caption to that case?

01:53

23 A. It says: Now comes Charles Wilson and Laura
24 Wilson, hereinafter referred to as Plaintiffs,
25 complaining of Rycoline Products, Inc., Rogersol, Inc.

01:54

1 Q. I'm sorry, Doctor, the top, the caption,
2 Charles Wilson v. Rycoline Products. I apologize.

3 A. Charles Wilson and Laura Wilson, Plaintiffs v.
4 Rycoline Products, Inc., Rogersol, Inc.,
5 Hostman-Steinberg, Inc., IC Compound Company, Ashland, 01:54
6 Inc., Company Individually, Ashland Oil & Refining
7 Company and Ashland Oil, Inc., Allied Photo Offset Supply
8 Corporation, Day International, Inc., Individually and
9 d/b/a Varn Products, Allied Photo Offsets Supply
10 Corporation; and Lastra American Corporation. 01:54

11 Q. Okay. And, Doctor, can you tell me the date on
12 the top of that petition that it was filed?

13 A. Filed 7-13-2006.

14 MR. WILLIAMS: Okay. We're going to mark
15 that as C-1, Ms. Reporter. 01:54

16 Q. (By Mr. Williams) And that's the case you have
17 listed as No. 54 on your expert summary?

18 A. Yes.

19 Q. Doctor, I'm going to next show you a witness
20 list to the case of Charles Wilson v. Rycoline Products, 01:55
21 and can you tell me if your name is listed as a witness
22 on that case?

23 A. Yes, it is.

24 Q. Okay. And could you tell me what date is on
25 the top of that witness list that it was filed? 01:55

1 A. It says filed 7-17-2007.

2 Q. Okay. Do you recall being a witness in this
3 case?

4 A. Vaguely.

5 Q. Okay. And that's marked as C-2. 01:55

6 Next, I'm going to show you a report from
7 that case, Doctor. Can you tell me if you recognize that
8 report?

9 A. Yes, this is a report on my letterhead.

10 Q. Can you tell me the date of that report, 01:55
11 Doctor?

12 A. June 22, 2007.

13 Q. Okay. And, Doctor, on the first page, it is
14 your opinion, the highlighted portion, that there are
15 several names for what we talked about earlier, ringed 01:56
16 sideroblast or RARS? Can you tell me what your opinion
17 is?

18 A. Yes, as I have written here: It is alleged
19 that his hemologic illness of refractory anemia with
20 ringed sideroblast, also known as acquired idiopathic 01:56
21 sideroblastic anemia, sideroachrestic anemia and by the
22 initials RARS and AISA has occurred subsequent to his
23 exposure in the workplace to benzene-containing solvents.

24 Q. And, Doctor, I want to return to Page 4 of the
25 report, you have a highlighted bolded portion. Can you 01:56

1 read that out loud, please?

2 A. Yes. In fact, I am not aware of a single
3 epidemiologic study or even an isolated case report in
4 the world's medical literature that shows RARS/AISA to be
5 a consequence of benzene exposure. 01:57

6 Q. And there was a reference number that you have
7 there?

8 A. Yes, No. 14.

9 Q. Can you tell us what No. 14 is?

10 A. That's the article that we've talked about 01:57
11 Benzene Exposure and Refractory Sideroblastic
12 Erythropoiesis: Is There an Association. And that was
13 the AMERICAN JOURNAL OF MEDICAL SCIENCE. At that time,
14 it was in press, in 2007.

15 Q. And "press" means that it's not published yet; 01:57
16 is that correct?

17 A. Well, it often is published on -- E-published.
18 In other words, you can see the article; but the journal
19 hasn't made the streets yet.

20 Q. Okay. Thank you. 01:57

21 Were you paid for preparing that report
22 there, Doctor?

23 A. I'm sure I was.

24 MR. SCOTT: Which exhibit is that?

25 MR. WILLIAMS: That's C-3. 01:58

1 Q. (By Mr. Williams) Were you paid to be an
2 expert in that case, Wilson v. Rycoline Products?

3 A. Yes.

4 Q. Do you remember how much money you were paid in
5 the Wilson case?

01:58

6 A. No.

7 Q. How long does it usually take you to review
8 records and write a report in a case like that?

9 A. It's variable from case to case because some
10 cases have a small amount of information, other cases 01:58
11 have a staggering amount of information. And once I have
12 all of the information together and then I sum up what
13 references I'd like to put into the letter and by the
14 time I go through revisions to the letter and
15 modifications of it, it might be from, starting a letter 01:58
16 to finishing a letter, easily seven or eight, ten hours.

17 Q. Okay. Doctor, I want to show you the next
18 exhibit, Exhibit D, a deposition from the Wilson v.
19 Rycoline Oil Products case; and if you turn the page to
20 the tabbed page. In the deposition are you offering 01:59
21 opinions that benzene does not cause RARS?

22 A. Yes, that's correct.

23 Q. Okay. And if you flip the page, in that
24 deposition, do you also testify that your journal article
25 will be published in November of 2007? 01:59

1 A. Yes.

2 Q. And what's the date of that deposition, Doctor?

3 A. 9-17-2007.

4 Q. Were you paid for that deposition in that case,
5 Doctor?

01:59

6 A. I'm sure I was, yes.

7 Q. Okay. Thank you, Doctor.

8 Doctor, I'm now going to show you a
9 subpoena that was issued to the -- David Ploth, the
10 editor of the AMERICAN JOURNAL OF MEDICAL SCIENCES, along 02:00
11 with a copy of your published paper.

12 Have you ever seen that subpoena before?

13 A. No.

14 Q. Do you know who David Ploth is?

15 A. Is his name written? 02:00

16 Q. Ploth, I think I'm mispronouncing, on the front
17 page. David Ploth, I apologize.

18 A. According to this thing, he is the current
19 editor of the AMERICAN JOURNAL OF MEDICAL SCIENCES.

20 Q. Doctor, I'm going to provide you with a copy of 02:01
21 the response that we received.

22 It's a copy of the response that we
23 received from the journal; and if you flip the page,
24 there is a document -- the second page right there. Is
25 that your handwriting, Doctor? 02:01

1 A. It is.

2 Q. And can you identify the title of this
3 document?

4 A. It says: Authorship responsibility, financial
5 disclosure and copyright transfer form. 02:01

6 Q. And, Doctor, you filled out this form and
7 submitted it to the AMERICAN JOURNAL OF THE MEDICAL
8 SCIENCES; is that correct?

9 A. Yes.

10 Q. Okay. Doctor, if you go down to Section 2 02:01
11 under financial disclosures, the highlighted section, and
12 read that into the record for us?

13 A. I certify that any affiliations with or
14 involvement, either competitive or amiable, in any
15 organization or entity with a direct financial interest 02:02
16 in the subject matter or materials discussed in the
17 manuscript, for example, employment, consultancies, stock
18 ownership, honoraria and expert testimony, are noted
19 below. Otherwise, my signature indicates that I have no
20 such financial interest. All financial research or 02:02
21 project support is identified in an acknowledgment in the
22 manuscript.

23 Q. Okay. And my question to you is, Doctor, I
24 don't see where you disclosed that you had any expert
25 testimony relating to the subject matter in that 02:02

1 document?

2 MR. SCOTT: Object to the form of the
3 question.

4 A. That would be true.

5 Q. (By Mr. Williams) Okay. And I don't believe 02:02
6 the article identifies that you were serving as an expert
7 witness in RARS cases; is that correct?

8 MR. SCOTT: Objection, form.

9 A. That's correct.

10 Q. (By Mr. Williams) And am I correct that you 02:02
11 were serving as an expert witness in benzene, RARS cases
12 prior to starting the article?

13 A. Yes.

14 Q. As we have just evidenced through the
15 depositions and the reports, while the article was under 02:03
16 publication; is that correct?

17 A. Possibly. Look at those dates. As I say, we
18 have the date I submitted it, yes.

19 Q. And you were serving as an expert witness in
20 benzene, RARS cases after the article was published; is 02:03
21 that correct?

22 A. Yes.

23 Q. If you flip the page please, Doctor --

24 A. (Witness complies.)

25 Q. -- and let me ask you one more question. What 02:03

1 did you understand "certifying" to mean, under oath, or
2 do you know what certifying means?

3 MR. SCOTT: Object to the form.

4 A. I'm not sure I know what it means. In other
5 words, this article was a review. It was not original 02:03
6 work. It's a review of literature and I'm just putting
7 it together and I don't see that that offers any conflict
8 of interest to anybody. And it's a common practice in
9 writing articles that one reviews other people's work and
10 puts it in there and that, to me, is not considered a 02:03
11 conflict of interest.

12 Q. (By Mr. Williams) And you don't agree that the
13 Journal required you to identify any potential conflict
14 of interest?

15 MR. SCOTT: Object to the form. 02:04

16 A. Well, I look at that as, was that article being
17 written about information in a particular case that I'm
18 testifying in? This is a general subject matter, and I
19 don't see that it has anything to do with a conflict of
20 interest. 02:04

21 Q. (By Mr. Williams) Doctor, do you know a
22 gentleman by the name of David Pyatt?

23 A. I've actually never met him but I've
24 corresponded with him and I've spoken with him on the
25 phone once or twice. 02:04

1 Q. Did you speak to him relating to this article
2 that you published?

3 A. I don't know that. I mean, at the time I wrote
4 it, I think that would be doubtful; but I couldn't say
5 "yes" or "no." 02:04

6 Q. Do you know if you've ever served as an expert
7 witness on a benzene myelodysplastic syndrome case with
8 David Pyatt who is a toxicologist?

9 A. Yes.

10 MR. SCOTT: Objection, form. 02:05

11 Q. (By Mr. Williams) Can you tell me which ones
12 you've served on? If you'd like to look at your list,
13 that would be fine.

14 A. I wouldn't be able to tell you that from this
15 list. 02:05

16 MR. SCOTT: Eric, I'm sorry. I've got some
17 objections to these questions.

18 And, Doctor, if you will let me --

19 THE WITNESS: I'm sorry.

20 MR. SCOTT: No, that's all right. If 02:05
21 you'll just pause for a second after his question is
22 done, I'll get my objection in and then I won't be
23 prancing all over your words; but I object to the form of
24 the last question.

25 Q. (By Mr. Williams) Doctor, have you ever told 02:05

1 the AMERICAN JOURNAL OF MEDICAL SCIENCES up until today
2 that you do work involving benzene RARS cases?

3 A. No.

4 MR. SCOTT: Object to the form.

5 Q. (By Mr. Williams) Can you tell me how many 02:05
6 benzene myelodysplastic syndrome cases you worked on with
7 Dr. Pyatt?

8 A. I couldn't.

9 Q. Can you tell me how many benzene cases you've
10 worked on with Dr. Pyatt? 02:06

11 A. I don't know.

12 Q. Can you tell me if it's more than ten?

13 A. I can't tell you that. I don't know. He's
14 been an expert witness on several cases; and, in fact,
15 I've written a paper with him, but I actually have never 02:06
16 met the man.

17 There are two papers. One is a paper that
18 he was the primary author that has to do with
19 formaldehyde, and it's in my CV. And the other is a
20 paper that was recently accepted for publication that has 02:06
21 to do with chemotherapy induced myelodysplasia.

22 Q. Doctor, do you know who the peer reviewers were
23 for the article that we're here for today, the Madison
24 2007?

25 A. No. 02:06

1 Q. Were you over told -- or did you ever
2 correspond with the peer reviewers?

3 A. Well, no, you're not told that. In other
4 words, you are given -- typically, the way the Journal
5 operates is that you may recommend -- they typically ask 02:07
6 you to recommend some people in the field; but then what
7 happens is that you get a blank paragraph back from each
8 of the reviewers or simply a letter saying the Journal
9 isn't interested. And you don't know which reviewer
10 wrote what, or if they used any of the people you 02:07
11 suggested; but they simply ask you to suggest some names.

12 Q. Do you know if you worked on any benzene cases
13 with Dr. Pyatt in 2007?

14 A. I think it's very doubtful.

15 Q. Okay. If you turn to a few pages where it says 02:07
16 to review letter --

17 MR. SCOTT: What's your exhibit number?
18 I'm sorry, Eric, so we can keep track of what we're
19 talking about --

20 MR. WILLIAMS: I apologize. All of this is 02:08
21 in Exhibit F. I need to change that number.

22 MR. SCOTT: F.

23 (Exhibit F was marked.)

24 Q. (By Mr. Williams) Doctor, have you seen this
25 page before? 02:08

1 A. No.

2 Q. Can you tell me what peer reviewer is
3 identified on this sheet?

4 A. David Pyatt, M.D.

5 Q. Okay. And if you turn the page, were you -- to 02:08
6 the highlighted section -- were you informed that David
7 Pyatt viewed your article as acceptable with minor
8 revisions and said that related issues and toxic tort
9 litigation are on the rise and MDS is frequently at
10 issue. Were you told that? 02:09

11 A. If I was given -- I certainly wouldn't be told
12 who reviewed it. I might have been given this paragraph
13 -- or a section of it, depending on what the editor
14 supplied me with.

15 Q. And did you recommend David Pyatt as a reviewer 02:09
16 of this article?

17 A. I probably did. I don't know that for a fact.
18 I gave them several names, and his name could have been
19 among them.

20 Q. Okay. Doctor, if you keep flipping until we 02:09
21 get to your article --

22 A. Yes.

23 Q. -- I believe you testified -- or you write in
24 your article -- and it's at the end, Page 359 -- that
25 there are certain forms of myelodysplastic syndrome that 02:09

1 you feel are caused by benzene exposure, the last
2 paragraph of 359.

3 A. Yes, I said: Despite these caveats, based on
4 considerable evidence presented here, benzene exposure
5 cannot be considered of potential etiology for RARS 02:10
6 although it remains a risk factor for certain forms of
7 the myelodysplasia such as RAEB, an unclassified and/or
8 hypocellular myelodysplasia syndromes, and for AML.

9 Q. Correct. And, Doctor, refractory anemia is a
10 form of myelodysplastic syndrome; is that correct? 02:10

11 A. RARS is classified as a form of myelodysplasia,
12 yes.

13 Q. No, just plain refractory anemia?

14 A. Oh, yes, you can have primary refractory anemia
15 that is a form of myelodysplasia. 02:10

16 Q. And then when one develops ringed sideroblast,
17 it would be RARS refractory with ringed sideroblastic?

18 A. Yes.

19 Q. And then when one develops RAEB, it would be
20 refractory anemia with excess blast; is that correct? 02:11

21 A. Yes, but if you're talking about the same case,
22 I don't think that you would see the transition from a
23 primary refractory anemia into an RARS. You would see
24 the progression from a primary refractory anemia into an
25 RAEB. You would see the progression from an RARS into an 02:11

1 RAEB.

2 Q. And cases of RAEB, refractory anemia with
3 excess blast would have excess amounts of ringed
4 sideroblastic, too; is that correct?

5 A. If they started out as an RARS and the natural 02:11
6 history of that illness is to, in some instances, move
7 toward a Leukemia, as they increase blast, they become,
8 by the classification system RAEB. They are the same
9 illness, as far as I'm concerned; but they are classified
10 as RAEB because they now have blast and they still have 02:12
11 ringed sideroblast.

12 Q. Okay. Doctor, would that be the same for
13 RAEB-T that you would have excessive blast and also
14 possibly excessive ringed sideroblastic; is that correct?

15 MR. SCOTT: Object to the form. 02:12

16 A. Well, again, talking about the progression, if
17 you had RARS-T, that's an illness which you are saying at
18 diagnosis it's a myeloproliferative disease. It has
19 excess ringed sideroblast. That disease may progress
20 toward an acute myeloleukemia, too, and accumulate large 02:12
21 numbers of blast and actually go into AML.

22 Q. (By Mr. Williams) Doctor, are there -- how
23 much money have you made serving as an expert witness for
24 various defendants in myelodysplastic syndrome cases?

25 MR. SCOTT: Object to the form. 02:12

1 A. I couldn't give you a number.

2 Q. (By Mr. Williams) And could you give us a
3 number for how much money you have made in RARS cases?

4 A. I wouldn't have a guess. It looks like there
5 were five, I think we saw, since 1982. I couldn't give a 02:13
6 guess.

7 Q. Do you have an average of what it takes you to
8 prepare a report and go through a deposition, average
9 price, a range?

10 A. It depends on how long the deposition is in 02:13
11 terms of how much that costs; and the preparation, my
12 guess would be that it -- and this would be a guess, that
13 it might be anywhere from six to ten hours, let's say,
14 depending on the simplicity of the case in terms of
15 reviewing the records. 02:13

16 Q. Okay. Have you ever treated a patient with
17 myelodysplastic syndrome that was exposed to -- that was
18 a chemist and was exposed to chemicals?

19 A. Yes.

20 Q. And was it your opinion that that chemist's 02:14
21 exposures to benzene and other chemicals was the cause of
22 his myelodysplastic syndrome?

23 A. I thought it was possible.

24 Q. Okay. Are there any studies, Doctor, in the
25 world's literature that focus on the fact benzene, 02:14

1 besides your own, can't cause RARS?

2 A. Well, there are many articles that read on that
3 point. In other words, there is the Dr. Ruiz article,
4 which I think I cited, where he did bone marrows on 33
5 people with heavy exposure to benzene and pancitopenia 02:14
6 and he specifically tells us there were no ringed
7 sideroblasts.

8 We have Dr. Irons article. He had two
9 articles. One, I think, in 2005 and one recently where
10 he's looked at a large number of people with heavy 02:14
11 benzene exposure and none have had ringed sideroblast.

12 We have Dr. Aksoy's work. And Dr. Aksoy
13 was trained, in part, here in the United States with
14 Dr. Damashek who was the world's expert on RARS. So, he
15 certainly knew about that illness. And he did bone 02:15
16 marrows on a number of people he thought had
17 benzene-related disease, and he makes no mention of ever
18 finding RARS in their marrows.

19 And I would not think that could be missed
20 by a person of his training. 02:15

21 We have the so-called Chinese benzene
22 study, the Haze benzene studies in which Dr. Larsen and
23 others reviewed slides, they claim, of seven people with
24 myelodysplasia from that large cohort; and they make no
25 description of seeing ringed sideroblasts. And all of 02:15

1 those people are very prominent hematologists and
2 certainly would recognize ringed sideroblasts.

3 So that if we look through the literature
4 in cohorts that have been studied by bone marrow analysis
5 by prominent people, there is no mention of the 02:16
6 occurrence of ringed sideroblast, and in many instances,
7 mention that they are not evident, even after having been
8 sought.

9 Q. Doctor, maybe you didn't understand my
10 question. I asked you were there any other studies that 02:16
11 are focused, the title or the objective is benzene
12 exposure and refractory sideroblastic erythropoiesis.

13 MR. SCOTT: Object to the form.

14 A. I think I understand the question. Yes, that
15 was the reason I wrote this article is because that was 02:16
16 because early on, Wintrobe had asked that question and
17 others had; and so, now, I was in the a position to
18 review that question and try to answer that question.

19 Q. (By Mr. Williams) Basically, your study is one
20 of a kind as to answering that question only? 02:16

21 A. Yes.

22 Q. Okay. Thank you.

23 A couple more questions, Doctor; and I
24 think we're done.

25 Have you spoken with -- besides myself, 02:16

1 Mr. Scott, Bob Scott over there, regarding this
2 deposition?

3 A. Yes, I've spoken with -- well, Mr. Asher called
4 me right after you did; and I spoke with him. And then I
5 spoke with Mr. Scott later on, several days later, I 02:17
6 believe. And I also spoke with Stan Perry. That's the
7 best I can remember.

8 Q. Okay. Start off telling us what you spoke with
9 Mr. Asher about.

10 A. Well, what had happened is you called and said 02:17
11 you wanted to depose me on my paper; and I specifically
12 asked you whether this had to do with a specific case.
13 And you told me, no, I just want to depose you about your
14 article. And then I thought that was very peculiar.

15 And then shortly thereafter, I got a call 02:17
16 from Mr. Asher saying you're going to be receiving a
17 subpoena, if you haven't already; and it's about this
18 Barry Wild case.

19 And I said, Well, I'm told I'm going to
20 receive a subpoena but not that it's about a particular 02:18
21 case.

22 And he said, Oh, yes, it is. It's about a
23 particular case; and I'm going to send you a summary of
24 the case, which he did. And that was the sum and
25 substance of the conversation. 02:18

1 Q. And when you say "summary," are you referring
2 to an expert report prepared by Defendant Fisher
3 Scientific's expert, Gregory Sona?

4 A. Yes.

5 Q. And did you review that paper? 02:18

6 A. Yes, I did review the report.

7 Q. And when you say Ross Asher, you mean the
8 gentleman to my right who represents Fisher Scientific.
9 He is the one that contacted you?

10 A. Yes. 02:18

11 Q. Next you said Mr. Bob Scott contacted you.
12 Tell me about that conversation.

13 A. Well, Mr. Scott said that -- I've forgotten
14 what initiated the conversation because we had done other
15 cases; but I mentioned this situation to him, and he 02:18
16 said, Well, that's very interesting because I'm involved
17 in that Barrios case. And I didn't know that. Mr. Asher
18 hadn't mentioned that to me.

19 And so, he said, When are you going to give
20 this deposition? 02:19

21 And I told him and that was the -- in
22 general, that was the substance of that case.

23 Q. And what cases have you worked on for
24 Mr. Scott, what defendants was he representing?

25 A. I'm terrible on names, but we testified on a 02:19

1 case that was in -- was it -- New Mexico, I believe, that
2 was a myelodysplasia case that comes to mind. I know
3 there were probably several others, but I can't remember
4 it by name.

5 Q. Was RARS an issue in any of the cases that you 02:19
6 worked for with Mr. Scott?

7 A. I don't remember that. I think, yes, I think
8 that case had to do with RARS.

9 Q. In New Mexico?

10 A. Yes, I believe so. That was an issue in that 02:19
11 case.

12 Q. And did you testify at trial?

13 A. Yes.

14 MR. SCOTT: It was actually a Daubert
15 hearing. I'm sure Dr. Natelson didn't understand the 02:20
16 niceties of that.

17 Q. (By Mr. Williams) And have you served for
18 Mr. Scott as an expert on several occasions?

19 A. I'm sure I have. I can't remember all of the
20 cases. 02:20

21 Q. And then, I believe, you just told me that Stan
22 Perry, that's the gentleman that's the national counsel
23 for Shell Oil Company, called you?

24 A. Yes.

25 MR. SCOTT: Object to the form. 02:20

1 Q. (By Mr. Williams) What did Mr. Perry have to
2 say?

3 A. I'm trying to recall what he specifically said.
4 There was nothing -- he said, Well -- I asked him, I
5 said, Isn't this a little bit peculiar to get subpoenaed 02:20
6 about a case you're not involved in?

7 And he said, Well, it does sound a little
8 peculiar; but I would just recommend you going ahead and
9 giving the testimony, whatever you're asked. And he
10 said, I don't have a clue why this has occurred. 02:20

11 Q. Do you know why Mr. Stan Perry, the national
12 counsel for Shell Oil Company, contacted you when, in
13 fact, Shell Oil is not a defendant in this case?

14 A. No, I was talking with him on another issue;
15 and I brought it up. So, I said, How would you look at 02:21
16 this issue? I said, isn't this somewhat peculiar?

17 And he said, Well, this does sound a little
18 peculiar; but my advice is just go ahead and give the
19 testimony.

20 MR. SCOTT: Object to the form of the last 02:21
21 question.

22 Q. (By Mr. Williams) Did any of the attorneys
23 that contacted you tell you to testify or lean one way or
24 the other in this deposition?

25 A. No, none of them said, Don't Testify. All of 02:21

1 them said, theoretically -- I think, in fact, Mr. Asher
2 said to me, he said, You know, you could really hire an
3 attorney and try to get out of this?

4 And I said, Well, it just sounds like that
5 would be more trouble than it would be worth. And so -- 02:21
6 but no one suggested I do that.

7 Q. Right. Besides Mr. Asher?

8 A. Well, he didn't suggest. He said I could.

9 Q. You could do that, right. Okay. Give me a
10 second. That's it. 02:22

11 Do you have anything, Mr. Asher?

12 MR. SCOTT: Yeah, I definitely have some.

13 EXAMINATION

14 BY MR. SCOTT:

15 Q. Good afternoon, Dr. Natelson, and thank you for 02:22
16 being here.

17 You mentioned earlier that your first
18 thoughts about benzene and any association with a disease
19 known as refractory anemia with ringed sideroblast or
20 RARS, as it's been called, came after reading something 02:22
21 that Wintrobe wrote.

22 Did I get that right?

23 A. Yes.

24 Q. Who is Wintrobe?

25 A. Well, Dr. Maxwell Wintrobe was the -- was a 02:22

1 hematologist, self-trained really, who was the chief of
2 medicine in hematology in Salt Lake City at one time. He
3 actually worked in Louisiana at one time and I believe he
4 went to Rochester Medical School, but he became
5 internationally known because he wrote the first major 02:23
6 textbook in hematology and was a very renowned and also
7 very famous for having an enormous research -- reprint
8 library. In the days prior to the Internet, if you
9 wanted to have an article, you would write a letter or a
10 postcard to an author and they would send you back a 02:23
11 signed copy; and Dr. Wintrobe had a massive research
12 library where you could get all of your reprints there.

13 Q. This was before the Internet, I take it?

14 A. This is long before the Internet, yes.

15 Q. Is Dr. Wintrobe still with us? 02:23

16 A. No, he died a number of years ago.

17 Q. Does his hematology textbook continue to be
18 with us, new editions from time to time?

19 A. Yes.

20 Q. And is it one of the hematology textbooks that 02:24
21 is used in medical schools, certainly in this country and
22 perhaps around the world?

23 A. Yes.

24 Q. And exactly what is it that Dr. Wintrobe wrote
25 or reported that piqued your interest with regard to 02:24

1 benzene and RARS?

2 A. Well, Dr. Wintrobe was aware of this illness.
3 He was not the first discoverer of it. Some other
4 doctors in the decade prior to when he wrote about it had
5 made mention of this illness. And he decided that he 02:24
6 would study all the cases he had at Salt Lake City. I
7 don't remember the numbers. They are in this article.
8 Let's say, 19 cases or so that he had; and then I think
9 he abstracted about 44 more cases from the world's
10 literature. And he looked to see how you made this 02:24
11 diagnosis; how many ringed sideroblasts there were in the
12 bone marrow; could there be known causes for this looking
13 at drugs, looking at alcohol because it was known that
14 alcohol could produce ringed sideroblasts.

15 And so, he looked to see if there was a 02:25
16 unifying feature in these patients that explained their
17 illness. And he found what we really know today that a
18 number of these people went on to develop acute Leukemia,
19 that there was no particular relationship with alcohol,
20 there was no relationship with lead poisoning which could 02:25
21 also give ringed sideroblasts. There was no association
22 with benzole, as he put it, which he knew caused bone
23 marrow depression. And so, he termed the illness
24 idiopathic meaning that none of the known bone marrow
25 toxins that he was aware of could produce this illness. 02:25

1 Q. You also mentioned an author, a Doctor named
2 Aksoy.

3 A. Yes.

4 Q. And as I recall, he was a Turkish doctor; is
5 that correct?

02:26

6 A. Yes.

7 Q. You indicated that he trained with
8 Dr. Damashek. How do you know that?

9 A. Well, I happen to know that because Dr. Aksoy
10 wrote many articles; and these were -- most of them were 02:26
11 written, I think, in the '70s, up until about 1982, I
12 think, was his last article. And after he died, I have a
13 review article by some of his colleagues that wrote about
14 it. And they went in that article into his background
15 and pointed out that he had studied with Dr. Damashek 02:26
16 doing a fellowship. And so, I learned a little bit more
17 about his background. He was not -- I don't think his
18 hematology training was in the United States but his
19 fellowship was.

20 Q. And what is it that Dr. Aksoy wrote about that 02:26
21 was related, in your view, to the question of whether
22 benzene is associated -- causally associated with the
23 development of RARS?

24 A. Well, Dr. Aksoy studied a large number of
25 patients. His patient base was about 29,000 people. And 02:26

1 I don't recall the exact number of how many had what he
2 called pre-Leukemic syndromes and acute Leukemia, but
3 let's say it was in the 30s to 40s of individuals that he
4 personally studied. And I think in one of his articles
5 he said he does bone marrows on 11 of them. And those 02:27
6 were ones that he did, and I assume he looked at bone
7 marrows that other people did on other cases.

8 In the era when he was writing those
9 articles, the iron stain, the so-called Prussian blue
10 stain, or pearls blue stain was a standard practice in 02:27
11 hematology. And so, he would be familiar with looking at
12 iron stains.

13 He also studied with Dr. Damashek who one
14 of his favorite topics was sideroblastic anemia. So,
15 certainly, it's reasonable to expect that a trained 02:27
16 hematologist who studies with someone interested in this
17 disease could recognize a ringed sideroblastic.

18 And in a normal bone marrow, one doesn't
19 see a single ringed sideroblast. And in RARS, one may
20 see 40, 50, 70 percent of the cells may be ringed 02:28
21 sideroblast. I brought a cover here of a magazine to
22 show how striking it is.

23 So, when Dr. Aksoy writes an article and he
24 says, These are the abnormalities that I saw in
25 benzene-related illnesses, he didn't have to tell me that 02:28

1 he looked for ringed sideroblasts. He had seen them, he
2 would have commented that that was an abnormality.

3 In other words, it was just as though he
4 doesn't say he didn't see malaria parasites or this or
5 that. In other words, he said what he saw; and included 02:28
6 in that was not ringed sideroblasts.

7 Q. You use the term "sideroblastic anemia." What
8 relationship is sideroblastic anemia to refractory anemia
9 with ringed sideroblasts or RARS?

10 A. Well, sideroblastic anemia is a general topic; 02:28
11 and prior to the use of the term myelodysplasia and even
12 subsequent to it, if you went to a hematology textbook,
13 you would see a chapter on sideroblastic anemia. And
14 that chapter would be divided into those that are
15 hereditary, which there are some, and those that are 02:29
16 acquired illness.

17 And then under the acquired illnesses,
18 there would be broken down as to what the causes might
19 be. For example, lead poisoning gives you a sideroblastic
20 anemia, very heavy arsenic poisoning can give you a 02:29
21 sideroblastic anemia. Alcohol can give you a
22 sideroblastic anemia.

23 Those all acquired sideroblastic anemias;
24 but only, perhaps, in the arsenic related might they go
25 on to a Leukemia. They are not a pre-Leukemia state. 02:29

1 But certain of the sideroblastic anemias
2 for which there are no obvious causes, no drugs, no
3 chemicals, they fall under the title Wintrobe called
4 idiopathic sideroblastic anemia. And that was a group
5 that he followed and he commented that they could live 02:30
6 many years, and they often died of iron overload. They
7 didn't always die of Leukemia. In fact, only
8 occasionally did they die of Leukemia. Dr. Damashek
9 thought about half of them would die of Leukemia, but
10 Dr. Wintrobe realized that that was too big a number and 02:30
11 it was much smaller than that that went on to develop
12 Leukemia.

13 So, that would be what you would find in
14 the textbook chapter. It would give you a discussion of
15 all the different types of sideroblastic anemias. 02:30

16 Q. You say you have a cover that shows us a
17 refractory anemia with ringed sideroblast or at least a
18 ringed sideroblast?

19 A. Yes.

20 Q. Is that something that we can mark for this 02:30
21 deposition and have it sent back to you?

22 A. Certainly.

23 (Exhibit No. G was marked.)

24 Q. (By Mr. Williams) And, Doctor, if you don't
25 mind, would you hold that up for the camera; and we'll 02:31

1 see if he can zoom in on the cover here of Exhibit G.

2 A. This is a cover of a magazine called BLOOD, and
3 Dr. Damashek was the founder of that magazine. He was
4 the original editor.

5 Q. And is the journal BLOOD the JOURNAL OF THE 02:31
6 AMERICAN SOCIETY OF HEMATOLOGY?

7 A. Yes, it is.

8 Q. Or SOCIETY OF HEMATOLOGY?

9 A. Yes.

10 Q. Now, can you point at -- it may be tough to do 02:31
11 on the -- on the camera, I don't know, because you can't
12 see the other side of it; but can you point out --

13 A. I think I can.

14 Basically, when you prepare a slide to do
15 an iron stain, what you like is to make a fairly thin 02:31
16 film of the bone marrow; and that spreads out the mother
17 cells that give rise to red cells. And they're counter
18 stained with a slightly red stain. So, everything you
19 see red is the nucleus of a cell that is going to be
20 circulating a red blood cell. 02:31

21 Q. And that's sometimes called an erythroid cell;
22 is that right?

23 A. These are called erythroid blasts in the bone
24 marrow. And when you're staining them with the Prussian
25 blue stain, any iron in the cytoplasm forms a blue 02:32

1 granule color. And in a normal bone marrow, all you
2 should see is the red counter stain. There wouldn't be a
3 single one of these cells with these multiple little blue
4 dots around them. So, this smacks you in the face if you
5 were looking at an iron stain on a bone marrow. 02:32

6 Q. This is not the kind of thing Dr. Aksoy would
7 miss if he had seen it?

8 A. I'm confident Dr. Aksoy would recognize this,
9 just as Dr. Damashek and many others have.

10 Q. I want to -- we've talked about Dr. Wintrobe 02:32
11 and Dr. Aksoy. What other -- you have written a review
12 article. What is a review article? You distinguish that
13 between a review recall and a research. Can you describe
14 for us what a review recall is and what the purpose of it
15 is? 02:33

16 A. Well, a review article is to provide education
17 for people in the medical community about a particular
18 issue. And you take a subject and you try to review the
19 literature intensively and find what you think are the
20 pertinent articles to answer a particular question. And 02:33
21 then you review those articles and mention why you're
22 selecting them and why these articles help you come
23 toward a conclusion.

24 In this particular case, we're talking
25 about sideroblastic anemia and causation; and that's what 02:33

1 the purpose of this review was.

2 Q. And I take it that in preparing that article
3 and writing that article, you did some sort of literature
4 search to see what was available in the medical and
5 scientific literature regarding benzene and refractory 02:33
6 anemia with ringed sideroblast?

7 A. Yes.

8 Q. You've told us about Wintrobe and Aksoy. What
9 other original work was in the literature that led you to
10 your conclusions that benzene is not associated with the 02:34
11 development of RARS?

12 A. Well, there were several articles; and some of
13 these are referenced in the paper, and some of these are
14 already discussed. One we didn't discuss, for example,
15 is we discussed, let's say, the Ruiz study where he had 02:34
16 people heavily exposed to benzene and he selected a group
17 of 33 that he thought would be most reflective of that
18 poisoning and he did bone marrows on them. And he tells
19 us that none of them have ringed sideroblasts.

20 Q. Not a single one? 02:34

21 A. Not a single one.

22 Then you could look at that in reverse, and
23 one of the articles I cited took a large collection of
24 people with RARS, I think there were 84 of them. And
25 they went back and interviewed those people and studied 02:34

1 their files to see how many of those 84 might have had it
2 from benzene exposure. Did they have a chemical
3 background that could have been causative? And in that
4 article, they claim they found one person who alleged
5 exposure to benzole; but that person had also received 02:35
6 radiation therapy for a malignancy. And so, it did not
7 appear that looking at a cohort of people with this
8 illness that benzene stood out as a potential cause and
9 effect.

10 Q. What was the article where they took the 02:35
11 collection of people with RARS and went back to see if,
12 in their history, they had benzene or solvent exposure?

13 A. Let me see if I can find that. Let's see where
14 I reference that. I probably better find it from looking
15 at my references. I believe it's reference 19, but let 02:36
16 me see if that's correct.

17 Yes, it's my reference 19, which is called
18 -- is by Garand, G-A-R-A-N-D.

19 Q. That was in the 1992, it looks like, from your
20 reference list, correct? That was -- that article 02:36
21 appeared in LEUKEMIA RESEARCH?

22 A. That article appeared in LEUKEMIA RESEARCH,
23 Volume 16, Page 463 to 486, 1992.

24 Q. Are you familiar with a series of papers
25 arising out of a study conducted by the National Cancer 02:36

1 Institute in conjunction with the Chinese Academy of
2 preventative maintenance -- preventative medicine -- I've
3 got a car problem. I keep saying "maintenance" instead
4 of "medicine" -- of a large group of workers in China?

5 A. Yes.

02:36

6 Q. Does that article shed any light or provide any
7 information that is helpful on the question of whether or
8 not benzene has been associated with the development of
9 RARS?

10 A. Yes, I think so. That was a very large cohort, 02:37
11 I believe, about 74,000 workers in China exposed to what
12 are thought to be very large amounts of benzene in an
13 occupational environment. And in that group, the --
14 there were seven cases identified as having forms of
15 myelodysplasia. And according to the articles, those 02:37
16 cases were reviewed by hematopathologists. And they list
17 the diagnosis of these seven, and none of them are RARS.

18 There is also a comment in one of the
19 articles I cited about what the typical bone marrow
20 looked like in these people, and there is no mention of 02:37
21 ringed sideroblast in that comment.

22 MR. SCOTT: What's our next exhibit?

23 THE COURT REPORTER: H.

24 (Exhibit No. H was marked.)

25 Q. (By Mr. Scott) Dr. Natelson, I'm going to hand 02:38

1 you what I've marked as -- actually, the court reporter
2 has marked as Exhibit H, which is an Internet search form
3 and then an article with a lead author Travis; and it was
4 published in 1994.

5 Have you seen that article before? 02:38

6 A. Yes.

7 Q. Is that one of the papers out of this NCI CADM
8 or Chinese Preventative Medicine Study?

9 A. Yes.

10 Q. On page -- the second page of that article 02:38
11 which is numbered, I think, 92 -- and Lois Travis is the
12 lead author; am I correct?

13 A. Yes.

14 Q. And in the right-hand column, there is a
15 description in the first full paragraph that says: 02:39
16 Evidence of dyserythropoiesis included the presence of --
17 and it lists a number of items, ringed sideroblasts,
18 multinuclearity, nuclear fragmentation, megaloblastoid
19 changes and so on.

20 What are those? What is dyserythropoiesis, 02:39
21 and what are those items?

22 A. Well, dyserythropoiesis would be a general term
23 meaning, in lay language, that the cell line looks
24 abnormal; and it may be abnormal because it's too large.
25 It may be abnormal because the cytoplasm is very 02:39

1 irregular on the cells. It may be abnormal because the
2 colors -- the stain colors are abnormal. It may be
3 abnormal because they are inclusions, like ringed
4 sideroblasts, something that shouldn't be in there. It
5 may be abnormal because the nucleus is splitting, that 02:39
6 you have two nuclei in a single red cell precursor, for
7 example.

8 So, dyserythropoiesis is a general term
9 means abnormal, morphology, funny-looking cells. And
10 then they go on to say what some of those were, for 02:40
11 example, ringed sideroblasts we've discussed.
12 Multinuclearity meaning there were multiple nuclei
13 instead of a single one in the cell.

14 Karyorrhexis, what that means is the
15 nucleus is fragmenting instead of being very well 02:40
16 defined.

17 Abnormal nuclear shape, I think I mentioned
18 it should be like a bulls eye. It looks very round. It
19 may be irregular.

20 Impaired hemoglobinization, what that means 02:40
21 is that as the cell matures, the cytoplasm becomes redder
22 and redder as hemoglobin is manufactured. And so,
23 impaired hemoglobinization means the cell looks very
24 pale. It's not making it's complement of the hemoglobin.

25 Megaloblastoid changes meaning simulating 02:40

1 what we see with Vitamin B-12 deficiency where the cells
2 are very large and abnormal looking.

3 And so, those are the things that they
4 mention as would come under the heading of
5 dyserythropoiesis.

02:41

6 Q. And part of the -- one of the items or things
7 they were looking for as evidence of dyserythropoiesis is
8 the existence or observation of ringed sideroblasts?

9 A. Yes.

10 Q. Can you turn to Table 5 of the Travis article, 02:41
11 Exhibit H, which I think is on Page 97. Can you first
12 confirm that Table 5 is a listing of the various -- among
13 other things, the various items of dyserythropoiesis that
14 the National Cancer Institute investigators had been
15 looking for?

02:41

16 A. Yes.

17 Q. And under the cases of MDS, how many instances
18 did they observe ringed sideroblasts?

19 A. None, according to this. They have looked for
20 them, but they don't cite any cases as having them.

02:42

21 Q. And they do cite, if you can confirm,
22 observation of megaloblastoid changes, abnormal nuclear
23 change, impaired hemoglobinization and multinuclearity as
24 you described for us earlier; correct?

25 A. Yes, that is correct.

02:42

1 Q. Is that the same thing as saying they look to
2 see if there were ringed sideroblasts among their MDS
3 cases and saw none?

4 A. Correct.

5 Q. And then finally the Irons article or articles, 02:42
6 what do Dr. Irons and his group's articles in 2005 and I
7 think it was titled something along the lines of benzene
8 induces a unique form of dysplasia or something like
9 that. And then in more recent 2009 article which we
10 don't have marked -- do you have that article? 02:43

11 MR. WILLIAMS: It's right here.

12 A. Yes.

13 MR. SCOTT: Let's mark that as Exhibit I
14 just so we have a sticker on it.

15 (Exhibit No. I was marked.)

02:43

16 Q. (By Mr. Scott) How did Dr. Irons' 2005 and
17 2009 articles or reports inform your view on whether
18 benzene causes refractory anemia with ringed
19 sideroblasts?

20 A. Well, in this particular article, he comments 02:43
21 about how they looked at the bone marrows, that they did
22 iron stains on the bone marrows. Let's see if I can find
23 where he discusses that, but I know that he says that.

24 He says: Bone marrow aspirate and
25 peripheral blood smears were prepared from fresh tissue 02:44

1 and evaluated using Wright-Giemsa stained preparations
2 and special stains, including an iron stain.

3 So, he was doing an iron stain on all of
4 this material.

5 And then he comments and I have to look to 02:44
6 see what page this might be that -- here it is, Page 10
7 of the article. He says: There was no evidence of
8 increased ringed sideroblasts.

9 Q. And was this among a group of people who had a
10 myelodysplastic syndrome and had known and, in some 02:44
11 cases, very high benzene exposure?

12 A. Yes, according to Dr. Irons, these were his
13 signal cases, as he used that term, meaning that they had
14 unequivocal enormous benzene exposure and abnormal bone
15 marrows. 02:45

16 Q. Are there -- from your knowledge and review of
17 the scientific literature -- and I want to turn away from
18 RARS, at this point; but myelodysplastic syndromes, you
19 have said that some myelodysplastic syndromes are
20 associated with exposure to benzene? 02:45

21 A. Yes, I think that's true.

22 Q. Are there features, clinical features,
23 morphologic features, cytogenetic features, type of
24 features that, sort of thing, of the benzene-caused
25 myelodysplastic syndromes? 02:45

1 (Mr. Trull enters the deposition room at
2 this time.)

3 A. Well, I suppose the two best articles that
4 would read on that would be the Ruiz article with his
5 large number of cases, 33 cases that were studied and the 02:45
6 Richard Irons article. And the results of those two
7 articles are quite similar. They also are in line with
8 the description that's in the cases seen in the Hayes of
9 benzene study.

10 The description is that the bone marrows 02:46
11 generally show reduced total cellularity or what we call
12 hypocellularity, that they have abnormal morphology of
13 the red cell precursors, that they have the presence of
14 increased numbers of eosinophils, which are a cell that
15 we see in inflammatory conditions, and that these 02:46
16 eosinophils look peculiar. They are granules. They are
17 very unusually colored and large, as we see in certain
18 forms of acute Leukemia.

19 And the bone marrow also contains
20 phagocytic cells, histiocytes that are prominent in these 02:46
21 bone marrows. And the absence of ringed sideroblasts,
22 for example, in these bone marrows.

23 Q. You say histiocytes or phagocytic cells, are
24 those sometimes referred to as -- is that condition
25 sometimes referred to as hemophagocytosis? 02:47

1 A. Yes.

2 Q. And the abnormal eosinophils, increased
3 eosinophils and peculiar appearance, morphologic
4 appearance, are those in the peripheral blood or in the
5 bone marrow? 02:47

6 A. Well, in the case of Leukemias, they can be
7 both in the peripheral blood and bone marrow in certain
8 forms of Leukemia.

9 In the case of benzene bone marrows that
10 are described, they are confined to the bone marrow. 02:47

11 Q. And are these sometimes called precursors
12 because they are in the bone marrow?

13 A. Well, a general statement would be that most of
14 the cells that you see in the bone marrow are precursors
15 to cells that eventually come out and circulate in the 02:48
16 peripheral blood.

17 Q. In normal MDS, myelodysplastic syndrome case,
18 is the bone marrow hypercellular, that is, greater
19 cellularity or more cells in the marrow or hypocellular?

20 A. I think in general, you might find the figure 02:48
21 that looking at all types of myelodysplasia, perhaps
22 20 percent are very hypocellular, sometimes referred to
23 as hypocellular myelodysplasia. Many have a normal
24 cellularity, and many have increased cellularity.

25 Q. Are you familiar with a disorder known as -- or 02:48

1 referred to as myelodysplastic
2 syndrome/myeloproliferative disorder or sometimes
3 myeloproliferative neoplasm?

4 A. Yes.

5 Q. What is that disorder or disorders?

02:49

6 A. That classification is a relatively new
7 classification by the World Health Organization, and this
8 really came about because what the World Health
9 Organization has been trying to do is to become as
10 specific as it can about a particular diagnosis. For 02:49
11 example, we had the illness chronic myeloid Leukemia,
12 which, for many years, we considered most of them to have
13 a positive Philadelphia chromosome but also some of them
14 to be missing that chromosome, but we still called them
15 chronic myeloid Leukemia. 02:49

16 Well, the World Health Organization took
17 the position that only chronic myeloid Leukemia with a
18 Philadelphia chromosome is the real thing and we've got
19 to do something else with these cases of chronic myeloid
20 Leukemia that lack the Philadelphia chromosome. And 02:49
21 there is another illness called chronic myelomonocytic
22 Leukemia, which is another myeloproliferative disease,
23 which the cause is unknown. And the question was, where
24 are we going to place that.

25 So, they came up with a category called 02:50

1 myeloproliferative myelodysplastic syndromes. And the
2 best known in this category to be chronic myelomonocytic
3 Leukemia, what's called atypical CML -- that is CML
4 lacking the Philadelphia chromosome, an unusual illness
5 called juvenile myeloid Leukemia. And eosinophilic 02:50
6 Leukemia would be another in this category.

7 And a provisional member of this is once
8 called RARS-T. These are illnesses for which they are
9 all myeloproliferative illnesses. They are not
10 myelodysplasia. They are all myeloproliferative 02:50
11 diseases. However, they can have funny-looking cells.
12 So, they can have some degree of myelodysplasia; but they
13 are quite different from the illnesses we classify as
14 myelodysplasia. And those illnesses are all thought to
15 be of unknown cause at this time. So, the articles on 02:51
16 that subject tell us that the diseases in that category
17 of myelodysplasia, myeloproliferative disease are all of
18 unknown cause.

19 Q. I want to hand you -- I'm going to hand you two
20 things here, one a very poor color print that I have 02:51
21 made.

22 (Exhibit No. J was marked.)

23 Q. (By Mr. Williams) Dr. Natelson, I've marked as
24 Exhibit J, two pages out of what I will represent to you
25 as the World Health Organization's 2008 classification of 02:51

1 tumors of hematopoietic and lymphoid issues. And I'm
2 going to turn to the book -- mine is sort of messed up
3 here so that we can copy it, but can you just confirm
4 that, one, this is, in fact, the 2008 World Health
5 Organization classification book; and second, that the 02:52
6 pages I've handed you are, albeit poor, but copies of
7 Pages 85 and 86 from that book?

8 A. Yes, I'm glad you're not checking books out of
9 my library. Yes, that's what these are from.

10 Q. And what is this particular -- what disease or 02:52
11 disease entities do these pages deal with, Exhibit J,
12 that I've handed you?

13 A. What you've handed me are Pages 85 and 86; and
14 they are referred to as
15 myelodysplastic/myeloproliferative neoplasm, 02:52
16 unclassifiable.

17 Q. Now, is that the disease entity that -- or
18 entities that you were describing for us a moment ago
19 before I handed you that document?

20 A. Yes. 02:52

21 Q. Now, is MDS/MPN, I think WHO calls it, is that
22 a myelodysplastic syndrome?

23 A. All of these diseases in this category are
24 myeloproliferative disease or neoplasms, whichever term
25 you like; but they may have myelodysplastic features. 02:53

1 Q. What is the difference for a layperson between
2 MDS or myelodysplastic features and myeloproliferative
3 features?

4 A. Well, the easiest way to think about it is this
5 way. Myelodysplasia is characterized by what we call 02:53
6 ineffective myelopoiesis. What that means is -- a simple
7 example is, if I take a person and inject them with
8 radioactive iron, within about 30 minutes or so, that
9 iron disappears from the circulation. It's gone. It
10 goes right into the bone marrow. 02:53

11 Now, if I sample the blood over the course
12 of a week, by the time you get out to seven to ten days,
13 all of that iron has reappeared out into the circulating
14 blood; but now it's inside the red cells in the
15 hemoglobin. 02:54

16 In other words, the bone marrow took that
17 iron, built it into new red blood cells and all of that
18 radioactive label came out circulating. That's effective
19 erythropoiesis.

20 Now, if I do that same experiment on 02:54
21 someone with RARS, I inject them with the same amount of
22 radioactive iron. In the same sort of period of time, it
23 will go right into the bone marrow. Now, if I look to
24 see where that iron is at seven to ten days, sometimes as
25 little as 5 percent of it will be back out and 02:54

1 circulating red cells.

2 What's happening is the iron gets into the
3 red cell precursors and it churns in the bone marrow and
4 the cells are made and die and made and die in the bone
5 marrow and it's ineffective. The production is -- the 02:54
6 machinery looks like it's there, but it's not efficient.
7 The cells aren't coming out. That's ineffective
8 erythropoiesis. The same would be true if you're looking
9 at white cells or platelets. The general term is
10 ineffective myelopoiesis. That's a very strong 02:55
11 characteristic of all myelodysplastic disorders.

12 When you look at myeloproliferative
13 disorders, like atypical chronic myeloid Leukemia, for
14 example, or chronic myelomonocytic Leukemia, the bone
15 marrow is very efficient. You look in the bone marrow, 02:55
16 it's full of white cells. They are coming right out and
17 circulating. So, they don't have this problem. They
18 have -- they have a very proliferative disease.

19 So, in myelodysplasia, typically,
20 everything is low. We have what we call cytopenias -- 02:55
21 low red cells in the peripheral blood, low numbers of
22 white cells, low numbers of platelets.

23 On the other hand, in the
24 myeloproliferative diseases, you may have white counts of
25 300,000 because the bone marrow is quite efficient. It's 02:55

1 making these cells, and they are coming out and
2 circulating. And so, that's a major difference between
3 those two illnesses.

4 Q. We have talked about your opinions and views on
5 whether benzene is causally associated or causes RARS -- 02:55
6 refractory anemia ringed sideroblast. What is the
7 evidence as to whether benzene causes myeloproliferative
8 disorders?

9 A. Well, to my knowledge, there is none. In other
10 words, this has been looked at by a number of people, 02:56
11 particularly in illnesses like chronic myeloid Leukemia
12 and myelomonocytic Leukemia, chronic myelomonocytic
13 Leukemia; and there isn't evidence that those
14 myeloproliferative diseases can be caused by excessive
15 benzene exposure. 02:56

16 So, the general dogma in hematology would
17 be that myelodysplasia, that category, certain types can
18 be caused by excessive benzene exposure. In fact, the
19 World Health Organization booklet says that.

20 Myeloproliferative diseases, on the other 02:56
21 hand, there isn't evidence that benzene can cause those.

22 Q. The same question for this MDS/MPN
23 myelodysplastic syndrome/myeloproliferative disorder or
24 neoplasm, what is the evidence that benzene causes those
25 disorders? 02:57

1 A. Well, there is none. And, in fact, the
2 reviewers on that, the latest reviews that are perhaps a
3 year or so old tell us the cause of all of those
4 illnesses in that category, the etiology is unknown.

5 MR. SCOTT: Doctor, that's all I have. 02:57
6 Thank you very much.

7 EXAMINATION

8 BY MR. ASHER:

9 Q. Dr. Doctor, my name is Ross Asher.

10 Did I hear you correctly earlier to say 02:57
11 that myelodysplastic syndrome or myelodysplasia is a term
12 for a classification of a group of diseases?

13 A. Yes, it's a classification system that was
14 first proposed around 1982.

15 Q. So, if someone is diagnosed with 02:57
16 myelodysplastic syndrome or myelodysplastic disorder, is
17 that a general diagnosis; or is that a diagnosis of some
18 specific disease?

19 A. Well, it's a little of both. It's a general
20 term. It might be, like, akin to saying hepatitis; but 02:58
21 there are many forms of hepatitis. It's a general
22 category of bone marrow failure; but there are many, many
23 different forms of myelodysplasia.

24 Q. I want to go back and ask just a couple of
25 questions about -- pardon me -- the article that you were 02:58

1 asked about earlier, Benzene Exposure Refractory
2 Sideroblastic Erythropoiesis: Is There an Association,
3 that article, I believe, was published in the AMERICAN
4 JOURNAL OF MEDICAL SCIENCE?

5 A. Yes.

02:58

6 Q. Is the AMERICAN JOURNAL OF MEDICAL SCIENCE a
7 peer-reviewed publication?

8 A. Yes.

9 Q. And can you explain for the ladies and
10 gentlemen of the jury what it means for an article to
11 undergo peer review? 02:58

12 A. Yes, well, this particular journal is one of
13 the oldest journals in the country, medical journals; and
14 what happens is that when you send an article into a
15 journal, they have an internal editorial board. And 02:59
16 their people review the article and see if they feel that
17 it has merit. And many times when you send an article
18 into a journal, it will never get out of the journal. In
19 other words, the internal review board turns it down
20 flat. They say it's not of interest to the general 02:59
21 public. It's poorly written. We're not even going to
22 bother to send this out to a reviewer not connected with
23 our journal.

24 And ultimately, if they decide it has
25 potential, they will send it out, typically, to three 02:59

1 reviewers. And, for example, I, just a few weeks ago got
2 an e-mail from a journal called HEMATOLOGICA.

3 And they said, Would you be willing to
4 review an article for us?

5 And I said, okay.

03:00

6 And so, they sent me that article, all
7 electronically.

8 And what happens is they then gather the
9 comments of the reviewers they send it out to; and if
10 there is a disagreement, they may send it out to a few 03:00
11 more reviewers. And then they come to some decision and
12 will send a letter back to you saying what they feel you
13 should do with your article.

14 Q. And what's the purpose, generally, of peer
15 review before publication? 03:00

16 A. Well, it's multiple eyes. In other words, they
17 are sending it out to people who don't necessarily think
18 alike, have different expertise and might find something
19 that's incorrect that another reviewer might gloss over.
20 And so, you're looking for several people to look at a 03:00
21 study and see if you feel it has merit.

22 Q. And the article we're talking about here that
23 you've written on benzene exposure, that was peer
24 reviewed; is that right?

25 A. Yes.

03:00

1 Q. And it was published by that -- by the AMERICAN
2 JOURNAL OF MEDICAL SCIENCE after being peer reviewed; is
3 that right?

4 A. Yes.

5 Q. I wasn't quite certain, did you say that when 03:01
6 you spoke to Mr. Williams, he told you that your
7 deposition today wasn't for use in any specific case?

8 A. Yes, as I recall, the conversation was
9 something; and, of course, I don't have a recording.

10 But he said that you're going to receive a 03:01
11 subpoena, and I want to question you about your article.

12 And I said, About my article?

13 He said, yes.

14 I said, Well, are we talking about a
15 particular case or -- he said, No, no, I want to question 03:01
16 you about your article.

17 And I said, Okay. I hadn't received the
18 subpoena at that point, but I said that sounds all right.
19 I'll be willing to do that.

20 Q. Have you come to find out that you are here 03:01
21 today because of a specific case that's going on?

22 A. Well, you informed me of that when you called
23 me.

24 Q. And I want to make sure we clear up one thing
25 that you mentioned earlier. 03:02

1 Did I ever suggest to you in a telephone
2 call that you should try to avoid this deposition today?

3 A. Absolutely not.

4 Q. And did I inform you that I represented a party
5 to the case and we had not designated you as an expert 03:02
6 witness and, therefore, I couldn't represent you?

7 A. Correct, you said that.

8 Q. Sir, I think that's all the questions I have
9 for you right now.

10 FURTHER EXAMINATION 03:02

11 BY MR. WILLIAMS:

12 Q. When we originally talked, I informed you that
13 this deposition didn't involve a case that you were an
14 expert in; is that correct?

15 A. I can't recall the exact language. You said 03:02
16 something to the effect -- when I asked you, Is this
17 regarding a case?

18 You said something, as best I can say, This
19 is no case -- this has nothing to do with any case you've
20 ever had anything to do with, or something to that 03:02
21 effect.

22 Q. Fair enough.

23 Doctor, do you recall one other thing you
24 told me on the phone when I explained that I wanted to
25 discuss your 2007 article dealing with RARS, do you 03:02

1 recall what you told me?

2 A. I don't recall.

3 Q. Do you recall what you told me about -- that
4 you couldn't call it a RARS case without looking at the
5 slide?

03:03

6 MR. SCOTT: Object to the form.

7 A. Oh, yes, I said -- I don't remember how we got
8 on that; but I said, if it's a particular case, I said, I
9 would have to look at the marrow slides to be convinced
10 that that was a diagnosis.

03:03

11 Q. (By Mr. Williams) Doctor, what percentage of
12 ringed sideroblasts do you need to have a RARS diagnosis?

13 A. Well, that's an interesting question. The
14 typical number given by bodies such as the WHO is
15 15 percent of all of the red cell precursors of the bone 03:03
16 marrow should be ringed sideroblasts.

17 Hematologists traditionally don't count
18 cells. We look at it. And many of these cases, there
19 are 60 and 70 percent ringed sideroblasts. It's obvious
20 what they have. It's like looking at an old friend. And 03:03
21 I think you would find very few hematologists who would
22 laboriously count whether it's 15 percent, 16 or 17
23 percent. Some pathologists might; but not too many of
24 them, either.

25 So, it's usually a visual diagnosis; but, 03:04

1 technically, the number is supposed to be 15 percent or
2 greater.

3 Q. And if there aren't 15 percent ringed
4 sideroblasts present, you couldn't make a diagnosis of
5 RARS; is that correct? 03:04

6 A. It does not meet the standard of care that this
7 diagnosis requires.

8 Q. And, Doctor, one final question: Did you
9 receive any type of compensation whatsoever for the
10 writing and drafting and publishing of your 2007 benzene 03:04
11 RARS article?

12 A. No. In fact, it cost me a few dollars, as I
13 gave you the receipt.

14 Q. As a matter of fact, this is your invoice --

15 A. That is my invoice. 03:04

16 Q. -- that you paid to get a published copy of the
17 book?

18 A. Yes, most journals will give you a charge per
19 page and a very large charge if you have color prints;
20 and so, it can be very expensive to publish an article 03:04
21 these days.

22 MR. WILLIAMS: We'd like to mark his
23 invoice. I don't have any further questions. Thank you,
24 Doctor.

25 (Exhibit No. K was marked.) 03:05

FURTHER EXAMINATION

BY MR. SCOTT:

Q. Dr. Natelson, on this issue of counting ringed sideroblasts, is this one of those issues where practicing clinicians and hematologists, such as yourself, basically don't need a weatherman to know which way the wind blows? 03:05

A. Well, when considered that way, I think in my career, I've probably, personally, looked at at least 7,000 bone marrows more. And so, usually, if I'm looking at a bone marrow, it doesn't take more than a few milliseconds to give me a general idea of what the bone marrow is going to show. 03:05

Now, I will study it for much longer than that, particularly if I'm photographing it to find a good feel to illustrate a point. But usually, to an experienced hematologist, just a short time under the microscope tells you what you need to know. 03:05

Q. And that's an interesting point. Is it accurate to say that even if one were to count sideroblasts, the counting must be done in representative fields from the bone marrow pathology? 03:06

A. Certainly, it's not only the representative fields; but also is the slide preparation proper? There is an art, as well as a science to making a good iron 03:06

1 stain of a bone marrow. It needs to be a relatively thin
2 film, and it needs to be incubated with the two reagents
3 that you use -- cyanide reagent and a hydrochloric acid
4 reagent, and it needs to be properly incubated and then
5 it needs to be properly counterstained because if you 03:06
6 over counterstain it, you may obscure a lot of things
7 there. And if you don't incubate it long enough, you
8 don't get the good blue color.

9 So, there is a bit of a science and an art
10 to making this; and I've seen many bone marrow slides 03:07
11 which are very thick. And you really can't tell whether
12 there is ringed sideroblasts there or not, and you may
13 have to repeat a stain.

14 Q. If staining is done in a way that the stain was
15 negative as a processing artifact, can that affect the 03:07
16 count, if you will, of ringed sideroblasts when you
17 observe the slides under the microscope?

18 A. Yes, because what happens is you flood the
19 slide with a stain; and sometimes, if there is a little
20 grease on the slide or it's not properly fixed with 03:07
21 alcohol, you will get uneven staining. Some areas will
22 be very densely stained. Other areas not well sustained
23 at all. So, you have to look sometimes at multiple
24 slides and you'll find a, quote, good area that looks
25 well sustained with good colors; and that's what you -- 03:07

1 if I were going to photograph something, that's what I
2 would seek.

3 Q. Did you bring a copy of your CV today?

4 A. I didn't. It wasn't asked for. So, I didn't
5 bring it. 03:08

6 Q. I understand. I neglected to do that myself.

7 Do you diagnose and treat patients with
8 Leukemia lymphoma, myelodysplastic syndromes essentially
9 every workday of your life?

10 A. Yes. 03:08

11 Q. How long have you been doing that?

12 A. I've been seeing hematology patients
13 exclusively since around 1969.

14 Q. Do you teach medical students and hematology
15 specifically to medical students? 03:08

16 A. Yes.

17 Q. And for how long have you been doing that?

18 A. Well, I've been in medical education my entire
19 career; and that might involve interns and residents.
20 And I'm a director of one of our residency programs, and 03:08
21 it might be students of various types.

22 MR. SCOTT: I believe that's everything I
23 have. Thank you, Doctor.

24 MR. WILLIAMS: Thank you, Doctor.

25 MR. ASHER: Whoa. 03:08

FURTHER EXAMINATION

BY MR. ASHER:

Q. Doctor, with regard to this question of
15 percent ringed sideroblasts in order to have a
diagnosis of RARS --

03:09

A. Yes.

Q. -- does that 15 percent count have to come in
any particular time? For example, if you have two bone
marrow samples taken at different times, an earlier bone
marrow sample doesn't show 15 percent but a later one
shows greater than 15 percent, is there any particular
time that 15 percent number has to appear?

03:09

A. No. And, of course, an earlier one might have
been a poor stain; but, in other words, you would have to
look at the case in total. But, typically, 15 percent or
greater makes a diagnosis along with the other features
of the illness.

MR. ASHER: Thank you, sir.

FURTHER EXAMINATION

BY MR. SCOTT:

03:09

Q. Since Ross has asked, now I have to. Do
repeated blood transfusions cause the development or
observation of ringed sideroblasts?

A. No.

MR. SCOTT: That's all I have. Thank you, 03:09

1 sir.

2 THE VIDEOGRAPHER: Going off the record.

3 The time now is 3:09.

4 (Signature requested.)

CHANGE AND SIGNATURE

PAGE	LINE	CHANGE	REASON
------	------	--------	--------

I, ETHAN A. NATELSON, M.D., have read the foregoing deposition and hereby affix my signature that same is true and correct, except as noted above.

ETHAN A. NATELSON, M.D.

THE STATE OF TEXAS

COUNTY OF

Before me, _____, on this day personally appeared ETHAN A. NATELSON, M.D., known to me (or provided to me under oath or through _____) to be the person whose name is subscribed to the foregoing instrument and acknowledged to me that they executed the same for the purposes and consideration therein expressed.

Given under my hand and seal of office this
day of _____, 2010.

NOTARY PUBLIC IN AND FOR
THE STATE OF

1 STATE OF TEXAS:

2 REPORTER'S CERTIFICATION
3 ORAL DEPOSITION OF ETHAN A. NATELSON, M.D.
4 TAKEN ON FEBRUARY 10, 2010

5 I, Minnie Cadena, Certified Shorthand
6 Reporter in and for the State of Texas, do
7 hereby certify that this deposition transcript is a true
8 record of the testimony given by the witness, ETHAN A.
9 NATELSON, M.D., after said witness was duly sworn by me.

10 The witness x was / ____ was not requested
11 to review the deposition.

12 I further certify that I am neither
13 attorney nor counsel for, related to, nor employed by any
14 of the parties to the action in which this testimony was
15 taken. Further, I am not a relative or employee of any
16 attorney of record in this cause, nor do I have a
17 financial interest in the action.

18 GIVEN under my hand and seal of office on
19 this the 15th day of February, 2010.
20

21
22 Minnie Cadena, CSR, RMR
23 CSR No. 5849
24 Expiration Date: 12-31-10
25 Preferred Legal Services, Inc.
Firm Registration No. 157
P.O. Box 551387
Dallas, Texas 75355

UNITED STATES DISTRICT COURT

for the
Southern District of Texas

Joyce Barrois, et al	)	
Plaintiff	)	
v.	)	Civil Action No. 09-380
Fireman's Fund Insurance Co., et al	)	
Defendant	)	(If the action is pending in another district, state where: Eastern District of Louisiana)

SUBPOENA TO TESTIFY AT A DEPOSITION IN A CIVIL ACTION

To: Ethan Natelson, MD.
6550 Fannin St., Suite 1001, Houston, Texas 77030

☒ **Testimony:** YOU ARE COMMANDED to appear at the time, date, and place set forth below to testify at a deposition to be taken in this civil action. If you are an organization that is *not* a party in this case, you must designate one or more officers, directors, or managing agents, or designate other persons who consent to testify on your behalf about the following matters, or those set forth in an attachment:

Place Houston Marriott at the Medical Center 6580 Fannin Street Houston, TX 77030	Date and Time: 02/10/2010 1:30 am
--	--------------------------------------

The deposition will be recorded by this method: Video and Oral Deposition

☒ **Production:** You, or your representatives, must also bring with you to the deposition the following documents, electronically stored information, or objects, and permit their inspection, copying, testing, or sampling of the material:

Documents identified in the attached Notice of Deposition and article entitled, Benzene Exposure and Refractory Sideroblastic Erythropoiesis: Is There an Association? by Ethan A. Natelson, MD.

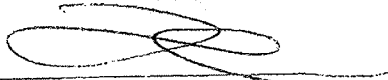
The provisions of Fed. R. Civ. P. 45(c), relating to your protection as a person subject to a subpoena, and Rule 45 (d) and (e), relating to your duty to respond to this subpoena and the potential consequences of not doing so, are attached.

Date: 1/27/10

CLERK OF COURT

OR

Signature of Clerk or Deputy Clerk


Attorney's signature

The name, address, e-mail, and telephone number of the attorney representing (name of party) Joyce Barrois, et al, who issues or requests this subpoena, are:
L. Eric Williams, Jr., Williams Law Office, LLC, 3000 W. Esplanade Ave., Ste. 200, Metairie, LA 70002, Tel: (504) 832-9898, eric@amlbenzene.net



Civil Action No. 09-380

PROOF OF SERVICE

(This section should not be filed with the court unless required by Fed. R. Civ. P. 45.)

This subpoena for (name of individual and title, if any) ETHAN NATELSON, M.D.
was received by me on (date) 1-28-2010 AT 7:00 AM CST.

☒ I served the subpoena by delivering a copy to the named individual as follows: IN PERSON
AT 6550 FANNIN STREET, SUITE 1001, HOUSTON, TEXAS 77030
on (date) 1-28-2010; OR AT 12:00 PM
NOON (CST)

☐ I returned the subpoena unexecuted because: _____

Unless the subpoena was issued on behalf of the United States, or one of its officers or agents, I have also
tendered to the witness fees for one day's attendance, and the mileage allowed by law, in the amount of
\$ 40.00 FEDERAL WITNESS FEE PLUS \$ 5.00 MILEAGE.

My fees are \$ 95.00 for travel and \$ _____ for services, for a total of \$ 95.00

PLUS \$ 45.00
WITNESS + MILEAGE
FEES.

I declare under penalty of perjury that this information is true.

Date: 1-28-2010

Jake Jacobsen - JAKE JACOBSEN
TEXAS Server's signature PROCESS SERVER

JAKE JACOBSEN - TEXAS PROCESS SERVER
Printed name and title LIC. # SCH-4317

Jake Jacobsen
Texas Process Server
Lic.# SCH-4317
STAR CIVIL PROCESS

Server's address

Additional information regarding attempted service, etc:

STAR CIVIL PROCESS
P.O. Box 133005
The Woodlands, TX
77393

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF LOUISIANA

JOYCE BARROIS, ET AL

Plaintiffs

versus

FIREMAN'S FUND INS. CO., ET AL

Defendants

*
*
*
*
*
*
*
*

CIVIL ACTION NO.: 09-380

SECTION: R

JUDGE: VANCE

MAGISTRATE: KNOWLES

VIDEO DEPOSITION NOTICE
OF ETHAN NATELSON, MD

TO: Ethan Natelson, MD
6550 Fannin St., Suite 1001
Houston, Texas 77030

PLEASE TAKE NOTICE that undersigned counsel for plaintiffs, Joyce Barrois, et al, pursuant to Federal Rules of Civil Procedure, shall conduct the video deposition upon oral examination of Ethan Natelson, MD, at 6550 Fannin St., Suite 1001, Houston, Texas, 77030, on February 10, 2010 at 1:30 p.m., and continuing from day to day until the deposition may be adjourned, concerning those areas of testimony and for the production of documents identified below.

The deponent is to produce the following documents at the time of the deposition;

- (1) A copy of all documentation regarding the article entitled, Benzene Exposure and Refractory Sideroblastic Erythropoiesis: Is There an Association? by Ethan A. Natelson, MD, including all rough drafts, peer reviewed comments, reference articles, funding sources, notes, invoices, payments, potential conflict of interest disclosures, a copy of the original article submitted to the journal.

RETURN OF SERVICE
ATTACHED

- (2) A list of all myelodysplastic syndrome cases that you have served as an expert or consultant in the last 10 years.
- (3) A copy of the scientific or medical literature that you reviewed in preparing this article.
- (4) A copy of all invoices that you have issued relating to any myelodysplastic syndrome cases that you have served as an expert or consultant in.
- (5) A list of all funding received for the preparation and publishing of this paper.
- (6) Your file regarding this article.
- (7) Documentation sufficient to establish your income for the last five years attributable for services rendered as an expert, and also to establish the percentage of your total income that is derived from providing expert witness services.
- (8) Documentation evidencing the total amount of income earned from litigation regarding myelodysplastic syndrome in the past 20 years.
- (9) Copies of all expert reports that you have submitted in myelodysplastic syndrome cases.
- (10) A list of all cases that you have served as an expert witness involving myelodysplastic syndrome.

RESPECTFULLY SUBMITTED:

L. Eric Williams, Jr.

L. ERIC WILLIAMS, JR. # 26773
WILLIAMS LAW OFFICE, LLC
3000 W. Esplanade Ave., Ste. 200
Metairie, Louisiana 70002
Telephone: (504) 832-9898
Facsimile: (504) 832-9838
eric@amlbcnzene.net

And

**RETURN OF SERVICE
ATTACHED**

/s/Richard J. Fernandez
Richard J. Fernandez, LA Bar # 05532
RICHARD J. FERNANDEZ, LLC
3000 West Esplanade Ave., Ste. 200
Metairie, Louisiana 70002
Telephone: (504) 834-8500
Facsimile: (504) 834-1511
rick@rjfernandezlaw.com
Attorneys for Plaintiffs

CERTIFICATE OF SERVICE

I HEREBY CERTIFY that a copy of the foregoing pleading has been served upon all known counsel of record, via electronic filing, this 27th day of January, 2010.

L. Eric Williams, Jr.

**RETURN OF SERVICE
ATTACHED**

Benzene Exposure and Refractory Sideroblastic Erythropoiesis: Is There an Association?

ETHAN A. NATELSON, MD

ABSTRACT: The myelodysplastic syndromes (MDS) consist of a group of diverse hematological disorders that carry an increased risk of transforming into acute myeloid leukemia. They may appear de novo and without obvious cause (primary or de novo MDS) or be induced by certain mutagenic environmental or therapeutic toxins (secondary MDS). Excessive exposures to benzene are generally considered to be a potential environmental risk factor for both MDS and acute myeloid leukemia. However, such risk is unproven for each disease component within the MDS classification. A critical review

of the refractory sideroblastic disorders strongly suggests that benzene exposure is not a potential cause of this distinct and still-evolving subset of MDS. The widely disparate nature of MDS suggests that epidemiologic studies can only provide meaningful data on associations and potential causation of its component syndromes by a disease-specific analysis, as is currently advocated for other hematological malignancies. **KEY INDEXING TERMS:** Benzene; Myelodysplasia; MDS; Refractory Sideroblastic Anemia. [Am J Med Sci 2007; 334(5):356-360.]

The terms myelodysplasia and the myelodysplastic syndromes (MDS) refer to a classification of heterogeneous and distinct disease forms linked by the presence of oligoclonal hematopoietic stem cell abnormalities, ineffective hematopoiesis characterized by abnormal differentiation and maturation of myeloid cells, and a variable but increased risk of progression toward acute myeloid leukemia.¹⁻⁶ A common etiology among each of the various myelodysplastic disorders that is also shared with acute myeloid leukemia (AML) has not been proposed, and little is known about the major causes of MDS.^{6,7} Unfortunately, epidemiological surveys seeking statistical information on hematological malignancies in cohorts potentially exposed to environmental chemicals or toxins seldom provide specific data on MDS, despite its higher incidence in the general population than AML.⁴ Moreover, in rare instances when information on MDS is collected and presented, it is usually treated as a single, distinct disease entity, and its numbers may be combined with those of AML or even other unrelated hematological malignancies in an attempt to achieve statistical significance in the analysis.⁸ Such approach obscures identification of potential etiologic risk fac-

tors that might be specific to the individual disease components within MDS and to the various AML syndromes. Thus, under certain circumstances, benzene exposure is an accepted, although uncommon, potential risk factor for both MDS and AML.^{1,6,7,9} However, when carefully studied (vide infra), such risk does not necessarily apply to all components of the MDS. This report reviews the clinical observations that provide specific information concerning the question of causal associations between benzene as an environmental toxin and the acquired refractory sideroblastic disorders, a readily identifiable subset of the MDS classification system.^{10,11}

Discussion

Refractory anemia with ringed sideroblasts (RARS) was a well-described and stand-alone hematopoietic disorder until 1982, when it was included among other hematological syndromes grouped under a then newly defined heading of MDS.¹²⁻¹⁵ Typically discussed in hematologic text chapters dealing with congenital and acquired sideroblastic anemias of diverse cause, RARS has been described under a variety of titles including acquired idiopathic refractory sideroblastic anemia and sideroachrestic anemia. Its unifying morphological feature is the presence of ringed sideroblasts, as identified by iron stains, in at least 15% of the bone marrow erythroid precursors throughout multiple areas of the bone marrow films or biopsy.^{1,4} Such histologic stains have been a part of the routine evaluation of bone marrow specimens for nearly 60 years.¹⁶ The variable but clearly preleukemic nature of RARS has

From the Transitional Residency Program, The Methodist Hospital, and Weill Medical College of Cornell University at The Methodist Hospital, Houston, Texas.

Submitted January 16, 2007; accepted in revised form May 2, 2007.

Correspondence: Ethan A. Natelson, MD, 6550 Fannin Street, Smith Tower 1001, Houston, TX 77030 (E-mail: enatelson@tmhs.org).

Table 1. Myelodysplastic Syndromes

Original FAB Divisions	Current WHO Divisions
Refractory anemia	Refractory anemia
RA-Ringed sideroblasts	RC-Multilineage dysplasia
RA-Excess (5-20%) blasts	RA-Ringed sideroblasts
RA-Excess (21-30%) blasts in transition	RC-RS-Multilineage dysplasia
Chronic myelomonocytic leukemia	RA-Excess (5-9%) blasts type I
	RA-Excess (9-19%) blasts type II
	MDS isolated deletion 5 q
	MDS unclassifiable

FAB, French-American-British format; WHO, World Health Organization; RA, refractory anemia; RC, refractory cytopenia; RS, ringed sideroblasts.

also been known since its earliest descriptions.^{13,15} In the original MDS classification scheme, the subset of individuals with RARS comprised about 10% to 20% of the total cases in most series, with the relative frequency, perhaps, age of onset-related.¹⁷ They exhibit the lowest incidence of classical chromosomal aberrations of all MDS subsets and the least frequency of progression to AML—approximately 15%.¹⁸⁻²¹ Certain chromosomal aberrations have been associated with RARS including long arm deletions of chromosomes 5, 11, and 20, as well as trisomy 8.²¹ None are specific, however, and particularly deletions of 20q and trisomy 8 are identified in a number of diverse hematological disorders.²¹⁻²³

Modern revised classification systems of MDS attempt to separate RARS into 2 general subsets, 1 currently referred to as refractory cytopenia with multilineage dysplasia-ringed sideroblasts (RCMD-RS), and a second entity with little evident morphologic cytologic dysplasia outside the erythroid cell line, and a lesser risk of AML (Table 1). It remains under the designation of RARS.^{1,11,19,20,24} Recently, a further clinically-useful separation of the refractory sideroblastic disorders has been suggested, segregating all patients with ringed sideroblasts and markedly elevated platelet counts into yet another subset designated RARS-T or RST to emphasize the presence of thrombocytosis.²⁴⁻²⁷ Many of the individuals in this third grouping may also possess the newly described JAK-2 V617F chromosomal abnormality, commonly identified in polycythemia vera and other myeloproliferative disorders.²⁶⁻²⁸ RARS-T could then also be listed under the newly suggested descriptive designation of myelodysplastic/myeloproliferative syndromes.²⁵ The recognition that some individuals with RARS and marked thrombocytosis might exhibit a clinical course more in keeping with a myeloproliferative disorder, with megakaryocytic hyperplasia and bone marrow fibrosis, similar to the natural history of polycythemia vera, primary thrombocythemia and agnogenic myeloid metaplasia, is not a new observation.²⁹ The presence of the JAK-2 V617F mutation among the RARS-T group provides a unifying molecular explanation. Importantly, my-

eloproliferative disorders have not been epidemiologically linked with exposures to either benzene or to modern mutagenic chemotherapy agents.

The frequency distribution of these 3 refractory sideroblastic syndromes, particularly between RARS and RCMD-RS, is clearly observer-dependent and also varies with the alternate classifications systems for MDS of the World Health Organization and the French-American-British (FAB) format.^{10,30} An estimate would place about 10% of the total as RARS-T. However, if the bone marrow blast cell count increases above 5%, and even if large numbers of ringed sideroblasts are retained, under these classification schemes individuals are now moved from an RARS syndrome into another MDS category, refractory anemia with excess blasts (RAEB). In effect, this movement arbitrarily diminishes the pool of cases with refractory sideroblastic hematopoiesis available for epidemiological or clinical analysis, and is a weakness of all MDS classifications.¹⁶ Importantly, occasional patients with RARS, even those with apparent multilineage cytologic dysplasia, may favorably respond to immunosuppressive therapy, and in rare instances the hematologic syndrome is actually consequent to unusual deficiency states.³¹⁻³⁴ Thus, progression to AML may not be a part of the natural history in certain forms of acquired sideroblastic anemia, emphasizing that all such disorders do not necessarily represent hematologic malignancies.

From the earliest descriptions, authors reporting on RARS pondered potential causes of this uncommon disorder. Wintrobe's experience in a single institution along with review of many additional cases led him and his associates to conclude that no specific drugs, environmental chemicals, alcohol, or cytostatic agents, could be confirmed as potential risk factors, and that the cause of RARS was unknown.¹² Benzene had previously been used as an oral chemotherapeutic agent in forms of chronic leukemia, and it was well known to cause bone marrow damage and potentially eventuate in AML. Exposure to this agent was specifically sought in an analysis of 84 patients with RARS, but only 1 of these subjects could recall any previous benzene exposure. Furthermore, that patient also had received radiation therapy.¹⁹ The collective experience now involving thousands of reported patients having received chemotherapy and then developing secondary hematologic syndromes including MDS, has only supplied rare case reports describing a chronic acquired sideroblastic process. This phenomenon has usually occurred in the presence of an underlying hematological malignancy, such as multiple myeloma or Hodgkin's disease, and is then noted after treatment including both alkylating agents and radiation.³⁵ Here, the acquired sideroblastic process, itself, is often transient and not evident in follow-up bone marrow examinations.^{36,37} Thus, neither exposure to

benzene nor to modern chemotherapeutic mutagenic agents has been shown to be a risk factor for RARS.

There are 3 major epidemiological studies often cited as offering detailed observations, including bone marrow analysis, which routinely includes iron stains, concerning the hematological effects of chronic, high-level benzene exposure. In the Hayes⁸ report of about 74,000 factory workers, primarily immersion painters in China, 28 individuals with either AML or MDS were cited. Analysis of the individual slide material from these MDS cases, and which specifically described bone marrow iron examination, showed no examples of RARS.³⁸ In the Aksoy³⁹ report of 29,000 Turkish shoe workers heavily exposed to benzene-containing glues, 42 individuals were described as developing forms of AML, among other hematological disorders. Yet, in his description of the specific hematologic abnormalities in this cohort, there is no observation consistent with RARS.⁴⁰ Finally, in the frequently-analyzed United States Pliofilm factory cohort of about 1,800 individuals exposed to large concentrations of pure benzene for many years, there are no reported details of bone marrow examinations, but no instance of a listed diagnosis consistent with RARS.⁴¹ A recent report from The MD Anderson Cancer Center also could not confirm solvent exposure as a significant predisposing event in their patients with RARS, or with chronic myelomonocytic leukemia, an original, and now former, member within the MDS classification system.⁷ In that study, such exposures were apparent risk factors for other forms of MDS such as refractory anemia with increased blasts (RAEB). In reality, there does not appear to be a single epidemiological study or even an isolated case report in the world's medical literature that links RARS with benzene exposure.

Recently, Irons et al⁴² carefully analyzed blood counts and serial bone marrow examinations on a small cohort of 23 Chinese workers heavily exposed to benzene. They reaffirmed earlier sporadic observations of marrow hypoplasia and eosinophilia in benzene-exposed workers but failed to identify the presence of ringed sideroblasts. Similarly, an absence of ringed sideroblasts was noted in careful bone marrow studies of 33 additional individuals with chronic benzene poisoning.⁴³ These marrow studies also demonstrated eosinophilia and dyspoietic erythroblasts. In general, the type of MDS bone marrow histology usually described in both heavily benzene-exposed individuals and therapy-related MDS is a hypocellular bone marrow with cellular dyspoiesis, and distinct from the usual findings in RARS which typically reflect a normocellular to hypercellular bone marrow pattern.^{38,44}

Cigarette smoke is considered a risk factor for both AML and MDS, but the specific element or mechanism involved is unknown.^{9,45-53} Cigarette smoke does contain some benzene, but the cumula-

tive dose achieved by smokers is less than thought necessary to increase the risk of AML, and the chromosomal anomalies identified in smokers with AML are somewhat different from those typically reported for benzene-induced and other secondary forms of AML.^{9,48-53} The chromosomal aberrations seen in the vast majority of benzene-induced AML and modern day chemotherapy-induced AML, or t-AML, are similar, with a predominance of deletions in chromosomes 5 and 7.⁹ This is not surprising, since postulated mechanisms of leukemogenesis in benzene-induced and t-AML, are also thought to be similar, if not identical.^{54,55} Some reports have suggested cigarette smoking is linked with RARS, although the mechanism is not known.^{7,46}

One feature of MDS that further confounds epidemiological analysis of its individual disease components is the fact that unlike AML, MDS is not a final illness designation, and individuals frequently move within the MDS classification over time. This is particularly true with respect to RARS syndromes. Thus, it would be expected that as the often slow progression to AML from the 3 refractory sideroblastic variants described here occurs, the percentage of blast cells in the bone marrow may increase gradually from its initially normal values. As previously mentioned, ringed sideroblasts are often still present when the bone marrow blast percentage reaches 5% to 10%, but the MDS diagnosis now moves to RAEB.^{17,56} When the blast percentage eventually reaches 20%, by convention, the diagnosis of AML is now allowed. Even if ringed sideroblasts remain evident in excess along with marked erythroid dyspoiesis, the specific diagnosis would be an FAB-M6 AML or erythroleukemia. Obviously, for such individual, this transition reflects a single disease process, and not 3 separate illnesses. This logic was first explained by Dameshek¹⁵ in 1965. For epidemiological purposes, should such a patient remain an example of an RARS syndrome or be considered to have the same illness as one with a sudden appearance of FAB-M6 AML without ringed sideroblasts or a prior diagnosis of MDS?

As our understanding of the molecular events leading to MDS and AML increases, epidemiologists and clinicians should work together to carefully analyze representative cohorts so that truly like illnesses are compared, in order to better identify potential risk factors. Simply abstracting a diagnosis from an often misleading and incomplete death certificate should become obsolete. A disease-specific approach is currently the rule in clinical studies that analyze the natural history and responses to therapy among the various disorders that make up the MDS classification.⁵⁷ Similar coordinated analyses by epidemiologists, pathologists and clinicians have been advocated and implemented for epidemiologic studies of the lymphoproliferative disorders, which also appear to have a number of distinct and disease

pattern-specific potential causes.^{58,59} Despite these caveats, based upon the considerable evidence presented here, benzene exposure cannot be considered a potential etiology for RARS, although it remains a risk factor for certain forms of MDS such as RAEB and unclassified and/or hypocellular MDS syndromes, and for AML.

References

1. Catenacci DVT, Schiller GJ. Myelodysplastic (sic) syndromes: a comprehensive review. *Blood Rev* 2005;19:301-19.
2. Kantarjian H. Myelodysplastic syndromes (MDS): what is new? *Leukemia Insights* 2006;11:1-7.
3. Aul C, Bowen DT, Yoshida Y. Pathogenesis, etiology and epidemiology of myelodysplastic syndromes. *Haematol* 1998; 83:71-86.
4. Cazzola M, Malcovati I. Myelodysplastic syndromes: coping with ineffective hematopoiesis. *N Engl J Med* 2005;352: 536-8.
5. Heaney M, Golde DW. Myelodysplasia. *N Engl J Med* 1999; 340:1649-60.
6. Breccia M, Mengarelli A, Mancini M, et al. Myelodysplastic syndromes in patients under 50 years old: a single institution experience. *Leuk Res* 2005;29:749-54.
7. Strom SS, Gu Y, Gruschkus SK, et al. EH Risk factors of myelodysplastic syndrome: a case control study. *Leukemia* 2005;19:1912-8.
8. Hayes RB, Yin S-N, Dosemici M, et al. Benzene and the dose-related incidence of hematologic neoplasms in China. *J Natl Cancer Inst* 1997;89:1065-71.
9. Estey E, Döhner H. Acute myeloid leukaemia. *Lancet* 2006; 368:1894-907.
10. Malcovati L, Della Porta MG, Pascutto C, et al. Prognostic factors and life expectancy in myelodysplastic syndromes classified according to WHO criteria: a basis for clinical decision making. *J Clin Oncol* 2005;23:7594-603.
11. Müller-Berndorff H, Haas PS, Kunzmann R, et al. Comparison of five prognostic scoring systems, the French-American-British (FAB) and World Health Organization (WHO) classifications in patients with myelodysplastic syndromes: results of a single-center analysis. *Ann Hematol* 2006;85: 502-13.
12. Kushner JP, Lee GR, Wintrobe MM, et al. Idiopathic refractory sideroblastic anemia: clinical and laboratory investigation of 17 patients and review of the literature. *Medicine* 1971;50:139-59.
13. Cheng DS, Kushner JP, Wintrobe MM. Idiopathic refractory sideroblastic anemia: incidence and risk factors for leukemic transformation. *Cancer* 1979;44:724-51.
14. Cazzola M, Barosi G, Gobbi PG, et al. Natural history of idiopathic refractory sideroblastic anemia. *Blood* 1988;71: 305-12.
15. Dameshek W. Sideroblastic anaemia: is this a malignancy? *Br J Haematol* 1965;11:52-8.
16. Beutler E, Robson MJ, Bittenwieser B. A comparison of the plasma iron, iron-binding capacity, sternal marrow iron and other methods in the clinical evaluation of iron stores. *Ann Intern Med* 1958;48:60-82.
17. Kuendgen A, Strupp C, Aivado M, et al. Myelodysplastic syndromes in patients younger than age 50. *J Clin Oncol* 2006;24:5358-65.
18. Vandermolen L, Rice L, Rose MA, et al. Ringed sideroblasts in primary myelodysplasia: leukemic propensity and prognostic factors. *Ann Intern Med* 1988;148:653-6.
19. Garand R, Gardais J, Bizet M, et al. Heterogeneity of acquired idiopathic sideroblastic anaemia (AISA). *Leukemia Res* 1992;16:463-8.
20. Germing U, Gattermann N, Arvedo M, et al. Two types of acquired idiopathic sideroblastic anaemia (AISA): a time tested distinction. *Br J Haematol* 2000;108:724-8.
21. Schwartz S, Jiji R, Meekins J, et al. Chromosome abnormalities in acquired idiopathic sideroblastic anemia with subsequent leukemic transformation. *Can Gen Cytogenet* 1986;19:291-9.
22. Olney HJ, Le Beau MM. Evaluation of recurring cytogenetic abnormalities in the treatment of myelodysplastic syndromes. *Leuk Res* 2007;31:427-34.
23. Kurtin PJ, Dewald GW, Shields DJ, et al. Hematologic disorders associated with deletions of chromosome 20q: a clinicopathologic study of 107 patients. *Am J Clin Pathol* 1996;106:680-8.
24. Cabello AI, Collado R, Ruiz MA, et al. A retrospective analysis of myelodysplastic syndromes with thrombocytosis: reclassification of the cases by WHO proposals. *Leuk Res* 2005;29:365-70.
25. Shaw GR. Ringed sideroblasts with thrombocytosis: an uncommon mixed myelodysplastic/myeloproliferative disease of older adults. *Br J Haematol* 2005;31:180-4.
26. Szpurka R, Tiu G, Murugesan S, et al. Refractory anemia with ringed sideroblasts associated with marked thrombocytosis (RARS-T), another myeloproliferative condition characterized by JAK2 V617F mutation. *Blood* 2006;2173-31.
27. Boissinot M, Garand R, Hamidou M, et al. The JAK2-V617F mutation and essential thrombocythemia features in a subset of patients with refractory anemia with ring sideroblasts (RARS). *Blood* 2006;108:1781-2.
28. Villeval J-L, James C, Pisani DF, et al. New insights into the pathogenesis of JAK2 V617F-positive myeloproliferative disorders and consequences for the management of patients. *Semin Thromb Haemost* 2006;32:341-351.
29. Scully RE, Mark EJ, McNeely WF, et al. BU Weekly Clinicopathological Exercises (case 17-1992). *N Engl J Med* 1992;326:1137-46.
30. Malcovati L, Germing U, Kuendgen A, et al. Time-dependent prognostic scoring system for predicting survival and leukemic evolution in myelodysplastic syndromes. *J Clin Oncol* 2007;25:3503-10.
31. Zervas J, Geary CG, Olesky S. Sideroblastic anemia treated with immunosuppressive therapy. *Blood* 1974;44: 117-23.
32. Lin J-T, Wang W-S, Yen C-C, et al. Myelodysplastic syndrome complicated by autoimmune hemolytic anemia: remission of refractory anemia following mycophenolate mofetil. *Ann Hematol* 2002;81:723-6.
33. Natelson E. Pregnancy-induced pancytopenia: distinctive hematological features. *Am J Med Sci* 2006;332:205-7.
34. Huff JD, Keung Y, Thakuri M, et al. Copper deficiency causes reversible myelodysplasia. *Am J Hematol* 2007;82 advance e-publication.
35. Kitahara M, Cosgriff TM, Eyre HJ. Sideroblastic Anemia as a preleukemic event in patients treated for Hodgkin's disease. *Ann Intern Med* 1980;92:625-7.
36. Magalhães SMM, Durate FB, Ribeiro SCC, et al. Sideroblastic anemia following treatment of chronic myeloid leukemia with busulfan. *Leukemia* 2002;14:214-5.
37. Fernandez LA, Zayed E. Busulfan-induced sideroblastic anemia. *Am J Hematol* 1998;28:199-200.
38. Linet MS, Yin S-N, Travis LB, et al. Clinical features of hematopoietic malignancies and related disorders among

Benzene and Refractory Sideroblastic Erythropoiesis

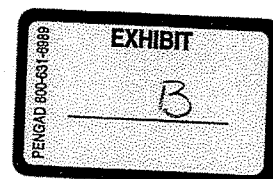
- benzene exposed workers in china. *Environ Health Perspect* 1996;104:1353-64.
39. Aksoy M. Different types of malignancies due to occupational exposure to benzene: a review of recent observations in Turkey. *Environ Res* 1980;23:181-90.
40. Aksoy M, Dinçol K, Akgün T, et al. Haematological effects of chronic benzene poisoning in 217 workers. *Br J Indust Med* 1971;28:296-302.
41. Rinsky RA, Hornung RW, Silver SR, et al. Benzene exposure and hematopoietic mortality: a long-term epidemiologic risk assessment. *Am J Indust Med* 2002;42:474-80.
42. Irons RD, Lv L, Gross SA, et al. Chronic exposure to benzene results in a unique form of dysplasia. *Leukemia Res* 2005;29:1371-80.
43. Ruiz MA, Augusto LGS, Vassallo J, et al. Bone marrow morphology in patients with neutropenia due to chronic exposure to organic solvents (benzene): early lesions. *Path Res Pract* 1994;190:151-4.
44. Orazi A. Histopathology in the diagnosis and classification of acute myeloid leukemia, myelodysplastic syndromes and myelodysplastic/myeloproliferative diseases. *Pathobid* 2007;74: 97-114.
45. Björk J, Albin M, Mauritzson N, et al. Smoking and myelodysplastic syndromes. *Epidemiol* 2000;11:285-91.
46. Pasqualetti P, Festucia V, Acitelli P, et al. Tobacco smoking and risk of haematological malignancies in adults: a case-control study. *Br J Haematol* 1997;97:659-62.
47. Carmona R. The Surgeon General's 2004 report, The Health Consequences of Smoking. US Dept Health and Human Services, Chap 2, p 254.
48. Chelghoum Y, Danaïla C, Belhabri A, et al. Influence of cigarette smoking on the presentation and course of acute myeloid leukemia. *Ann Oncol* 2002;13:1621-7.
49. Lichtman MA. Cigarette smoking, cytogenetic abnormalities, and acute myelogenous leukemia. *Leuk* 2007;21: 1137-40.
50. Thomas X, Chelghoum Y. Cigarette smoking and acute leukemia. *Leuk Lymphoma* 2004;45:1103-9.
51. Kane EV, Roman E, Cartwright R, et al. Tobacco and the risk of acute leukaemia in adults. *Br J Cancer* 1999;81:1228-33.
52. Davico L, Sacerdote C, Ciccone G, et al. Chromosome 8, occupational exposures, smoking, and acute nonlymphocytic leukemias: a population-based study. *Can Epidemiol Biomarkers Prev* 1998;7:1123-5.
53. Moorman AV, Roman E, Cartwright RA, et al. Smoking and the risk of acute myeloid leukaemia in cytogenetic subgroups. *Br J Cancer* 2002;86:60-2.
54. Smith MA, McCaffrey RP, Karp JE. The secondary leukemias: challenges and research directions. *J Natl Cancer Inst* 1996;88:407-18.
55. Morgan GJ, Alvares CL. Benzene and the hematopoietic stem cell. *Chemico-Biol Interact* 2005;153-154:217-222.
56. Yoshida Y, Oguma S, Tohyama K, et al. Diagnostic and biological significance of sideroblastic erythropoiesis in the myelodysplastic syndromes. *Int J Hematol* 1998;67:137-44.
57. List A, Kurtin S, Roe DJ, et al. Efficacy of Lenalidomide in myelodysplastic syndromes. *N Engl J Med* 2005;352: 549-57.
58. Alexander DD, Mink PJ, Adami HO, et al. The non-Hodgkin lymphomas: A review of the epidemiologic literature. *Int J Can* 2007;120:1-39.
59. Wang SS, Slager SL, Brennan P, et al. Family history of hematopoietic malignancies and risk of non-Hodgkin lymphoma (NHL): a pooled analysis of 10211 cases and 11905 controls from the International Lymphoma Epidemiology Consortium (InterLymph). *Blood* 2007;109:3479-88.

10/74 MDS
5/79 RAAS

Testimony Given by Dr. Ethan A. Natelson

The following is a list of cases in which I have testified at trial or by deposition, since Jan. 1992.

1. *Elbert M. Mims vs. Amoco Oil Co.* circa Oct. 1992. This was Texas Worker's Comp. Commission Docket No. GA-91-1701-10-CC-GA41. I testified at a hearing for the defendant, concerning the issue of benzene and chronic granulocytic leukemia.
2. *Lee Cheshire* case. I have no remaining information about the specific court. I testified both by deposition and at trial held in civil court in Dallas, Texas, testifying for the plaintiff, circa Nov. 1994. The plaintiff attorney was Mr. Stephen A. Khoury. The case had to do with death following coronary artery bypass surgery alleged to be from an adverse reaction to protamine.
3. *Brenda Jones, et al. vs. Sisters of Charity of the Incarnate Word, et al.*, in the 133rd Judicial District Court of Harris County, Texas, #92053234, circa 6-15-1994. I testified as to responsibilities of interns and residents, by deposition, for the defendants.
4. *Jerry Smothers vs. Reliance National Company.* Texas Worker's Comp. Commission Docket No. HE/94-179074-02-CC-SA44. Also U.S. District Court for the Southern District of Texas. Case had to do with acute lymphoblastic leukemia and benzene exposure. I testified at a hearing, for the defendant, circa May 30, 1995.
5. *Lillie Poston vs. Monsanto*, 10th Judicial District Court of Galveston County, Texas. Case had to do with multiple myeloma and its relation to benzene exposure. I testified by deposition, for the defendant, circa 12-4-1995.
6. *Michael N. Forino vs. Charles Mooney*, 15th Judicial District Court of Grayson County, Texas. Case had to do with a death following splenectomy for thrombocytopenia. I testified by deposition, for the plaintiff, circa 7-5-95.
7. *Karen Camp vs. Harris Methodist Ft. Worth Hosp.*, 352nd Judicial District Court of Tarrant County, Texas. Case had to do with death following failure to appropriately treat severe anemia. I testified by deposition, for the plaintiff, circa 12/1995.
8. *Terry Joe Groom vs. Schlumberger.* Case had to do with Hodgkin's disease and causation. I testified for the defendant, by deposition, circa 1/1996. I do not have the court citation but this was Fulbright & Jaworski, Cause No. 94-42682.
9. *Lottie Rene Carter vs. Jerry Darrell Martin*, 12th Judicial District Court, Walker County, Texas. I testified for the defendant, by deposition, on July 24, 1996. Case had to do with death following orthopedic surgery.



10. *Jesus Valentine Frias vs. Shell Oil*. In District Court of Harris County, Texas, 270th Judicial District Court. Case had to do with benzene and causation of aplastic anemia. I testified for the defendant, by deposition on Sept. 25, 1996.
11. *Lester Barrett, et al. v. Mobil Oil, et al.*, in the 60th District Court of Jefferson County, Texas. Case had to do with causation of gastric lymphoma. I testified by deposition on 10-22-97, for the defendant.
12. *Stacy Lynn Wolff, et al. v. Mario Villafani, et al.*, in the 201st Judicial District Court of Travis County, Texas. I testified by deposition on 6-4-97, and later in live trial, in Austin, testifying for a defendant, St. Joseph Hospital, on the responsibilities of interns and residents assigned to Brackenridge Hospital in Austin, Texas.
13. *York vs. Texaco, et al.*, Fulbright & Jaworski Case No. E149519. Testifying by deposition on 1-26-98, as the treating physician. Case had to do with allegations of benzene exposure as a cause of aplastic anemia.
14. *Runnels, et al. vs. Catholic Charities, et al.*, in the 172nd Judicial District Court of Jefferson County, Texas. Testified by deposition on Feb. 23, 1998, for the plaintiff. Case involves accidental injury and allegations concerning the health effects of sickle cell trait and anemia. Woodard, Hall & Primm was plaintiff's firm.
15. *Tarin vs. Exxon*, in the 122nd Judicial District Court, Galveston County, Texas. Testified by deposition on July 6, 1998, for the defendant. Case had to do with allegations of benzene exposure as a cause of lymphoma.
16. *Brenda Brown, et al. vs. The Women's Hospital of Texas, et al.*, Case No. 97-02708 in the 133rd Judicial District Court of Harris County, Texas. Testified by deposition at the invitation of plaintiff's attorney in Feb. 1999. Case had to do with maternal death following a term pregnancy.
17. *Estella Sanchez v. Magnetek, Inc., et al.*, in the United States District Court for the Southern District of Texas, Brownsville Division. Testified by deposition on July 26, 1999, for the defendant. Case had to do with allegations that exposure to chemicals caused cerebral non-Hodgkin's lymphoma.
18. *Mike Adalis, et al. v. Exxon, et al.*, in the 269th Judicial District Court of Harris County, Texas. Testified for defendant by deposition on 8-11-99, and at trial on 11-16-99. Case had to do with allegations of disease causation by chemicals, including benzene, in the water supply.
19. *James Elmer Warren, Jr. vs. Sabine Towing, et al.*, in the 14th Judicial District Court of Calcasieu Parish, Louisiana. Testified for defendant by deposition on 3-15-2000, and in court on 10-27-2000. Case had to do with allegations of benzene as a cause of myeloproliferative disease.

20. *Arthur Jones, et al. vs. Harold Mullins, M.D., et al.*, in the 55th Judicial District Court of Harris County, Texas. Testified as a treating physician (non-suited) as requested by the Defendant, by deposition on April 10, 2000. Case had to do with allegations of inadequate care by a primary care physician.
21. *Deborah Hamill vs. Sisters of Charity, et al.*, in the 189th Judicial District Court of Harris County, Texas. Testified by deposition on June 28, 2000. Case had to do with allegations concerning the non-renewal of a general surgery resident's contract with St. Joseph Hospital.
22. *Donald Ward, et ux vs. Atlantic Richfield Co., et al.*, in the 60th Judicial District Court, Jefferson County, Texas. Testified by deposition on January 18, 2002. Case had to do with allegations of chemical cause for idiopathic sideroblastic anemia.
23. *Adene Hill vs. Crown Central Petroleum, et al.*, in the U.S. District Court for the Eastern District of Virginia, No. 01-CV-1395-A. Testified by deposition for the defendant on April 22, 2002, and at trial on Aug. 2, 2002. Case had to do with causation in acute myeloid leukemia.
24. *Howard Collins vs. American Petrofina, Inc., et al.*, in the 136th Judicial District Court of Jefferson County, Texas. Testified by deposition for the defendant on May 17, 2002. Case had to do with allegations that chemical exposure to benzene caused refractory sideroblastic anemia.
25. *Geneva Parsley, et al. vs. Terminix International, et al.*, in the U.S. District Court of Ohio, Western Division-Dayton, Ohio. Testified by deposition for the defense on August 21, 2002, and before a binding arbitration panel on Oct. 11, 2002, in Cincinnati, Ohio. Case had to do with allegations that Isophenphos exposure resulted in the illness of agnogenic myeloid metaplasia.
26. *Bonnie Wilcox and Charles Wilcox vs. Memorial Hermann Baptist Beaumont Hospital*. Testified by deposition for the defendant on Oct. 23, 2002. Case had to do with allegations that an intravenous infiltration caused loss of an extremity and death.
27. *Ivan Merritt, et ux vs. Mallinckrodt, Inc., et al.*, in the 214th Judicial District Court, Nueces County, Texas. Testified for the defendant by deposition on 4-16-03. Case had to do with allegations that chronic lymphocytic leukemia was caused by chemical exposures.
28. *Jacob Cave v. Exxon Mobil Corporation, et al.*, in the Circuit Court of Marshall County, West Virginia, Civil Action No. 01-C-19M. Testified for the defendant by deposition on 10-24-03, and at trial on 2-25-04. Case had to do with allegations that benzene and aromatic hydrocarbons caused non-Hodgkin's lymphoma.

29. *Patrick Davis, et al. vs. Houston Northwest Partners, et al.*, No. 202-17939, in the 165th Judicial District Court of Harris County, Texas. Testified for the defendants by deposition on 11-21-03. Case had to do with allegations of improper care of sickle cell disease and treatment of pneumonia.
30. *James Cowey, et al. vs. Radiator Specialty Company, et al.*, in the 58th Judicial District Court of Jefferson County, Texas. Testified by deposition for the defendant on Dec. 3, 2003. Case had to do with allegations of chemical (benzene) exposure as a cause of myelodysplastic syndrome.
31. *Ronald E. Awalt, et al. vs. Applied Energy Services, Inc., et al.*, in the Circuit Court of the Third Judicial Circuit, Madison County, Illinois. Testified by deposition for the defense on Dec. 22, 2003. Case had to do with allegations of causation of myelodysplastic syndrome.
32. *Lavon S. Lee, et al. vs. Christine M. Eady, et al.*, in the 250th Judicial District Court of Travis County, Texas. Testified for the defense by deposition on 4-23-04. Case had to do with allegations of failure to properly diagnose and treat peripheral vascular disease.
33. *Stella Jean Patterson, et al. vs. Jagathia Challagalla, M.D., et al.*, Cause No. 157,578-C, in the 89th Judicial District Court of Wichita County, Texas. Testified at trial for the defense on 9-3-2004. Case had to do with allegation of failure to properly diagnose Budd-Chiari Syndrome in a patient with non-Hodgkin's lymphoma.
34. *James Boren, et al. vs. The Dow Chemical Company, et al.*, Cause No. 17958*JG01, in the 239th Judicial District Court of Brazoria County, Texas. Testified by deposition for the defense on Sept. 17, 2004. Case had to do with allegations of causation of acute promyelocytic leukemia.
35. *Federico Tagle vs. Citgo Refining & Marketing, Inc., et al.*, Cause No. 01-4891-E, in the 148th Judicial District Court of Nueces County, Texas. Testified by deposition for the defense on Oct. 4, 2004. Case had to do with allegation of causation in idiopathic sideroblastic anemia.
36. *Daniel T. Minnehan, et al. vs. American Oil Company, et al.*, Cause No. 21916*JG02, in the 239th Judicial District Court of Brazoria County, Texas. Testified for the defense by deposition on October 20, 2004. Case had to do with allegations that benzene caused AML.
37. *Michael A. Lebron, et al. vs. Shell Oil Company, et al.*, Civil Action 00L10021, in the Circuit Court of Cook County, Illinois, County Department – Law Division, State of Illinois. Testified by deposition for the defendant on Oct. 27, 2004. Testified again by deposition on November 11, 2008 with restyling as Cause No. 05 L 9246. Case had to do with a dispute concerning diagnosis and allegations of causation of disease in a patient with hepatitis B and renal failure.

38. *Patrick Sean Murphy, et al. vs. Robert Weinstein, DDS, MS, et al.*, Cause 03-7749-C, in the County Court at Law No. 3, Dallas County, Texas. Testified by deposition for the plaintiff on 3-28-05. Case had to do with allegation of improperly administered parenteral dental anesthesia causing acute compartment syndrome and loss of an arm.
39. *Denizilye M. Douglas, et al. vs. Ashland, Inc., et al.*, Civil Action No. 01-CI-00392, Commonwealth of Kentucky, Greenup Circuit Court, Civil Division. Testified by deposition for the defendant on June 1, 2005. Case had to do with allegations of chemicals in causation of multiple myeloma.
40. *Robert E. Scherer, et ux, et al. vs. S&S Automotive, Inc., et al.*, in the Circuit Court of the 19th Judicial Circuit, Lake County, Illinois. Testified by deposition for the defendant on September 15, 2005. Case had to do with allegations of a chemical causation of chronic myelomonocytic leukemia (CMML).
41. *Melissa Daville vs. German Newall, M.D.*, Cause No. 2004-35094, in the Judicial District Court of Harris County, Texas. Testified by deposition for the plaintiff on Oct. 19, 2005. Case had to do with allegations of complications of liposuction as a cause of pulmonary and cerebral venous sinus thrombosis and blindness.
42. *Edward Crofton, et al. vs. Amoco Chemical Company, et al.*, Cause No. 95CV1352, in the 10th Judicial District Court of Galveston County, Texas. Testified by deposition for the defendant on Dec. 12, 2005. Case had to do with allegations of causation, by chemical exposures, of various lymphoproliferative disorders.
43. *Doris Sue Scott, et al. vs. Radiator Specialty Company, et al.*; In the District Court of Brazoria County, Texas; 23rd Judicial District. Testified for the defendant, by deposition, on Feb 13, 2006. Case has to do with allegations of chemical causation of acute myeloid leukemia (AML).
44. *John Ringstaff and Karen Ringstaff, et al. v AMOCO Chemical Co., et al.*, CA. No. 03-CV-0551, In the 56th Judicial District, Galveston County, Texas. Testified for the defense, by deposition on 2-22-06, and at trial on 3/27-3/28, 2006. Case had to do with allegations of benzene as causation of chronic lymphocytic leukemia (CLL).
45. *George Loveless, et al v. Ashland, Inc., et al*; Cause No. 4:04CV00972 GTE, In the United States District Court, Eastern District of Arkansas, Western Division. Testified by deposition for the defense on 4-19-06, Case has to do with allegations of causation of chronic lymphocytic leukemia (CLL) and non-Hodgkin lymphoma (NHL).
46. *Herbert W. Wilkinson and Peggy S. Hebert vs. Radiator Specialty Company, et al*; Cause No A030272-GC and *Ann Stubbs, Individually, and as Representative of the Estate of and as Wrongful Death Beneficiary of Ben L. Stubbs vs Radiator Specialty Co., et al*; Cause No. A030272-CC; In the 128th Judicial District Court

of Orange County, Texas. Testified for the defense on 5-10-2006 by deposition. Case has to do with allegations that benzene caused Hodgkin's disease, non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukemia.

47. *Cause 00-5021E, Debra Angell v. Oxychem Corp., et al* In the District Court of Nueces County, Texas 148th Judicial District. Testified for the defense on August 11, 2006, by deposition. Case has to do with allegations of causation in acute myeloid leukemia.
48. *Case No. 04-00545; Donna Cashiola, et al vs. American Petroleum, et al.* In the District Court of Dallas County, Texas 298th Judicial District. Testified by deposition for the defense on 10-27-06, and at trial on 11-28-06. Case has to do with allegation of causation in acute myeloid leukemia.
49. *Cause CL98152; Margaret J. Mielke, et al. v. Ashland, Inc., et al.;* In the Iowa District Court in and for Polk County, Fifth Judicial District. Testified by deposition on 11-27-06. Case has to do with allegations concerning causation of acute myeloid leukemia in a patient with underlying polycythemia rubra vera.
50. *Theresa Frazier, Administrator of Estate of Robert Frazier, Deceased, Plaintiff vs. Fairfield Medical Center, et al., Defendants,* Case No 06 CV285, In the Court of Common Pleas, Fairfield County, Ohio. Testified by deposition on 4-11-07 and 8-8-07, at the request of the plaintiff's attorney. My testimony was limited to issues relating to the use of the term, coumadin (Warfarin) resistance, as it appears in the medical literature and in common medical usage. Case has to do with death from unrecognized myocardial infarction and allegations of improper emergency clinic medical evaluation.
51. *Aubrey Clark and Wife, Kelly Clark v. Kellogg Brown & Root, LLC and Halliburton Company; In the District Court of Matagorda County, Texas 23rd Judicial District. Cause No. 06-H-0395-C.* Testified by deposition on April 30, 2007. The case was restyled as *No. 2:07-CV-191(TJW-CE); Aubrey Clark v. Kellogg Brown & Root, L.L.C., et al; in the United States District Court; Eastern District of Texas*, and I testified in court for the defendant on January 17, 2008. Action had to do with allegations of causation in AML with 6;9 translocation.
52. *Guy Hamman, et al. v. American Oil Company, et al:* Cause No. E-173418: In the 172nd Judicial District Court of Jefferson County, Texas. Testified by deposition on July 31, 2007. Case has to do with allegations of causation in a patient with acquired refractory sideroblastic anemia evolving into erythroleukemia.
53. *Ruth Vettrus, as Trustee for the Heirs and Next of Kin of Robert Vettrus, Decedent, et al vs. Ashland, Inc., et al;* In the District Court, 3rd Judicial District, County of Rice, State of Minnesota. Cause C9-04-000817. Testified by deposition on 8-8-2007. Case has to do with allegations of causation in AML.
54. *Charles Wilson and Laura Wilson v. Rycoline Products, Inc., et al.,* In the United States District Court for the Eastern District of Texas, Marshall Division. Civil

Action No. 2-06CV-286. Testified by deposition for the defense on 9-17-2007. Case has to do with allegations concerning the causation of refractory anemia with ringed sideroblasts (RARS).

55. *Dorsey McCann vs. The Sherwin Williams Co., et al.*; Cause No. 33871, In the Parish of LaSalle, State of Louisiana, 28th Judicial District Court. Testified by deposition for the defense in a case alleging benzene exposure as a cause of AML, on September 26, 2007.
56. *Duane Draper, et al., v. PPG Industries, Inc., et al.* Cause No. 199-02538-04, In the District Court of Collin County, Texas 199th Judicial District. Testified by deposition for the defense in a case alleging benzene exposure in paints as a cause for AML on December 10, 2007.
57. *Karen White, Individually and as Representative of the Estate of Mack Ivory White, deceased, et a. vs. Syed J.Zaheer, M.D., Victoria Gordon, M.D., et al.*, In the 60th Judicial District Court of Jefferson County, Texas. Testified for the plaintiff on January 30, 2008, by deposition. Case has to do with allegations concerning the emergency treatment of thrombotic thrombotic purpura (TTP).
58. *Arnold Wayne Russell and Pamela Russell v. Ashland Chemical, Inc., UNOCAL, and Monochem, Inc.*; Cause No. 04-4116, In the United States District Court, Western District of Arkansas, Texarkana Division. Testified for the defense by deposition on Feb-29-2008, and at trial on August 26th 2008. Case has to do with allegations of AML caused by benzene exposure during work in the tire building industry.
59. *Neil Henriksen and Maurita Henriksen, v. Chevron Phillips Chemical Company, LP, et al., NO. CV-07-224-JLQ.* In The United States District Court Eastern District of Washington at Spokane. Testified by deposition for the defense on April 11, 2008. Case has to do with allegation of AML caused by exposure to gasoline and diesel fuels.
60. *Bryn Duffy, et al. v. Rodolfo E. Martinez, M.D., et al., Cause No. 2005-532,528;* In the 237th District Court in and for Lubbock County, Texas. Testified by deposition for the defense on May 19, 2008. Case has to do with allegations concerning pulmonary thromboemboli in a patient with the primary anti-phospholipid syndrome.
61. *Walton Wayne Segree, Individually and as Executor of the Estate of Brenda Ruth Segree, Deceased, et al. v. CVS Pharmacy, Inc.; Civil Action No. 9:07cv189;* In the United States District Court for the Eastern District of Texas, Lufkin Division. Testified by deposition for the defense on 6-25-2008. Case has to do with allegations concerning the cause and the date of onset of a subdural hematoma which was identified shortly prior to death.
62. *Civil Action No.: CV-06-1258; Connie Lea Gibson Andrews, Individually and as personal Representative of Tommy Lindell Andrews, Deceased vs. United States*

Steel Corporation, et al; In the Fifth Judicial District Court, County of Chaves, State of New Mexico. Testified for the defense in a hearing for summary judgment in a case concerning allegations of solvent exposure as a cause of myelodysplasia (RARS), on August 18th, 2008.

63. *Eugene and Patricia Salmieri, vs. Sunoco, Inc., f/k/a Sun Company, Inc. et al.*, CCP, Philadelphia County, April Term, 2006, No.:002439. Testified for the defense by deposition on September 19, 2008. Case had to do with allegations of causation of small cell lymphocytic lymphoma (SLL) by exposure to gasoline.
64. *Rosalinda Kerwin, Individually and as Representative of the Estate of Maria Del Rosario Rico, Deceased vs. Mansur Nathoo, M.D.; and CHCA Clear Lake, L.P.* In The District Court of Harris County, Texas 164th Judicial District. Testified for the defense by deposition on 10-24-2008. Case has to do with allegations of poor treatment by a general internist concerning the post-operative death of a patient undergoing orthopedic surgery for a severe, displaced hip fracture.
65. *Robert B. Oakley and Irene Oakley vs. Air Products and Chemicals, et al.; Cause No. 2:07-CV-00351*; In the United States District Court for the Eastern District of Texas; Marshall Division. Testified for the defense by deposition on 11-5-2008. Case has to do with allegations of causation in acute myeloid leukemia.
66. *Isabel Hollister, et al. v. BP Amoco Chemical Company, et al.*; In the County Court at Law No. 3 of Galveston County, Texas. Testified for the defense by deposition on 4-24-2009. Case has to do with allegations of causation of Inv 16 AML by benzene and other chemicals.
67. *Joann V. Bishop, Individually, and as the legal representative of James Manuel Bishop, Jr., et al. vs. Shell Oil Company, et al.*, In the United States District Court Eastern District of Louisiana, Civil Action No. 07-2832. Testified for the defense on 6-5-2009. Case has to do with allegations of chemical causation of multiple myeloma.
68. *Bonnie L. Mallory, Executrix of the Estate of Robert E. Mallory, Deceased v. The Goodyear Tire & Rubber Company, et al. Court of Common Pleas of Summit County, Ohio.* Case No. 2007-11-8033. Testified by deposition on June 24, 2009. Case has to do with allegations of causation of MDS and AML.
69. *Andrew Wolfe and Denise Wolfe, vs. E.I. DuPont de Nemours and Company et al. In the General Court of Justice Superior Court Division, County of Forsyth, State of North Carolina.* Civil Action 07-CVS-3370. Testified by deposition on July 16, 2009. Case has to do with allegations of causation of acute promyelocytic leukemia.
70. *Fred M. Cantu and Ruth Cantu vs. Amoco Chemical Company, et al; In the 56th Judicial District Court of Galveston County.* Cause No: 07-CV-0594. Testified for the defense on July 27th 2009. Case has to do with allegations of causation in primary gastric MALT non-Hodgkin's lymphoma.

71. *Barbara Barker, as Personal Representative of the Estate of Terry Barker, Deceased, v. Go-Mart, Inc., et al.* Cause No: 04-C-75K; *In the Circuit Court of Marshall County, West Virginia.* Testified for the defense by deposition on August 14, 2009. Case has to do with allegations of causation in acute myeloid leukemia.
72. *Raul Zendejas and Araceli Zendejas vs. Shell Oil Co., et al;* Cause No. CV 2007-005399; *In the Superior Court of Arizona, Maricopa County.* Testified by deposition for the defense on September 25, 2009, and at trial on November 12, 2009. Case has to do with allegations that exposure to gasoline caused the myeloproliferative disorder known as Philadelphia chromosome negative BCR/ABL negative, chronic myeloid leukemia (aka atypical chronic myeloid leukemia).
73. *Darla J. Lemaire, Individually and as Independent Executrix of the Estate of Michael Lemaire, deceased, and Logan Lemaire v. Berryman Products, Inc, et al;* Cause No. E-0178440; *In the 172nd Judicial District Court of Jefferson County, Texas.* Testified for the defense by deposition on October 9, 2009. Case has to do with allegations of benzene-induced causation in AML.
74. *Mary Ellen Hall(John O'Neal Hall, deceased) vs. Radiator Specialty Company, et al;* Cause No. 08CV0161; *In the 212th Judicial District Court of Galveston County, Texas.* Testified for the defense by deposition on January 18, 2010. Case has to do with allegations of benzene-induced causation in myelodysplasia (MDS).

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF TEXAS
MARSHALL DIVISION

06 JUL 13 AM 11:07

120 E. HILL

CHARLES WILSON and
LAURA WILSON

Plaintiffs,

vs.

RYCOLINE PRODUCTS, INC.;
ROGERSOL, INC.;
HOSTMAN-STEINBERG, INC.;
I C COMPOUND COMPANY;
ASHLAND, INC , individually and f/k/a
ASHLAND OIL & REFINING
COMPANY and ASHLAND OIL, INC.;
ALLIED PHOTO OFFSET SUPPLY
CORPORATION;
DAY INTERNATIONAL, INC., individually
and d/b/a VARN PRODUCTS;
ALLIED PHOTO OFFSET SUPPLY
CORPORATION; and
LASTRA AMERICA CORPORATION,

Defendants

CIVIL ACTION FILE NO:

BY _____

2-06 CV-286

LED

ORIGINAL PETITION

TO THE HONORABLE JUDGE OF SAID COURT:

NOW COMES CHARLES WILSON and LAURA WILSON, hereinafter referred to as Plaintiffs, complaining of RYCOLINE PRODUCTS, INC; ROGERSOL, INC.; HOSTMAN-STEINBERG, INC.; I C. COMPOUND COMPANY; ASHALND, INC., individually and f/k/a ASHLAND OIL & REFINING COMPANY and ASHLAND OIL, INC.; ALLIED PHOTO OFFSET SUPPLY CORPORATION; DAY INTERNATIONAL, INC , individually and d/b/a VARN PRODUCTS; and LASTRA AMERICA CORPORATION, hereinafter referred to as "Defendants,"



and for cause of action would respectfully show this Court and Jury the following:

VENUE, PARTIES AND JURISDICTION

Plaintiffs Charles Wilson and wife Laura Wilson ("Plaintiffs") are residents of the state of Texas.

This Court has jurisdiction over the lawsuit pursuant to 28 U.S.C. §1332(a)(1) because Plaintiffs and Defendants are citizens of different states and the amount in controversy exceeds \$75,000.00 excluding interest and costs.

Venue is proper pursuant to 28 U.S.C. §1391(a) as a substantial part of the acts and omissions occurred in this judicial district.

ALLEGATIONS COMMON TO ALL COUNTS

1 Defendants RYCOLINE PRODUCTS, INC.; ROGERSOL, INC.; HOSTMAN-STEINBERG, INC.; I.C. COMPOUND COMPANY; ASHALND, INC., individually and f/k/a ASHLAND OIL & REFINING COMPANY and ASHLAND OIL, INC.; ALLIED PHOTO OFFSET SUPPLY CORPORATION; DAY INTERNATIONAL, INC., individually and d/b/a VARN PRODUCTS; and LASIRA AMERICA CORPORATION are hereinafter referred to collectively as "Defendants".

2 Plaintiff Charles Wilson and his wife Laura Wilson ("Plaintiff") are residents of the State of Texas.

3 Defendant, **RYCOLINE PRODUCTS, INC.** is a Delaware Corporation doing business in the State of Texas and may be served with citation through its registered agent for service, to wit: Leonard Allen, 4421 Garland Road, Fort Worth, TX 76117-1812.

4 **ROGERSOL, INC.** is a Delaware Corporation doing business in the State of Texas but does not maintain a registered agent for service in Texas. Defendant, **ROGERSOL, INC.** may

be served with process by serving the Texas Secretary of State with process to be forwarded to: Rogersol, Inc , 5540 North Northwest Highway, Chicago, IL 60630.

5. Defendant, **HOSTMAN-STEINBERG, INC.** is a Georgia Corporation doing business in the State of Texas and may be served with citation by serving its registered agent, to wit: CSC-Lawyers Incorporating Service Company, 701 Brazos Street, Suite 1050, Austin, TX 78701

6. Defendant, **I.C. COMPOUND COMPANY** is a California Corporation doing business in the State of Texas, but does not maintain a registered agent for service in Texas. Defendant, **I.C. COMPOUND COMPANY**, may be served with process by serving the Texas Secretary of State with process to be forwarded to: I.C. Compound Company, 120 E 163rd Street, P.O. Box 66, Gardena, CA 90248.

7. Defendant, **ASHLAND, INC.**, individually and f/k/a **ASHLAND OIL & REFINING COMPANY** and **ASHLAND OIL, INC.** is a Kentucky corporation doing business in the State of Texas and may be served with citation by serving its registered agent, to wit: CSC-Lawyers Incorporating Service Company, 701 Brazos Street, Suite 1050, Austin, TX 78701

8. Defendant, **ALLIED PHOTO OFFSET SUPPLY CORPORATION** is a foreign corporation doing business in the State of Texas but does not maintain a registered agent for service in Texas. Defendant, **ALLIED PHOTO OFFSET SUPPLY CORPORATION**, may be served with process by serving the Texas Secretary of State with process to be forwarded to 2040 Lee Street, Hollywood, FL 33020

9. Defendant, **DAY INTERNATIONAL, INC.**, individually and d/b/a **VARN PRODUCTS**, is a Delaware corporation doing business in the State of Texas and may be served with citation by serving its registered agent, to wit: Jerry B. Mabry, Three Riverway Suite 400, Houston, TX 77056.

10. Defendant, **LASTRA AMERICA CORPORATION**, is a Delaware Corporation doing business in the State of Texas and may be served with citation by serving its registered agent, to wit: CI Corporation System, 350 N. St. Paul Street, Dallas, TX 75201.

11. CHARLES WILSON worked as a pressman at Frankston Packaging Company in Frankston, Texas from 1978-2005. During this time and in the course of his work, through inhalation, breathing, smelling and/or direct contact with skin, he was exposed to benzene and benzene-containing products including, but not limited to: blanket washes, press washes, varnish removers, plate cleaners, roller washers and other solvents and chemicals (hereinafter referred to as "Products") CHARLES WILSON was diagnosed with Myelodysplastic Syndrome in December 2005. LAURA WILSON is CHARLES WILSON's wife.

COUNT ONE – NEGLIGENCE

12. Plaintiffs would show that CHARLES WILSON was exposed to a deadly situation by all the Defendants in this case. Plaintiff alleges, as more specifically set out below, that CHARLES WILSON contracted Myelodysplastic Syndrome, and such illness was proximately caused by Defendants' negligent acts, and by CHARLES WILSON's exposure to products designed, produced, manufactured, marketed, placed into the system of commerce, sold or used by Defendants.

13. CHARLES WILSON's illness and Plaintiffs' subsequent damages are a direct and proximate result of the negligence of each Defendant or, where applicable, the employee or the agent of one or more Defendants

14. Defendants, at all times material to this action, had a duty to any and all consumers and workers, including CHARLES WILSON, to exercise reasonable care in creation, manufacturing, production, and distribution of their respective products into the stream of commerce, including a duty to assure the products did not pose a significantly increased risk of injury, including, without

limitation, myelodysplastic syndrome. Defendants breached the duty owed to Plaintiffs and were negligent in the following respects:

- a. Defendants knew that the products they utilized, distributed, marketed, and/or manufactured were deleterious, poisonous, carcinogenic, and highly harmful to Wilson's body and health; notwithstanding which, Defendants failed to take any precautions or to warn Wilson of the dangers and harm to which he was exposed while handling these products;
- b. Defendants knew that products used by or in proximity to Wilson were carcinogenic, deleterious, and highly harmful to his body and health and that Wilson would not have known of such dangerous properties; notwithstanding which, the Defendants failed to provide Wilson with sufficient knowledge as to what would be reasonably safe and sufficient wearing apparel and proper protective equipment and appliances to protect him from being damaged by exposure to such products;
- c. Defendants knew that the products used by or in proximity to Wilson contained carcinogenic and highly harmful substances to the human body and health; notwithstanding which, the Defendants failed to take any precautions or to exercise care by placing any warnings or cautions on the containers of such products or the products themselves to warn the handlers thereof the dangers to health in coming into contact with these products;
- d. The Defendants knew that the products used by or in proximity to Wilson contained deleterious and carcinogenic substances; notwithstanding which, the Defendants failed to take reasonable care to warn Wilson of said danger and/or instruct Wilson in the proper handling of said products or to take proper precautions or exercise care to protect Wilson from harm and failed to timely adopt and enforce a safety plan method of handling products;
- e. Defendants knew or should have known that their products that they introduced into the stream of commerce were carcinogenic and failed to adequately warn;
- f. Defendants supplied products with marketing, design, and/or manufacturing defects; and
- g. Such other acts or omissions of negligence, gross negligence, malice and/or strict products liability that may be proven at trial.

15. Such acts and omissions constituting negligence were a proximate cause of the illness of CHARLES WILSON and injuries and damages sustained by Plaintiffs.

COUNT TWO – STRICT LIABILITY

16. All of the allegations contained in the previous paragraphs are re-alleged herein. This count is applicable to all Defendants

17. The products and/or materials to which CHARLES WILSON was exposed were designed, produced, manufactured, marketed, sold and/or otherwise put into the stream of commerce by Defendants, and were used for their intended purpose.

18. Plaintiff would further show that the products in question were defective and not reasonably fit for the purposes and uses for which they were intended at the time they left the hands of the Defendants, in that Defendants failed to give the users adequate warnings or instructions concerning product dangers that were known or should have been known to the Defendants by the application of reasonably developed skill and foresight. The failures to warn on the part of the Defendants rendered such products unreasonably dangerous at the time they left the hands of the Defendants and were the proximate cause of CHARLES WILSON's resulting disease and the damages sustained by Plaintiffs.

COUNT THREE – BREACH OF WARRANTY

19. This count is applicable to all Defendants. The Defendants were merchants with respect to their benzene-containing products. In connection with the manufacture, design, assembly, sales, supply, delivery, handling, marketing, advertising and instructing in the use of benzene-containing products, Defendants warranted, either expressly or impliedly, that their products were merchantable, when in fact they were not. These products were unfit for the ordinary purpose or uses for which their products were intended, including their use and handling by human beings. Further, these Defendants breached express and implied warranties under the Texas Uniform Commercial Code.

COUNT FOUR – GROSS NEGLIGENCE

20 All of the allegations contained in the previous paragraphs are re-alleged herein. This count is applicable to all Defendants.

21 The actions and inactions of all the Defendants, and or alternatively the employees or agents of Defendants and their predecessors-in-interest, whether taken separately or together, were of such a character as to constitute a pattern or practice of intentional wrongful conduct and/or malice resulting in the damages sustained by Plaintiffs. More specifically, Defendants, or alternatively the employee or agent of Defendants and their predecessors-in-interest, consciously and/or deliberately engaged in fraud, wantonness and/or malice with regard to CHARLES WILSON.

22. Defendants had actual awareness of the extreme degree of risk associated with exposure to the carcinogenic and poisonous products they utilized, manufactured, processed, and/or distributed, and nevertheless proceeded with conscious indifference to the rights, safety, and welfare of CHARLES WILSON by failing to act to minimize or eliminate these risks. Therefore, Defendants are guilty of gross negligence for which they should be held liable for punitive and exemplary damages to Plaintiffs.

RELIEF SOUGHT

23. CHARLES WILSON was diagnosed with myelodysplastic syndrome in December 2005 and underwent extensive treatment for his disease. The conduct of Defendants, as alleged hereinabove, was a direct, proximate and producing cause of the injuries and illness to CHARLES WILSON, and the following general and special damages that Plaintiffs sustained:

- a. Reasonable and necessary medical expenses incurred by CHARLES WILSON in the past;
- b. Reasonable and necessary medical expenses to be incurred by CHARLES WILSON in the future;

- c. The conscious physical pain and suffering and mental anguish sustained by CHARLES WILSON in the past and future;
- d. The physical impairment suffered by CHARLES WILSON;
- e. The disfigurement suffered by CHARLES WILSON;
- f. Loss of earnings suffered by CHARLES WILSON, past and future;
- g. Loss of consortium, companionship and society, including the loss of the positive benefits flowing from the love, comfort, companionship, consortium, and society that LAURA WILSON would have received from CHARLES WILSON if not for his illness and injuries;
- h. The mental anguish suffered by Plaintiffs due to the injuries and illness of CHARLES WILSON;
- i. Plaintiffs seek punitive and exemplary damages.

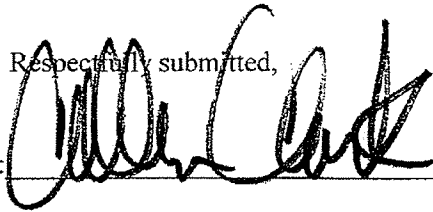
JURY DEMAND

24. Plaintiffs have requested a jury trial and tendered the jury fee.

CONCLUSION

WHEREFORE, PREMISES CONSIDERED, Plaintiffs demand that Defendants answer herein as the law directs, and that upon final hearing, this Court enter Judgment against all Defendants for actual, special and exemplary or punitive damages together with interest thereon at the legal rate, costs of court, and for other such additional and further relief, special and general, at law and in equity, which Plaintiffs show just and proper in accordance with the law.

Respectfully submitted,

By: 

SCHMIDT & CLARK

Collen A. Clark

Texas Bar No. 04309100

Michael E. Schmidt

Texas Bar No. 00785361

Keith E. Patton

Texas Bar No. 24032821

2911 Turtle Creek Blvd.

Suite 1400

Dallas, Texas 75219

(214) 521-4895

(214) 521-9995 (fax)

DURHAM & PITTARD, LLP

F. Leighton Durham, III

Texas Bar No. 24012569

Kirk L. Pittard

Texas Bar No. 24010313

P. O. Box 190310

Dallas, Texas 75219

(214) 946-8000

(214) 946-8433 (fax)

COUNSEL FOR PLAINTIFFS

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF TEXAS
MARSHALL DIVISION

CHARLES WILSON AND WIFE,
LAURA WILSON,
Plaintiffs,

v.

RYCOLINE PRODUCTS, et al.
Defendants.

§ Civil Action No. 2-06CV-286

§

§

§

§

§ JURY DEMANDED

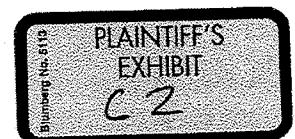
§

§

DEFENDANT ASHLAND INC., INDIVIDUALLY AND F/K/A ASHLAND OIL &
REFINING COMPANY AND ASHLAND OIL INC.'S
PRELIMINARY TRIAL WITNESS LIST

TO: Plaintiffs Charles and Laura Wilson by and through their attorneys of record Colleen A. Clark, Michael E. Schmidt and Keith E. Patton of Schmidt & Clark, 2911 Turtle Creek Blvd., Suite 1400 Dallas, Texas 75219 and F. Leighton Durham, III and Kirk L. Pittard of Durham & Pittard, LLP, P.O. Box 190310 Dallas, Texas 75219

Ashland Inc., Individually and f/k/a Ashland Oil & Refining Company and Ashland Oil Inc., ("Ashland") a defendant in the above referenced case, makes the following preliminary identification of Trial Witnesses in accordance with Federal Rule of Civil Procedure 26A(3)(a) and by Court order. This identification is preliminary and Defendant Ashland reserves the right to supplement it. Defendant Ashland hereby identifies the following trial witnesses which Ashland expects to or may call at the trial of the above-referenced matter (see attached Exhibit "A" hereto which is incorporated herein by reference as though fully set forth herein).



Respectfully submitted,

By: /s/Ricky A. Raven

Ricky A. Raven
State Bar # 16585500
Thompson & Knight LLP
333 Clay Street, Suite 3300
Houston, Texas 77002
Phone: 713.654.8111
Fax: 713.654.1871
Email: Ricky.Raven@tklaw.com

ATTORNEY IN CHARGE FOR
DEFENDANT ASHLAND INC.

OF COUNSEL:

THOMPSON & KNIGHT, LLP
333 Clay Street, Suite 3300
Houston, Texas 77002-4499
Telephone: (713) 654-8111
Telecopier: (713) 654-1871

CERTIFICATE OF SERVICE

Pursuant to Fed.R.Civ.P. 5(b), this is to certify that a true and correct copy of Defendant Ashland Inc.'s Preliminary Trial Witness List has been served upon all counsel of record by the Court mandated electronic filing system on this 17th day of July, 2007.

/s/ Ricky A. Raven

Ricky A. Raven

Collen Clark
Michael E. Schmidt
Keith A. Patton
Schmidt & Clark, LLP
2911 Turtle Creek Boulevard, Suite 1400
Dallas, TX 75225
Phone: (214) 521-4898
Fax: (214) 521-9995
COUNSEL FOR PLAINTIFFS

F. Leighton Durham, III
Kirk L. Pittard
Durham & Pittard, L.L.P.
P.O. Box 190310
Dallas, TX 75219
Phone: (214) 946-8000
Fax: (214) 946-8433
COUNSEL FOR PLAINTIFFS

James N. Isbell
James Louis Hordern, Jr
Janis H. Detloff
Jason M. Yacuk
Thompson Coe Cousins & Irons
One Riverway, Suite 1600
Houston, TX 77056
Phone: 713-403-8210
Fax: 713-403-8299
***COUNSEL FOR DEFENDANTS RYCOLINE PRODUCTS, INC. AND
ROGERSOL, INC.***

Jason Todd Wagner
Wesson H. Tribble
Tribble Ross & Wagner
3050 Post Oak Blvd., Suite 1350
Houston, TX 77056
Phone: 713-622-0444
Fax: 713-622-0555
***COUNSEL FOR DEFENDANTS DAY INTERNATIONAL, INDIVIDUALLY AND
D/B/A VARN PRODUCTS***

George Read Carlton
Paul Milton Bass, III
Godwin Pappas Langley Ronquillo
1201 Elm St., Suite 1700
Dallas, TX 75270
Phone: 214-939-4400
Fax: 214-760-7332
COUNSEL FOR DEFENDANT HOSTMANN-STEINBERG, INC.

Dale B. McMath
Sheehy Serpe & Ware
909 Fannin Street, Suite 2500
Houston, TX 77010-1003
Phone: 713-951-1071
Fax: 713-951-1199

COUNSEL FOR DEFENDANT I.C. COMPOUND COMPANY

C. Robert Dorsett, Jr.
State Bar No. 24029524
Damon Robertson
State Bar No. 24005285
Savrick Schumann Johnson McGarr Kaminski & Shirley
4330 South Mopac, Suite 150
Austin, TX 78735
Phone: 512-347-1604
Fax: 512-347-1676

***COUNSEL FOR DEFENDANT
ALLIED PHOTO OFFSET SUPPLY CORPORATION***

James L Moore
Gregory C. Ulmer
Baker & Hostetler
1000 Louisiana, Suite 2000
Houston, TX 77002-5009
Phone: 713-646-1374
Fax: 713-276-1626
***COUNSEL FOR DEFENDANT
LASTRA AMERICA CORPORATION
(AGFA CORPORATION)***

Gregory W. Carboy
David A. Johnson
Cowles & Thompson, P.C.
901 Main Street, Suite 4000
Dallas, Texas 75202
Phone: 214-672-2169
Fax: 214-672-2369
***COUNSEL FOR THIRD-PARTY DEFENDANT
FPBOT CORPORATION***

William O. Ashcraft, Esq.
Ashcraft Law Firm
3900 Republic Center
325 North St. Paul Street
Dallas, Texas 75201
Phone: 214-987-0660
Fax: 214-987-3847

***COUNSEL FOR THIRD-PARTY DEFENDANT
FRANKSTON PACKAGING COMPANY, L.P.***

EXHIBIT A

Defendant Ashland Inc.'s Preliminary Trial Witness List

Defendant Ashland reserves the right to supplement this list of Trial Witnesses should additional witnesses be identified before trial. To the extent that a witness expresses an opinion at trial or in discovery that has not been divulged prior to the time that this designation was served on counsel and which creates a need for additional areas of rebuttal testimony or proof, Defendant Ashland reserves the right to supplement this identification.

I. Defendant Ashland expects to present the following persons as witnesses at the time of trial:

Ethan A. Natelson, M.D.

- Defendant Ashland's retained expert

Wayne R. Snodgrass, M.D., Ph.D.

- Defendant Ashland's retained expert

John W. Spencer, CIH, CST

- Defendant Ashland's retained expert

Gerhard K. Raabe, M.D.

- Defendant Ashland's retained expert

Tom Keenan

- Ashland Inc.

Buddy Whitlock

- Ashland Inc.

David Pemberton

- Ashland Inc.

II. Defendant Ashland may present the following persons, either live or through deposition testimony, as witnesses at the time of trial should the need arise:

Charles Wayne Wilson, Sr. - Plaintiff

- Defendant Ashland may call Mr. Wilson as an adverse witness to question him regarding the factual bases for Plaintiffs' claims.

Laura Wilson - Plaintiff

- Defendant Ashland may call Mrs. Wilson as an adverse witness to question her regarding the factual bases for Plaintiffs' claims.

Mark Nicas, Ph.D., MPH, CIH

- Plaintiffs' Retained Expert Witness

Peter F. Infante, D.D.S., Dr.P.H.

- Plaintiffs' Retained Expert Witness

Dr. Richard A. Parent, Ph.D., D.A.B.T., F.A.T.S., R.A.C., E.R.T.

- Plaintiffs' Retained Expert Witness

Dale Funderburk, Ph.D.

- Plaintiffs' Retained Expert Witness

Aubrey Underhill

- Employee, supervisor, and co-worker of Mr. Wilson at the Frankston Box Company facility

Edwin Adcock

- Frankston Plant Manager from September 2003 - October 2006

Norm Bullock

Kyle Eldred

- Owners of Frankston Box Company and/or Frankston Packaging

Bill McCamm

- Plant manager for Frankston Box Company facility who hired Charles Wilson to work at the Frankston facility

Dave Tiechmann

- General manager for Frankston Box Company facility: approximately 2001-2003

Duane Odom

- Employee and salesman for Frankston Box Company facility

Patrick Debusk

- Employee and designer at Frankston Box Company facility

Mark Wilkins

- Employee and quality control manager at Frankston Box Company facility

Jason Jacobs

- Employee and cutting supervisor at Frankston Box Company facility

Troy House

- Employee and helper to Mr. Wilson at Frankston Box Company facility

Joyce McClain

- Employee of Frankston

Michael Warren

- Employee and co-worker with Mr. Wilson at Frankston Box Company facility

Jay Taylor

- Employee and first pressman with Mr. Wilson at Frankston Box Company facility

O.J. Boatfield

Tony Muddle

James McBride

Kenny Patterson

- Employees and co-workers with Mr. Wilson at Frankston Box Company facility

Randy Burshett

- Employee and gluer operator at the Frankston Box Company facility

Barbara Reeves

- Employee, bookkeeper and customer service at the Frankston Box Company facility

Tracy Black

Michelle Hutchins

Cindy Pace

- Employees in purchasing department at the Frankston Box Company facility

Custodian of Records for Frankston Packaging Company

- Employer of Plaintiff

Les Johnson

- Frankston Packaging Company

Unidentified employees of Frankston Packaging Company

- Employer of Plaintiff

Shop Rite Foods, Inc. - Custodian of Records (Personnel and Payroll) c/o Registered Agent G. Nash Lamb

- Former employer of Plaintiff

George Consolidated, Inc. - Custodian of Records (Personnel and Payroll) c/o LD George

- Former employer of Plaintiff

Pepsi-Cola Company- Custodian of Records (Personnel and Payroll)

- Former employer of Plaintiff

Precision Inspection, Inc.- Custodian of Records (Personnel and Payroll) c/o Joe Sink, Jr.

- Former employer of Plaintiff

Texas Sanitation Co. - Custodian of Records (Personnel and Payroll)

- Former employer of Plaintiff

United Stevedoring Corporation- Custodian of Records (Personnel and Payroll)

- Former employer of Plaintiff

Metils, Inc. - Custodian of Records (Personnel and Payroll) c/o Linda Lundgren

- Former employer of Plaintiff

Naylor Industries Inc.- Custodian of Records (Personnel and Payroll) - c/o William Naylor

- Former employer of Plaintiff

Aerojet-General Corporation - Custodian of Records (Personnel and Payroll)

- Former employer of Plaintiff

Big Three Industries, Inc. - Custodian of Records (Personnel and Payroll) c/o Corporation Services Company

- Former employer of Plaintiff

Superior Insulation Company - Custodian of Records (Personnel and Payroll) c/o Registered Agent Roy Jacobie, Jr.

- Former employer of Plaintiff

East Texas Drilling Company, Inc. - Custodian of Records (Personnel and Payroll) c/o B. Keith Bristow

- Former employer of Plaintiff

Unidentified Corporate Representatives, Custodians of Records, and/or Current/Former Employees of the Texas Natural Resources Conservation Commission

- May have records of materials at the Frankston facility

Unidentified Corporate Representatives, Custodians of Records, and/or Current/Former Employees of Safety-Kleen

- May have records of materials at the Frankston facility

Dr. Charles Haas

- Charles Wilson's treating physician

Gary E. Gross, M.D.

- Charles Wilson's treating physician

Custodian of Records/Representative of Mother Francis Hospital

- Charles Wilson's treating physician

Dr. Gary Babbitt

- Charles Wilson's treating physician

Dr. David Johnson

- Charles Wilson's treating physician

Custodian of Records of Azalea Orthopaedics and Sports Medicine Clinic

- Medical provider

Unidentified Corporate Representative and Employees of Azalea Orthopaedics and Sports Medicine Clinic

- Medical provider

Custodian of Records of Cardiovascular Consultants of Tyler

- Medical provider

Unidentified Corporate Representative and Employees of Cardiovascular Consultants of Tyler

- Medical provider

Custodian of Records of Robert J. Carney, M.D.

- Medical provider

Unidentified Corporate Representative and Employees of Robert J. Carney, M.D.

- Medical provider

Custodian of Records of Family Healthcare of East Texas

- Medical provider

Unidentified Corporate Representative and Employees of Family Healthcare of East Texas

- Medical provider

Pathology Associates of Tyler, P.A. – medical provider

- Andrew D. Kulaga, M.D.
- Arthur W. Zieske, M.D.

Unidentified Corporate Representative and Employees of Pathology Associates of Tyler, P.A.

- Medical provider

Custodian of Records of Pulmonary Associates of East Texas

- Medical provider

Unidentified Corporate Representative and Employees of Pulmonary Associates of East Texas

- Medical provider

Custodian of Records of Quest Diagnostics, Inc.

- Medical provider

Unidentified Corporate Representative and Employees of Quest Diagnostics, Inc.

- Medical provider

Custodian of Records of Thomas Lyles, M.D.

- Medical provider

Unidentified Corporate Representative and Employees of Thomas Lyles, M.D.

- Medical provider

Richard Kronenberg, M.D.

- Medical provider

Custodian of Records of Trinity Clinic

- Medical provider

Unidentified Corporate Representative and Employees of Trinity Clinic

- Medical provider

Custodian of Records of Trinity Mother Francis Clinic – Lake Palestine

- Medical provider

Trinity Cardiology

- David Dick, M.D. – treating physician
- Roderick B. Meese, M.D. – treating physician
- Unidentified employees – provided medical care
- Custodian of Records – provided medical care

Trinity Mother Francis Clinic – Lake Palestine

- Unidentified Corporate Representative and Employees – medical providers
- Charles E. Jones, M.D. – treating physician
- Sam Raborn, M.D. – treating physician
- Carrie Moore - Custodian of Records
- Ann Calvert-White - Custodian of Billing Records

Trinity Mother Francis Hospital - medical providers

- Robert J. Carney, M.D.
- Bill J. Wright, M.D.
- Royal Becker, M.D.
- Kevin Short, M.D.
- Mark Anderson, M.D.
- David Hector, M.D.
- Charles D. Haas, M.D.
- Edward Dominguez, M.D.
- Peter K. Meyers, M.D.
- Lazel B. Augustus, M.D.
- Paul J. Lim, M.D.
- Robert Gaddy, M.D.
- Pete Andrews, M.D.
- Doug Macha, M.D.
- Kent Walker, M.D.
- Ralph Gutierrez, M.D.
- Thomas Arnold, M.D.
- E. Stroupe, M.D.
- Unidentified employees

Trinity Mother Francis Hospital

- Laura Thompson - Custodian of Medical Records
- Leavern Walker Custodian of Billing Records

The Trinity Clinic Pulmonary Disease Division

- Lazel Augustus, M.D. – treating physician
- Unidentified employees – medical provider
- Custodian of Records

Tyler Radiology Associates

- E. Maxey Abernathy, M.D. – treating physician
- Unidentified Employees – medical providers
- Custodian of Records

Tyler Cardiovascular Consultants

- David A. Hector, M.D. – treating physician
- Frank Navetta, M.D. – treating physician

East Texas Orthopedics

- M. Joseph Shepherd, M.D. – treating physician
- Unidentified employees – healthcare providers
- Custodian of Records

Family Healthcare of East Texas

- Julie T. Haygood, M.D. – treating physician
- Unidentified employees – health care providers
- Custodian of records

Quest Diagnostics

- R.E. Reitz, M.D. – treating physician
- Unidentified employees – health care providers
- Custodian of records

Custodian of Records of M.D. Anderson Cancer Center

- Medical provider

Unidentified Corporate Representative and Employees of M.D. Anderson Cancer Center

- Medical provider

Custodian of Records of East Texas Medical Center at Athens

- Medical provider

Unidentified Corporate Representative and Employees of East Texas Medical Center at Athens

- Medical provider

Custodian of Records of Linda S. O'Brien, M.D.

- Medical provider

Unidentified Corporate Representative and Employees of Linda S. O'Brien, M.D.

- Medical provider

Custodian of Records of Urology Tyler/Stanton Champion, M.D.

- Medical provider

Unidentified Corporate Representative and Employees of Urology Tyler/Stanton Champion, M.D.

- Medical provider

Custodian of Records of Mutual of Omaha Insurance Company and/or United of Omaha Life Insurance Company

- Insurer

Unidentified Corporate Representative and Employees of Mutual of Omaha Insurance Company and/or United of Omaha Life Insurance Company

- Insurer

Custodian of Records of Blue Cross Blue Shield of Texas

- Insurer

Unidentified Corporate Representative and Employees of Blue Cross Blue Shield of Texas

- Insurer

Heritage Health Plans

- Insurer

Custodian of Records of Trustmark Companies

- Insurer

Texas Department of Assistive and Rehabilitative Services- Disability Determination Services Plan

- Paul Zapata
- Unidentified employees
- Custodian of records

Unidentified Corporate Representative and Employees of Trustmark Companies

- Insurer

Custodian of Records of Metils, Inc.

- Former employer

Unidentified Corporate Representative and Employees of Metils, Inc.

- Former employer

Custodian of Records of Kellogg Brown & Root

- Former employer

Unidentified Corporate Representative and Employees of Kellogg Brown & Root

- Former employer

Custodian of Records of Texas Workforce Commission

- Benefits provider

Unidentified Corporate Representative and Employees of Texas Workforce Commission

- Benefits provider

Steven Donnell, Custodian of Records of Social Security Administration

- Benefits provider

Unidentified Corporate Representative and Employees of Social Security Administration

- Benefits provider

Unidentified Corporate Representative and Employees of FPBOT, Inc.

- Former employer of Plaintiff

Custodian of Records of Blood and Cancer Center of East Texas

- Medical provider

Unidentified Employees of Blood and Cancer Center of East Texas

- Medical provider

Sherry Wells

- Custodian of Medical and Billing Records at Blood and Cancer Center of East Texas

Unidentified Corporate Representative and Employees of Blood and Cancer Center of East Texas

- Medical provider

Custodian of Records, Unidentified Corporate Representative, and Employees of Texas Workers Compensation Commission – Division of Workers' Health & Safety, including Ed Blakemore

- Investigated work environment

Custodian of Records, Unidentified Corporate Representative, and Employees of Texas Department of Health – Toxic Substances Control Division – Hazard Communication Branch

- Investigated work environment

Custodian of Records, Unidentified Corporate Representative, and Employees of Anchor Risk Management Services, Inc., including Joyce A. Witham

- Investigated work environment

III. Additional Witnesses

Defendant Ashland reserves the right to call any and all treating physicians, custodians of records, hospitals and other healthcare providers of Charles Wilson identified in Plaintiffs' responses to discovery, depositions, and medical records obtained from said treating physicians, hospitals, and other healthcare providers, including but not limited to any and all appropriately qualified documents custodians as to Plaintiffs' medical records, and all records made or kept by such witnesses. These witnesses and exhibits will relate to the course of Charles Wilson's medical treatment, any and all health conditions suffered by Charles Wilson, and the diagnosis and causes of Charles Wilson's illness.

Defendant Ashland reserves the right to call any and all witnesses identified at any time in any way in discovery in these actions by Plaintiffs, and any and all witnesses necessary to provide rebuttal evidence. By this designation, Defendant Ashland does not agree that such witnesses are qualified, or necessarily agree with any of their opinions. Defendant Ashland simply makes this designation in order to have the ability to use or elicit testimony or cross-examination from such person.

Defendant Ashland reserves the right to call any person designated by any other party in this case as an expert witness, whether or not such party is still a party at the time of trial as well as all expert witnesses listed by Plaintiffs, custodians of records of any and all physicians, health care facilities, hospitals, clinics and health care providers who have treated or examined Charles Wilson in this case who may have records concerning Charles Wilson, and any physician who has examined and/or treated Charles Wilson not identified.

Defendant Ashland explicitly designates all expert witnesses designated by any defendant in this case, whether or not that defendant is still a party at the time of trial.

Defendant Ashland designates any expert witness deposed in this case.

Defendant Ashland designates any physician or records custodians, who have examined, treated, and/or evaluated Charles Wilson.

Defendant Ashland designates any doctor, records custodians, or medical provider identified by Plaintiffs in deposition testimony or any discovery response.

Defendant Ashland designates any and all health care providers and records custodians, not listed, who have examined or treated Charles Wilson.

Defendant Ashland designates any other witnesses not listed whom Plaintiffs have named, or current and/or former Defendants in this litigation, as adverse witnesses.

Defendant Ashland reserves the right to amend and supplement this response as additional information is located.

**Methodist Methodist Academic
Medicine Associates**

Ethan A. Natelson, MD, FACP
Director, Transitional Residency
6550 Fannin Street
Smith Tower, Suite 1001
Houston, Texas 77030
Direct Dial 713-441-5154
Clinic 713-441-0006
Fax 713-790-2727
enatelson@tmh.tmc.edu
www.methodisthealth.com

June 22, 2007

Mr. Kevin J. Parks
Thompson & Knight LLP
Three Allen Center
333 Clay Street, Suite 3300
Houston, Texas 77002-4499

RE: Civil Action No: 2-06CV-286, Charles Wilson and Laura Wilson vs. Rycoline Products, Inc.
et al. In The United States District Court For the Eastern District of Texas, Marshall Division

Dear Mr. Parks,

Thank you for allowing me to review the medical records and additional materials that you provided concerning the above action. As you are aware, I am a Board-certified hematologist in clinical practice at The Methodist Hospital, in Houston, Texas, where I also serve as Director of the Transitional Residency Program. I have clinical faculty appointments to Baylor College of Medicine, University of Texas Health Science Center at Houston and Weill Medical College of Cornell University. I am a member of the Board of Directors of the Christus/Stehlin Foundation for Cancer Research, and of the Gulf Coast Regional Blood Center where I chair the Education and Research Committee. I am a past President of the Gulf Coast Hematology Society and of the Houston Society of Internal Medicine. I have more than 38 years experience in clinical hematology and am familiar with hematological disorders classified as leukemias, including the various forms of acute myeloid leukemia (AML) and the myelodysplastic syndromes (MDS), and what is known concerning their etiology, diagnosis, clinical course and therapy. The opinions expressed herein are my own and should not be construed in any way to also represent the opinions and/or judgments of The Methodist Hospital System or any of its associated institutions and subsidiaries. My medical license is current and on file with the appropriate authorities. You have a copy of my curriculum vitae. My testimony has never been excluded by any court.

This action concerns Mr. Charles Wayne Wilson, Sr. (SSN 460-74-8667, DOB 5-29-1950) who was employed in the printing industry from 1981-1994. It is alleged that his hematologic illness of refractory anemia with ringed sideroblasts (also known as acquired idiopathic sideroblastic anemia, sideroachrestic anemia, and by the initials, RARS and AISA) has occurred consequent to his exposure in the workplace to benzene-containing solvents used in various inks and proprietary products such as Rogersol and Rycoline and as cleaning agents such as Stoddard-type solvents. I will briefly review his clinical history as contained in the medical records and deposition that I have received and then comment on what is known concerning causation of his specific illness.



Mr. Wilson has a long history of ischemic heart disease and underwent angioplasties of his coronary arteries in 1988, and again in 1992. Either in 1992 or 1993 he underwent a triple vessel coronary artery bypass. A cardiac catheterization performed in 1997, revealed that two of these bypasses were occluded, and he is currently being treated medically with anti-platelet agents such as Plavix. In 1998, he had an episode of thrombophlebitis and was treated for a time with coumadin anticoagulation. He has a strong family history of ischemic heart disease. He has no siblings. He denies a history of smoking.

His blood counts on 9-7-1998, showed a hemoglobin concentration of 14.4 gm/dl, total leukocyte count of 6,900/cu mm, and a platelet count of 171,000/cu mm. The mean corpuscular volume (MCV) of his red blood cells was slightly increased at 95 Fl. He first was found to be anemic in December of 2005, and also had a right lower lobe pneumonia, at that time. During a workup for the anemia, it was established that he was hypothyroid with an elevated TSH of 13.2 and reduced free T-4 of 0.61. He also required transfusion of 2 units of blood. Endoscopic studies showed focal distal esophagitis but no active bleeding. The MCV had increased to 109 Fl. His serum iron was reported as greatly reduced at 9 µg/100 ml with a normal total iron-binding-capacity (TIBC). The actual lab slips are not in the material I received, but quoted in the discharge summaries. There is no mention of a serum ferritin value. A bone marrow examination disclosed a diagnosis of refractory anemia with ringed sideroblasts (RARS) without evidence of multilineage dysplasia (*vide infra*). He was placed on oral iron supplements for his iron deficiency, gastric acid blockers, thyroid, and also given Aranesp (erythropoietin) injections. A blood count on 6-22-2006, showed a hemoglobin concentration of 12.6 gm/dl, total leukocyte count of 7,000/cu mm and an MCV of 101 Fl. He has not required further blood transfusions, according to these records. I have no material from 2007.

RARS or AISA has been a well-described and well-studied unique hematological illness for more than 50 years (1-7). In 1982, it was placed in a newly-minted classification of myelodysplasia (MDS) along with several other diverse hematological disorders. This classification system has been revised many times since 1982, with certain syndromes added and others syndromes removed (9-13). The classification has emphasized certain commonalities among these separate illnesses, including the propensity to manifest multiple cytopenias, a variable tendency to demonstrate chromosomal abnormalities and evolution in acute myeloid leukemia (AML) syndromes. There is no evidence that these illnesses have a common etiology, and articles concerning their therapy typically illustrate responses by disease type, rather than as a single illness. One may read about RARS in hematology texts in chapters dealing with the various types of diverse congenital and acquired sideroblastic anemias or under the heading of MDS. Similarly, modern scientific papers deal specifically with RARS syndromes, or discuss this illness in comparison with other syndromes in the MDS classification (14).

In discussing causation in this case, it is important at the outset to emphasize that the specific illness in question is RARS, not other disease entities in the MDS classification. To illustrate the importance of this distinction, one needs only to read the following series of quotes. "The myelodysplastic syndromes (MDS) represent a heterogenous group of disorders with different biology and prognosis" (15). "From clinical, cytomorphologic, cytogenetic, and

molecular aspects the myelodysplastic syndromes (MDS) are heterogenous diseases" (16). "The hallmark of myelodysplastic syndromes (MDS) is ineffective erythropoiesis...MDS is heterogenous and represents many different disease forms" (17). "The World Health Organization (WHO) classification...is...useful for defining the different subtypes of myelodysplastic syndrome. These variants show impressive clinical heterogeneity, ranging from conditions with a near-normal standardized mortality ratio...to entities that are very close to acute myeloid leukemia" (18). Frequently, plaintiff's attorneys and experts, as well as epidemiologists and statisticians unfamiliar with clinical medicine, attempt to use a broad brush to claim MDS is a single illness. Even a casual review of the scientific medical literature shows this claim to be without merit, and this approach often seems disingenuous. Other selected panels have addressed this issue, and from one multi-authored review we learn, concerning MDS, "For exposure to specific solvents, such as benzene, the rarity of the disease and the difficulty in classifying MDS as a separate entity have limited the evaluation of associations in most studies...The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to benzene and myelodysplastic syndromes" (19). Thus, in my discussion of causation, I will focus only on RARS, the specific hematological disorder affecting Mr. Wilson. There is ample and continuing scientific literature on this specific illness which has fascinated hematologists for many years.

RARS/AISA is, perhaps, the easiest of the myelodysplastic syndromes to accurately diagnose because of its unusual bone marrow iron distribution within the red blood cell precursors. By convention, at least 15% of the bone marrow erythroblasts as seen on the iron stain of the bone marrow must be ringed sideroblasts in order to establish this diagnosis, and this finding was described in Mr. Wilson's bone marrow. Among large series of patients classified as having MDS, about 10-30 % fit into the RARS/AISA category (2-7, 20-21). Some believe there are at least two major subcategories among the RARS/AISA group that separate those individuals with an excellent prognosis, and rare conversion to AML, from those with a more progressive course and higher risk of transition to AML (4-5). The latter group typically exhibits Pelger-Huët type peripheral blood leukocyte abnormalities, multiple cytopenias, and chromosome abnormalities. In the newer proposed WHO classification scheme for MDS, an attempt is made to separate these two forms into simple RARS/AISA and RARS with considerable morphologic cellular abnormalities (multilineage dysplasia) or RARS-MD (18). A still newer subset of RARS associated with an elevated platelet count and the presence of the JAK-2 molecular chromosomal aberration seems to represent a 3rd subset of RARS/AISA (22-24). Taken as a whole, patients with RARS/AISA syndromes evolve into AML about 10-16 % of the time, and the median survival of all patients with this diagnosis is generally thought to be about 60-80 months, although some patients, particularly those in the WHO RARS category, may have a very prolonged course. Because many affected individuals are elderly when the diagnosis is established, they may not die directly from, but with, the illness. Still others die as a consequence of treatment and, in particular, from complications of iron overload, particularly in heavily transfused individuals (3, 7, 25). The transition from RARS/AISA to AML, with preservation of the extensive sideroblastic marrow findings, is well-described (8).

Iron overload is a significant problem in RARS, even prior to institution of transfusion therapy, so that in Mr. Wilson's case, where an extremely low serum iron was identified, his initial finding of anemia likely related to the combination of chronic blood loss and hypothyroidism, rather than bone marrow dysplasia. He simply may not have had active bleeding at the time of endoscopy, which is a common event in patients with known gastrointestinal blood loss. He is currently receiving therapy with Aranesp, an erythropoietin preparation, but only about 20-30 % of people with RARS would be expected to improve their hemoglobin concentration with such treatment.

While the general statement that certain forms of MDS may be secondary to major exposure to chemicals, such as benzene, may be correct, many lines of evidence suggest that this is not the case for the specific category of RARS/AISA (as well as for chronic myelomonocytic leukemia, another original and now former member of the MDS grouping). For example, the large Hayes study of around 74,000 Chinese factory workers exposed to disputed, but probably massive doses of benzene and other solvents, contained 7 cases of MDS with slide review, but none could be classified as RARS/AISA (26-27). Similarly, in the Plofilm cohort, relied upon by the EPA as the benchmark study for hematological diseases potentially caused by benzene, there is no description of sideroblastic anemia (28). In the hematologic descriptions by Aksoy of shoe workers exposed to glues and solvents containing enormous concentrations of benzene, no evidence of sideroblastic anemia was described (29-30). In more recent studies, again of Chinese workers with prolonged benzene exposure studied by comprehensive bone marrow examinations, no increase in ringed sideroblasts was noted, although the marrow morphology was abnormal (31). The presence of ringed sideroblasts in another large group with benzene poisoning was sought, and found absent (32). Moreover, in one report analyzing 84 patients with an established diagnosis of RARS/AISA, possible benzene exposure was identified in only one of these individuals, and he had also received radiation therapy (4). This lack of association of chemical exposure with both RARS/AISA and chronic myelomonocytic leukemia (CMML), was also noted in an MD Anderson Cancer Center retrospective patient analysis (33). **In fact, I am not aware of a single epidemiological study or even an isolated case report in the world's medical literature that shows RARS/AISA to be a consequence of benzene exposure (14).** This should not be surprising, because it has been consistently observed that the bone marrow findings observed in examples of MDS noted after prolonged and intense benzene exposure are different than those of typical *de novo* MDS and generally reveal less bone marrow cellularity than found in *de novo* forms of MDS and have other unique features, such as increases in eosinophils (26, 31-32). By contrast, RARS/AISA bone marrows, as present in Mr. Wilson's case, are generally quite cellular.

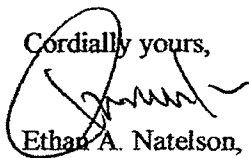
Mr. Wilson had a normal standard chromosome analysis, which is unusual for a suspected chemical-induced (including benzene-associated AML) MDS/AML syndrome (34-36). For example, **"Recurring chromosomal abnormalities occur in 40-70 % of patients with primary MDS and in 95 % with t-MDS"** (36). Dr. Nicas, a plaintiff's expert, estimates the cumulative dose of benzene for Mr. Wilson to be 18.1 ppm. Even if this estimate is correct, it is well below the cumulative benzene dosage that has been associated with AML (27, 37). A statistically increased incidence of AML has not been noted in the petrochemical industry for

many years, even with known cumulative benzene dose levels up to 40 ppm (38). There is also no evidence that low dose exposures to benzene can cause AML (39-40). There is also no evidence that exposure to Stoddard solvents used in cleaning and containing small amounts of benzene may cause AML (41-42).

In summary, and in my opinion, and in all medical probability, the cause for RARS/AISA in Mr. Wilson remains unknown, as it typically occurs in members of the general population without any history of toxic chemical exposures. Based on observations in many other individuals with RARS/AISA, Mr. Wilson's general prognosis is good, and his risk for conversion to AML is small, although increased over the standard age-adjusted rates in the population. His serum ferritin level needs to be followed to allow initiation of treatment should he develop iron-overload. He has long-standing coronary heart disease which is probably the greatest threat to his longevity.

Please let me know if I can provide any additional information. I would be pleased to review the bone marrow slides, should they be available.

Cordially yours,



Ethan A. Natelson, M.D.

References:

1. Kushner IP, et al. Idiopathic refractory sideroblastic anemia. Clinical and laboratory investigation of 17 patients and review of the literature. *Medicine* 50:139-159, 1971.
2. Cheng DS, et al. Idiopathic refractory sideroblastic anemia. Incidence and risk factors for leukemic transformation. *Cancer* 44:724-751, 1979.
3. Cazzola M, et al. Natural history of idiopathic refractory sideroblastic anemia. *Blood* 71:305-312, 1988.
4. Garand R, et al. Heterogeneity of acquired idiopathic sideroblastic anaemia (AISA). *Leukemia Research* 16:463-468, 1992.
5. Germing D, et al. Two types of acquired idiopathic sideroblastic anaemia (AISA): a time tested distinction. *Brit J Haematol* 108:724-728, 2000.
6. Alcindor T, et al. Sideroblastic Anemia. *Brit J Haematol* 116:733-743, 2002.
7. Vandermolen L, et al. Ringed sideroblasts in primary myelodysplasia. Leukemia propensity and prognostic factors. *Arch Int Med* 148:653-656, 1988.

8. Yoshida Y, et al. Diagnostic and biological significance of sideroblastic erythropoiesis in the myelodysplastic syndromes *Int J Hematol* 67:137-144, 1998.
9. Heaney M., et al. Myelodysplasia. *New Eng J Med* 340:1649-1660, 1999.
10. Aul C, et al. Pathogenesis, etiology and epidemiology of myelodysplastic syndromes. *Haematol* 83:71-86, 1998.
11. Nosslinger T, et al. Myelodysplastic syndromes, from French-American-British to World Health Organization: comparison of classifications on 432 unselected patients from a single institution. *Blood* 98:2936-2941, 2001.
12. Cheson BD, et al. Report of an international working group to standardize a response criteria for myelodysplastic syndromes. *Blood* 96:3671-3674, 2000.
13. Howe RB, et al. The WHO classification of MDS does make a difference. *Blood* 103:3265-3270, 2004.
14. Natelson EA. Benzene exposure and refractory sideroblastic erythropoiesis – is there an association. *Am J Med Sci* (in press), 2007.
15. Golshayan A-R, Jin T, Maciejewski J, et al. Efficacy of growth factors compared to other therapies for low-risk myelodysplastic syndromes. *Brit J Haematol* 137:125-132, 2007.
16. Bacher U, Haferlach T, Kern W, et al. A comparative study of molecular mutations in 381 patients with myelodysplastic syndrome and in 4130 patients with acute myeloid leukemia. *Haematol* 92:744-752, 2007.
17. Kantarjian H. Myelodysplastic syndrome (MDS): What is new? *Leukemia Insights-MD Anderson Cancer Center* 11:1-3, 2006.
18. Cazzola M, Malcovati I. Myelodysplastic syndromes – coping with ineffective hematopoiesis. *New Eng J Med* 352:536-538, 2005.
19. Grossblatt N, Kelly K, (Editors) Committee on Gulf War and Health: Literature Review of Pesticides and Solvents Board on Health Promotion and Disease Prevention, Gulf War and Health, Volume 2, Insecticides and Solvents, The National Academies Press, Washington, D.C. pp 326-331, 2003.
20. Greenberg P, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood* 89:2079-2088, 1997.
21. Maes B, et al. Application of the international prognostic scoring system for myelodysplastic syndromes. *Ann Oncol* 34:473-478, 1995.

22. Shaw GR. Ringed sideroblasts with thrombocytosis: an uncommon mixed myelodysplastic/myeloproliferative disease of older adults. *Brit J Haematol* 31:180-184, 2005.
23. Szpurka R, Tiu G, Murugesan S, et al. Refractory anemia with ringed sideroblasts associated with marked thrombocytosis (RARS-T), another myeloproliferative condition characterized by JAK2 V617F mutation. *Blood* 2173-2181. 2006.
24. Boissinot M, Garand R, Hamidou M, et al. The JAK2-V61F mutation and essential thrombocythemia features in a subset of patients with refractory anemia with ring sideroblasts (RARS). *Blood* 108:1781-1782, 2006.
25. Jensen, PD. The effect of iron chelation on haematopoiesis in MDS patients with transfusional iron overload. *Brit J Haematol* 94:288-299, 1996.
26. Linet MS, et al. Clinical features of hematopoietic malignancies and related disorders among benzene exposed workers in china. *Environ Health Perspect* 104: 1353-1364, 1996.
27. Wong O. Investigations of benzene exposures benzene poisoning and malignancies in China. *Reg Tox Pharm* 35:126-135, 2002.
28. Wong O. Risk of acute myeloid leukemia and multiple myeloma in workers exposed to benzene. *Occup Environ Med* 52:380-384, 1995.
29. Aksoy M, et al. Haematological effects of chronic benzene poisoning in 217 workers. *Brit J Indust Med* 28:296-302, 1971.
30. Aksoy M. Different types of malignancies due to occupational exposure to benzene: A review of recent observations in Turkey. *Environ Res* 23:181-190, 1980.
31. Irons, RD, et al. Chronic exposure to benzene results in a unique form of dysplasia. *Leukemia Res* 29:1371-1380, 2005.
32. Ruiz MA, Augusto LGS, Vassallo J, et al. Bone marrow morphology in patients with neutropenia due to chronic exposure to organic solvents (benzene): Early lesions. *Path Res Pract* 190:151-154, 1994.
33. Strom SS, et al Risk factors of myelodysplastic syndrome: a case control study. *Leukemia* 19:1912-1918, 2005.
34. Zang L, Eastmond DA, Smith MT. The nature of chromosomal aberrations detected in human exposed to benzene. *Crit Rev Toxicol* 37:1-42, 2002.
35. Olney HJ, Le Beau MM. Evaluation of recurring cytogenetic abnormalities in the treatment of myelodysplastic syndromes. *Leuk Res* 31:427-434, 2007.

36. Catenacci DVT, Schiller GJ. Myelodysplastic (sic) syndromes: A comprehensive review. *Blood Rev* 19:301-319, 2005.
37. Bergsagel DE, Wong O, Bergsagel PL, et al. Benzene and multiple myeloma: Appraisal of the scientific evidence. *Blood*. 94:1174-1182, 1999.
38. Bloemen LJ, Youk A, Bradley TD, et al. Lymphohaematopoietic cancer risk among chemical workers exposed to benzene. *Occup Environ Med*. 61:270-274, 2004.
39. Gum RT, Pratt N, Ryan P, et al. Update of mortality and cancer incidence in the Australian petroleum industry cohort. *Occup Environ Med* 63:476-481, 2006.
40. Scheinberg D.A., et al Acute Leukemias, Chapter 46.2 In: *Cancer Principles & Practices of Oncology*, Editor DeVita, V.TJr., 6th Edition, pgs. 2404-2433, 2001.
41. Madl AK, Paustenbach DJ. Airborne concentrations of benzene and mineral spirits (Stoddard Solvent) during cleaning of a locomotive generator and traction motor. *J Toxicol Environ Health, Part A* 1965-1979, 2002.
42. Fedoruk MJ, Bronstein R, Kerger BD. Benzene exposure assessment for use of a mineral spirits-based degreaser. *Appl Occup Environ Hygiene* 18:764-771, 2003.

Curriculum Vitae

Ethan A. Natelson, M.D.

March 10, 2001

Present Title: Medical Director of Quality Assurance and Director of the Transitional Internship program, St. Joseph Hospital, Clinical Associate Professor, University of Texas Health Science Center at Houston, Associate Director, Stehlin Foundation for Cancer Research, St. Joseph Hospital, Houston, Texas.

Business Address: Department of Medical Education, St. Joseph Hospital, 1919 LaBranch, Houston, Texas 77002. Phone (713) 652-3161, Fax (713) 659-1503, e-mail (natelson@pipeline.com).

Home Address: 8707 Wateka Drive, Houston, Texas 77074.

Birthdate: January 22, 1942, Kings County, New York State.

Marital Status: Wife (Kathy), two children (Laura, Marcia).

Citizenship: United States.

Social Security: 318-34-1941, EIN 76-0165770.

Undergraduate Education: B.S., Haverford College, Haverford, Pennsylvania, 1958-62.

Graduate Education: M.D., Baylor College of Medicine, Houston, Texas, 1962-1966.

Post-Graduate Training: Straight Medicine Internship, The Methodist Hospital, 1966-7, Residency in internal medicine, Baylor Affiliated Hospitals, Houston, Texas 1967-1969, Fellowship in Hematology, Department of Medicine, Baylor Medical School and The Methodist Hospital, Houston Texas.

Military Service: Major, USAF, Lackland AFB, San Antonio, Texas, 1970-1972.

Academic Appointments:

1971 Clinical Instructor, University of Texas Medical at San Antonio.

1972-3 Instructor in Medicine, Baylor College of Medicine.

1973-5 Assistant Professor of Medicine, Baylor College of Medicine.

1975-80 Adjunct Associate Professor of Biomedical Engineering, Rice University, Houston, Texas.

1975- Associate Professor of Medicine, University of Texas Health Science Center at Houston.

Hospital Appointments:

1972-5 Active Staff, The Methodist Hospital, Houston, Texas - since 1975, Consulting Staff.

1972-5 Consulting Staff, The Veterans Hospital, Houston, Texas.

1975- Active Staff, St. Joseph Hospital, Houston, Texas.

Licensure: Texas (D-9036), Illinois (36-42274 inactive).

Certification: 1967 National Board of Medical Examiners.

1970 American Board of Internal Medicine

1974 American Board of Internal Medicine-Hematology

Memberships:

Harris County Medical Society

American Society of Hematology

Fellow, American College of Physicians

American Federation for Clinical Research

American Medical Association

Houston Society of Internal Medicine (past president, current treasurer)

Gulf Coast Society of Hematology (past president)

Gulf Coast Regional Blood Center (member, educational and technical advisory committees)

International Society of Thrombosis and Hemostasis

American Association for the Advancement of Science

New York Academy of Sciences

Texas Club of Internists

California Rare Fruit Growers

International Dwarf Fruit Tree Association

Southern Fruit Fellowship (current president)

North American Fruit Explorers (current president)

Urban Harvest - Member, Advisory Board

Editorial Positions: Reviewer, Annals of Internal Medicine and Archives of Internal Medicine.

Awards: Intern of the year, The Methodist Hospital, Houston, Texas, Best Teacher Award, St. Joseph Hospital, Houston, Texas. 1984, 1995.

Publications:

1. Natelson, E.A., Lynch, E.C., Hettig, R.A. and Alfrey, C.P., Jr. Histiocytic Medullary Reticulosis. The Role of Phagocytosis in Pancytopenia. *Arch. Int. Med.* 122:223-229, 1968.
2. Fred, H.L. and Natelson, E.A. Selection of Patients for pulmonary embolectomy. *Dis. Chest* 56:139-142, 1969.
3. Natelson, E.A., Allen, T.A., Riggs, S. and Fred, H.L. Bloody ascites: diagnostic implications. *Am. J. Gast.* 52:523-527, 1969.
4. Natelson, E.A., Lynch, E.C., Alfrey, C.P., Jr. and Gross, J.F. Heparin induced thrombocytopenia: an unexpected response to treatment of consumption coagulopathy. *Ann. Int. Med.* 71:1121-1125, 1969.
5. Natelson, E.A., Duncan, W.C., Macossay, C.R. and Fred, H.L. Amyloidosis palpebrarum. *Arch. Int. Med.* 125:304-307, 1970.
6. Dickson, J., Natelson, E.A. and Fred, H.L. Myxedema ascites. *Am. Fam. Phy/GP.* 1:93, 1970.
7. Natelson, E.A., Watts, H.D. and Fred, H.L. Cystic medionecrosis of the pulmonary arteries. *Chest* 57:333-335, 1970.
8. Friedwald, V.E., Davis, P., Roehm, J., Jr., Fechner, R.E., Natelson, E.A., Lane, M. and Spjut, J.H. Clinicopathological conference. *Tex. Med.* 66:78-85, 1970.
9. Natelson, E.A., Lynch, E.C., Hettig, R.A. and Alfrey, C.P., Jr. Acquired factor IX deficiency in the nephrotic syndrome. *Ann. Int. Med.* 73:373-378, 1970.
10. Cohen, A.A., Natelson, E.A. and Fechner, R.E. Fibrosing interstitial pneumonitis in ankylosing spondylitis. *Chest* 59:369-371, 1971.
11. Natelson, E.A., Blumenthal, B.J. and Fred, H.L. Acute mercury vapor poisoning in the home. *Chest* 59:677-678, 1971.
12. Natelson, E.A., Lynch, E.C., Britton, H.A. and Alfrey, C.P., Jr. Polycythemia vera in childhood. A case with chromosomal abnormality, immunoglobulin deficiency and chronic consumption coagulopathy. *Am. J. Dis. Child.* 122:241-244, 1971.
13. Girard, D.E., Carlson, V., Natelson, E.A. and Fred, H.L. Pneumomediastinum in diabetic acidosis: Comments on mechanism, incidence and management. *Chest* 60:455-459, 1971.
14. Fred, H.L. and Natelson, E.A. Gonococcal dermatitis. *Hum. Sex.* 6:183-191, 1972.
15. Cypus, G.S., Natelson, E.A. Hematological manifestations of systemic lupus erythematosus.

- St. Jos. Hosp. Med. Surg. Bull. 8:193-202, 1973.
16. Natelson, E.A. and Dooley, D.F. Rapid determination of fibrinogen by thrombokinetics. *Am. J. Clin. Path.* 61:828-833, 1974.
 17. Brown, C.H. III, Natelson, E.A., Bradshaw, M.W., Williams, T.W., Jr., and Alfrey, C.P. Jr. The hemostatic defect induced by carbenicillin. *New Eng. J. Med.* 265-270, 1974.
 18. Kidd, C.R., Fred, H.L., Natelson, E.A. Bilateral hilar adenopathy in amyloidosis. *New Eng. J. Med.* 290 972, 1974.
 19. Glover, C.J., McIntire, L.V., Leverett, L.B., Hellums, J.D., Brown, C.H. III and Natelson, E.A. Effect of shear stress on clot structure formation. *Trans. Am. Soc. Art. Int. Org.* 20:463-469, 1974.
 20. Brown, C.H. III, Weisberg, R.J., Natelson, E.A. and Alfrey, C.P. Jr. Glanzmann's thrombasthenia: Assessment of the response to platelet transfusions. *Transfusion* 15:124-131, 1975.
 21. Rahman, F., Zanger, B. and Natelson, E.A. Factor IX deficiency in the nephrotic syndrome. Studies with prothrombin complex concentrate. *J. Urol.* 113:853-855, 1975.
 22. Natelson, E.A., Shapiro, D.M. and Smith, D.F. Detection of mild factor VIII deficiency by thrombocytochemistry. *Am. J. Clin. Path.* 64:95-100, 1975.
 23. Brown, C.H. III, Natelson, E.A., Bradshaw, M.W., Alfrey, C.P., Jr., and Williams, T.W., Jr. A study of the effects of ticarcillin on blood coagulation and platelet function. *Antimicrob. Ag. Chemother.* 7:652-657, 1975.
 24. Natelson, E.A., Cyprus, G.S. and Hettig, R.A. Absent factor II in systemic lupus erythematosus. Immunological studies and response to corticosteroid therapy. *Arth. Rheum.* 19:79-82, 1976.
 25. Glover, C.J., McIntire, L.V., Brown, C.H. III, and Natelson, E.A., Dynamic coagulation studies: Influence of normal and abnormal platelets on clot structure formation. *Thromb. Res.* 7:185-198, 1975.
 26. Glover, C.J., McIntire, L.V., Brown, C.H. III, Natelson, E.A. Dynamic coagulation studies. Effects of fibrinogen concentration, factor XIII deficiency and factor XIII inhibition. *J. Lab. Clin. Med.* 85:644-656, 1975.
 27. Shapiro, D.M., Zeluff, G.W., Wilson, L., Natelson, E.A. and Lynch, E.C. Thrombotic thrombocytopenic purpura despite splenic absence. Report of a case. *Am. J. Osteop.* 75:798-802, 1976.
 28. Siebart, W.T., Natelson, E.A. Chronic consumption coagulopathy accompanying abdominal

- aortic aneurysm. *Arch. Surg.* 111:539-541, 1976.
29. Natelson, E.A., Brown, C.H. III, Bradshaw, M.W., Alfrey, C.P., Jr. and Williams, T.W. Influence of cephalosporin antibiotics on blood coagulation and platelet function. *Antimicrob. Ag. Chemother.* 9:91-93, 1976.
30. Noor, G.P., Solis, R.T. and Natelson, E.A. A simple method of intraoperative autotransfusion. *Surg. Gyn. Obstet.* 143:65-70, 1976.
31. Fred, H.L., Blakely, R.W. and Natelson, E.A. Roentgenogram of the month. *Chest* 71:381-382, 1977.
32. Brown, C.H. III, Bradshaw, M.W., Natelson, E.A., Alfrey, C.P., Jr. and Williams, T.W. Defective platelet function following the administration of penicillin compounds. *Blood* 47:949-956, 1976.
33. Natelson, E.A., and Fred, H.L. Lead poisoning from cocktail glasses. Observations on two patients. *JAMA* 236:2527-2529, 1976.
34. Natelson, E.A. Sustained thrombocytosis: Clinical significance and therapeutic considerations. *St. Joseph Hosp. Med. J.* 11:109-117, 1976.
35. Moake, J.L., Cimo, P.L., Peterson, D.M., Roper, P. and Natelson, E.A. Inhibition of ristocetin-induced platelet aggregation and agglutination by vancomycin. *Blood* 50:397-495, 1977.
36. Fred, H.L. and Natelson, E.A. Grossly bloody urine of runners. *South. Med. J.* 70:1394-1396, 1977.
37. Zeff, G.W., Natelson, E.A. and Jackson, D. Thrombocytopenic purpura - idiopathic and thrombotic. *Heart & Lung* 7:327-334, 1978.
38. Natelson, E.A. Treatment of iron overload in patients with chronic anemias. *St. Joseph Hosp. Med. J.* 3:78-83, 1978.
39. Crook, J.E., Woosley, R.L., Leftwich, R.B. and Natelson, E.A. Agranulocytosis during combined antiarrhythmic therapy with procainamide and phenytoin. *South. Med. J.* 72:1599-1601, 1979.
40. Cimo, P.L., Moake, J.L., Sonzaes, M.F., Natelson, E.A. and Fox, K.R. Inherited combined deficiency of factor V and factor VIII: Report of a case with normal factor VIII antigen and ristocetin-induced platelet aggregation. *Am. J. Hematol.* 2:385-391, 1977.
41. Natelson, E.A. Current concepts of anticoagulant therapy. *St. J. Hosp. Med. J.* 14:77-86, 1979.

42. Novy, S.R., Natelson, E.A., Whitlock S.L. Gaucher's disease in black adults. *Am. J. Roentgen.* 133:947-949, 1979.
43. Kurumukula, M.S., McIntire, L.V., Natelson, E.A. A rheological study of the kinetics of coagulation in normal and hemophilic blood plasma. *Biorheology* 16:403-410, 1979.
44. Natelson, E.A., Siebert, W.T., Williams, T.W., Bradshaw, M.W. Combined effects of ticarcillin and cefazolin on blood coagulation and platelet function. *Am. J. Med. Sci.* 278:217-221, 1980.
45. Gentry, L.O., Jamsek, J.G., and Natelson, E.A. The effects of sodium piperacillin on platelet function in normal volunteers. *Antimicrob. Ag. Chemother.* 19:532-533, 1981.
46. Natelson, E.A. An update on blood and component therapy. *St. Joseph Hosp. Med. J.* 16:41-46, 1981.
47. Natelson, E.A. Hemorrhagic and thrombotic disorders. *St. Joseph Hosp. Med. J.* 18:5-18, 1983.
48. Natelson, E.A. Human blood coagulation: Clinical and laboratory correlation. *Clin. Physiol. & Biochem.* 1:214-224, 1983.
49. Eoides, M., Natelson, E.A. and Sher, M. Extrahepatic biliary obstruction in multiple myeloma. *Houston Med. J.* 1:31-34, 1985.
50. Natelson, E.A., and White, D. Recurrent thrombotic thrombocytopenic purpura (TTP) in early pregnancy: Effect of uterine evacuation. *Obster. Gynecol.* 66:(suppl) 54S-56S, 1985.
51. Sudashan, A., Natelson, E.A. and Gordon, C. Hereditary hemorrhagic telangiectasia and factor VIII inhibitor. *South. Med. J.* 78:623-624, 1985.
52. Gentry, L.O., Wood, B.A. and Natelson, E.A. The effects of apalcillin on platelet function in normal volunteers. *Antimicrob. Ag. Chemother.* 27:683-684, 1985.
53. Natelson, E.A. Current therapy of aplastic anemia. *Houston Med. J.* 1:53-59, 1985.
54. Sterr, L.D., Natelson, E.A., Lee C.K. Cardiac tamponade as the first clinical feature of multiple myeloma. *Houston Med. J.* 2:101-104, 1985.
55. Cassa, D., Natelson, E.A., Williams, B.V., Braden, D. Splenosis: A case report. *Houston Med. J.* 2:141-144, 1986.

56. Natelson, E.A., Bullock, A.C., Jr., Siebert, W.T., and Kupor, L.R. Recovery from allopurinol-induced agranulocytosis. *Houston Med. J.* 3:93-96, 1987.
57. Farmer, K., Natelson, E.A., Stephanou, N. HELLP syndrome as the only manifestation of preeclampsia: Therapeutic considerations. *Houston Med. J.* 4:37-40, 1988.
58. Stehlin, J.S., Greeff, P.J., DeIpolyi, P.D., Giovanella, B.C., Klein, G.C., McGaff, C.J., Davis, B.R., Williams, L.J., Natelson, E.A. and Anderson, R.F. Heat as an adjuvant in the treatment of advanced melanoma: An immune stimulant? *Houston Med. J.* 4:61-82, 1988.
59. Natelson, S., Natelson, E.A. Preparation of D-, DL-, and L-Homoserine Lactone from Methionine. *Microchemical J.* 40:116-132, 1989.
60. Natelson, E.A., Young, D.J., Greeff, P.J. Splenectomy in paroxysmal nocturnal hemoglobinuria. *Houston Medicine* 6:186-188, 1990.
61. Pantazis, P., Mendoza, J.T., Early, J.A., Kozielski, A.J., Natelson, E.A. and Giovanella, B.C. 9-nitro camptothecin delays growth of U-937 leukemia tumors in nude mice and is cytotoxic or cytostatic for human myelomonocytic leukemia cell lines *in vitro*. *Europ. J. Haematol.* 50:81-89, 1993.
62. Hinz, H.R., Harris, N.J., Natelson, E.A., and Giovanella, B.C. Pharmacokinetics of the *in vivo* and *in vitro* conversion of 9-nitro-20(S)-camptothecin to 9-amino-20(S)-camptothecin in human, dog and mouse. *Cancer Research* 54:3096-3100, 1994.
63. Natelson, S., Pantazis, P., and Natelson, E.A. L-homoserine hydroxamic acid as an anti-tumor agent. *C in. Chim. Acta* 229:133-145, 1994.
64. Natelson, E.A., Fred, H.L. Fever, leukocytosis and an enlarging flank mass. *Hospital Practice* 29:(4) 37-34, 1994.
65. Tschien, L.F., Tschien, J.A., Natelson, E.A. Photophobia and thickened eyelids in a healthy-appearing nurse. *Hospital Practice* 31:(2) 73-74, 1996.
66. Triana, Z., Tschien, J., Natelson, E.A. Multiple subcutaneous nodules on the torso and leg. *Arch. Derm.* 134:1477-1482, 1998.
67. Giovanella, B. C., Natelson, E., Harris, N., Vardeman, D., and Stehlin, J. Protocols for the treatment of human tumor xenografts with camptothecins. *Ann. N.Y. Acad. Sci.* 803:181-187, 1996.
68. Natelson, E.A., Giovanella, B.C., Verschraegen, C.F., Fehir, K.M., De Ipolyi, P.D., Harris, N., Stehlin, J.S. Phase I Clinical and Pharmacological Studies of 20-(S)-Camptothecin and 2-(S)-9-

Nitrocamptothecin as Anticancer Agents. *Ann. N.Y. Acad. Sci.* 803:224-230, 1996.

69. Vershraegen, C.F., Natelson, E.A., Giovanella, B.C., Kavanagh, J.J., Kudelka, A.P., Freedman, R.S., Edwards, C.L., Ende, K., Harris, N., Stehlin, J.S. Phase I Clinical and Pharmacological Study of Oral 9-Nitrocamptothecin, a Novel Water-Insoluble Topoisomerase-I Inhibitor. *Anticancer Drugs* 9:36-44, 1998.

70. Gupta, E., Toppmeyer, D., Zamek, R., Much, J., Ibrahim, N., Goodin, S., Kane, M., Aisner, J., Li, X., Hluska, Jr., P., Medina, M., Cornfield, A., Vyas, V., Natelson, E., Giovanella, B., Saleem, A., and Lubin, E. Clinical evaluation of sequential topoisomerase targeting in the treatment of advanced malignancy. *Cancer Therapeutics* 1:292-301, 1998.

71. Stehlin, J.S., Giovanella, B.C., Natelson, E.A., de Ipolyi, P.D., Coil, D., Davis, B., Wolk, D., Wallace, P., Trojacek, A. A Phase II Study of 9-nitrocamptothecin (RFS-2000) in patients with advanced pancreatic cancer: A Preliminary Report. *Internat. J. Oncol.* 14:821-31, 1999.

72. Trizna, Z., Tschien, J., Natelson, E.A. Atypical Mycobacterial Infection in a Patient With Hairy Cell Leukemia. *Cutis* 67:241-2, 2001.

BOOKS

1. Fred, H.L., Natelson, E.A.: Pulmonary thromboembolism in Chapter 5, Crises in Medicine, R.D. Eichorn and E.F. Beard (eds) Chas. C. Thomas: Springfield, Illinois. 1973. Pp 56-75.

2. Natelson, S., Natelson, E.A. Principles of Applied Clinical Chemistry: Chemical Background and Medical Applications. Volume I Maintenance of Fluid and Electrolyte Balance. Plenum Press, New York, 1975. 393 pp.

3. Ibid. Volume II. The erythrocyte, chemical composition and metabolism. Plenum Press, New York, 1978. 560 pp.

4. Ibid. Volume III. Plasma Proteins in Nutrition and Transport. Plenum Press. 1980. 554 pp.

5. Natelson, S., Natelson, E.A. Regulation of Water and Electrolyte Balance. Pg. 3-42 in CRC Handbook of Clinical Chemistry. Volume IV. Ed. Werner, M. CRC Press Inc. Boca Raton, Florida. 1989.

6. Stehlin, J.S., Natelson, E.A., Hinz, H.R., Giovanella, B.C., de Ipolyi, P.D., Fehir, K.M., Trezone, T.P., Varleman, D.M., Harris, N.J., Marcee, A.K., Kozielski, A.J. and Ruiz-Razura, A. Chapter 5 in Camptothecins: New Anticancer Agents. Ed. Potmesil, M. And Pinedo, H., CRC Press Inc. Boca Raton, Florida. Pg 59-65, 1995.

Teaching Videocassettes

1. Natelson, E.A., Williams, T.W. Critical decisions in medicine. #7 Park Row Publishers, New York, New York. 1984.

Horticultural Articles

1. Natelson, E.A. More on Fireblight Control. Pomona 22: No. 4, 36-7, 1989.
2. Natelson, E.A. Pear and Apples Together. Pomona 31: No. 1, 56, 1998.
3. Natelson, E.A. Pear Interstem Length. Pomona 31: No 3, 25-27, 1998.

1 IN THE UNITED STATES DISTRICT COURT
2 FOR THE EASTERN DISTRICT OF TEXAS
3 MARSHALL DIVISION

4 CHARLES WILSON and)
5 LAURA WILSON)
6 Plaintiffs,)

6 VS.) Case No. 2:06:CV-286

7 RYCOLINE PRODUCTS,)
8 INC.; et al.,)
9 Defendants.)

11 *****

12 ORAL DEPOSITION OF

13 DR. ETHAN NATELSON

14 SEPTEMBER 17, 2007

15 *****

16
17 ORAL DEPOSITION of DR. ETHAN NATELSON, produced as
18 a witness at the instance of the Plaintiffs, and duly
19 sworn, was taken in the above-styled and numbered cause
20 on SEPTEMBER 17, 2007, from 2:16 p.m. to 5:07 p.m.,
21 before Denyce M. Sanders, CSR, RPR, in and for the
22 State of Texas, recorded by machine shorthand, at the
23 offices of THOMPSON & KNIGHT, 333 Clay Street, Suite
24 3300, Houston, Texas, pursuant to the Federal Rules of
25 Civil Procedure and the provisions stated on the record
 or attached hereto; that the deposition shall be read
 and signed before any notary public.



Page 2		Page 4	
1	APPEARANCES	1	NATELSON EXHIBIT NO. 12
2		2	NATELSON EXHIBIT NO. 13
3	FOR THE PLAINTIFFS:	3	NATELSON EXHIBIT NO. 14
4	SCHMIDT & CLARK	4	NATELSON EXHIBIT NO. 15
5	2911 Turtle Creek Boulevard, Suite 1400	5	NATELSON EXHIBIT NO. 16
6	Dallas, Texas 75219	6	NATELSON EXHIBIT NO. 17
7	Mr. Keith Patton	7	NATELSON EXHIBIT NO. 18
8		8	NATELSON EXHIBIT NO. 19
9	FOR THE DEFENDANT ASHLAND, INC.:	9	NATELSON EXHIBIT NO. 20
10	THOMPSON & KNIGHT	10	NATELSON EXHIBIT NO. 21
11	333 Clay Street, Suite 3300	11	NATELSON EXHIBIT NO. 22
12	Houston, Texas 77002	12	NATELSON EXHIBIT NO. 23
13	Mr. Kevin Parks	13	NATELSON EXHIBIT NO. 24
14		14	NATELSON EXHIBIT NO. 25
15		15	NATELSON EXHIBIT NO. 26
16		16	NATELSON EXHIBIT NO. 27
17		17	NATELSON EXHIBIT NO. 28
18		18	NATELSON EXHIBIT NO. 29
19		19	NATELSON EXHIBIT NO. 30
20		20	NATELSON EXHIBIT NO. 31
21		21	NATELSON EXHIBIT NO. 32
22		22	NATELSON EXHIBIT NO. 33
23		23	NATELSON EXHIBIT NO. 34
24		24	NATELSON EXHIBIT NO. 35
25		25	NATELSON EXHIBIT NO. 36
Page 3		Page 5	
1	EXAMINATION INDEX	1	NATELSON EXHIBIT NO. 37
2		2	NATELSON EXHIBIT NO. 38
3	WITNESS: DR. ETHAN NATELSON	3	NATELSON EXHIBIT NO. 39
4	EXAMINATION PAGE	4	NATELSON EXHIBIT NO. 40
5	BY MR. PATTON 6	5	NATELSON EXHIBIT NO. 41
6	BY MR. PARKS 103	6	NATELSON EXHIBIT NO. 42
7		7	NATELSON EXHIBIT NO. 43
8	FURTHER EXAMINATION	8	NATELSON EXHIBIT NO. 44
9	BY MR. PATTON 108	9	NATELSON EXHIBIT NO. 45
10	SIGNATURE REQUESTED 111	10	NATELSON EXHIBIT NO. 46
11	REPORTER'S CERTIFICATION 113	11	NATELSON EXHIBIT NO. 47
12		12	NATELSON EXHIBIT NO. 48
13	EXHIBIT INDEX	13	NATELSON EXHIBIT NO. 49
14	PAGE	14	NATELSON EXHIBIT NO. 50
15	NATELSON EXHIBIT NO. 1	15	
16	NATELSON EXHIBIT NO. 2 57	16	
17	NATELSON EXHIBIT NO. 3 58	17	
18	NATELSON EXHIBIT NO. 4 59	18	
19	NATELSON EXHIBIT NO. 5 60	19	
20	NATELSON EXHIBIT NO. 6 60	20	
21	NATELSON EXHIBIT NO. 7 61	21	
22	NATELSON EXHIBIT NO. 8 62	22	
23	NATELSON EXHIBIT NO. 9 63	23	
24	NATELSON EXHIBIT NO. 10 63	24	
25	NATELSON EXHIBIT NO. 11 64	25	

Page 6

Page 8

1 DR. ETHAN NATELSON,
2 having been first duly sworn, testified as follows:
3 EXAMINATION
4 BY MR. PATTON:
5 Q. Please introduce yourself for the record.
6 A. My name is Ethan A. Natelson.
7 Q. You are a doctor, correct?
8 A. Correct.
9 Q. Tell us what kind of doctor you are.
10 MR. PARKS: Before we get into that,
11 we'll agree that the deposition is pursuant to the
12 Federal Rules and the witness will read and sign the
13 transcript?
14 MR. PATTON: Agreed.
15 Q. (BY MR. PATTON) Please introduce yourself.
16 A. I'm -- as I said, my name is Ethan A.
17 Natelson. I'm a hematologist.
18 Q. And how long have you been a hematologist?
19 A. I did a fellowship in 1969; and since that
20 time, I've more exclusively seen hematology-type
21 patients.
22 Q. As we sit here today, do you have a clinical
23 practice where you see hematology patients on a daily
24 and weekly basis?
25 A. Yes.

Page 7

Page 9

1 Q. And where is your practice at?
2 A. At the Methodist Hospital. The address is
3 6550 Fannin Street.
4 Q. You are a hired expert in this case, correct?
5 A. Yes.
6 Q. Hired by Ashland, correct?
7 A. Indirectly. Hired by Ricky Raven, but Ashland
8 is the company of record.
9 Q. Okay. How much are you being paid for your
10 time on the case?
11 A. I normally charge \$250 an hour to review
12 records and \$400 an hour for deposition testimony.
13 Q. And as we sit here today, we marked some
14 exhibits before we started; and Exhibit 50 appears to
15 be your invoicing and billing records, correct?
16 A. Yes.
17 Q. How much time did you spend on this case prior
18 to writing your report?
19 A. I can't tell you that exactly. It's not noted
20 on here, but the total hours are about 15 hours that
21 are listed here; and probably between 10 and 15 hours,
22 I would say, when the report was actually written.
23 Q. Before September 8, appears you've had ten
24 hours total in the case?
25 A. Yes.

1 Q. And since September 8, you've spent about five
2 hours before coming here for your deposition?
3 A. Yes.
4 Q. And that includes four hours to prepare for
5 your deposition?
6 A. Yes.
7 Q. Have you been asked to testify at trial in
8 this case?
9 A. I don't recall that. But that's, essentially,
10 a given. In other words, if I agree to be involved in
11 a case, I typically agree to testify at trial.
12 Q. Do you know when this case is set for trial?
13 A. No.
14 Q. You have served as an expert witness in
15 benzene cases before, correct?
16 A. Yes.
17 Q. Have you ever testified in any cases involving
18 MDS or myelodysplastic syndrome?
19 A. I have to look at the list to be certain about
20 that.
21 Q. Okay. We can go over that a little bit later.
22 Before we go on to it more later, have you ever
23 testified on behalf of a plaintiff in a chemical
24 exposure case?
25 A. No.

1 Q. Have you ever given the opinion in any
2 litigation that benzene caused a person's given
3 disease, whatever that disease may be?
4 A. No.
5 Q. Is it your opinion in this case that Charles
6 Wilson's MDS is not related to any benzene exposure?
7 A. He has a form -- he has an illness that can be
8 classified as a form of MDS. I don't believe that
9 particular illness can be caused by benzene.
10 Q. Just so I have your opinions clear. It's your
11 opinion in this case, that Charles Wilson's MDS/RARS is
12 not related to any exposure to benzene?
13 A. Yes. That's correct.
14 Q. Stated another way, you will testify at trial
15 in this case that benzene exposure played absolutely
16 zero causative factor in Charles Wilson's MDS or RARS,
17 correct?
18 A. There's no "or." He has one illness, which is
19 RARS; and I don't believe that benzene is related to
20 that illness.
21 Q. Okay. My question is a little more specific.
22 Do you believe that benzene in any way caused or
23 contribute or played any causative factor in Charles
24 Wilson's RARS?
25 A. No.

3 (Pages 6 to 9)

Page 106 1 do with sideroblastic anemia; and then within that 2 chapter, RARS is a subheading. 3 Q. And in the Wintrobe text, is benzene 4 identified as a potential cause of RARS? 5 A. No. 6 Q. The article that you've written that is 7 planned for publication, when -- when do you expect 8 that will be published? 9 A. Well, it's listed as November -- in the 10 November edition. 11 Q. And was that article peer reviewed? 12 A. Yes. 13 Q. What was your purpose in writing that article? 14 A. Well, my purpose was this: I don't think this 15 is a question that has been discussed much in the 16 hematologic literature. In other words, there are a 17 number of articles out there that deal with the 18 subject; but I don't think anybody, since the time of 19 Dr. Damashek, has written a general discussion about 20 this situation. 21 Q. And by this general subject, do you mean 22 whether benzene can cause RARS? 23 A. Yes. 24 Q. And what is the conclusion in your article? 25 A. Well, my conclusion is that there's no	Page 108 1 not cause that? 2 A. That's correct. 3 MR. PARKS: Thank you for your time. 4 I'll pass the witness. 5 FURTHER EXAMINATION 6 BY MR. PATTON: 7 Q. Dr. Natelson, what is the multiple hit theory 8 as it relates to bone marrow diseases? 9 A. Well, the notion is that, for example, someone 10 gets, let's say, damage to a chromosome. It may be 11 minor damage or major damage. And that changes the 12 milieu, for example. It produces a growth factor or a 13 growth factor that has a certain advantage and starts 14 proliferating cells in the bone marrow; and then a 15 second genetic event occurs which takes those 16 proliferating cells and makes them leukemic. 17 And so it takes multiple hits to drive a 18 normal bone marrow to a leukemic bone marrow because of 19 the fact that the bone marrow has tremendous reparative 20 processes. And it's very difficult to -- to sustain 21 damage in the bone marrow because of the fact that even 22 chromosome defects can be repaired. 23 Q. Would you agree with me that some individuals 24 are more susceptible or more likely to take those hits 25 to the bone marrow, so to speak, a little harder than
Page 107 1 epidemiologic evidence or case report data to suggest 2 that benzene can cause RARS and considerable data that 3 would suggest that it can't. 4 Q. Mr. Patton also asked you questions, for 5 instance, as to whether benzene can cause AML? 6 A. Yes. 7 Q. And you agreed that it could? 8 A. Yes. 9 Q. And then he asked you questions about the fact 10 that RARS can develop into AML as the natural -- in the 11 natural history -- in the course of the disease, if you 12 will? 13 A. Yes. 14 Q. But if you have a patient who has been 15 diagnosed with RARS who then develops AML, wouldn't you 16 rule out benzene as a potential cause because you know 17 that benzene does not cause RARS? 18 A. Both situations. We know that AML is the 19 natural progression of a number of cases of RARS, and 20 we also know that there is no relationship between 21 benzene and RARS. So if a person with RARS develops 22 AML, I would think that's just simply the natural 23 progression of the illness. 24 Q. So even if Mr. Wilson does proceed on to 25 develop AML, your opinion would remain that benzene did	Page 109 1 others? 2 A. That's theoretically possible, yes. 3 Q. Is it theoretically likely, as far as the 4 concept of susceptibility goes, for people who have 5 different forms of cancer. Some people are more likely 6 to get cancer than others for one reason or another, 7 right? 8 A. That is so. We don't know the reasons for 9 that. But that is true, that in some instances there's 10 genetic predisposition, but -- but those -- the 11 research in that is really in its infancy. 12 Q. But you agree with me that some people have a 13 genetic predisposition to be more susceptible to 14 contracting, say, leukemia or a bone marrow disease 15 from exposure to benzene than other people would be; 16 fair statement? 17 A. Well, certainly. I don't know the answer to 18 that. I would say it's quite -- it's possible. I 19 don't know that for a fact. 20 MR. PATTON: All right. Thank you for 21 your time. 22 MR. PARKS: Reserve the rest of our 23 questions until the time of trial. 24 MR. PATTON: And for the record, can we 25 have the agreement, Kevin, that you will, for cost

28 (Pages 106 to 109)

Page 110

1 sake, take the exhibits, copy them, return the original
2 to Dr. Natelson, send me a copy within, say, five days;
3 is that fair?

4 MR. PARKS: That's fair.
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25

Page 112

SIGNATURE OF WITNESS

1
2
3 I, DR. ETHAN NATELSON, solemnly swear or affirm
4 under the pains and penalties of perjury that the
5 foregoing pages contain a true and correct transcript
6 of the testimony given by me at the time and place
7 stated with the corrections, if any, and the reasons
8 therefor noted on the foregoing correction page(s), and
9 that I am signing this before a Notary Public.
10
11

12 DR. ETHAN NATELSON
13

STATE OF TEXAS *

COUNTY OF _____ *

SUBSCRIBED AND SWORN TO BEFORE ME BY

17 _____ on this, the _____ day of
18 _____, 2007.
19
20
21

22 Notary Public, State of Texas
23

My Commission Expires: _____

Job 2-64038

25

Page 111

WITNESS CORRECTIONS AND SIGNATURE

1 Please indicate changes on this sheet of paper,
2 giving the change, page number, line number and reason
3 for the change. Please sign each page of changes.
4 PAGE/LINE CORRECTION REASON FOR CHANGE
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23

24 DR. ETHAN NATELSON
25

Page 113

1 THE STATE OF TEXAS:
2 COUNTY OF HARRIS:
3 I, DENYCE SANDERS, a Certified Shorthand
4 Reporter and Notary Public in and for the State of
5 Texas, do hereby certify that the facts as stated by me
6 in the caption hereto are true; that the above and
7 foregoing answers of the witness, DR. ETHAN NATELSON,
8 to the interrogatories as indicated were made before me
9 by the said witness after being first duly sworn to
10 testify the truth, and same were reduced to typewriting
11 under my direction; that the above and foregoing
12 deposition as set forth in typewriting is a full, true,
13 and correct transcript of the proceedings had at the
14 time of taking of said deposition.
15 I further certify that I am not, in any
16 capacity, a regular employee of the party in whose
17 behalf this deposition is taken, nor in the regular
18 employ of this attorney, and I certify that I am not
19 interested in the cause, nor of kin or counsel to
20 either of the parties.
21 That the amount of time used by each party at
22 the deposition is as follows:
23 Mr. Keith Patton - 02:28:54
24 Mr. Kevin Parks - 00:05:48
25

15 GIVEN UNDER MY HAND AND SEAL OF OFFICE, on
16 this, the 25th day of September, 2007.
17

18 DENYCE SANDERS, CSR, RPR
19 Notary Public in and for
20 Harris County, T E X A S
21

My Commission Expires: 4-6-09

Certification No.: 4038

Expiration Date: 12-31-07

U.S. LEGAL Support, Inc.

363 N. Sam Houston Parkway, 9th Floor,

Houston, Texas 77060; 713.653.7100

Firm No. 122

25

29 (Pages 110 to 113)

U. S. Legal Support, Inc./MillerParker
214.741.6001

UNITED STATES DISTRICT COURT

for the

District of South Carolina

Joyce Barrois, et al

Plaintiff

v.

Fireman's Fund Insurance Company, et al

Defendant

Civil Action No. 09-380

(If the action is pending in another district, state where:

Eastern District of Louisiana)

SUBPOENA TO PRODUCE DOCUMENTS, INFORMATION, OR OBJECTS
OR TO PERMIT INSPECTION OF PREMISES IN A CIVIL ACTION

To: David W. Ploth, Editor, The American Journal of the Medical Sciences, 2491 River Bluff Ln, Mount Pleasant, SC 29466 or 1088 Johnnie Dodds Blvd., Mount Pleasant, SC 29464

☒ **Production: YOU ARE COMMANDED** to produce at the time, date, and place set forth below the following documents, electronically stored information, or objects, and permit their inspection, copying, testing, or sampling of the material: A certified, true, correct copy of the cover page, title page and manuscript of "Benzene Exposure and Refractory Sideroblastic Erythropoiesis: Is There An Association?" by Ethan A. Natelson, MD, The Am J of the Med Sci., 2007, 334(5):356-360 attached as Exhibit A. Please include all supporting documentation, rough drafts, funding sources, notes, possible conflict of interest disclosures and peer review comments.

Place: Williams Law Office, LLC
3000 W. Esplanade Ave., Ste. 200
Metairie, Louisiana 70002

Date and Time:

02/01/2010 5:00 pm

☐ **Inspection of Premises: YOU ARE COMMANDED** to permit entry onto the designated premises, land, or other property possessed or controlled by you at the time, date, and location set forth below, so that the requesting party may inspect, measure, survey, photograph, test, or sample the property or any designated object or operation on it.

Place:

Date and Time:

The provisions of Fed. R. Civ. P. 45(c), relating to your protection as a person subject to a subpoena, and Rule 45 (d) and (e), relating to your duty to respond to this subpoena and the potential consequences of not doing so, are attached.

Date:

1/19/10

CLERK OF COURT

OR

Signature of Clerk or Deputy Clerk

Attorney's signature

The name, address, e-mail, and telephone number of the attorney representing (name of party) Joyce Barrois, et al, who issues or requests this subpoena, are:

L. Eric Williams, Jr., Williams Law Office, LLC, 3000 W. Esplanade Ave., Ste. 200, Metairie, LA 70002, Tel: (504) 832-9898, eric@amlbenzene.net



Civil Action No. 09-380

PROOF OF SERVICE

(This section should not be filed with the court unless required by Fed. R. Civ. P. 45.)

This subpoena for *(name of individual and title, if any)* _____
was received by me on *(date)* _____.

☐ I served the subpoena by delivering a copy to the named person as follows: _____
_____ on *(date)* _____; or

☐ I returned the subpoena unexecuted because: _____

Unless the subpoena was issued on behalf of the United States, or one of its officers or agents, I have also
tendered to the witness fees for one day's attendance, and the mileage allowed by law, in the amount of
\$ _____.

My fees are \$ _____ for travel and \$ _____ for services, for a total of \$ 0.00 .

I declare under penalty of perjury that this information is true.

Date: _____

Server's signature

Printed name and title

Server's address

Additional information regarding attempted service, etc:

Federal Rule of Civil Procedure 45 (c), (d), and (e) (Effective 12/1/07)

(c) Protecting a Person Subject to a Subpoena.

(1) Avoiding Undue Burden or Expense; Sanctions. A party or attorney responsible for issuing and serving a subpoena must take reasonable steps to avoid imposing undue burden or expense on a person subject to the subpoena. The issuing court must enforce this duty and impose an appropriate sanction — which may include lost earnings and reasonable attorney's fees — on a party or attorney who fails to comply.

(2) Command to Produce Materials or Permit Inspection.

(A) Appearance Not Required. A person commanded to produce documents, electronically stored information, or tangible things, or to permit the inspection of premises, need not appear in person at the place of production or inspection unless also commanded to appear for a deposition, hearing, or trial.

(B) Objections. A person commanded to produce documents or tangible things or to permit inspection may serve on the party or attorney designated in the subpoena a written objection to inspecting, copying, testing or sampling any or all of the materials or to inspecting the premises — or to producing electronically stored information in the form or forms requested. The objection must be served before the earlier of the time specified for compliance or 14 days after the subpoena is served. If an objection is made, the following rules apply:

(i) At any time, on notice to the commanded person, the serving party may move the issuing court for an order compelling production or inspection.

(ii) These acts may be required only as directed in the order, and the order must protect a person who is neither a party nor a party's officer from significant expense resulting from compliance.

(3) Quashing or Modifying a Subpoena.

(A) When Required. On timely motion, the issuing court must quash or modify a subpoena that:

(i) fails to allow a reasonable time to comply;

(ii) requires a person who is neither a party nor a party's officer to travel more than 100 miles from where that person resides, is employed, or regularly transacts business in person — except that, subject to Rule 45(c)(3)(B)(iii), the person may be commanded to attend a trial by traveling from any such place within the state where the trial is held;

(iii) requires disclosure of privileged or other protected matter, if no exception or waiver applies; or

(iv) subjects a person to undue burden.

(B) When Permitted. To protect a person subject to or affected by a subpoena, the issuing court may, on motion, quash or modify the subpoena if it requires:

(i) disclosing a trade secret or other confidential research, development, or commercial information;

(ii) disclosing an unretained expert's opinion or information that does not describe specific occurrences in dispute and results from the expert's study that was not requested by a party; or

(iii) a person who is neither a party nor a party's officer to incur substantial expense to travel more than 100 miles to attend trial.

(C) Specifying Conditions as an Alternative. In the circumstances described in Rule 45(c)(3)(B), the court may, instead of quashing or modifying a subpoena, order appearance or production under specified conditions if the serving party:

(i) shows a substantial need for the testimony or material that cannot be otherwise met without undue hardship; and

(ii) ensures that the subpoenaed person will be reasonably compensated.

(d) Duties in Responding to a Subpoena.

(1) Producing Documents or Electronically Stored Information. These procedures apply to producing documents or electronically stored information:

(A) Documents. A person responding to a subpoena to produce documents must produce them as they are kept in the ordinary course of business or must organize and label them to correspond to the categories in the demand.

(B) Form for Producing Electronically Stored Information Not Specified. If a subpoena does not specify a form for producing electronically stored information, the person responding must produce it in a form or forms in which it is ordinarily maintained or in a reasonably usable form or forms.

(C) Electronically Stored Information Produced in Only One Form. The person responding need not produce the same electronically stored information in more than one form.

(D) Inaccessible Electronically Stored Information. The person responding need not provide discovery of electronically stored information from sources that the person identifies as not reasonably accessible because of undue burden or cost. On motion to compel discovery or for a protective order, the person responding must show that the information is not reasonably accessible because of undue burden or cost. If that showing is made, the court may nonetheless order discovery from such sources if the requesting party shows good cause, considering the limitations of Rule 26(b)(2)(C). The court may specify conditions for the discovery.

(2) Claiming Privilege or Protection.

(A) Information Withheld. A person withholding subpoenaed information under a claim that it is privileged or subject to protection as trial-preparation material must:

(i) expressly make the claim; and

(ii) describe the nature of the withheld documents, communications, or tangible things in a manner that, without revealing information itself privileged or protected, will enable the parties to assess the claim.

(B) Information Produced. If information produced in response to a subpoena is subject to a claim of privilege or of protection as trial-preparation material, the person making the claim may notify any party that received the information of the claim and the basis for it. After being notified, a party must promptly return, sequester, or destroy the specified information and any copies it has; must not use or disclose the information until the claim is resolved; must take reasonable steps to retrieve the information if the party disclosed it before being notified; and may promptly present the information to the court under seal for a determination of the claim. The person who produced the information must preserve the information until the claim is resolved.

(e) Contempt. The issuing court may hold in contempt a person who, having been served, fails without adequate excuse to obey the subpoena. A nonparty's failure to obey must be excused if the subpoena purports to require the nonparty to attend or produce at a place outside the limits of Rule 45(c)(3)(A)(ii).

Benzene Exposure and Refractory Sideroblastic Erythropoiesis: Is There an Association?

ETHAN A. NATELSON, MD

ABSTRACT: The myelodysplastic syndromes (MDS) consist of a group of diverse hematological disorders that carry an increased risk of transforming into acute myeloid leukemia. They may appear de novo and without obvious cause (primary or de novo MDS) or be induced by certain mutagenic environmental or therapeutic toxins (secondary MDS). Excessive exposures to benzene are generally considered to be a potential environmental risk factor for both MDS and acute myeloid leukemia. However, such risk is unproven for each disease component within the MDS classification. A critical review

of the refractory sideroblastic disorders strongly suggests that benzene exposure is not a potential cause of this distinct and still-evolving subset of MDS. The widely disparate nature of MDS suggests that epidemiologic studies can only provide meaningful data on associations and potential causation of its component syndromes by a disease-specific analysis, as is currently advocated for other hematological malignancies. **KEY INDEXING TERMS:** Benzene; Myelodysplasia; MDS; Refractory Sideroblastic Anemia. [Am J Med Sci 2007; 334(5):356-360.]

The terms myelodysplasia and the myelodysplastic syndromes (MDS) refer to a classification of heterogeneous and distinct disease forms linked by the presence of oligoclonal hematopoietic stem cell abnormalities, ineffective hematopoiesis characterized by abnormal differentiation and maturation of myeloid cells, and a variable but increased, risk of progression toward acute myeloid leukemia.¹⁻⁶ A common etiology among each of the various myelodysplastic disorders that is also shared with acute myeloid leukemia (AML) has not been proposed, and little is known about the major causes of MDS.^{6,7} Unfortunately, epidemiological surveys seeking statistical information on hematological malignancies in cohorts potentially exposed to environmental chemicals or toxins seldom provide specific data on MDS, despite its higher incidence in the general population than AML.⁴ Moreover, in rare instances when information on MDS is collected and presented, it is usually treated as a single, distinct disease entity, and its numbers may be combined with those of AML or even other unrelated hematological malignancies in an attempt to achieve statistical significance in the analysis.⁸ Such approach obscures identification of potential etiologic risk fac-

tors that might be specific to the individual disease components within MDS and to the various AML syndromes. Thus, under certain circumstances, benzene exposure is an accepted, although uncommon, potential risk factor for both MDS and AML.^{1,6,7,9} However, when carefully studied (vide infra), such risk does not necessarily apply to all components of the MDS. This report reviews the clinical observations that provide specific information concerning the question of causal associations between benzene as an environmental toxin and the acquired refractory sideroblastic disorders, a readily identifiable subset of the MDS classification system.^{10,11}

Discussion

Refractory anemia with ringed sideroblasts (RARS) was a well-described and stand-alone hematopoietic disorder until 1982, when it was included among other hematological syndromes grouped under a then newly defined heading of MDS.¹²⁻¹⁵ Typically discussed in hematologic text chapters dealing with congenital and acquired sideroblastic anemias of diverse cause, RARS has been described under a variety of titles including acquired idiopathic refractory sideroblastic anemia and sideroachrestic anemia. Its unifying morphological feature is the presence of ringed sideroblasts, as identified by iron stains, in at least 15% of the bone marrow erythroid precursors throughout multiple areas of the bone marrow films or biopsy.^{1,4} Such histologic stains have been a part of the routine evaluation of bone marrow specimens for nearly 60 years.¹⁶ The variable but clearly preleukemic nature of RARS has

From the Transitional Residency Program, The Methodist Hospital, and Weill Medical College of Cornell University at The Methodist Hospital, Houston, Texas.

Submitted January 16, 2007; accepted in revised form May 2, 2007.

Correspondence: Ethan A. Natelson, MD, 6550 Fannin Street, Smith Tower 1001, Houston, TX 77030 (E-mail: enatelson@tmhs.org).



Table 1. Myelodysplastic Syndromes

Original FAB Divisions	Current WHO Divisions
Refractory anemia	Refractory anemia
RA-Ringed sideroblasts	RC-Multilineage dysplasia
RA-Excess (5–20%) blasts	RA-Ringed sideroblasts
RA-Excess (21–30%) blasts in transition	RC-RS–Multilineage dysplasia
Chronic myelomonocytic leukemia	RA-Excess (5–9%) blasts type I
	RA-Excess (9–19%) blasts type II
	MDS isolated deletion 5 q
	MDS unclassifiable

FAB, French-American-British format; WHO, World Health Organization; RA, refractory anemia; RC, refractory cytopenia; RS, ringed sideroblasts.

also been known since its earliest descriptions.^{13,15} In the original MDS classification scheme, the subset of individuals with RARS comprised about 10% to 20% of the total cases in most series, with the relative frequency, perhaps, age of onset-related.¹⁷ They exhibit the lowest incidence of classical chromosomal aberrations of all MDS subsets and the least frequency of progression to AML—approximately 15%.^{18–21} Certain chromosomal aberrations have been associated with RARS including long arm deletions of chromosomes 5, 11, and 20, as well as trisomy 8.²¹ None are specific, however, and particularly deletions of 20q and trisomy 8 are identified in a number of diverse hematological disorders.^{21–23}

Modern revised classification systems of MDS attempt to separate RARS into 2 general subsets, 1 currently referred to as refractory cytopenia with multilineage dysplasia-ringed sideroblasts (RCMD-RS), and a second entity with little evident morphologic cytologic dysplasia outside the erythroid cell line, and a lesser risk of AML (Table 1). It remains under the designation of RARS.^{1,11,19,20,24} Recently, a further clinically-useful separation of the refractory sideroblastic disorders has been suggested, segregating all patients with ringed sideroblasts and markedly elevated platelet counts into yet another subset designated RARS-T or RST to emphasize the presence of thrombocytosis.^{24–27} Many of the individuals in this third grouping may also possess the newly described JAK-2 V617F chromosomal abnormality, commonly identified in polycythemia vera and other myeloproliferative disorders.^{26–28} RARS-T could then also be listed under the newly suggested descriptive designation of myelodysplastic/myeloproliferative syndromes.²⁵ The recognition that some individuals with RARS and marked thrombocytosis might exhibit a clinical course more in keeping with a myeloproliferative disorder, with megakaryocytic hyperplasia and bone marrow fibrosis, similar to the natural history of polycythemia vera, primary thrombocythemia and agnogenic myeloid metaplasia, is not a new observation.²⁹ The presence of the JAK-2 V617F mutation among the RARS-T group provides a unifying molecular explanation. Importantly, my-

eloproliferative disorders have not been epidemiologically linked with exposures to either benzene or to modern mutagenic chemotherapy agents.

The frequency distribution of these 3 refractory sideroblastic syndromes, particularly between RARS and RCMD-RS, is clearly observer-dependent and also varies with the alternate classifications systems for MDS of the World Health Organization and the French-American-British (FAB) format.^{10,30} An estimate would place about 10% of the total as RARS-T. However, if the bone marrow blast cell count increases above 5%, and even if large numbers of ringed sideroblasts are retained, under these classification schemes individuals are now moved from an RARS syndrome into another MDS category, refractory anemia with excess blasts (RAEB). In effect, this movement arbitrarily diminishes the pool of cases with refractory sideroblastic hematopoiesis available for epidemiological or clinical analysis, and is a weakness of all MDS classifications.¹⁸ Importantly, occasional patients with RARS, even those with apparent multilineage cytologic dysplasia, may favorably respond to immunosuppressive therapy, and in rare instances the hematologic syndrome is actually consequent to unusual deficiency states.^{31–34} Thus, progression to AML may not be a part of the natural history in certain forms of acquired sideroblastic anemia, emphasizing that all such disorders do not necessarily represent hematologic malignancies.

From the earliest descriptions, authors reporting on RARS pondered potential causes of this uncommon disorder. Wintrobe's experience in a single institution along with review of many additional cases led him and his associates to conclude that no specific drugs, environmental chemicals, alcohol, or cytostatic agents, could be confirmed as potential risk factors, and that the cause of RARS was unknown.¹² Benzene had previously been used as an oral chemotherapeutic agent in forms of chronic leukemia, and it was well known to cause bone marrow damage and potentially eventuate in AML. Exposure to this agent was specifically sought in an analysis of 84 patients with RARS, but only 1 of these subjects could recall any previous benzene exposure. Furthermore, that patient also had received radiation therapy.¹⁹ The collective experience now involving thousands of reported patients having received chemotherapy and then developing secondary hematologic syndromes including MDS, has only supplied rare case reports describing a chronic acquired sideroblastic process. This phenomenon has usually occurred in the presence of an underlying hematological malignancy, such as multiple myeloma or Hodgkin's disease, and is then noted after treatment including both alkylating agents and radiation.³⁵ Here, the acquired sideroblastic process, itself, is often transient and not evident in follow-up bone marrow examinations.^{36,37} Thus, neither exposure to

benzene nor to modern chemotherapeutic mutagenic agents has been shown to be a risk factor for RARS.

There are 3 major epidemiological studies often cited as offering detailed observations, including bone marrow analysis, which routinely includes iron stains, concerning the hematological effects of chronic, high-level benzene exposure. In the Hayes⁹ report of about 74,000 factory workers, primarily immersion painters in China, 28 individuals with either AML or MDS were cited. Analysis of the individual slide material from these MDS cases, and which specifically described bone marrow iron examination, showed no examples of RARS.³⁸ In the Aksoy³⁹ report of 29,000 Turkish shoe workers heavily exposed to benzene-containing glues, 42 individuals were described as developing forms of AML, among other hematological disorders. Yet, in his description of the specific hematologic abnormalities in this cohort, there is no observation consistent with RARS.⁴⁰ Finally, in the frequently-analyzed United States Pliofilm factory cohort of about 1,800 individuals exposed to large concentrations of pure benzene for many years, there are no reported details of bone marrow examinations, but no instance of a listed diagnosis consistent with RARS.⁴¹ A recent report from The MD Anderson Cancer Center also could not confirm solvent exposure as a significant predisposing event in their patients with RARS, or with chronic myelomonocytic leukemia, an original, and now former, member within the MDS classification system.⁷ In that study, such exposures were apparent risk factors for other forms of MDS such as refractory anemia with increased blasts (RAEB). In reality, there does not appear to be a single epidemiological study or even an isolated case report in the world's medical literature that links RARS with benzene exposure.

Recently, Irons et al⁴² carefully analyzed blood counts and serial bone marrow examinations on a small cohort of 23 Chinese workers heavily exposed to benzene. They reaffirmed earlier sporadic observations of marrow hypoplasia and eosinophilia in benzene-exposed workers but failed to identify the presence of ringed sideroblasts. Similarly, an absence of ringed sideroblasts was noted in careful bone marrow studies of 33 additional individuals with chronic benzene poisoning.⁴³ These marrow studies also demonstrated eosinophilia and dyspoietic erythroblasts. In general, the type of MDS bone marrow histology usually described in both heavily benzene-exposed individuals and therapy-related MDS is a hypocellular bone marrow with cellular dyspoiesis, and distinct from the usual findings in RARS which typically reflect a normocellular to hypercellular bone marrow pattern.^{38,44}

Cigarette smoke is considered a risk factor for both AML and MDS, but the specific element or mechanism involved is unknown.^{9,45-53} Cigarette smoke does contain some benzene, but the cumula-

tive dose achieved by smokers is less than thought necessary to increase the risk of AML, and the chromosomal anomalies identified in smokers with AML are somewhat different from those typically reported for benzene-induced and other secondary forms of AML.^{9,48-53} The chromosomal aberrations seen in the vast majority of benzene-induced AML and modern day chemotherapy-induced AML, or t-AML, are similar, with a predominance of deletions in chromosomes 5 and 7.⁹ This is not surprising, since postulated mechanisms of leukemogenesis in benzene-induced and t-AML, are also thought to be similar, if not identical.^{54,55} Some reports have suggested cigarette smoking is linked with RARS, although the mechanism is not known.^{7,45}

One feature of MDS that further confounds epidemiological analysis of its individual disease components is the fact that unlike AML, MDS is not a final illness designation, and individuals frequently move within the MDS classification over time. This is particularly true with respect to RARS syndromes. Thus, it would be expected that as the often slow progression to AML from the 3 refractory sideroblastic variants described here occurs, the percentage of blast cells in the bone marrow may increase gradually from its initially normal values. As previously mentioned, ringed sideroblasts are often still present when the bone marrow blast percentage reaches 5% to 10%, but the MDS diagnosis now moves to RAEB.^{17,56} When the blast percentage eventually reaches 20%, by convention, the diagnosis of AML is now allowed. Even if ringed sideroblasts remain evident in excess along with marked erythroid dyspoiesis, the specific diagnosis would be an FAB-M6 AML or erythroleukemia. Obviously, for such individual, this transition reflects a single disease process, and not 3 separate illnesses. This logic was first explained by Dameshek¹⁵ in 1965. For epidemiological purposes, should such a patient remain an example of an RARS syndrome or be considered to have the same illness as one with a sudden appearance of FAB-M6 AML without ringed sideroblasts or a prior diagnosis of MDS?

As our understanding of the molecular events leading to MDS and AML increases, epidemiologists and clinicians should work together to carefully analyze representative cohorts so that truly like illnesses are compared, in order to better identify potential risk factors. Simply abstracting a diagnosis from an often misleading and incomplete death certificate should become obsolete. A disease-specific approach is currently the rule in clinical studies that analyze the natural history and responses to therapy among the various disorders that make up the MDS classification.⁵⁷ Similar coordinated analyses by epidemiologists, pathologists and clinicians have been advocated and implemented for epidemiologic studies of the lymphoproliferative disorders, which also appear to have a number of distinct and disease

pattern-specific potential causes.^{58,59} Despite these caveats, based upon the considerable evidence presented here, benzene exposure cannot be considered a potential etiology for RARS, although it remains a risk factor for certain forms of MDS such as RAEB and unclassified and/or hypocellular MDS syndromes, and for AML.

References

1. Catenacci DVT, Schiller GJ. Myelodysplastic (sic) syndromes: a comprehensive review. *Blood Rev* 2005;19:301-19.
2. Kantarjian H. Myelodysplastic syndromes (MDS): what is new? *Leukemia Insights* 2006;11:1-7.
3. Aul C, Bowen DT, Yoshida Y. Pathogenesis, etiology and epidemiology of myelodysplastic syndromes. *Haematol* 1998; 83:71-86.
4. Cazzola M, Malcovati L. Myelodysplastic syndromes: coping with ineffective hematopoiesis. *N Engl J Med* 2005;352: 536-8.
5. Heaney M, Golde DW. Myelodysplasia. *N Engl J Med* 1999; 340:1649-60.
6. Breccia M, Mengarelli A, Mancini M, et al. Myelodysplastic syndromes in patients under 50 years old: a single institution experience. *Leuk Res* 2005;29:749-54.
7. Strom SS, Gu Y, Gruschkus SK, et al. EH Risk factors of myelodysplastic syndrome: a case control study. *Leukemia* 2005;19:1912-8.
8. Hayes RB, Yin S-N, Dosemici M, et al. Benzene and the dose-related incidence of hematologic neoplasms in China. *J Natl Cancer Inst* 1997;89:1065-71.
9. Estey E, Döhner H. Acute myeloid leukaemia. *Lancet* 2006; 368:1894-907.
10. Malcovati L, Della Porta MG, Pascutto C, et al. Prognostic factors and life expectancy in myelodysplastic syndromes classified according to WHO criteria: a basis for clinical decision making. *J Clin Oncol* 2005;23:7594-603.
11. Müller-Berndorff H, Haas PS, Kunzmann R, et al. Comparison of five prognostic scoring systems, the French-American-British (FAB) and World Health Organization (WHO) classifications in patients with myelodysplastic syndromes: results of a single-center analysis. *Ann Hematol* 2006;85: 502-13.
12. Kushner JP, Lee GR, Wintrobe MM, et al. Idiopathic refractory sideroblastic anemia: clinical and laboratory investigation of 17 patients and review of the literature. *Medicine* 1971;50:139-59.
13. Cheng DS, Kushner JP, Wintrobe MM. Idiopathic refractory sideroblastic anemia: incidence and risk factors for leukemic transformation. *Cancer* 1979;44:724-51.
14. Cazzola M, Barosi G, Gobbi PG, et al. Natural history of idiopathic refractory sideroblastic anemia. *Blood* 1988;71: 305-12.
15. Dameshek W. Sideroblastic anaemia: is this a malignancy? *Br J Haematol* 1965;11:52-8.
16. Beutler E, Robson MJ, Buttnerwieser B. A comparison of the plasma iron, iron-binding capacity, sternal marrow iron and other methods in the clinical evaluation of iron stores. *Ann Intern Med* 1958;48:60-82.
17. Kuendgen A, Strupp C, Aivado M, et al. Myelodysplastic syndromes in patients younger than age 50. *J Clin Oncol* 2006;24:5358-65.
18. Vandermolen L, Rice L, Rose MA, et al. Ringed sideroblasts in primary myelodysplasia: leukemic propensity and prognostic factors. *Ann Intern Med* 1988;148:653-6.
19. Garand R, Gardais J, Bizet M, et al. Heterogeneity of acquired idiopathic sideroblastic anaemia (AISA). *Leukemia Res* 1992;16:463-8.
20. Germing U, Gattermann N, Arvedo M, et al. Two types of acquired idiopathic sideroblastic anaemia (AISA): a time tested distinction. *Br J Haematol* 2000;108:724-8.
21. Schwartz S, Jiji R, Meekins J, et al. Chromosome abnormalities in acquired idiopathic sideroblastic anemia with subsequent leukemic transformation. *Can Gen Cytogenet* 1986;19:291-9.
22. Olney HJ, Le Beau MM. Evaluation of recurring cytogenetic abnormalities in the treatment of myelodysplastic syndromes. *Leuk Res* 2007;31:427-34.
23. Kurtin PJ, Dewald GW, Shields DJ, et al. Hematologic disorders associated with deletions of chromosome 20q: a clinicopathologic study of 107 patients. *Am J Clin Pathol* 1996;106:680-8.
24. Cabello AI, Collado R, Ruiz MÁ, et al. A retrospective analysis of myelodysplastic syndromes with thrombocytosis: reclassification of the cases by WHO proposals. *Leuk Res* 2005;29:365-70.
25. Shaw GR. Ringed sideroblasts with thrombocytosis: an uncommon mixed myelodysplastic/myeloproliferative disease of older adults. *Br J Haematol* 2005;31:180-4.
26. Szpurka R, Tiu G, Murugesan S, et al. Refractory anemia with ringed sideroblasts associated with marked thrombocytosis (RARS-T), another myeloproliferative condition characterized by JAK2 V617F mutation. *Blood* 2006;2173-81.
27. Boissinot M, Garand R, Hamidou M, et al. The JAK2-V61F mutation and essential thrombocythemia features in a subset of patients with refractory anemia with ring sideroblasts (RARS). *Blood* 2006;108:1781-2.
28. Villeval J-L, James C, Pisani DF, et al. New insights into the pathogenesis of JAK2 V617F-positive myeloproliferative disorders and consequences for the management of patients. *Semin Thromb Haemost* 2006;32:341-351.
29. Scully RE, Mark EJ, McNeely WF, et al. BU Weekly Clinicopathological Exercises (case 17-1992). *N Engl J Med* 1992;326:1137-46.
30. Malcovati L, Germing U, Kuendgen A, et al. Time-dependent prognostic scoring system for predicting survival and leukemic evolution in myelodysplastic syndromes. *J Clin Oncol* 2007;25:3503-10.
31. Zervas J, Geary CG, Oleesky S. Sideroblastic anemia treated with immunosuppressive therapy. *Blood* 1974;44: 117-23.
32. Lin J-T, Wang W-S, Yen C-C, et al. Myelodysplastic syndrome complicated by autoimmune hemolytic anemia: remission of refractory anemia following mycophenolate mofetil. *Ann Hematol* 2002;81:723-6.
33. Natelson E. Pregnancy-induced pancytopenia: distinctive hematological features. *Am J Med Sci* 2006;332:205-7.
34. Huff JD, Keung Y, Thakuri M, et al. Copper deficiency causes reversible myelodysplasia. *Am J Hematol* 2007;82 advance e-publication.
35. Kitahara M, Cosgriff TM, Eyre HJ. Sideroblastic Anemia as a preleukemic event in patients treated for Hodgkin's disease. *Ann Intern Med* 1980;92:625-7.
36. Magalhães SMM, Durate FB, Ribeiro SCC, et al. Sideroblastic anemia following treatment of chronic myeloid leukemia with busulfan. *Leukemia* 2002;14:214-5.
37. Fernandez LA, Zayed E. Busulfan-induced sideroblastic anemia. *Am J Hematol* 1998;28:199-200.
38. Linet MS, Yin S-N, Travis LB, et al. Clinical features of hematopoietic malignancies and related disorders among

- benzene exposed workers in china. *Environ Health Perspect* 1996;104:1353-64.
39. Aksoy M. Different types of malignancies due to occupational exposure to benzene: a review of recent observations in Turkey. *Environ Res* 1980;23:181-90.
40. Aksoy M, Dinçol K, Akgün T, et al. Haematological effects of chronic benzene poisoning in 217 workers. *Br J Indust Med* 1971;28:296-302.
41. Rinsky RA, Hornung RW, Silver SR, et al. Benzene exposure and hematopoietic mortality: a long-term epidemiologic risk assessment. *Am J Indust Med* 2002;42:474-80.
42. Irons RD, Lv L, Gross SA, et al. Chronic exposure to benzene results in a unique form of dysplasia. *Leukemia Res* 2005;29:1371-80.
43. Ruiz MA, Augusto LGS, Vassallo J, et al. Bone marrow morphology in patients with neutropenia due to chronic exposure to organic solvents (benzene): early lesions. *Path Res Pract* 1994;190:151-4.
44. Orazi A. Histopathology in the diagnosis and classification of acute myeloid leukemia, myelodysplastic syndromes and myelodysplastic/myeloproliferative diseases. *Pathobid* 2007;74: 97-114.
45. Björk J, Albin M, Mauritzson N, et al. Smoking and myelodysplastic syndromes. *Epidemiol* 2000;11:285-91.
46. Pasqualetti P, Festucia V, Acitelli P, et al. Tobacco smoking and risk of haematological malignancies in adults: a case-control study. *Br J Haematol* 1997;97:659-62.
47. Carmona R. The Surgeon General's 2004 report, The Health Consequences of Smoking. US Dept Health and Human Services, Chap 2, p 254.
48. Chelghoum Y, Danaïla C, Belhabri A, et al. Influence of cigarette smoking on the presentation and course of acute myeloid leukemia. *Ann Oncol* 2002;13:1621-7.
49. Lichtman MA. Cigarette smoking, cytogenetic abnormalities, and acute myelogenous leukemia. *Leuk* 2007;21: 1137-40.
50. Thomas X, Chelghoum Y. Cigarette smoking and acute leukemia. *Leuk Lymphoma* 2004;45:1103-9.
51. Kane EV, Roman E, Cartwright R, et al. Tobacco and the risk of acute leukaemia in adults. *Br J Cancer* 1999;81:1228-33.
52. Davico L, Sacerdote C, Ciccone G, et al. Chromosome 8, occupational exposures, smoking, and acute nonlymphocytic leukemias: a population-based study. *Can Epidemiol Biomarkers Prev* 1998;7:1123-5.
53. Moorman AV, Roman E, Cartwright RA, et al. Smoking and the risk of acute myeloid leukaemia in cytogenetic subgroups. *Br J Cancer* 2002;86:60-2.
54. Smith MA, McCaffrey RP, Karp JE. The secondary leukemias: challenges and research directions. *J Natl Cancer Inst* 1996;88:407-18.
55. Morgan GJ, Alvares CL. Benzene and the hematopoietic stem cell. *Chemico-Biol Interact* 2005;153-154:217-222.
56. Yoshida Y, Oguma S, Tohyama K, et al. Diagnostic and biological significance of sideroblastic erythropoiesis in the myelodysplastic syndromes. *Int J Hematol* 1998;67:137-44.
57. List A, Kurtin S, Roe DJ, et al. Efficacy of Lenalidomide in myelodysplastic syndromes. *N Engl J Med* 2005;352: 549-57.
58. Alexander DD, Mink PJ, Adami HO, et al. The non-Hodgkin lymphomas: A review of the epidemiologic literature. *Int J Can* 2007;120:1-39.
59. Wang SS, Slager SL, Brennan P, et al. Family history of hematopoietic malignancies and risk of non-Hodgkin lymphoma (NHL): a pooled analysis of 10211 cases and 11905 controls from the International Lymphoma Epidemiology Consortium (InterLymph). *Blood* 2007;109:3479-88.

Eric Williams

From: Kindy J.D., Lisa Zokas [kindylz@musc.edu]
Sent: Monday, February 01, 2010 3:25 PM
To: 'eric@amlbenzene.net'; 'erika@amlbenzene.net'
Cc: Ploth, David W.; Medical Sciences, American Journal of
Subject: Barrois v. Fireman's Fund Subpoena to Ploth Editor
Attachments: CTA.PDF; Acknowledgement Ltr.PDF; Ltr to AU 4.25.07.PDF; Ltr to AU.PDF; Natelson Ltr.PDF; Published Article.PDF; Re-Review.PDF; Response to Reviewer.PDF; Review.PDF; Instructions to Authors (2).pdf

Importance: High

Joyce Barrois v. Fireman's Fund Insurance Co, et al
US District Court District of SC Civil Action No. 09-380
Pending Eastern District Louisiana
Subpoena to David W. Ploth, Editor, The American Journal of the Medical Sciences
Subpoena dated 1/19/10.

Dear Mr. Williams:
Attached are the documents responsive to the above referenced Subpoena.
Please contact me if you have any questions.
Thank you,
Lisa Zokas Kindy JD
General Counsel's Office MUSC
3 Doughty Street
Charleston, SC 29425
(843) 792-9089



07-031

The American Journal of the Medical Sciences
Published by Lippincott Williams & Wilkins
Authorship Responsibility, Financial Disclosure, and Copyright Transfer

Manuscript Title: Benzene Exposure and Leukemia: Erythroblastosis - IS THERE AN ASSOCIATION?

Corresponding Author's Name: ETHAN A. NATELSON, MD MMS Number:

Address: 6550 Fannin Street
Suite 1001
Houston Texas

Telephone Number: 713-441-5154

Fax Number: 713-790-2727

E-Mail Address: e.natelson@fwh.tmc.edu

Each author must read and sign the following statements: (1) Authorship Responsibility; (2) Financial Disclosure; and (3) Copyright Transfer or (3-b) Federal Employment. If necessary, photocopy this document and distribute to co-authors for their original ink signatures. Please compile all forms and send to AJMS Editorial Offices, Medical University of South Carolina, Division of Nephrology, CSB 829, 96 Jonathan Lucas Street, Charleston, SC 29425.

1. **Authorship Responsibility:** I certify that I have participated sufficiently in the conception and design of this work, the analysis of the data (where applicable), as well as the writing of the manuscript, to take public responsibility for it. I believe the manuscript represents valid work. I reviewed this manuscript (original version) and approve its submission. If I am listed above as corresponding author, I will provide all authors with information regarding this manuscript and will obtain their approval before submitting any revision. Neither this manuscript nor one with substantially similar context under my authorship has been published or will be submitted for publication elsewhere while under consideration by *The American Journal of the Medical Sciences*, except as described in an attachment. Furthermore, I attest that I shall produce the data on which the manuscript is based for examination by the editors or their assignees should they request it.

Authors' Signatures	Date
<u>[Signature]</u>	<u>1-16-2007</u>

Authors' Signatures	Date

2. **Financial Disclosure:** I certify that any affiliations with or involvement (either competitive or amiable) in any organization or entity with a direct financial interest in the subject matter or materials discussed in the manuscript (e.g. employment, consultancies, stock ownership, honoraria, and expert testimony) are noted below. Otherwise, my signature indicates that I have no such financial interest. All financial research or project support is identified in an acknowledgment in the manuscript.

Statement of Financial Interest: (If more space is needed, submit a signed attachment.) _____

Authors' Signatures	Date
<u>[Signature]</u>	<u>1-16-2007</u>

Authors' Signatures	Date

Authors need to complete either section a or b:

- 3a. **Copyright:** In consideration of reviewing and editing this submission, the author(s) undersigned hereby transfer(s) or otherwise convey(s) all copyright ownership to The Southern Society for Clinical Investigation in the event that such work is published in the *Journal*.

Authors' Signatures	Date
<u>[Signature]</u>	<u>1-16-2007</u>

Authors' Signatures	Date

- 3b. **U.S. Federal Employment:** I was an employee of the U.S. Federal Government when this work was conducted and prepared for publication. Therefore, it is not protected by the Copyright Act and there is no copyright. Thus, ownership cannot be transferred.

Authors' Signatures	Date

Authors' Signatures	Date

View Letter

[Close](#)[Resend](#)

Date: 02/13/2007
To: "Ethan Allen Natelson" enatelson@tmh.tmc.edu
From: "The American Journal of the Medical Sciences" ajms@musc.edu
Subject: A manuscript number has been assigned (AJMS 07-031)

Feb 13, 2007

Associate Professor Natelson,

Thank you for submitting your manuscript to The The American Journal of the Medical Sciences. Your submission entitled "Benzene Exposure and Refractory Sideroblastic Erythropoiesis - Is There an Association?" has been assigned the following manuscript number: AJMS 07-031.

We will be sending your manuscript to the Editorial Board shortly and from there it may be sent out for a comprehensive review. Should your manuscript be accepted, the publisher will bill you a charge of \$40 (USD) per printed page.

You will be able to check on the progress of your paper by logging on to Editorial Manager as an author.

<http://maj.edmgr.com/>

Your username is: *****
Your password is: *****

Thank you again for your contribution. I look forward to receiving your response to this e-mail and to working with you throughout our review process.

Kind regards,

Kathleen Kelly
Managing Editor
The American Journal of the Medical Sciences

[Close](#)[Resend](#)

View Letter

[Close](#)[Resend](#)

Date: 04/25/2007
To: "Ethan Allen Natelson" enatelson@tmh.tmc.edu
From: "The American Journal of the Medical Sciences" ajms@musc.edu
Subject: AJMS 07-031 Decision

April 25, 2007

RE: AJMS 07-031, entitled "Benzene Exposure and Refractory Sideroblastic Erythropoiesis - Is There an Association?"

Good Morning Dr. Natelson,

I am pleased to inform you that your paper has been found acceptable for publication pending minor revision. Below you will find the reviewers comments for your review. I anticipate that you will easily be able to answer the criticisms of the reviewers in a satisfactory manner and will verify those changes upon receipt of the revised manuscript.

Please include with your revised (highlighted) submission an itemized, point-by-point response to the comments of each reviewer. Thank you, I look forward to receiving your completed revisions by May 09, 2007.

To submit a revision, go to <http://maj.edmgr.com/> and log in as an Author. You will see a menu item called "Submission Needing Revision." Please click on this item to obtain your submission record and begin the revision process.

Your username is: *****
Your password is: *****

With kind regards,
Ms. Kathleen Kelly
Managing Editor
The American Journal of the Medical Sciences

Reviewer Comments:

Reviewer #1: I found this to be a very interesting, if somewhat abbreviated review of this subject. This topic is also quite timely as benzene related issues (mostly toxic tort litigation) are on the rise and MDS is frequently at issue. Most epidemiologists and toxicologists consider MDS to be a single disease entity, particularly from an etiological point of view. Therefore, this review makes a useful contribution to the scientific literature by providing a needed, informed opposing viewpoint. Additionally, physicians are becoming increasingly involved in this discussion (both formally and informally), and in many cases they come in with a very poor background or understanding of benzene toxicology or pathology. In both of these areas, this review provides something of value and would likely be widely read and appreciated.

General Comments:

The abstract is perhaps overly concise and would benefit from a bit more information.

I think this manuscript would also benefit from a more robust discussion of MDS and the FAB method of classification (the 'FAB' 5). A more detailed discussion regarding the accepted and suspected risk factors for the various subtypes of MDS would also be very germane to this review. How might this change within the WHO classification system?

There were several areas where some light editing is needed. Additionally, the draft tends to have a lot of technical terms with (in some cases) insufficient introduction to that topic. I have provided a few examples below.

There was a great deal of effort on the part of the author to identify the 3 subtypes of RARS, but that didn't seem to influence the overall conclusions of the manuscript, namely that MDS is not a single disease and that benzene exposure is not associated with one type, RARS. Perhaps a rationale for why the 3 different forms of RARS are important epidemiologically might be included for clarity.

Specific Comments:

P3: Is myelodysplasia the same as myelodysplastic syndrome? I think the author's answer would be yes, but this needs to be made clear at the outset of the introduction.

P3, L4: Suggested edit...delete "That there is"...and begin the sentence with "a".

P3, L15: The sentence needs some additional justification. The approach as described only 'blurs' things if, in fact, the various diseases under the rubric of MDS actually have different etiologies. Later, some evidence is offered that supports this sentence, but at this point in the progression of the discussion, no data has been discussed.

P5, L12: The sentence that starts with 'RARS' is somewhat confusing.

P6, L9: Please define the T in RARS-T...it is identified later in the section.

P7, L11: What does 'obvious multi-lineage dysplasia' have to do with IS therapy. This section jumped around a bit too much for a non-hematologist to follow. Also, does it indicate the different forms of RARS have diverse causes or really just evidence of a diverse response to treatment?

P8: Is the point of this section that neither benzene nor chemotherapy exposure is associated with an increased risk of RARS?

P9: Were the pathological descriptions published in Aksoy's work sufficiently detailed to determine if any RARS cases were present? Did they use the appropriate assays and stains? Also, the 'pliofilm' cohort was based on death certificates. Is it possible that some had RARS and then progressed and died from AML without RARS being identified (or identifiable)? If so, does this change the authors position?

P10: If topoisomerase inhibition is a potential mechanism for benzene and AML, why is there no involvement of chromosomes 11 in any benzene exposure worker or occupational AML case? Involvement with (11q23) is extremely common in topoisomerase inhibition induced t-AML, but not in benzene cohorts? This reviewer has serious doubts about this mechanism playing a role in benzene induced AML.

P12: What are the recommendations of the author regarding MDS epidemiology? How should the hypothetical patient discussed on page 11-12 be handled in epidemiology studies? How would that ever be identified by the investigators...particularly in a retrospective mortality study? I totally agree that this is a significant issue and would

therefore be interested in reading any recommendations regarding this short-coming in available or forthcoming studies.

P12: Last line: I would suggest the following editorial change...although it remains a risk factor for other certain forms of AML and for AML. This line also begs the question...which forms of MDS might be positively associated with benzene? Perhaps a table could be included with the various diseases and the relative strength of the epidemiology evidence.

Complete Revision Instructions:

PRELIMINARY STEPS:

1. Click on the "Submissions Needing Revision" link.
2. To view the previous decision letter and reviewer comments, please click the blue decision term listed under the View Decision menu.
2. If you would like to download the previous manuscript in order to make revisions, click on "Download Files" under the Action menu.

RESUBMISSION STEPS:

3. To BEGIN the RESUBMISSION: Click "Submit Revision" under the Action menu.
4. Proof each screen to ensure the information is still correct (the Title, Authors, etc), then click Next at the bottom of each page.
5. On the Attach Files screen, be sure to click beside each previous submission item that you would like included in the following submission. BE SURE TO CHOOSE TO CARRY OVER YOUR COPYRIGHT FORM.
6. Now, as you did previously, simply upload the parts of your manuscript. When you are finished, please click Next.
7. Click "Build PDF for My Approval."
8. Click "Go to Submissions Waiting for Authors Approval."
9. Wait for the PDF to Build. When it has been built, you will see the link "View Submission" in the Action menu. Click "View Submission," and open the manuscript in order to proof your work.
10. If you find problems with the manuscript, please click "Edit Submission" from the Action menu. Make the appropriate changes, beginning again at step 3.
11. If you find no problems with the manuscript, please click "Approve Submission" from the Action menu. Your re-submission is now complete!

[Close](#)[Resend](#)

[Cancel](#)[Save and Close](#)**AJMS 07-031R1****"Benzene Exposure and Refractory Sideroblastic Erythropoiesis - Is There an Association?"****Revision 1****David Pyatt, MD (Reviewer 1)**[Edit Reviewer Comments](#)**Reviewer Recommendation Term:**

Accept as is

Rate Review: Please enter a number from 1-100

How would you rate this manuscript for priority of publication 1-10; [1- 9
10 being excellent 10]

Comments to Editor:

Part I. COMMENTS AND SUMMARY OF REVIEWER FOR EDITORIAL OFFICE ONLY. This part will NOT be sent to authors.

Scientific Quality: Excellent Good Fair Poor**Manuscript Issues to be Addressed:**Grammar Yes No Length Yes No **Comments to Author:**

Additional Comments to Editorial Office:

I think it will be an important addition to the literature.

[More Reviewer Details](#)[Cancel](#)[Save and Close](#)

[Cancel](#)[Save and Close](#)**AJMS 07-031****"Benzene Exposure and Refractory Sideroblastic Erythropoiesis - Is There an Association?"
Original Submission****David Pyatt, MD (Reviewer 1)**[Edit Reviewer Comments](#)**Reviewer Recommendation Term:** Accept with Minor Revision**Rate Review:** Please enter a number from 1-100How would you rate this manuscript for priority of publication 1-10; [1- 9
10 being excellent 10]**Comments to Editor:** Part I. COMMENTS AND SUMMARY OF REVIEWER FOR EDITORIAL OFFICE ONLY. This part will NOT be sent to authors.

Scientific Quality:

☐ X_ Excellent☐ X_ Good☐ Fair☐ Poor

Manuscript Issues to be Addressed:

Grammar Yes___ a few No___

Length Yes_X___ No___

Comments to Author:

Additional Comments to Editorial Office:

I found this to be a very interesting, if somewhat abbreviated review of this subject. This topic is also quite timely as benzene related issues (mostly toxic tort litigation) are on the rise and MDS is frequently at issue. Most epidemiologists and toxicologists consider MDS to be a single disease entity, particularly from an etiological point of view. Therefore, this review makes a useful contribution to the scientific literature by providing a needed, informed opposing viewpoint. Additionally, physicians are becoming increasingly involved in this discussion (both formally and informally), and in many cases they come in with a very poor background or understanding of benzene toxicology or pathology. In both of these areas, this review provides something of value and would likely be widely read and appreciated.

General Comments:

The abstract is perhaps overly concise and would benefit from a bit more information.

I think this manuscript would also benefit from a more robust discussion of MDS and the FAB method of classification (the 'FAB' 5). A more detailed discussion regarding the accepted and suspected risk factors for the various subtypes of MDS would also be very germane to this review. How might this change within the WHO classification system?

There were several areas where some light editing is needed. Additionally, the draft tends to have a lot of technical terms with (in some cases) insufficient introduction to that topic. I have provided a few examples below.

There was a great deal of effort on the part of the author to identify the 3 subtypes of RARS, but that didn't seem to influence the overall conclusions of the manuscript, namely that MDS is not a single disease and that benzene exposure is not associated with one type, RARS. Perhaps a rationale for why the 3 different forms of RARS are important epidemiologically might be included for clarity.

Specific Comments:

P3: Is myelodysplasia the same as myelodysplastic syndrome? I think the author's answer would be yes, but this needs to be made clear at the outset of the introduction.

P3, L4: Suggested edit...delete "That there is"...and begin the sentence with "a".

P3, L15: The sentence needs some additional justification. The approach as described only 'blurs' things if, in fact, the various diseases under the rubric of MDS actually have different etiologies. Later, some evidence is offered that supports this sentence, but at this point in the progression of the discussion, no data has been discussed.

P5, L12: The sentence that starts with 'RARS' is somewhat confusing.

P6, L9: Please define the T in RARS-T...it is identified later in the section.

P7, L11: What does 'obvious multi-lineage dysplasia' have to do with IS therapy. This section jumped around a bit too much for a non-hematologist to follow. Also, does it indicate the different forms of RARS have diverse causes or really just evidence of a diverse response to treatment?

P8: Is the point of this section that neither benzene nor chemotherapy exposure is associated with an increased risk of RARS?

P9: Were the pathological descriptions published in Aksoy's work sufficiently detailed to determine if any RARS cases were present? Did they use the appropriate assays and stains? Also, the 'pliofilm' cohort was based on death certificates. Is it possible that some had RARS and then progressed and died from AML

without RARS being identified (or identifiable)? If so, does this change the authors position?

P10: If topoisomerase inhibition is a potential mechanism for benzene and AML, why is there no involvement of chromosomes 11 in any benzene exposure worker or occupational AML case? Involvement with (11q23) is extremely common in topoisomerase inhibition induced t-AML, but not in benzene cohorts? This reviewer has serious doubts about this mechanism playing a role in benzene induced AML.

P12: What are the recommendations of the author regarding MDS epidemiology? How should the hypothetical patient discussed on page 11-12 be handled in epidemiology studies? How would that ever be identified by the investigators... particularly in a retrospective mortality study? I totally agree that this is a significant issue and would therefore be interested in reading any recommendations regarding this short-coming in available or forthcoming studies.

P12: Last line: I would suggest the following editorial change... although it remains a risk factor for other certain forms of AML and for AML. This line also begs the question...which forms of MDS might be positively associated with benzene? Perhaps a table could be included with the various diseases and the relative strength of the epidemiology evidence.

[More Reviewer Details](#)

[Cancel](#)

[Save and Close](#)

2-1-2010
THIS IS A TRUE COPY OF published
MANUSCRIPT from ADMS 334:356, 2007

Benzene Exposure and Refractory Sideroblastic Erythropoiesis: Is There an Association?

ETHAN A. NATELSON, MD

Donna J. Piantadosi
Editor in Chief

ABSTRACT: The myelodysplastic syndromes (MDS) consist of a group of diverse hematological disorders that carry an increased risk of transforming into acute myeloid leukemia. They may appear de novo and without obvious cause (primary or de novo MDS) or be induced by certain mutagenic environmental or therapeutic toxins (secondary MDS). Excessive exposures to benzene are generally considered to be a potential environmental risk factor for both MDS and acute myeloid leukemia. However, such risk is unproven for each disease component within the MDS classification. A critical review

of the refractory sideroblastic disorders strongly suggests that benzene exposure is not a potential cause of this distinct and still-evolving subset of MDS. The widely disparate nature of MDS suggests that epidemiologic studies can only provide meaningful data on associations and potential causation of its component syndromes by a disease-specific analysis, as is currently advocated for other hematological malignancies. **KEY INDEXING TERMS:** Benzene; Myelodysplasia; MDS; Refractory Sideroblastic Anemia. [Am J Med Sci 2007; 334(5):356-360.]

The terms myelodysplasia and the myelodysplastic syndromes (MDS) refer to a classification of heterogeneous and distinct disease forms linked by the presence of oligoclonal hematopoietic stem cell abnormalities, ineffective hematopoiesis characterized by abnormal differentiation and maturation of myeloid cells, and a variable but increased, risk of progression toward acute myeloid leukemia.¹⁻⁶ A common etiology among each of the various myelodysplastic disorders that is also shared with acute myeloid leukemia (AML) has not been proposed, and little is known about the major causes of MDS.^{6,7} Unfortunately, epidemiological surveys seeking statistical information on hematological malignancies in cohorts potentially exposed to environmental chemicals or toxins seldom provide specific data on MDS, despite its higher incidence in the general population than AML.⁴ Moreover, in rare instances when information on MDS is collected and presented, it is usually treated as a single, distinct disease entity, and its numbers may be combined with those of AML or even other unrelated hematological malignancies in an attempt to achieve statistical significance in the analysis.⁸ Such approach obscures identification of potential etiologic risk fac-

tors that might be specific to the individual disease components within MDS and to the various AML syndromes. Thus, under certain circumstances, benzene exposure is an accepted, although uncommon, potential risk factor for both MDS and AML.^{1,6,7,9} However, when carefully studied (vide infra), such risk does not necessarily apply to all components of the MDS. This report reviews the clinical observations that provide specific information concerning the question of causal associations between benzene as an environmental toxin and the acquired refractory sideroblastic disorders, a readily identifiable subset of the MDS classification system.^{10,11}

Discussion

Refractory anemia with ringed sideroblasts (RARS) was a well-described and stand-alone hematopoietic disorder until 1982, when it was included among other hematological syndromes grouped under a then newly defined heading of MDS.¹²⁻¹⁵ Typically discussed in hematologic text chapters dealing with congenital and acquired sideroblastic anemias of diverse cause, RARS has been described under a variety of titles including acquired idiopathic refractory sideroblastic anemia and sideroachrestic anemia. Its unifying morphological feature is the presence of ringed sideroblasts, as identified by iron stains, in at least 15% of the bone marrow erythroid precursors throughout multiple areas of the bone marrow films or biopsy.^{1,4} Such histologic stains have been a part of the routine evaluation of bone marrow specimens for nearly 60 years.¹⁶ The variable but clearly preleukemic nature of RARS has

From the Transitional Residency Program, The Methodist Hospital, and Weill Medical College of Cornell University at The Methodist Hospital, Houston, Texas.

Submitted January 16, 2007; accepted in revised form May 2, 2007.

Correspondence: Ethan A. Natelson, MD, 6550 Fannin Street, Smith Tower 1001, Houston, TX 77030 (E-mail: enatelson@tmhs.org).

Table 1. Myelodysplastic Syndromes

Original FAB Divisions	Current WHO Divisions
Refractory anemia	Refractory anemia
RA-Ringed sideroblasts	RC-Multilineage dysplasia
RA-Excess (5-20%) blasts	RA-Ringed sideroblasts
RA-Excess (21-30%) blasts in transition	RC-RS-Multilineage dysplasia
Chronic myelomonocytic leukemia	RA-Excess (5-9%) blasts type I
	RA-Excess (9-19%) blasts type II
	MDS isolated deletion 5q
	MDS unclassifiable

FAB, French-American-British format; WHO, World Health Organization; RA, refractory anemia; RC, refractory cytopenia; RS, ringed sideroblasts.

also been known since its earliest descriptions.^{13,15} In the original MDS classification scheme, the subset of individuals with RARS comprised about 10% to 20% of the total cases in most series, with the relative frequency, perhaps, age of onset-related.¹⁷ They exhibit the lowest incidence of classical chromosomal aberrations of all MDS subsets and the least frequency of progression to AML—approximately 15%.¹⁸⁻²¹ Certain chromosomal aberrations have been associated with RARS including long arm deletions of chromosomes 5, 11, and 20, as well as trisomy 8.²¹ None are specific, however, and particularly deletions of 20q and trisomy 8 are identified in a number of diverse hematological disorders.²¹⁻²³

Modern revised classification systems of MDS attempt to separate RARS into 2 general subsets, 1 currently referred to as refractory cytopenia with multilineage dysplasia-ringed sideroblasts (RCMD-RS), and a second entity with little evident morphologic cytologic dysplasia outside the erythroid cell line, and a lesser risk of AML (Table 1). It remains under the designation of RARS.^{1,11,19,20,24} Recently, a further clinically-useful separation of the refractory sideroblastic disorders has been suggested, segregating all patients with ringed sideroblasts and markedly elevated platelet counts into yet another subset designated RARS-T or RST to emphasize the presence of thrombocytosis.²⁴⁻²⁷ Many of the individuals in this third grouping may also possess the newly described JAK-2 V617F chromosomal abnormality, commonly identified in polycythemia vera and other myeloproliferative disorders.²⁶⁻²⁸ RARS-T could then also be listed under the newly suggested descriptive designation of myelodysplastic/myeloproliferative syndromes.²⁵ The recognition that some individuals with RARS and marked thrombocytosis might exhibit a clinical course more in keeping with a myeloproliferative disorder, with megakaryocytic hyperplasia and bone marrow fibrosis, similar to the natural history of polycythemia vera, primary thrombocythemia and agnogenic myeloid metaplasia, is not a new observation.²⁹ The presence of the JAK-2 V617F mutation among the RARS-T group provides a unifying molecular explanation. Importantly, my-

eloproliferative disorders have not been epidemiologically linked with exposures to either benzene or to modern mutagenic chemotherapy agents.

The frequency distribution of these 3 refractory sideroblastic syndromes, particularly between RARS and RCMD-RS, is clearly observer-dependent and also varies with the alternate classifications systems for MDS of the World Health Organization and the French-American-British (FAB) format.^{10,30} An estimate would place about 10% of the total as RARS-T. However, if the bone marrow blast cell count increases above 5%, and even if large numbers of ringed sideroblasts are retained, under these classification schemes individuals are now moved from an RARS syndrome into another MDS category, refractory anemia with excess blasts (RAEB). In effect, this movement arbitrarily diminishes the pool of cases with refractory sideroblastic hematopoiesis available for epidemiological or clinical analysis, and is a weakness of all MDS classifications.¹⁸ Importantly, occasional patients with RARS, even those with apparent multilineage cytologic dysplasia, may favorably respond to immunosuppressive therapy, and in rare instances the hematologic syndrome is actually consequent to unusual deficiency states.³¹⁻³⁴ Thus, progression to AML may not be a part of the natural history in certain forms of acquired sideroblastic anemia, emphasizing that all such disorders do not necessarily represent hematologic malignancies.

From the earliest descriptions, authors reporting on RARS pondered potential causes of this uncommon disorder. Wintrobe's experience in a single institution along with review of many additional cases led him and his associates to conclude that no specific drugs, environmental chemicals, alcohol, or cytostatic agents, could be confirmed as potential risk factors, and that the cause of RARS was unknown.¹² Benzene had previously been used as an oral chemotherapeutic agent in forms of chronic leukemia, and it was well known to cause bone marrow damage and potentially eventuate in AML. Exposure to this agent was specifically sought in an analysis of 84 patients with RARS, but only 1 of these subjects could recall any previous benzene exposure. Furthermore, that patient also had received radiation therapy.¹⁹ The collective experience now involving thousands of reported patients having received chemotherapy and then developing secondary hematologic syndromes including MDS, has only supplied rare case reports describing a chronic acquired sideroblastic process. This phenomenon has usually occurred in the presence of an underlying hematological malignancy, such as multiple myeloma or Hodgkin's disease, and is then noted after treatment including both alkylating agents and radiation.³⁵ Here, the acquired sideroblastic process, itself, is often transient and not evident in follow-up bone marrow examinations.^{36,37} Thus, neither exposure to

benzene nor to modern chemotherapeutic mutagenic agents has been shown to be a risk factor for RARS.

There are 3 major epidemiological studies often cited as offering detailed observations, including bone marrow analysis, which routinely includes iron stains, concerning the hematological effects of chronic, high-level benzene exposure. In the Hayes⁸ report of about 74,000 factory workers, primarily immersion painters in China, 28 individuals with either AML or MDS were cited. Analysis of the individual slide material from these MDS cases, and which specifically described bone marrow iron examination, showed no examples of RARS.³⁸ In the Aksoy³⁹ report of 29,000 Turkish shoe workers heavily exposed to benzene-containing glues, 42 individuals were described as developing forms of AML, among other hematological disorders. Yet, in his description of the specific hematologic abnormalities in this cohort, there is no observation consistent with RARS.⁴⁰ Finally, in the frequently-analyzed United States Pliofilm factory cohort of about 1,800 individuals exposed to large concentrations of pure benzene for many years, there are no reported details of bone marrow examinations, but no instance of a listed diagnosis consistent with RARS.⁴¹ A recent report from The MD Anderson Cancer Center also could not confirm solvent exposure as a significant predisposing event in their patients with RARS, or with chronic myelomonocytic leukemia, an original, and now former, member within the MDS classification system.⁷ In that study, such exposures were apparent risk factors for other forms of MDS such as refractory anemia with increased blasts (RAEB). In reality, there does not appear to be a single epidemiological study or even an isolated case report in the world's medical literature that links RARS with benzene exposure.

Recently, Irons et al⁴² carefully analyzed blood counts and serial bone marrow examinations on a small cohort of 23 Chinese workers heavily exposed to benzene. They reaffirmed earlier sporadic observations of marrow hypoplasia and eosinophilia in benzene-exposed workers but failed to identify the presence of ringed sideroblasts. Similarly, an absence of ringed sideroblasts was noted in careful bone marrow studies of 33 additional individuals with chronic benzene poisoning.⁴³ These marrow studies also demonstrated eosinophilia and dyspoietic erythroblasts. In general, the type of MDS bone marrow histology usually described in both heavily benzene-exposed individuals and therapy-related MDS is a hypocellular bone marrow with cellular dyspoiesis, and distinct from the usual findings in RARS which typically reflect a normocellular to hypercellular bone marrow pattern.^{38,44}

Cigarette smoke is considered a risk factor for both AML and MDS, but the specific element or mechanism involved is unknown.^{9,45-53} Cigarette smoke does contain some benzene, but the cumula-

tive dose achieved by smokers is less than thought necessary to increase the risk of AML, and the chromosomal anomalies identified in smokers with AML are somewhat different from those typically reported for benzene-induced and other secondary forms of AML.^{9,46-53} The chromosomal aberrations seen in the vast majority of benzene-induced AML and modern day chemotherapy-induced AML, or t-AML, are similar, with a predominance of deletions in chromosomes 5 and 7.⁹ This is not surprising, since postulated mechanisms of leukemogenesis in benzene-induced and t-AML, are also thought to be similar, if not identical.^{54,55} Some reports have suggested cigarette smoking is linked with RARS, although the mechanism is not known.^{7,45}

One feature of MDS that further confounds epidemiological analysis of its individual disease components is the fact that unlike AML, MDS is not a final illness designation, and individuals frequently move within the MDS classification over time. This is particularly true with respect to RARS syndromes. Thus, it would be expected that as the often slow progression to AML from the 3 refractory sideroblastic variants described here occurs, the percentage of blast cells in the bone marrow may increase gradually from its initially normal values. As previously mentioned, ringed sideroblasts are often still present when the bone marrow blast percentage reaches 5% to 10%, but the MDS diagnosis now moves to RAEB.^{17,56} When the blast percentage eventually reaches 20%, by convention, the diagnosis of AML is now allowed. Even if ringed sideroblasts remain evident in excess along with marked erythroid dyspoiesis, the specific diagnosis would be an FAB-M6 AML or erythroleukemia. Obviously, for such individual, this transition reflects a single disease process, and not 3 separate illnesses. This logic was first explained by Dameshek¹⁵ in 1965. For epidemiological purposes, should such a patient remain an example of an RARS syndrome or be considered to have the same illness as one with a sudden appearance of FAB-M6 AML without ringed sideroblasts or a prior diagnosis of MDS?

As our understanding of the molecular events leading to MDS and AML increases, epidemiologists and clinicians should work together to carefully analyze representative cohorts so that truly like illnesses are compared, in order to better identify potential risk factors. Simply abstracting a diagnosis from an often misleading and incomplete death certificate should become obsolete. A disease-specific approach is currently the rule in clinical studies that analyze the natural history and responses to therapy among the various disorders that make up the MDS classification.⁵⁷ Similar coordinated analyses by epidemiologists, pathologists and clinicians have been advocated and implemented for epidemiologic studies of the lymphoproliferative disorders, which also appear to have a number of distinct and disease

pattern-specific potential causes.^{58,59} Despite these caveats, based upon the considerable evidence presented here, benzene exposure cannot be considered a potential etiology for RARS, although it remains a risk factor for certain forms of MDS such as RAEB and unclassified and/or hypocellular MDS syndromes, and for AML.

References

1. Catenacci DVT, Schiller GJ. Myelodysplastic (sic) syndromes: a comprehensive review. *Blood Rev* 2005;19:301-19.
2. Kantarjian H. Myelodysplastic syndromes (MDS): what is new? *Leukemia Insights* 2006;11:1-7.
3. Aul C, Bowen DT, Yoshida Y. Pathogenesis, etiology and epidemiology of myelodysplastic syndromes. *Haematol* 1998; 83:71-86.
4. Cazzola M, Malcovati I. Myelodysplastic syndromes: coping with ineffective hematopoiesis. *N Engl J Med* 2005;352: 536-8.
5. Heaney M, Golde DW. Myelodysplasia. *N Engl J Med* 1999; 340:1649-60.
6. Breccia M, Mengarelli A, Mancini M, et al. Myelodysplastic syndromes in patients under 50 years old: a single institution experience. *Leuk Res* 2005;29:749-54.
7. Strom SS, Gu Y, Gruschus SK, et al. EH Risk factors of myelodysplastic syndrome: a case control study. *Leukemia* 2005;19:1912-8.
8. Hayes RB, Yin S-N, Dosemici M, et al. Benzene and the dose-related incidence of hematologic neoplasms in China. *J Natl Cancer Inst* 1997;89:1065-71.
9. Estey E, Döhner H. Acute myeloid leukaemia. *Lancet* 2006; 368:1894-907.
10. Malcovati L, Della Porta MG, Pascutto C, et al. Prognostic factors and life expectancy in myelodysplastic syndromes classified according to WHO criteria: a basis for clinical decision making. *J Clin Oncol* 2005;23:7594-603.
11. Müller-Berndorff H, Haas PS, Kunzmann R, et al. Comparison of five prognostic scoring systems, the French-American-British (FAB) and World Health Organization (WHO) classifications in patients with myelodysplastic syndromes: results of a single-center analysis. *Ann Hematol* 2006;85: 502-13.
12. Kushner JP, Lee GR, Wintrobe MM, et al. Idiopathic refractory sideroblastic anemia: clinical and laboratory investigation of 17 patients and review of the literature. *Medicine* 1971;50:139-59.
13. Cheng DS, Kushner JP, Wintrobe MM. Idiopathic refractory sideroblastic anemia: incidence and risk factors for leukemic transformation. *Cancer* 1979;44:724-51.
14. Cazzola M, Barosi G, Gobbi PG, et al. Natural history of idiopathic refractory sideroblastic anemia. *Blood* 1988;71: 305-12.
15. Dameshek W. Sideroblastic anaemia: is this a malignancy? *Br J Haematol* 1965;11:52-8.
16. Beutler E, Robson MJ, Bittenwieser B. A comparison of the plasma iron, iron-binding capacity, sternal marrow iron and other methods in the clinical evaluation of iron stores. *Ann Intern Med* 1958;48:60-82.
17. Kuendgen A, Strupp C, Aivado M, et al. Myelodysplastic syndromes in patients younger than age 50. *J Clin Oncol* 2006;24:5358-65.
18. Vandermolen L, Rice L, Rose MA, et al. Ringed sideroblasts in primary myelodysplasia: leukemic propensity and prognostic factors. *Ann Intern Med* 1988;148:653-6.
19. Garand R, Gardais J, Bizet M, et al. Heterogeneity of acquired idiopathic sideroblastic anaemia (AISA). *Leukemia Res* 1992;16:463-8.
20. Germing U, Gattermann N, Arvedo M, et al. Two types of acquired idiopathic sideroblastic anaemia (AISA): a time tested distinction. *Br J Haematol* 2000;108:724-8.
21. Schwartz S, Jiji R, Meekins J, et al. Chromosome abnormalities in acquired idiopathic sideroblastic anemia with subsequent leukemic transformation. *Can Gen Cytogenet* 1986;19:291-9.
22. Olney HJ, Le Beau MM. Evaluation of recurring cytogenetic abnormalities in the treatment of myelodysplastic syndromes. *Leuk Res* 2007;31:427-34.
23. Kurtin PJ, Dewald GW, Shields DJ, et al. Hematologic disorders associated with deletions of chromosome 20q: a clinicopathologic study of 107 patients. *Am J Clin Pathol* 1996;106:680-8.
24. Cabello AI, Collado R, Ruiz MÁ, et al. A retrospective analysis of myelodysplastic syndromes with thrombocytosis: reclassification of the cases by WHO proposals. *Leuk Res* 2005;29:365-70.
25. Shaw GR. Ringed sideroblasts with thrombocytosis: an uncommon mixed myelodysplastic/myeloproliferative disease of older adults. *Br J Haematol* 2005;31:180-4.
26. Szpurka R, Tiu G, Murugesan S, et al. Refractory anemia with ringed sideroblasts associated with marked thrombocytosis (RARS-T), another myeloproliferative condition characterized by JAK2 V617F mutation. *Blood* 2006;2173-81.
27. Boissinot M, Garand R, Hamidou M, et al. The JAK2-V61F mutation and essential thrombocythemia features in a subset of patients with refractory anemia with ring sideroblasts (RARS). *Blood* 2006;108:1781-2.
28. Villeval J-L, James C, Pisani DF, et al. New insights into the pathogenesis of JAK2 V617F-positive myeloproliferative disorders and consequences for the management of patients. *Semin Thromb Haemost* 2006;32:341-351.
29. Scully RE, Mark EJ, McNeely WF, et al. BU Weekly Clinicopathological Exercises (case 17-1992). *N Engl J Med* 1992;326:1137-46.
30. Malcovati L, Germing U, Kuendgen A, et al. Time-dependent prognostic scoring system for predicting survival and leukemic evolution in myelodysplastic syndromes. *J Clin Oncol* 2007;25:3503-10.
31. Zervas J, Geary CG, Oleesky S. Sideroblastic anemia treated with immunosuppressive therapy. *Blood* 1974;44: 117-23.
32. Lin J-T, Wang W-S, Yen C-C, et al. Myelodysplastic syndrome complicated by autoimmune hemolytic anemia: remission of refractory anemia following mycophenolate mofetil. *Ann Hematol* 2002;81:723-6.
33. Natelson E. Pregnancy-induced pancytopenia: distinctive hematological features. *Am J Med Sci* 2006;332:205-7.
34. Huff JD, Keung Y, Thakuri M, et al. Copper deficiency causes reversible myelodysplasia. *Am J Hematol* 2007;82 advance e-publication.
35. Kitahara M, Cosgriff TM, Eyre HJ. Sideroblastic Anemia as a preleukemic event in patients treated for Hodgkin's disease. *Ann Intern Med* 1980;92:625-7.
36. Magalhães SMM, Durate FB, Ribeiro SCC, et al. Sideroblastic anemia following treatment of chronic myeloid leukemia with busulfan. *Leukemia* 2002;14:214-5.
37. Fernandez LA, Zayed E. Busulfan-induced sideroblastic anemia. *Am J Hematol* 1998;28:199-200.
38. Linet MS, Yin S-N, Travis LB, et al. Clinical features of hematopoietic malignancies and related disorders among

- benzene exposed workers in china. *Environ Health Perspect* 1996;104:1353-64.
39. Aksoy M. Different types of malignancies due to occupational exposure to benzene: a review of recent observations in Turkey. *Environ Res* 1980;23:181-90.
40. Aksoy M, Dinçol K, Akgün T, et al. Haematological effects of chronic benzene poisoning in 217 workers. *Br J Indust Med* 1971;28:296-302.
41. Rinsky RA, Hornung RW, Silver SR, et al. Benzene exposure and hematopoietic mortality: a long-term epidemiologic risk assessment. *Am J Indust Med* 2002;42:474-80.
42. Irons RD, Lv L, Gross SA, et al. Chronic exposure to benzene results in a unique form of dysplasia. *Leukemia Res* 2005;29:1371-80.
43. Ruiz MA, Augusto LGS, Vassallo J, et al. Bone marrow morphology in patients with neutropenia due to chronic exposure to organic solvents (benzene): early lesions. *Path Res Pract* 1994;190:151-4.
44. Orazi A. Histopathology in the diagnosis and classification of acute myeloid leukemia, myelodysplastic syndromes and myelodysplastic/myeloproliferative diseases. *Pathobid* 2007;74: 97-114.
45. Björk J, Albin M, Mauritzson N, et al. Smoking and myelodysplastic syndromes. *Epidemiol* 2000;11:285-91.
46. Pasqualetti P, Festucia V, Acitelli P, et al. Tobacco smoking and risk of haematological malignancies in adults: a case-control study. *Br J Haematol* 1997;97:659-62.
47. Carmona R. The Surgeon General's 2004 report, The Health Consequences of Smoking. US Dept Health and Human Services, Chap 2, p 254.
48. Chelghoum Y, Danaïla C, Belhabri A, et al. Influence of cigarette smoking on the presentation and course of acute myeloid leukemia. *Ann Oncol* 2002;13:1621-7.
49. Lichtman MA. Cigarette smoking, cytogenetic abnormalities, and acute myelogenous leukemia. *Leuk* 2007;21: 1137-40.
50. Thomas X, Chelghoum Y. Cigarette smoking and acute leukemia. *Leuk Lymphoma* 2004;45:1103-9.
51. Kane EV, Roman E, Cartwright R, et al. Tobacco and the risk of acute leukaemia in adults. *Br J Cancer* 1999;81:1228-33.
52. Davico L, Sacerdote C, Ciccone G, et al. Chromosome 8, occupational exposures, smoking, and acute nonlymphocytic leukemias: a population-based study. *Can Epidemiol Biomarkers Prev* 1998;7:1123-5.
53. Moorman AV, Roman E, Cartwright RA, et al. Smoking and the risk of acute myeloid leukaemia in cytogenetic subgroups. *Br J Cancer* 2002;86:60-2.
54. Smith MA, McCaffrey RP, Karp JE. The secondary leukemias: challenges and research directions. *J Natl Cancer Inst* 1996;88:407-18.
55. Morgan GJ, Alvares CL. Benzene and the hematopoietic stem cell. *Chemico-Biol Interact* 2005;153-154:217-222.
56. Yoshida Y, Oguma S, Tohyama K, et al. Diagnostic and biological significance of sideroblastic erythropoiesis in the myelodysplastic syndromes. *Int J Hematol* 1998;67:137-44.
57. List A, Kurtin S, Roe DJ, et al. Efficacy of Lenalidomide in myelodysplastic syndromes. *N Engl J Med* 2005;352: 549-57.
58. Alexander DD, Mink PJ, Adami HO, et al. The non-Hodgkin lymphomas: A review of the epidemiologic literature. *Int J Can* 2007;120:1-39.
59. Wang SS, Slager SL, Brennan P, et al. Family history of hematopoietic malignancies and risk of non-Hodgkin lymphoma (NHL): a pooled analysis of 10211 cases and 11905 controls from the International Lymphoma Epidemiology Consortium (InterLymph). *Blood* 2007;109:3479-88.

4-27-07

Ms. Kathleen Kelly
Managing Editor
The American Journal of the Medical Sciences

RE: Manuscript AJMS 07-031, Response to Reviewers

Dear Ms. Kelly,

Thank you for the opportunity to respond to the reviewer's comments and suggestions. I must say that I appreciate the detailed analysis and the time spent in this review. I hope you will agree that the revised manuscript flows more easily as it is read and more clearly highlights the points I am trying to make. This improves its usefulness to both general physicians and epidemiologists who are not always familiar with the descriptive and often confusing language used in discussing MDS. My point by point responses to the specific comments are as follows:

P3: Yes, myelodysplasia, myelodysplastic syndrome, myelodysplastic disorders and myelodysplastic syndromes all refer to the same process and classification, and are terms used interchangeably throughout the medical literature. I have clarified this in the abstract and the opening sentence of the introduction.

P3, L4: I have modified this sentence as suggested.

P3, L15: I have clarified this language and added the term, *vide infra*, to emphasize that while no data has yet been presented, it is to follow.

P5, L12: This confusing sentence has been re-worked.

P6, L9: The T, as used in RARS-T, has been defined in the sentence.

P7, L11: This sentence has been re-worked and added to in order to make the point clear that even a very dyspoietic and sick appearing RARS marrow, with obvious multilineage dysplasia, does not mean that the patient has a neoplastic condition destined to evolve into leukemia. Thus, the RARS syndromes are very heterogenous in causation. Truthfully, in my and other hematologist's opinions, they should exit MDS as has chronic myelomonocytic leukemia, but this is too big a leap to propose in a focused article like this one.

P8: Yes, that is the point. I have added a summation sentence to the paragraph to emphasize this conclusion.

P9: Here the reviewer reveals that he/she is not a clinician. The Aksoy and Pliofilm studies were done in the 1970's and 1980's. As a medical student in 1963-4 I was doing

iron stains on bone marrows, as they were already a routine procedure at that time. I did add a reference from 1958 (now 16), by Dr. Ernst Beutler, who, almost 50 years later, remains an eminent hematologist, clinician and lecturer, and who reviewed the subject of bone marrow iron stains at that time. I also discussed the use of iron stains and death certificates in the text.

P10: The reviewer is alluding to a topic that, "has not yet been introduced in evidence", as the lawyers often say. Nowhere in the manuscript did I use the term Topoisomerase II inhibitor. Actually, I agree with the reviewer on this concept. Thus, I removed the 2 references (original 48-49) that specifically deal with Topoisomerase II inhibition as a possible mechanism of benzene leukemogenic action, and used alternate references (now 54-55) that state that the leukemogenic effects of benzene and modern chemotherapy are thought to be identical, without specifying the proposed Topoisomerase II related mechanism that the reviewer finds controversial.

P12: This is an important topic and has been more and more emphasized in the medical literature, but, until recently, been given more lip service than application. I added a few sentences and a very new reference (now 59) that shows, in concert with the preceding reference (now 58) how this was suggested and then actually has been implemented in the field of lymphoma epidemiology and causation.

P12, Last Line: I did add a comment as to which types of MDS might be benzene-induced. I did add a table to show how the classification of MDS began, and what it consists of today. There is simply no data to define the strength of the evidence for each subtype of MDS – this can only be addressed as I have done to exclude RARS and CMML (an entity now removed from the original classification system) and plea for specific data in all of the categories.

Going back to the general comments, I have expanded the abstract, adding information, and in the table show how the MDS classification has been modified from the original "FAB 5" the reviewer mentions.

Please let me know if these revisions and additions have satisfactorily addressed the reviewer's comments.

Cordially yours,

Ethan A. Natelson, M.D.

View Letter

[Close](#)[Resend](#)

Date: 05/02/2007
To: "Ethan Allen Natelson" enatelson@tmh.tmc.edu
From: "The American Journal of the Medical Sciences" ajms@musc.edu
Subject: AJMS 07-031R1 Decision

May 02, 2007

RE: AJMS 07-031R1, entitled "Benzene Exposure and Refractory Sideroblastic Erythropoiesis - Is There an Association?"

Good Morning Dr. Natelson,

I am pleased to inform you that your work has now been accepted for publication in The American Journal of the Medical Sciences. Congratulations to you and your co-authors!

While there are no additional changes to be made at this time, there may be some minor changes which may need to be addressed once you receive the proofs back from the publisher. When you receive the page proofs, please check both the text and bibliography carefully as we must rely on the authors for the accuracy of the references.

Your manuscript materials will now be forwarded to production for placement in an upcoming issue.

Thank you for submitting your interesting and important work to The Journal. It has been a pleasure working with you during the review process, and I do hope we will have a future opportunity of working with you again.

<http://maj.edmgr.com/>

Your username is: *****

Your password is: *****

With kind regards,

Ms. Kathleen Kelly
Managing Editor
The American Journal of the Medical Sciences

[Close](#)[Resend](#)

The American Journal of the Medical Sciences

Online Submission and Review System

Author Resources

[Instructions for Authors \(this page\)](#)

[Copyright Transfer \(PDF\)](#)

[Reprint Ordering](#)

[Permissions Requests](#)

[ePrints](#)

[Reprints](#)

The American Journal of the Medical Sciences considers manuscripts reporting original clinical or laboratory investigations, reviews and case reports. Papers on all subspecialties are invited. Each manuscript must be accompanied by a statement indicating that the material has not been previously published elsewhere and is being considered solely by AJMS. In addition, the submission must be accompanied by a completed copyright transfer form. All clinical research should be conducted in accordance with the guiding principles for human experimentation summarized in the latest version of the Helsinki Declaration. When reporting experiments on animals, indicate which guideline on the care and use of laboratory animals was followed. Include permission to reproduce previously published material or to use illustrations that may identify human subjects.

Manuscripts

All manuscripts should be submitted electronically with appropriate attachments, i.e. figures and tables. The page size configuration should be 8 1/2" x 11". The entire manuscript should be typed double-space with 1-inch margins. All pages should be numbered, including the title page. The format should be as follows: title page, abstract, introduction, methods, results, discussion, acknowledgments, references, tables (each on a separate page), figure legends and figures. Begin each section or component on a new page. Figures should be no larger than 8 x 10 inches. Use Arabic numerals.

Compliance with NIH and Other Research Funding Agency Accessibility Requirements

A number of research funding agencies now require or request authors to submit the post-print (the article after peer review and acceptance but not the final published article) to a repository that is accessible online without charge. As a service to our authors, Lippincott Williams & Wilkins will identify to the National Library of Medicine (NLM) articles that require deposit and will transmit the post-print of an article based on research funded in whole or in part by the National Institutes of Health, Wellcome Trust, Howard Hughes Medical Institute, or other funding agencies to PubMed Central. The revised Copyright Transfer Agreement provides the mechanism.

Images in the Medical Sciences

This section will contain one or more images with a short narrative description of the image and its relationship to the clinical case. The goal of this series is to display an important or unique pictorial representation of a disease, e.g. x-ray, biopsy or photograph. The discussion should be limited to one relatively short paragraph with no more than 1 or 2 references, such that the image or images and the text together do not exceed 1 published manuscript pages. An abstract is not required.

Cover Letter

The cover letter should include: (1) full title of the paper; (2) full authorship and all institutional affiliations; (3) clear statement that the paper has not been submitted elsewhere, is not under review, or published previously, except in abstract form; (4) any possible conflict of interest should be clearly stated; and (5) a statement to the effect of "all the authorship are aware of and approve the manuscript being submitted to this journal".

Title Page

The title page should carry (1) the title of the article, which should be concise but informative; (2) each author's name, with his or her highest academic degree and institutional affiliation; (3) the name, address, phone, fax and e-mail address of the corresponding author; (4) sources of support in the form of grants, equipment, or drugs, including any funding received for this work

from any of the following organizations: National Institutes of Health (NIH), Wellcome Trust, Howard Hughes Medical Institute (HHMI), or other(s); (5) disclaimers, if any, including notices of the manuscript's prior appearance as a preliminary report or abstract; and (6) a short title of no more than 40 characters and spaces.

Abstract

The abstract should not exceed 150 words [250 words for structured abstracts (Background, Methods, Results, Conclusions), which are required for reports of original investigations]. The abstract should state the purposes of the study or investigation, basic procedures, main findings and the principal conclusions. It should emphasize new and important aspects of the study.

Key Words

A list of no more than 5 key words or short phrases that will assist in cross-indexing should be provided.

References

References should be numbered consecutively in the order in which they are first mentioned in the text. There should be no more than 40 references. Identify references in text, tables, and legends by superscript Arabic numerals. Avoid using abstracts as references. References to papers accepted but not yet published should be designated as "in press"; authors should obtain written permission to cite such papers as well as verification that they have been accepted for publication. Information from manuscripts submitted but not accepted should be cited in the text as "unpublished observations" with written permission from the source. Avoid citing a personal communication unless it provides essential information not available from a public source, in which case the name of the person and date of communication should be cited in parentheses in the text. Authors should obtain written permission and confirmation of accuracy from the source. The permission document should be submitted with the manuscript. Use the style of the examples below. In all cases, list the first three authors and/or editors, followed by "et al." The titles of journals should be abbreviated according to the style used in Index Medicus. Abbreviations can be obtained from PubMed <<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed>>.

Parkin DM, Clayton D, Black RJ, et al. Childhood leukaemia in Europe after Chernobyl: 5 year follow-up. *Br J Cancer* 1996;73:1006-12.

Phillips SJ, Whisnant JP. Hypertension and stroke. In: Laragh JH, Brenner BM, editors. *Hypertension: pathophysiology, diagnosis, and management*. 2nd ed. New York: Raven Press; 1995. p. 465-78.

Bengtsson S, Solheim BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, et al, editors. *MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics*; 1992 Sep 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. p. 1561-5.

Figures

Number figures consecutively in the order of their first citation in the text. **Please reference "5 Steps to Creating Digital Artwork (pdf)" available at www.editorialmanager.com/maj/, specifically steps 2 and 3, when creating figures for submission.** Sharp, black-and-white photographic images, no larger than 8 x 10 inches, are preferred. Letters, numbers, and symbols should be clear and even throughout and of sufficient size that each item will still be legible when reduced for publication. Titles and detailed explanations belong in the legends for figures, not on the figures themselves. Photomicrographs should have internal scale markers; symbols, arrows or letters used should contrast with the background. If photographs of people are used, the subjects must be unidentifiable or the subjects must have provided written permission to use the photograph. This permission document should also be submitted with the manuscript. If a figure has been published, acknowledge the original source and submit written permission from the copyright holder to reproduce the material. Permission is required irrespective of authorship or publisher, except for documents in the public domain.

Supplemental Digital Content

Supplemental Digital Content (SDC): Authors may submit SDC via Editorial Manager to LWW journals that enhance their article's text to be considered for online posting. SDC may include standard media such as text documents, graphs, audio, video, etc. On the Attach Files page of the submission process, please select Supplemental Audio, Video, or Data for your uploaded file as the Submission Item. If an article with SDC is accepted, our production staff will create a URL with the SDC file. The URL will be placed in the call-out within the article. SDC files are not copy-edited by LWW staff, they will be presented digitally as submitted. For a list of all available file types and detailed instructions, please visit <http://links.lww.com/A142>.

SDC Call-outs

Supplemental Digital Content must be cited consecutively in the text of the submitted manuscript. Citations should include the type of material submitted (Audio, Figure, Table, etc.), be clearly labeled as "Supplemental Digital Content," include the sequential list number, and provide a description of the supplemental content. All descriptive text should be included in the call-out as it will not appear elsewhere in the article.

Example:

We performed many tests on the degrees of flexibility in the elbow (see Video, Supplemental Digital Content 1, which demonstrates elbow flexibility) and found our results inconclusive.

List of Supplemental Digital Content

A listing of Supplemental Digital Content must be submitted at the end of the manuscript file. Include the SDC number and file type of the Supplemental Digital Content. This text will be removed by our production staff and not be published.

Example:

Supplemental Digital Content 1. wmv

SDC File Requirements

All acceptable file types are permissible up to 10 MBs. For audio or video files greater than 10 MBs, authors should first query the journal office for approval. For a list of all available file types and detailed instructions, please visit <http://links.lww.com/A142>.

Tables

Submit each table, double-spaced, as a separate document. Number tables consecutively in the order of their first citation in the text and supply a brief title for each. Be sure that each table is cited in the text. Do not use internal horizontal and vertical rules. Place explanatory matter in footnotes, not in the heading. Explain in footnotes all abbreviations used in each table. For footnotes, use superscript lowercase letters. If you use data from another published or unpublished source, obtain permission and acknowledge them fully.

Abbreviations and Nomenclature

Abbreviations and nomenclature should conform to the American Medical Association Manual of Style, 9th ed. Abbreviations should be kept to a minimum in the text and should be defined at first usage. Periods are not used after abbreviations (eg, mm, mL). Generic names are preferred for drugs. Use of SI (Système International) units is preferred but not required.

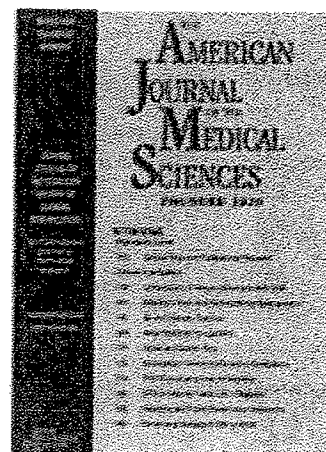
Submit Manuscripts On-Line To:

<http://www.editorialmanager.com/maj/>

Please do not submit hard-copy manuscripts as they will not be entered into the system or returned to the author.

Page Charges

Authors will be billed a publication page rate of \$40 per printed page. Authors will also be charged for color figures. Page charges and color charges will be billed by, and are payable to, the publisher.



Copyright 2009, Lippincott Williams & Wilkins. All rights reserved.

Published by Lippincott Williams & Wilkins

Copyright/Disclaimer Notice • Privacy Policy

blood

JOURNAL OF
THE AMERICAN
SOCIETY OF
HEMATOLOGY

VOLUME 108
NUMBER 7
1 OCTOBER 2006

Therapy of myeloma

Hyperhomocysteinemia and
arterial thrombosis

NEMO and dendritic cell
function

Significance of homozygous
V617F JAK2 mutation

IL-15, GVHD, and
graft-versus-tumor activity

Cover:

JAK2 V617F and refractory
anemia with thrombocytosis

www.bloodjournal.org

D 000-631-6969

EXHIBIT

6

Neulasta® (pegfilgrastim)

Start with support

BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

Neulasta® is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia.

CONTRAINDICATIONS

Neulasta® is contraindicated in patients with known hypersensitivity to *E. coli*-derived proteins, pegfilgrastim, filgrastim, or any other component of the product.

WARNINGS

General

The safety and efficacy of Neulasta® for peripheral blood progenitor cell (PBPC) mobilization has not been evaluated in adequate and well-controlled studies. Neulasta® should not be used for PBPC mobilization.

Splenic Rupture

RARE CASES OF SPLENIC RUPTURE HAVE BEEN REPORTED FOLLOWING THE ADMINISTRATION OF NEULASTA®. SPLENIC RUPTURE, IN SOME CASES RESULTING IN DEATH, HAS ALSO BEEN ASSOCIATED WITH FILGRASTIM, THE PARENT COMPOUND OF NEULASTA®. PATIENTS RECEIVING NEULASTA® WHO REPORT LEFT UPPER ABDOMINAL AND/OR SHOULDER TIP PAIN SHOULD BE EVALUATED FOR AN ENLARGED SPLEEN OR SPLENIC RUPTURE.

Adult Respiratory Distress Syndrome (ARDS)

Adult respiratory distress syndrome (ARDS) has been reported in neutropenic patients with sepsis receiving Filgrastim, the parent compound of Neulasta®, and is postulated to be secondary to an influx of neutrophils to sites of inflammation in the lungs. Neutropenic patients receiving Neulasta® who develop fever, lung infiltrates, or respiratory distress should be evaluated for the possibility of ARDS. In the event that ARDS occurs, Neulasta® should be discontinued and/or withheld until resolution of ARDS and patients should receive appropriate medical management for this condition.

Allergic Reactions

Allergic reactions to Neulasta®, including anaphylaxis, skin rash, and urticaria, have been reported in post-marketing experience. The majority of reported events occurred upon initial exposure. In some cases, symptoms recurred with rechallenge, suggesting a causal relationship. In rare cases, allergic reactions including anaphylaxis, occurred within days after initial anti-allergic treatment was discontinued. If a serious allergic reaction occurs, appropriate therapy should be administered, with close patient follow-up over several days. Neulasta® should be permanently discontinued in patients with serious allergic reactions.

Sickle Cell Disease

Severe sickle cell crises have been associated with the use of Neulasta® in patients with sickle cell disease. Severe sickle cell crises, in some cases resulting in death, have also been associated with Filgrastim, the parent compound of pegfilgrastim. Only physicians qualified by specialized training or experience in the treatment of patients with sickle cell disease should prescribe Neulasta® for such patients, and only after careful consideration of the potential risks and benefits.

PRECAUTIONS

General

Use With Chemotherapy and/or Radiation Therapy

Neulasta® should not be administered in the period between 14 days before and 24 hours after administration of cytotoxic chemotherapy (see **DOSE AND ADMINISTRATION**) because of the potential for an increase in sensitivity to rapidly dividing myeloid cells to cytotoxic chemotherapy.

The use of Neulasta® has not been studied in patients receiving chemotherapy associated with delayed myelosuppression (eg, nitrosoureas, mitomycin C).

The administration of Neulasta® concomitantly with 5-fluorouracil or other antineoplastic agents has not been evaluated in patients. Administration of pegfilgrastim at 0, 1, and 3 days before 5-fluorouracil resulted in increased mortality in mice; administration of pegfilgrastim 24 hours after 5-fluorouracil did not adversely affect survival.

The use of Neulasta® has not been studied in patients receiving radiation therapy.

Potential Effect on Malignant Cells

Pegfilgrastim is a growth factor that primarily stimulates neutrophils and neutrophil precursors; however, the G-CSF receptor through which pegfilgrastim and Filgrastim act has been found on tumor cell lines, including some myeloid, T-lymphoid, lung, head and neck, and bladder tumor cell lines. The possibility that pegfilgrastim can act as a growth factor for any tumor type cannot be excluded. Use of Neulasta® in myeloid malignancies and myelodysplasia (MDS) has not been studied. In a randomized study comparing the effects of the parent compound of Neulasta®, Filgrastim, to placebo in patients undergoing remission induction and consolidation chemotherapy for acute myeloid leukemia, important differences in remission rate between the two arms were excluded. Disease-free survival and overall survival were comparable; however, the study was not designed to detect important differences in these endpoints.

Information for Patients

Patients should be informed of the possible side effects of Neulasta®, and be instructed to report them to the prescribing physician. Patients should be informed of the signs and symptoms of allergic drug reactions and be advised of appropriate actions. Patients should be counseled on the importance of compliance with their Neulasta® treatment, including regular monitoring of blood counts.

If it is determined that a patient or caregiver can safely and effectively administer Neulasta® (pegfilgrastim) at home, appropriate instruction on the proper use of Neulasta® (pegfilgrastim) should be provided for patients and their caregivers, including careful review of the "Information for Patients and Caregivers" insert. Patients and caregivers should be cautioned against the reuse of needles, syringes, or drug product, and be thoroughly instructed in their proper disposal. A puncture-resistant container for the disposal of used syringes and needles should be available.

Laboratory Monitoring

To assess a patient's hematologic status and ability to tolerate myelosuppressive chemotherapy, a complete blood count and platelet count should be obtained before chemotherapy is administered. Regular monitoring of hematocrit value and platelet count is recommended.

Drug Interaction

No formal drug interaction studies between Neulasta® and other drugs have been performed. Drugs such as lithium may potentiate the release of neutrophils; patients receiving lithium and Neulasta® should have more frequent monitoring of neutrophil counts.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No mutagenesis studies were conducted with pegfilgrastim. The carcinogenic potential of pegfilgrastim has not been evaluated in long-term animal studies. In a toxicity study of 6 months duration in rats given once weekly subcutaneous injections of up to 1000 mcg/kg of pegfilgrastim (approximately 23-fold higher than the recommended human dose), no precancerous or cancerous lesions were noted.

When administered once weekly via subcutaneous injections to male and female rats at doses up to 1000 mcg/kg prior to, and during mating, reproductive performance, fertility, and sperm assessment parameters were not affected.

Pregnancy Category C

Pegfilgrastim has been shown to have adverse effects in pregnant rabbits when administered subcutaneously every other day during gestation at doses as low as 50 mcg/kg/dose (approximately 4-fold higher than the recommended human dose). Decreased maternal food consumption, accompanied by a decreased maternal body weight gain and decreased fetal body weights were observed at 50 to 1000 mcg/kg/dose. Pegfilgrastim doses of 200 and 250 mcg/kg/dose resulted in an increased incidence of abortions. Increased post-implantation loss due to early resorptions was observed at doses of 200 to 1000 mcg/kg/dose, and decreased numbers of live rabbit fetuses were observed at pegfilgrastim doses of 200 to 1000 mcg/kg/dose, given every other day.

Subcutaneous injections of pegfilgrastim of up to 1000 mcg/kg/dose every other day during the period of organogenesis in rats were not associated with an embryotoxic or fetotoxic outcome. However, an increased incidence (compared to historical controls) of wavy ribs was observed in rat fetuses at 1000 mcg/kg/dose every other day. Very low levels (< 0.5%) of pegfilgrastim crossed the placenta when administered subcutaneously to pregnant rats every other day during gestation.

Once weekly subcutaneous injections of pegfilgrastim to female rats from day 6 of gestation through day 18 of lactation at doses up to 1000 mcg/kg/dose did not result in any adverse maternal effects. There were no deleterious effects on the growth and development of the offspring and no adverse effects were found upon assessment of fertility indices.

There are no adequate and well-controlled studies in pregnant women. Neulasta® should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether pegfilgrastim is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Neulasta® is administered to a nursing woman.

Pediatric Use

The safety and effectiveness of Neulasta® in pediatric patients have not been established. The 6 mg fixed dose single-use syringe formulation should not be used in infants, children, and smaller adolescents weighing less than 45 kg.

Geriatric Use

Of the 932 patients with cancer who received Neulasta® in clinical studies, 139 (15%) were age 65 and over, and 18 (2%) were age 75 and over. No overall differences in safety or effectiveness were observed between patients age 65 and older and younger patients.

ADVERSE REACTIONS

See WARNINGS sections regarding Splenic Rupture, ARDS, Allergic Reactions, and Sickle Cell Disease.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of Neulasta® cannot be directly compared to rates in the clinical trials of other drugs and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to Neulasta® use and for approximating rates.

The data described below reflect exposure to Neulasta® in 932 patients.

Neulasta® was studied in placebo- and active-controlled trials (n = 467 and n = 465, respectively). The population encompassed an age range of 21 to 88 years. Ninety-two percent of patients were female. The ethnicity of the patients was as follows: 75% Caucasian, 18% Hispanic, 3% Black, and 1% Asian. Patients with solid tumors (breast (n = 823), lung and thoracic tumors (n = 53)) or lymphoma (n = 58) received Neulasta® after nonmyeloblastic cytotoxic chemotherapy. Most patients received a single 100 mcg/kg (n = 259) or a single 6 mg (n = 546) dose per chemotherapy cycle over 4 cycles.

In the placebo-controlled trial, bone pain occurred at a higher incidence in Neulasta®-treated patients as compared to placebo-treated patients. The incidence of other commonly reported adverse events were similar in the Neulasta®- and placebo-treated patients, and were consistent with the underlying cancer diagnosis and its treatment with chemotherapy. The data in Table 1 reflect these adverse events occurring in at least 10% of patients treated with Neulasta® in the placebo-controlled study.

TABLE 1. Adverse Events Occurring in ≥ 10% of Patients in The Placebo-Controlled Study.

Event	Neulasta® (n = 467)	Placebo (n = 461)
Alopecia	45%	47%
Bone Pain*	31%	26%
Diarrhea	29%	28%
Pyrexia (not including febrile neutropenia)	23%	22%
Myalgia	21%	18%
Headache	16%	14%
Arthralgia	16%	13%
Vomiting	13%	11%
Asthenia	13%	11%
Edema peripheral	12%	10%
Constipation	10%	6%

*Events occurring in ≥ 10% of Neulasta®-treated patients and at a higher incidence as compared to placebo-treated patients.

*Bone pain is limited to the specified adverse event term, "bone pain."

In the active-controlled studies, common adverse events occurred at similar rates and severities in both treatment arms (Neulasta®, n = 465; Filgrastim, n = 331). These adverse experiences occurred at rates between 72% and 15% and included: nausea, fatigue, alopecia, diarrhea, vomiting, constipation, fever, anorexia, skeletal pain, headache, taste perversion, dyspepsia, myalgia, insomnia, abdominal pain, arthralgia, generalized weakness, peripheral edema, dizziness, granulocytopenia, stomatitis, mucositis, and neutropenic fever.

Bone Pain

The analysis of bone pain described below is based on a composite analysis using multiple, related, adverse event terms.

In the placebo-controlled study, the incidence of bone pain was 57% in Neulasta®-treated patients compared to 50% in placebo-treated patients. Bone pain was generally reported to be of mild-to-moderate severity.

Among patients experiencing bone pain, approximately 37% of Neulasta®- and 31% of placebo-treated patients utilized non-narcotic analgesics and 10% of Neulasta®- and 9% of placebo-treated patients utilized narcotic analgesics.

In the active-controlled studies, the use of non-narcotic and narcotic analgesics in association with bone pain was similar between Neulasta®- and Filgrastim-treated patients. No patient withdrew from study due to bone pain.

Laboratory Abnormalities

In clinical studies, leukocytosis (WBC counts > 100 x 10⁹/L) was observed in less than 1% of 932 patients with nonmyeloid malignancies receiving Neulasta®. Leukocytosis was not associated with any adverse effects. In the placebo-controlled study, reversible elevations in LDH, alkaline phosphatase, and uric acid that did not require treatment occurred at similar rates in Neulasta®- and placebo-treated patients.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The incidence of antibody development in patients receiving Neulasta® has not been adequately determined. While available data suggest that a small proportion of patients developed binding antibodies to Filgrastim or pegfilgrastim, the nature and specificity of these antibodies has not been adequately studied. No neutralizing antibodies have been detected using a cell-based assay in 46 patients who apparently developed binding antibodies. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay, and the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, concomitant medications, and underlying disease. Therefore, comparison of the incidence of antibodies to Neulasta® with the incidence of antibodies to other products may be misleading.

Cytopenias resulting from an antibody response to exogenous growth factors have been reported on rare occasions in patients treated with other recombinant growth factors. There is a theoretical possibility that an antibody directed against pegfilgrastim may cross-react with endogenous G-CSF, resulting in immune-mediated neutropenia, but this has not been observed in clinical studies.

OVERDOSAGE

The maximum amount of Neulasta® that can be safely administered in single or multiple doses has not been determined. Single subcutaneous doses of 300 mcg/kg have been administered to 8 healthy volunteers and 3 patients with non-small cell lung cancer without serious adverse effects. These patients experienced a mean maximum ANC of 55 x 10⁹/L with a corresponding mean maximum WBC of 67 x 10⁹/L. The absolute maximum ANC observed was 96 x 10⁹/L with a corresponding absolute maximum WBC observed of 120 x 10⁹/L. The duration of leukocytosis ranged from 6 to 13 days. Leukapheresis should be considered in the management of symptomatic individuals.

DOSE AND ADMINISTRATION

The recommended dosage of Neulasta® is a single subcutaneous injection of 6 mg administered once per chemotherapy cycle. Neulasta® should not be administered in the period between 14 days before and 24 hours after administration of cytotoxic chemotherapy (see **PRECAUTIONS**).

The 6 mg fixed-dose formulation should not be used in infants, children, and smaller adolescents weighing less than 45 kg.

No dosing adjustment is necessary for renal dysfunction (see **CLINICAL PHARMACOLOGY, Special Populations**).

Rx Only

This product, its production, and/or its use may be covered by one or more US Patents, including US Patent Nos. 5,824,784; 4,810,643; 4,999,291; 5,582,823; 5,580,755 as well as other patents or patents pending.

Reference

*Heil G, Hoelter D, Sanz MA, et al. A randomized, double-blind, placebo-controlled, phase III study of Filgrastim in remission induction and consolidation therapy for adults with de novo Acute Myeloid Leukemia. *Blood*. 1997;90:4710-4718.

Issue Date: 09/15/2005

References: 1. Neulasta® (pegfilgrastim) Prescribing Information. Thousand Oaks, Calif: Amgen. 2. Vogel CL, Wojtukiewicz MZ, Carroll RR, et al. First and subsequent cycle use of pegfilgrastim prevents febrile neutropenia in patients with breast cancer: a multicenter, double-blind, placebo-controlled phase III study. *J Clin Oncol*. 2005;23:1178-1184.

AMGEN®

Manufactured by:
Amgen Manufacturing Limited,
a subsidiary of Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
©2005 Amgen. All rights reserved.
NAC28552-B

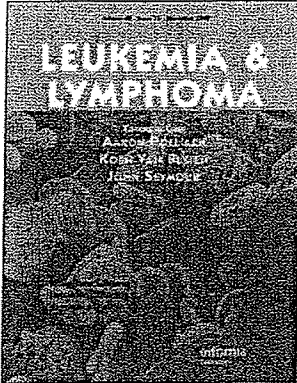
This article was downloaded by: [Tulane University]

On: 16 August 2009

Access details: Access Details: [subscription number 906389020]

Publisher Informa Healthcare

Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Leukemia and Lymphoma

Publication details, including instructions for authors and subscription information:
<http://www.informaworld.com/smpp/title-content=t713643806>

Hematopoietic Malignancies and Related Disorders Among Benzene-Exposed Workers in China

Lois B. Travis ^a; Chin-Yang Li ^b; Zhi-Nan Zhang ^c; De-Gao Li ^c; Song-Nian Yin ^c; Wong-Ho Chow ^a; Gui-Lan Li ^c; Mustafa Dosemeci ^a; William Blot ^a; Joseph F. Fraumeni Jr. ^a; Richard B. Hayes ^a; Martha S. Linet ^a
^a Epidemiology and Biostatistics Program, National Cancer Institute, National Institutes of Health, US Department of Health and Human Services, Bethesda, Maryland ^b Section of Hematopathology, Mayo Clinic, Rochester, Minnesota ^c Division of Hematology, Peking Union Medical College Hospital, Beijing University School of Medicine, Chinese Academy of Medical Sciences, Beijing, China ^d Department of Toxicology and Epidemiology, Institute of Occupational Medicine, Chinese Academy of Preventive Medicine, Beijing, China

Online Publication Date: 01 June 1994

To cite this Article Travis, Lois B., Li, Chin-Yang, Zhang, Zhi-Nan, Li, De-Gao, Yin, Song-Nian, Chow, Wong-Ho, Li, Gui-Lan, Dosemeci, Mustafa, Blot, William, Fraumeni Jr., Joseph F., Hayes, Richard B. and Linet, Martha S. (1994) 'Hematopoietic Malignancies and Related Disorders Among Benzene-Exposed Workers in China', *Leukemia and Lymphoma*, 14:1, 91 — 102

To link to this Article: DOI: 10.3109/10428199409049654

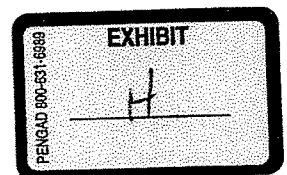
URL: <http://dx.doi.org/10.3109/10428199409049654>

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: <http://www.informaworld.com/terms-and-conditions-of-access.pdf>

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.



Leukemia and Lymphoma, Vol. 14, pp. 91-102
Reprints available directly from the publisher
Photocopying permitted by licence only

© 1994 Harwood Academic Publishers GmbH
Printed in the United States of America

Hematopoietic Malignancies and Related Disorders Among Benzene-Exposed Workers in China

LOIS B. TRAVIS,* CHIN-YANG LI,† ZHI-NAN ZHANG,‡ DE-GAO LI,‡ SONG-NIAN YIN,§
WONG-HO CHOW,* GUI-LAN LI,§ MUSTAFA DOSEMECI,* WILLIAM BLOT,*
JOSEPH F. FRAUMENI, JR.,* RICHARD B. HAYES* and MARTHA S. LINET*

*Epidemiology and Biostatistics Program, National Cancer Institute, National Institutes of Health, US Department of Health and Human Services, Bethesda, Maryland, †Section of Hematopathology, Mayo Clinic, Rochester, Minnesota, ‡Division of Hematology, Peking Union Medical College Hospital, Beijing University School of Medicine, Chinese Academy of Medical Sciences, Beijing, and §Department of Toxicology and Epidemiology, Institute of Occupational Medicine, Chinese Academy of Preventive Medicine, Beijing, China

(Received 1 September 1993)

Although the relationship between benzene and acute nonlymphocytic leukemia (ANLL) is well established, most of the analytic cohort investigations examining the relationship between benzene and hematologic neoplasms have evaluated only death certificates to validate diagnoses. In a follow-up study of 74,828 benzene-exposed and 35,805 non-exposed workers in China, pathology reports, medical records, and/or histopathologic material were reviewed for all patients with hematopoietic malignancies to ensure correct classification and to provide clinicopathologic descriptions. Eighty-two patients with hematopoietic neoplasms and related disorders were identified among benzene-exposed workers, including 32 cases of acute leukemia, 7—myelodysplastic syndrome (MDS), 9—chronic granulocytic leukemia (CGL), 20—malignant lymphoma or related disorder (ML), 9—aplastic anemia, and 5 others. Among the comparison group, 13 hematologic malignancies were observed, including 6 patients with acute leukemia, 2—CGL, 3—ML, and 2 others. The hematopathologic characteristics of the benzene-exposed ANLL cases resembled those following chemotherapy or radiotherapy. ANLL in workers exposed to benzene may represent a distinct clinicopathologic entity, with characteristics similar to treatment-related ANLL, including a preceding preleukemic phase in some patients. Results in our series, one of the largest to date, also indicate that a greater diversity of hematologic neoplasms is evident among benzene-exposed workers than previously described.

KEY WORDS: Benzene leukemia dysplasia

INTRODUCTION

The International Agency for Research on Cancer (IARC) concluded in the early 1980s that there was sufficient evidence that benzene could cause acute myelogenous leukemia (AML).¹ At that time, the ma-

jor studies implicating benzene in the occurrence of AML were two US cohort mortality investigations,^{2,3} a clinical series drawn from Turkish shoe and leather manufacturing workers,^{4,5} and case-control studies in France, Sweden and the US.⁶⁻⁹ Worldwide sources of exposure to benzene include its widespread use in industry and its presence in cigarette smoke, gasoline, and automobile exhaust,¹ thus potentially exposing a large population to its carcinogenic risks. Since the IARC report, investigators have also raised concerns about possible associations of benzene with non-

Address for correspondence: Lois B. Travis, M.D., National Cancer Institute, Executive Plaza North, Suite #408, Bethesda, MD 20892, USA.

Hodgkin's lymphoma,¹⁰ multiple myeloma,¹¹ and other hematopoietic malignancies.¹² Clarification of the role of benzene exposure in the etiology of various hematopoietic malignancies requires accurate classification. However, most of the investigations examining the relationship between benzene and hematologic neoplasms have evaluated only death certificates, with very few studies reviewing medical record or histologic data to provide detailed clinicopathologic descriptions and ensure correct categorization.^{4,6,13,14} Thus, a major objective of a recent epidemiologic study among a large number of benzene-exposed (and non-exposed) workers in China was to obtain medical record data and histopathologic specimens for patients with hematopoietic malignancies to enable classification according to recently published criteria and to identify unusual clinical and pathologic features.

SUBJECTS AND METHODS

A retrospective cohort study of incident cases of hematopoietic neoplasms and related disorders was conducted among 74,828 benzene-exposed workers employed between January 1, 1972 and December 31, 1987 in 672 factories in 12 Chinese cities (Shanghai, Tianjin, Chengdu, Chongqing, Harbin, Shenyang, Jinzhou, Zhengzhou, Luoyang, Guangzhou, Nanchang and Kaifeng).¹⁵ A concurrent comparison group consisted of 35,805 workers not occupationally exposed to benzene who were employed during the same period in 109 factories in the 12 cities. Careful review of factory records identified eligible exposed and unexposed persons. Data abstracted from these files included name, job title and information describing the types of work units and dates employed.

Since the factories usually provide all health care for current and retired workers, follow-up of benzene-exposed and unexposed subjects through December 31, 1987 was carried out utilizing factory occupational and medical records to ascertain hematopoietic malignancies and related disorders, vital status, and, for those deceased, cause of death. Additional means of follow-up were utilized for a small number of subjects who had left the factories prior to retirement. For workers reported to have developed hematologic neoplasms and related disorders, pertinent histopathologic material, pathology reports and medical records were requested for confirmation. Clinical, laboratory and pathology data for all patients were abstracted onto standardized forms by physician investigators who were

not aware of the exposure status of the subjects, nor of the numbers of exposed and non-exposed cases. All slides were reviewed systematically using structured, detailed abstract forms to objectively characterize hematopoiesis. Evaluation of the peripheral blood smear included review of polymorphonuclear (PMN) leukocytes for hypersegmentation, hyposegmentation (the pseudo-Pelger-Huet anomaly), hypogranularity, abnormal granules and the presence of vacuolization. Platelet size and granularity and red blood cell shape, size and general morphology were also noted. Eosinophilia was defined as an absolute count of more than 450 cells/uL; basophilia was defined as an absolute count of more than 200 cells/uL.¹⁶

Hematologic parameters recorded for bone marrow aspirates included the following: the estimated erythrocyte:granulocyte ratio, per cent blasts and morphologic changes. Evidence of dyserythropoiesis included the presence of ringed sideroblasts, multinuclearity, karyorrhexis, nuclear fragmentation, abnormal nuclear shape, impaired hemoglobinization, megaloblastoid changes or other nuclear or cytoplasmic abnormalities. Dysgranulopoiesis was characterized as for the peripheral blood smear. Dysmegakaryopoietic features included the presence of micromegakaryocytes, large mononuclear forms, multiple small nuclei, or giant or abnormal granules. The upper limit of the normal range for marrow basophils was defined as 0.2 per cent of total nucleated cells (TNC), and for eosinophils, 6.2 per cent of TNC.¹⁷

Diagnoses were assigned after evaluation of all available clinical, laboratory and pathologic data without knowledge of the patient's benzene exposure status. Published criteria were utilized to classify myelodysplastic syndrome (MDS),¹⁸ acute nonlymphocytic leukemia (ANLL),¹⁹⁻²¹ acute lymphoblastic leukemia (ALL),¹⁹ and non-Hodgkin's lymphoma (NHL).²² Since study objectives did not include quality control of the previously assigned Chinese diagnoses, which derived from a variety of sources, a systematic comparison of these diagnoses with the results of the current review was not undertaken.

RESULTS

Eighty-two hematopoietic malignancies and related disorders were documented among benzene-exposed workers, with 13 such cases identified among the non-exposed comparison group. Frequencies of the major diagnostic categories of hematologic neoplasms in

HEMATOPOIETIC MALIGNANCIES AMONG BENZENE WORKERS

93

benzene-exposed and non-exposed subjects are summarized in Table 1. Diagnoses confirmed by review of pathology reports and medical records for 51 benzene-exposed subjects included acute leukemia (17 patients [pts]), MDS (2 pts), chronic granulocytic leukemia (CGL) (5 pts), malignant lymphoma or related malignancy (ML) (16 pts), aplastic anemia (8 pts) and 3 other disorders. For an additional 31 benzene-exposed subjects, diagnoses based on evaluation of histopathologic material included 9 cases of ANLL; 5 acute leukemias which could not be classified further; 5 MDS; 4 CGL; 4 ML; 1 ALL; and 1 aplastic anemia (Tables 2–5). Findings in an additional patient were considered compatible with malignant histiocytosis and those in another subject were thought consistent with some type of toxic bone marrow effect.

Diagnoses confirmed by review of histopathologic material for the non-exposed comparison group included ANLL-M2 (1 pt), multiple myeloma (1 pt) and lymphoproliferative disorder (1 pt). Evaluation of medical records and pathology reports for 10 additional patients indicated diagnoses of acute leukemia (5 pts), CGL (2 pt), NHL (2 pt) and 1 leukemia, not otherwise specified. Diagnoses observed among only benzene-exposed cases included aplastic anemia and MDS (Table 1).

Preliminary analyses indicate that the age- and sex-adjusted relative risk of all confirmed lymphohematopoietic disorders in exposed versus unexposed workers is 3.4 (95% confidence interval: 1.9–6.1). The results of future analyses (which will evaluate risk by industry, occupational category, level of benzene exposure and type of hematologic malignancy) will

be reported separately. Available clinicopathologic data for 31 of the benzene-exposed cases are presented below by diagnostic subgroup; data for patients 32–34, who were not exposed to benzene, are summarized in Tables 2–4.

ANLL Histopathologic data were evaluated for 5 men and 4 women with ANLL (Table 2); patients typically presented with anemia and thrombocytopenia, with white blood cell counts ranging from 1,200 to 16,800 per uL (Table 3). Dyspoiesis was common (Tables 4 and 5). Three cases of ANLL-M2 and four of ANLL-M3 were included in the histopathologic review. In two patients (numbers 4 and 9), subtyping of ANLL was not possible. The leukemic bone marrow of Patient 4 was thought consistent with either ANLL-M2 or ANLL-M4. Review of bone marrow for Patient 9 revealed peroxidase-positive blasts, which demonstrated prominent nucleoli and a moderate amount of cytoplasm, some with granules. This patient was thought to have either a myelomonocytic or monocytic leukemia. An unusual increase in small, atypical basophils or mast cells was also noted in this patient, who had a prior diagnosis of chronic benzene poisoning.

Acute leukemia, not otherwise specified (AL, NOS) In five persons with acute leukemia, the cell type could not be established after review of histopathology, without the availability of additional cytochemical stains. Data available for two of these cases suggested blastic transformations of antecedent myeloproliferative disorders: Patient 10 presented with hepatosplenomegaly; basophilia and large platelets were among the features noted on the peripheral blood smear. Bone marrow examination revealed approximately 35 per cent blasts and right-shifted granulopoiesis with numerous PMNs, many of which were hypogranular. The peripheral blood smear for Patient 11 showed dacrocytes, basophilia and large platelets, many in aggregates, features consistent with the prior diagnosis of CGL noted in the medical record. Dysplasia was evident in peripheral blood and bone marrow, with undifferentiated blasts comprising approximately 30–35% of marrow cellularity. Other characteristics supporting the underlying diagnosis of CGL included bone marrow basophilia and available laboratory values (Table 3) which included a low leukocyte alkaline phosphatase (LAP) score.

More than 90% of marrow cellularity in Patient 12 consisted of blasts, which did not stain with peroxidase according to an accompanying report. The sig-

Table 1 Frequency of major diagnostic groups of all hematopoietic malignancies and related disorders among benzene-exposed and non-exposed workers

Diagnosis	Number of cases (%) ^a	
	Exposed workers	Non-exposed workers
Aplastic anemia	9 (11%)	0
Acute leukemia	32 (39%)	6 (46%)
Myelodysplastic syndrome	7 (9%)	0
Chronic granulocytic leukemia	9 (11%)	2 (15%)
Malignant lymphoma and related disorders	20 (24%)	3 (23%)
Other	5† (6%)	2‡ (15%)
Total	82	13

^aNumbers may not sum to 100 due to rounding error.

^bIncludes diagnoses of agranulocytosis (2), multiple myeloma (1), leukemia, not otherwise specified (NOS) (1), and toxic effect (1).

^cIncludes diagnoses of multiple myeloma (1) and leukemia, NOS (1).

Table 2 Clinical presentation of 34 patients with hematopoietic malignancies and related disorders*

Patient no.	Age/Sex (yr)	Symptoms/Signs	Physical examination		LN	Diagnosis
			HM	SM		
1	40/M	lower limb ulceration, ecchymoses, petechiae	—	—	+	ANLL-M2
2	45/F	vertigo, weakness, palpitations	—	—	—	ANLL-M2
3	24/M	fever	—	—	—	ANLL-M2
4	25/M	fever, malaise	—	—	—	ANLL-M2 or M4
5	43/M	sternal tenderness, gingival infiltration	—	—	+	ANLL-M3, microgranular
6	47/F	petechiae, sternal tenderness, gingival bleeding, ecchymoses	—	—	—	ANLL-M3
7	23/M	N/A	N/A	N/A	N/A	ANLL-M3
8	43/F	petechiae, ecchymoses	—	—	—	ANLL-M3
9†	53/F	fever, malaise, vertigo, pallor, dyspnea, mucosal ulceration	—	—	—	ANLL-M4 or M5
10	70/M	bronchitis	+	+	—	AL, NOS
11	64/M	N/A	N/A	N/A	N/A	AL, NOS
12	42/M	sternal tenderness, ecchymoses	+	—	+	AL, NOS
13	42/M	N/A	—	—	—	AL, NOS
14	42/M	fever	+	—	+	AL, NOS
15	53/M	N/A	—	—	—	RA
16‡	48/F	lower limb ulceration	—	N/A	+	CMML
17	30/F	N/A	—	—	—	RAEBT
18	41/F	N/A	N/A	N/A	N/A	MDS, NOS
19†	40/M	fever, joint pain	+	—	—	MDS, NOS
20	28/F	petechiae	+	+	+	CGL
21	62/M	abdominal mass, malaise, weight loss	+	+	—	CGL
22	30/M	N/A	—	—	—	CGL, atypical
23	N/A	N/A	N/A	N/A	N/A	CGL
24	20/M	fever, malaise vertigo	+	+	—	NHL (possible)
25	41/F	malnutrition, pallor	—	—	+	NHL
26	40/M	fever	—	—	+	NHL
27	34/M	fever	+	+	+	NHL
28	23/M	sternal tenderness, gingival pain	+	+	+	ALL
29	45/M	gingival bleeding, petechiae	+	N/A	N/A	Aplastic Anemia
30	58/M	fever, malaise	—	—	+	Malignant Histiocytosis (possible)
31‡	33/M	weakness, vertigo	+	+	—	Toxic effect
32	49/M	epistaxis, malaise, weight loss	—	—	+	ANLL-M2
33	52/M	chest wall mass	—	—	—	Multiple Myeloma
34	54/M	N/A	N/A	N/A	N/A	LPD

Abbreviations: AL: acute leukemia; ALL: acute lymphoblastic leukemia; ANLL: acute non-lymphocytic leukemia; CGL: chronic granulocytic leukemia; CMML: chronic myelomonocytic leukemia; HM: hepatomegaly; LN: lymphadenopathy; LPD: lymphoproliferative disorder; MDS: myelodysplastic syndrome; N/A: not ascertained; NHL: non-Hodgkin's lymphoma; NOS: not otherwise specified; RA: refractory anemia; RAEBT: refractory anemia with excess blasts in transformation; SM: splenomegaly; +: present; —: absent.

*This table is limited to those patients for whom histopathologic materials were reviewed (Tables 3–5). Patients 1–31 were occupationally exposed to benzene.

†Patient had been previously diagnosed with chronic benzene poisoning.

‡Available data preceded the reviewed bone marrow aspirate by 10 years.

nificant variation in blast size together with the presence of cytoplasmic granules and budding seemed suggestive of a megakaryocytic lineage. However, in the absence of immunohistochemical stains to evaluate a possible diagnosis of acute megakaryocytic leukemia (ANLL-M7),²¹ this patient was also considered to have AL, NOS.

An unusual feature of increased lymphocytes with large cytoplasmic granules was present in both the peripheral blood smear and marrow aspirate of Patient

13. Otherwise, findings in this patient were consistent with AL, NOS (Table 4).

MDS Myelodysplastic syndromes were evident in five subjects based upon review of histopathologic material. Findings in Patient 15 included bone marrow hypocellularity, with markedly dyserythropoietic features, including multinuclearity, megaloblastoid changes, and abnormal nuclear shape; the general

HEMATOPOIETIC MALIGNANCIES AMONG BENZENE WORKERS

95

Table 3 Laboratory data and peripheral blood morphologic findings in patients* with hematopoietic malignancies and related disorders†

Patient no.	Hemoglobin (g/dl)	WBC ($\times 10^3/\mu\text{L}$)	% blasts	Platelets ($\times 10^3/\mu\text{L}$)	Peripheral blood morphologic findings	Diagnosis
1	8.6	16.8	20	N/A	pseudo-Pelger-Huet PMNS, Auer rods, thrombocytopenia	ANLL-M2
2	4.4	4.4	0	105	N/A	ANLL-M2
4	3.0	13.7	0	N/A	anisocytosis, poikilocytosis, pseudo Pelger-Huet PMNs, pancytopenia, type II blasts	ANLL-M2 or M4
5	7.0	1.6	20	15	thrombocytopenia, hypogranular promyelocytes or monocytic cells	ANLL-M3, microgranular
6	8.8	1.2	10	66	N/A	ANLL-M3
8	5.2	3.1	0	40	N/A	ANLL-M3
9‡	4.6	3.4	38	10	N/A	ANLL-M4 or M5
10	8.0	15.2	23	56	polychromasia, NRBCs, hypersegmented, hyposegmented and hypogranular PMNs, large platelets, basophilia	AL, NOS
11§	N/A	84.6¶	4	350	dacryocytes, left-shifted granulopoiesis, large platelets, basophilia	AL, NOS
12	5.9	2.9	50	10	N/A	AL, NOS
13	14.7	2.3	0	86	oval macrocytes, neutropenia, thrombocytopenia, immature lymphoid cells with granules	AL, NOS
14	8.0	17.5	0	0.7	N/A	AL, NOS
15	4.0	1.8	0	16	N/A	RA
16‡	6.5	36.2	2	17	oval macrocytes, target cells, megaloblastic and megaloblastoid NRBCs, hypogranular PMNs, giant bands, basophilia, thrombocytopenia	CMML
17	8.1	4.6	N/A	36	N/A	RAEBT
19‡	10.0	4.7	0	50	N/A	MDS, NOS
20	7.0	198.0**	2	134	hypogranular PMNs and myelocytes, rodent nuclei, basophilia, eosinophilia	CGL
21	10.0	121.6	3	242	oval macrocytes, target cells, NRBCs, basophilia	CGL
22	7.0	32.8††	0	300	left-shifted granulopoiesis, no basophilia nor eosinophilia	CGL, atypical
23	N/A	N/A	N/A	N/A	left-shifted granulopoiesis with mild basophilia	CGL
24	8.4	2.6	0	37	N/A	NHL (possible)
25	8.5	16.8	0	N/A	N/A	NHL
26	11.0	8.3	0	210	N/A	NHL
27‡‡	7.0	5.5	0	N/A	N/A	NHL
28	9.5	23.0	96	51	oval macrocytes, thrombocytopenia	ALL
29	4.0	2.2	0	26	N/A	Aplastic Anemia
30	11.5	4.4	0	100	pancytopenia, large atypical monocytoid cells present	Malignant Histiocytosis (possible)
31§§	8.0	220.0¶¶	0	406	N/A	Toxic effect
32	6.0	4.9	64	N/A	anisocytosis, poikilocytosis, numerous Auer rods	ANLL-M2
33	5.5	2.9	0	76	rouleaux	Multiple Myeloma

Abbreviations: AL: acute leukemia; ALL: acute lymphoblastic leukemia; ANLL: acute non-lymphocytic leukemia; CGL: chronic granulocytic leukemia; CMML: chronic myelomonocytic leukemia; MDS: myelodysplastic syndrome; N/A: not available; NHL: non-Hodgkin's lymphoma; NOS: not otherwise specified; NRBC: nucleated red blood cells; PMN: polymorphonuclear leukocyte; RA: refractory anemia; RAEBT: refractory anemia with excess blasts in transformation; WBC: white blood cell.

*Neither laboratory data nor peripheral blood smears were available for patient nos. 3, 7, 18, and 34.

†Patients 1–31 were occupationally exposed to benzene.

‡Patient had been previously diagnosed with chronic benzene poisoning.

§Laboratory values preceded the reviewed peripheral blood and bone marrow specimens by 3 years.

¶WBC differential: 22% PMN, 33% bands, 8% metamyelocytes, 6% myelocytes, 5% promyelocytes, 4% blasts, 7% basophils, 4% eosinophils, 11% lymphocytes.

‡Patient was Philadelphia-chromosome positive.

**WBC differential: 27% PMN, 18% bands, 13% metamyelocytes, 25% myelocytes, 5% promyelocytes, 2% blasts, 4% eosinophils, 4% basophils, 2% lymphocytes.

††WBC differential: 49% PMN, 11% bands, 7.5% metamyelocytes, 20.5% myelocytes, 5% promyelocytes, 5% lymphocytes, 2% other.

‡‡Laboratory values were obtained approximately 1 month after lymph node biopsy.

§§Laboratory values preceded the reviewed bone marrow aspirate by 10 years.

¶¶WBC differential: 40% PMNs, 20% bands, 15% metamyelocytes, 25% promyelocytes.

Table 4 Bone marrow features in patients* with hematopoietic malignancies and related disorders††

Patient no.	E:G	Cellularity/Dyspoiesis			% blasts	Comments	Diagnosis
		Erythrocytes	Granulocytes	Megakaryocytes			
1	1:50	Decr/+	Incr/-	Decr/-	60	peroxidase stain: positive	ANLL-M2
2	1:30	Decr/+	Incr/-	Decr/+	30-35	—	ANLL-M2
3	1:10	Decr/-	Incr/-	Decr/+	40	—	ANLL-M2
4	1:100	Decr/+	Incr/-	Decr/+	40	numerous immature cells, either monocytes or granulocytes	ANLL-M2 or M4
5	1:20	NI/-	Incr/-	Decr/+	60	—	ANLL-M3, microgranular
6	1:20	Decr/+	Incr/-	Decr/+	—	hypergranular promyelocytes: 90%	ANLL-M3
7	1:15	Decr/+	Incr/-	Decr/+	—	hypergranular promyelocytes: 90%	ANLL-M3
8	50:1	Decr/+	Incr/+	Decr/-	—	hypergranular and hypogranular promyelocytes: 90%	ANLL-M3
9‡	1:100	Decr/+	Incr/+	Decr/+	80	increase in basophils or mast cells (5%), which are dysplastic; increase in monocytes; peroxidase stain: positive	ANLL-M4 or M5
10	1:8	Decr/+	Incr/+	Decr/+	35	preceding MPD	AL, NOS
11	1:100	Decr/+	Incr/-	Decr/+	30-35	undifferentiated blasts; preceding CGL	AL, NOS
12	§	§	Decr/-	Decr/-	90	blasts demonstrate cytoplasmic budding and granules	AL, NOS
13	1:1	N/A	N/A	N/A	see comment	immature lymphoid-like cells (some with granules): 90%	AL, NOS
14	1:50	Decr/-	Incr/-	Decr/+	90	—	AL, NOS
15	3:1	Incr/+	Decr/-	Decr/+	<5	significant dyserythropoiesis; marked granulocytic hypoplasia	Refractory Anemia
16‡	1:6	NI/+	Incr/+	Decr/+	5-10	incr. basophils: 1-2%; incr. monocytes: 20-25%	CMML
17	1:3	Incr//+	Incr/+	Decr/+	5-10	Auer rods noted	RAEBT
18	5:2	Incr//+	Decr/+	Decr/+	<5	—	MDS, NOS
19‡	N/A	N/A	N/A	N/A	N/A	pseudo-Pelger-Huet PMNs	MDS, NOS
21	1:15	NI/+	Incr/+	NI/-	<5	low LAP score, slight increase in basophils	CGL
22	1:10	NI/+	Incr/+	NI/-	<5	no basophilia nor eosinophilia, low LAP score	CGL, atypical
23	1:5	NI/+	Incr/-	NI/-	<5	eosinophilia: 5%; basophilia: <1%	CGL
24	1:1	Incr//+	Decr/+	NI/+	<5	increase in granular lymphocytes; hemophagocytosis	NHL (possible)
28	5:1	NI/-	Decr/+	Decr/+	90%	no Auer rods	ALL
29	10:1	Incr**/+	Decr/+	Decr/+	<5	megaloblastoid RBCs	Aplastic Anemia
30	1:2	NI/+	Decr/-	Decr/+	<5	—	Malignant Histiocytosis (possible)
31	1:18	NI/+	Incr/-	NI/-	<5	eosinophils: 5-8%; extensive dyserythropoiesis	Toxic effect
32	1:100	Decr/-	Incr/-	Decr/+	70	numerous Auer rods	ANLL-M2
33	1:3	Decr/-	Decr/-	NI/-	<5	myeloma cells: 50%	Multiple Myeloma
34	1:10	Decr/-	Decr/-	Decr/+	<5	lymphocytes: 50-60%	LPD

Abbreviations: AL: acute leukemia; ALL: acute lymphoblastic leukemia; ANLL: acute non-lymphocytic leukemia; CGL: chronic granulocytic leukemia; CMML: chronic myelomonocytic leukemia; Decr: decreased; E:G: erythrocyte: granulocyte ratio; Incr: increased; LAP: leukocyte alkaline phosphatase; LPD: lymphoproliferative disorder; MDS: myelodysplastic syndrome; MPD: myeloproliferative disorder; N/A: not ascertained; NHL: non-Hodgkin's lymphoma; NOS: not otherwise specified; PMN: polymorphonuclear leukocyte; RAEBT: refractory anemia with excess blasts in transformation; RBC: red blood cell; +: present; -: absent.

*Bone marrow was not available for review in Pt. 22. Lymph node biopsies (Pts. 25, 26, and 27) are not included in the table.

††Patients 1-31 were occupationally exposed to benzene.

‡Dyspoiesis could not be assessed since so few cells were available.

‡Patient had been previously diagnosed with chronic benzene poisoning.

§No erythroblasts were identified on the slide.

||Erythroblasts: 30%

¶Erythroblasts: 60%

**Erythroblasts: 80%

HEMATOPOIETIC MALIGNANCIES AMONG BENZENE WORKERS

97

Table 5 Summary of dysplastic morphologic findings in the peripheral blood or bone marrow of benzene-exposed workers with hematopoietic malignancies and related disorders*

Morphologic finding	Diagnostic category (no. of patients)								
	ANLL (9)	AL, NOS (4)	MDS (5)	CGL (4)	NHL (possible) (1)	ALL (1)	AA (1)	MH (possible) (1)	Toxic effect (1)
Dyserythropoiesis (all types)	6	3	5	3	1	0	1	1	1
Multinuclearity	0	0	2	1	1	0	0	0	1
Impaired hemoglobinization	5	2	3	1	1	0	1	1	1
Abnormal nuclear shape	0	0	3	0	0	0	0	0	1
Megaloblastoid changes	3	0	4	2	1	0	1	0	1
Dysgranulopoiesis (all types)	5	1	4	3	1	1	0	0	0
Hypersegmented PMNs	0	1	0	0	0	0	0	0	0
Hypogranulation	1	1	2	1	0	0	0	0	0
Pseudo-Pelger-Huet anomaly	2	0	3	0	1	0	0	0	0
Dysmegakaryocytopoiesis (Micromegakaryocytes)	0	1	0	0	1	0	0	0	0

Abbreviations: AA: aplastic anemia; ALL: acute lymphoblastic leukemia; AL, NOS: acute leukemia, not otherwise specified; ANLL: acute non-lymphocytic leukemia; CGL: chronic granulocytic leukemia; MDS: myelodysplastic syndrome; MH: malignant histiocytosis; NHL: non-Hodgkin's lymphoma.

*This table is limited to benzene-exposed subjects (patient numbers 1-31). Specimens from Patient 13 were not evaluable for dysplasia. The 3 subjects for whom lymph node biopsies were reviewed are not included in this table.

morphology of the red cells was dimorphic. Features of this case were consistent with refractory anemia (RA).

The findings in Patient 16, who had a prior diagnosis of chronic benzene poisoning, were most consistent with chronic myelomonocytic leukemia (CMML). Peripheral blood smear features included oval macrocytes, megaloblastoid nucleated red blood cells (NRBCs), hypogranular PMNs and monocytosis. Bone marrow demonstrated megaloblastoid dyserythropoiesis and giant bands and metamyelocytes, as well as an increase in monocytes (20-25%). Excess numbers of both peripheral blood and marrow basophils were also apparent. Information about the size of the spleen on physical examination was not available, and cytogenetic studies and a LAP score had not been performed to exclude a diagnosis of CGL. However, the extensive dyspoiesis evident on both the peripheral smear and the bone marrow, together with the increase in marrow monocytes, seemed to favor a diagnosis of CMML.

Although a marrow smear from Patient 17 contained only 5-10% blasts, the presence of Auer rods, together with other findings, met criteria for a diagnosis of refractory anemia with excess blasts in transformation (RAEBT). Dyserythropoiesis in this subject consisted of abnormal nuclear shape, megaloblastoid changes, and impaired hemoglobinization. Hypogran-

ular PMNs and the pseudo-Pelger-Huet anomaly were also evident.

For 2 of the cases, the MDS could not be subclassified further. Dyspoietic features in Patient 18 included megaloblastoid, multinucleated red cells, impaired hemoglobinization, and hypogranular and pseudo-Pelger-Huet granulocytes. Patient 19, who had a prior history of chronic benzene poisoning, was considered to have a possible MDS, based on the peripheral blood counts, presence of pseudo-Pelger-Huet cells on the reviewed slide, and a bone marrow report which noted 4 per cent blasts. Unfortunately, the available marrow aspirate was of poor quality.

CGL Four cases of CGL are summarized in Tables 2-5. Although a bone marrow aspirate was not available for examination in Patient 20, clinical findings and laboratory studies (which included the presence of the Philadelphia chromosome) were consistent with the diagnosis of CGL indicated in the medical record. Patient 21 presented with hepatosplenomegaly, a high white blood cell (WBC) count with basophilia and a LAP score of 8. Peripheral blood and bone marrow findings, which were consistent with CGL, also included dyspoiesis. Patient 22 had a medical record diagnosis of CGL. Given his peripheral blood counts, myelocyte bulge, LAP score of 6, and striking granulocytic hyperplasia on the marrow aspirate, we maintained CGL as the study diagnosis. However, in

the absence of basophilia, we considered this to be an atypical variant.

Malignant lymphoma Patient 24 presented with constitutional symptoms, hepatosplenomegaly and pancytopenia. Marrow review revealed hemophagocytosis, multinucleated and megaloblastoid dyserythropoiesis, slight impairment of hemoglobinization, pseudo-Pelger-Huet PMNs, hyposegmented eosinophils, eosinophils with pseudopodia and micromegakaryocytes. Several very large cells with cytoplasmic granules, possibly suggestive of malignant T-lymphocytes, were also present. Although this patient may have had an unusual peripheral T-cell lymphoma,²³ in the absence of additional immunohistochemical stains, only a diagnosis of possible non-Hodgkin's lymphoma (NHL) could be assigned.

Evaluation of lymph node biopsies disclosed three cases of NHL. Two patients (25 and 26) were both considered to have malignant lymphoma, diffuse mixed small and large cell, based on samples of tonsillar tissue and a cervical lymph node, respectively. Patient 27 was thought to have diffuse large cell lymphoma based on review of a supraclavicular lymph node biopsy.

Other diagnoses Bone marrow from Patient 28 generally demonstrated characteristic findings of ALL. The hypoplastic bone marrow of Patient 29, which was consistent with aplastic anemia, demonstrated impaired hemoglobinization and megaloblastoid dyserythropoiesis; the peripheral blood WBC differential was remarkable for a mild relative lymphocytosis (47%).

Patient 30, who presented with fever, malaise, lymphadenopathy and pancytopenia, had a medical record diagnosis of malignant histiocytosis. Although special stains to confirm this cell lineage were not available for our review, both the peripheral blood and marrow smears showed large, erythrophagocytic, monocytoïd cells suggestive of malignant histiocytes. Therefore, since the patient's clinical and pathologic features were consistent with the medical record diagnosis, we maintained it for study classification. Dyspoietic changes observed for this case included slightly impaired hemoglobinization.

Patient 31, a 33 year old man, had been exposed to benzene for approximately 11 years at the time the specimen described in Table 3 was obtained. This marrow aspirate demonstrated marked dyserythropoiesis, including multinuclearity, megaloblastoid changes, abnormal nuclear shape and cytoplasmic

vacuolization. These changes were thought most consistent with some type of toxic bone marrow effect, with further hematologic classification not possible.

DISCUSSION

The present report represents one of the largest series of benzene-related hematopoietic malignancies, identified from a cohort study, in which diagnoses were confirmed by review of pathology reports, medical records, and/or histopathologic material and in which individual clinicopathologic descriptions are provided.^{4,6,13,14} Important findings include the observation that the hematopathologic features of ANLL associated with benzene exposure resemble those following chemotherapy or radiotherapy, and documentation of diagnoses of MDS. Taken together, these observations suggest that benzene-related ANLL may represent a distinct clinicopathologic entity and perhaps display a preleukemic phase in some patients, as does therapy-related ANLL.

Another new finding in our study is the greater diversity of hematologic malignancies than usually reported with benzene exposure, perhaps due in part to the sizable number of subjects in a variety of occupational settings. In previous investigations of cancer risk among various groups of benzene-exposed workers, excesses of several forms of hematopoietic malignancies have been described, but only AML and aplastic anemia appear to be consistently increased.¹ Results have, otherwise, varied considerably between studies. For example, preleukemia and acute erythroleukemia were especially common among Turkish workers with chronic benzene poisoning,²⁴ and erythroleukemia was also noted among Italian workers exposed to benzene.²⁵ In the Paris region, CGL and CLL accounted for 26 and 16%, respectively, of all leukemias associated with benzene exposure.⁶ In addition, elevated risks for multiple myeloma, although based on only four cases, were reported among benzene-exposed workers in the US.²⁶ Reasons for the variation in the distribution of hematopoietic malignancies between studies may include the presence of concomitant exposures in the workplace, the duration and/or level of benzene exposure, or dissimilarities in case ascertainment and reporting. Furthermore, differences in genetic or other susceptibility factors in the at-risk populations may also affect the distribution of malignancies which are observed. For instance, although CLL was not seen among benzene-exposed

workers in our cohort and only one case of multiple myeloma was evident, population-based incidence data for China indicate that rates for these malignancies are very low.^{27,28} Similarly, acute erythroleukemia, also rare in our series, comprises only 5% of ANLL in China.²⁷ Otherwise, the spectrum of hematopoietic disorders in our series includes many of the conditions reported in prior studies of benzene-exposed workers. Clinicopathologic features of the benzene-exposed cases are discussed below by diagnostic subgroup and compared with observations in prior reports.

ANLL Although the presenting signs and symptoms of the benzene-exposed patients with ANLL typical of acute leukemia occurring *de novo*,²⁹ many of the hematologic features resembled those reported in leukemias secondary to chemotherapy or radiotherapy.³⁰ Characteristics typical of t-ANLL which were observed in our patients included the presence of dysmyelopoietic changes,³⁰⁻³³ the common occurrence of anemia and thrombocytopenia,³⁰⁻³² and increased bone marrow cellularity.^{30,31,33} Basophilia, which has been reported in t-ANLL,^{30,34} was evident in 2 of 3 patients with a prior history of chronic benzene poisoning, although other clinicopathologic series of benzene-induced leukemias have not noted increased numbers of basophils.^{4,13,14} Also, basophilia does not seem to be a typical feature of chronic benzene toxicity.³⁵

Treatment-related leukemias, which may demonstrate a preleukemic phase,³⁰⁻³³ are generally considered distinct clinicopathologic entities with characteristic non-random cytogenetic changes.^{30,36,37} Morphologic and hematologic similarities between our benzene-exposed cases and t-ANLL suggest an overlap in pathogenesis, perhaps including damage to marrow stem cells and to extra-medullary mediators of carcinogenesis. One of the metabolic products of benzene postulated to be leukemogenic includes trans-trans-muconaldehyde, which shares functional similarities with alkylating agents.³⁸ Non-random abnormalities of chromosomes 5 and 7 have been reported among patients with ANLL and past occupational exposure to either solvents or petroleum products,^{39,40} and subjects with t-ANLL following alkylating agent therapy.³⁶ More recently, Fagiolini *et al.*⁴¹ noted that the clinicopathologic features of ANLL following exposure to organic solvents also resembled those seen in t-ANLL. Another metabolite of benzene, hydroquinone, may inhibit the production of interleukin-1, a cytokine necessary for hematopoiesis.⁴² These and other

potential mechanisms of benzene hematotoxicity and carcinogenicity were recently reviewed by Cox.⁴³

Acute promyelocytic leukemia has been reported infrequently in benzene-exposed groups⁴ as well as in t-ANLL.³⁰⁻³³ Although ANLL-M3 occurred in at least 4 patients in this series, its general representation among the subtypes of ANLL was similar to its distribution in *de novo* ANLL in China.²⁷

MDS The occasional reports of preleukemia in association with benzene exposure^{4,14} have only rarely included descriptions of dysplasia, such as megaloblastoid dyserythropoiesis.⁴ To our knowledge, diagnoses of MDS *per se* have not been previously reported in benzene-exposed workers, perhaps due in part to the relatively recent recognition of some of these disorders.¹⁸ Among benzene-exposed workers in general, reports of dyspoiesis have usually been limited to the rare occurrence of the pseudo-Pelger-Huet anomaly.^{35,44} To date, dysplastic findings have not been observed in pancytopenic patients with chronic exposure to benzene.⁴⁵

It is likely that, with increasing appreciation of various types of hematologic dyspoiesis, MDS may be recognized more often among benzene-exposed subjects, enabling further characterization of the dysplastic features associated with benzene toxicity. Correlations between specific cytologic and cytogenetic aberrations might aid in understanding the genetic basis of morphologic dysplasia, as suggested by the possible association reported between pseudo-Pelger-Huet anomaly and monosomy 17.⁴⁶ A study of the natural history of benzene-related MDS, including its possible progression to acute leukemia as reported in t-ANLL,³⁰⁻³³ should help elucidate mechanisms of leukemogenesis.

CGL Although secondary CGL has been reported following chemotherapy,⁴⁷ it is mainly considered to be radiogenic.⁴⁸ Other clinicopathologic series of benzene-exposed workers have found variable proportions of CGL among reported hematopoietic malignancies.^{6,14} Among all benzene-exposed workers in our cohort, CGL accounted for approximately 11% of hematologic malignancies. The four patients with CGL included in our histopathologic review generally showed features characteristic of that diagnosis,⁴⁹ as reported in other benzene-exposed workers with this disorder.^{6,14} However, dysplastic changes were noted in all cases, and two subjects (numbers 20 and 22) were relatively young at diagnosis, given that CGL typically does not show a sharp increase in incidence

until after age 50.²⁷ The absence of basophilia in the latter patient was unusual, but has been noted in atypical CGL.⁵⁰

Malignant lymphoma Although lymphoma and related disorders (ML) accounted for approximately 24% of the hematopoietic malignancies among benzene-exposed patients in our series, to date there have been only scattered clinicopathologic reports of ML in benzene-exposed workers, as summarized recently by Aksoy.¹² Most of these descriptions have utilized older classification systems, thus limiting comparisons with our cases. It is noteworthy that two of the four cases of NHL among benzene-exposed patients in this series for whom slides were reviewed represent one subtype of lymphoma as classified by the Working Formulation, although this could represent a chance observation, given the small numbers. Further investigations including immunohistochemical studies as well as histopathologic review should help to clarify the relationship of NHL subtypes to benzene exposure.

Other diagnoses There have been occasional clinicopathologic descriptions of ALL in benzene-exposed workers.^{4,6,14,51} Leukocyte counts (median: 4,200/uL; range 1,700–39,000/uL) cited in these reports tend to be somewhat lower than in de novo ALL,⁵² but the cases seem otherwise typical. Clinicopathologic features of our patient were also similar to those of de novo ALL.⁵²

Although the association between benzene exposure and pancytopenia or aplastic anemia (AA) is well established,¹ there is considerable variability in bone marrow cellularity among pancytopenic patients, even when clinical and other hematologic features are similar.⁴⁵ Although benzene-related AA is frequently accompanied by an absolute lymphopenia,⁴⁵ a mild relative lymphocytosis was noted in the patient for whom histopathologic material was reviewed. Dyserythropoiesis was minimal in this subject, in accordance with previous reports of benzene-related AA.⁴⁵

The marked degree of toxic changes observed in erythropoietic cells in Patient 31 seems to have not been previously reported among benzene-exposed workers. Cytoplasmic vacuolization of erythroid ($n = 1$) or myeloid cells ($n = 2$) was noted on bone marrow examination in 3 apparently asymptomatic benzene-exposed workers with peripheral blood cytopenias, all of whom also demonstrated maturation arrests in the myeloid series.³⁵ Similarly, cytoplasmic vacuoliza-

tion has been reported in the bone marrow of benzene-intoxicated rats.⁵³

Marrow eosinophilia was also evident in Patient 31. Proportions of eosinophilic leukocytes greater than 8 per cent were noted in the peripheral blood of 6 of 217 benzene-exposed workers in one series,³⁵ and in 2 of 30 women with chronic benzene poisoning reported by Smith.⁵⁴ Relative or absolute numbers of eosinophils were not increased in the peripheral blood or bone marrow of the three patients in our series with prior diagnoses of chronic benzene poisoning.

Rapidly expanding knowledge of the importance of oncogenes in hematologic malignancies,⁵⁵ the application of molecular genetic techniques to hematology,⁵⁶ and characterization of the importance of the bone marrow stromal environment hold promise for identifying potential similarities, as well as differences, in the mechanisms of action of known leukemogens, such as benzene, radiation, and chemotherapy. It is hoped that the results of this clinicopathologic evaluation of hematologic neoplasms among benzene-exposed workers will encourage further incidence studies to clarify risks by subtype in the general population and in occupational cohorts with excessive hematopoietic malignancies. In addition, cytogenetic and molecular studies of benzene-related leukemias, along with corresponding studies of t-ANLL, should deepen our insights into the underlying mechanisms of leukemogenesis.

Acknowledgements We are indebted to the numerous participating investigators who generously provided clinical and laboratory data and histopathologic material for this study: Y.-Z. Wang, T.-R. Dai and X.-J. Chao of the Stations of Health and Anti-Infectious Disease in Shanghai, Chengdu, and Chong Qing, Z.-L. Jiang, W.-U. Zhang, P.-Z. Ye, Q.-R. Kou, Y.-H. Fan, X.-C. Zhang, X.-F. Lin, J.-F. Meng and J.-S. Zho of the Institutes of Labor Health and Occupational Disease in Tianjin Sichuan, Heilongjiang, Shenyang, Jinzhou, Henan, Guangzhou, Jiang Xi and Nanchang. We also thank Ms. Sandy Coopersmith and Ms. Denise Nguy for secretarial assistance, and Ms. Sara Brackett for technical support.

REFERENCES

1. International Agency for Research on Cancer (IARC) and International Association of Cancer Registries. (1982) Benzene. In *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: some industrial chemicals and dyestuffs*, vol. 29, pp. 93–148. Lyon, France: IARC.
2. Ott, M. G., Townsend, J. C., Rishbeck, W. A. et al. (1978) Mortality among individuals occupationally exposed to benzene. *Arch Environ. Health*, 33, 3–10.
3. Rinsky, R. A., Young, R. J. and Smith, A. B. (1981) Leukemia in benzene workers. *Am. J. Ind. Med.*, 2, 217–245.

HEMATOPOIETIC MALIGNANCIES AMONG BENZENE WORKERS

101

4. Aksoy, M., Erdem, S. and Dincol, G. (1974) Leukemia in shoe-workers exposed chronically to benzene. *Blood*, **44**, 837-841.
5. Aksoy, M. and Erdem, S. (1978) Follow-up study on the mortality and the development of leukemia in 44 pancytopenic patients with chronic benzene exposure. *Blood*, **44**, 285-292.
6. Goguel, P. A., Cavigneaux, A. and Bernard, J. (1967) Les Leucémies Benzéniques De La Région Parisienne Entre 1950 et 1965 (Etude de 50 observations). *Nouv. Rev. Fr. D'Hémat.*, **7**, 465-480.
7. Girard, P. R. and Revol, L. (1970) La fréquence d'une exposition benzenique au cours des hemopathies graves. *Nouv. Rev. Fr. Hematol.*, **10**, 477-484.
8. Brandt, L., Nilsson, P. G. and Mitelman, F. (1978) Occupational exposure to petroleum products in men with acute non-lymphocytic leukemia. *Br. Med. J.*, **1**, 553-554.
9. Linos, A., Kyle, R. A., O'Fallon, W. M. et al. (1980) A case-control study of occupational exposures and leukemia. *Int. J. Epidemiol.*, **9**, 131-135.
10. Young, N. (1989) Benzene and lymphoma. *Am. J. Ind. Med.*, **15**, 495-498.
11. Goldstein, B. D. (1990) Is exposure to benzene a cause of human multiple myeloma? *Ann. NY Acad. Sci.*, **609**, 225-234.
12. Aksoy, M. (1988) Benzene Carcinogenicity. In *Benzene Carcinogenicity*, edited by M. Aksoy, pp. 113-151. Boca Raton, Florida: CRC Press.
13. Aksoy, M., Dincol, K. and Erdem, S. (1972) Acute leukemia due to chronic exposure to benzene. *Am. J. Med.*, **52**, 160-166.
14. Aksoy, M., Erdem, S. and Dincol, G. (1976) Types of leukemia in chronic benzene poisoning. A study in thirty-four patients. *Acta Haematol.*, **55**, 65-72.
15. Yin, S.-N., Linet, M. S., Hayes, R. B. et al. A cohort study of benzene-exposed workers in China. I. General Methods and Resources. *Am. J. Indust. Med.*, (in press).
16. Lehmann, H. P. and Henry J. B. (1991) SI Units. In *Clinical Diagnosis and Management by Laboratory Methods*, edited by J. B. Henry, D. A. Nelson, R. H. Tomar, J. A. Washington and G. A. Threattle, pp. 1366-1382. Philadelphia: Saunders.
17. Jandl, J. H. (1987) Blood and blood forming tissues. In *Blood: Textbook of Hematology*, edited by J. H. Jandl, pp. 1-48. Boston: Little, Brown, and Co.
18. Bennett, J. M., Catovsky, D., Daniel, M. T. et al. (1982) Proposals for the classification of the myelodysplastic syndromes. *Br. J. Haematol.*, **51**, 189-199.
19. Bennett, J. M., Catovsky, D., Daniel, M. T. et al. (1976) Proposals for the classification of the acute leukaemias. *Br. J. Haematol.*, **33**, 451-458.
20. Bennett, J. M. (1980) Correspondence: A variant form of hypergranular promyelocytic leukaemia (M3). *Br. J. Haematol.*, **44**, 169-170.
21. Bennett, J. M., Catovsky, D., Daniel, M. T. et al. (1985) Criteria for the diagnosis of acute leukemia of megakaryocyte lineage (M7). *Ann. Intern. Med.*, **103**, 460-462.
22. National Cancer Institute Sponsored Study of Classifications of Non-Hodgkin's Lymphomas: (1982) Summary and Description of a Working Formulation for Clinical Usage. *Cancer*, **49**, 2112-2135.
23. Diez-Martin, J. L., Lust, J. A., Witzig, T. E., Banks, P. M. and Li, C. Y. (1991) Unusual presentation of extranodal peripheral T-cell lymphomas with multiple paraneoplastic features. *Cancer*, **68**, 834-841.
24. Aksoy, M. (1985) Malignancies due to occupational exposure to benzene. *Am. J. Indust. Med.*, **7**, 395-402.
25. Vigliani, E. C. (1978) Leukemia associated with benzene exposure. *Ann. NY Acad. Sci.*, **271**, 143-145.
26. Rinsky, R. A., Smith, A. B., Hornung, R. et al. (1987) Benzene and leukemia: An epidemiologic risk assessment. *N. Engl. J. Med.*, **316**, 1044-1050.
27. Yang, C. and Zhang, X. (1991) Incidence survey of leukemia in China. *Chin. Med. Sci. J.*, **6**, 65-70.
28. International Agency for Research on Cancer (IARC) and International Association of Cancer Registries. (1987) Age-specific and standardized incidence rates—China. In *Cancer Incidence in Five Continents*, edited by C. Muir, J. Waterhouse, T. Mack, J. Powell and S. Whelan, vol. V, pp. 394-401. Lyon, France: IARC.
29. Burns, C. P., Armitage, J. O., Frey, A. L. et al. (1981) Analysis of the presenting features of adult acute leukemia: The French-American-British Classification. *Cancer*, **47**, 2460-2469.
30. Michels, S. D., McKenna, R. W., Arthur, D. C. and Brunning, R. D. (1985) Therapy-related acute myeloid leukemia and myelodysplastic syndrome: A clinical and morphologic study of 65 cases. *Blood*, **65**, 1364-1372.
31. Pedersen-Bjergaard, J., Philip, P., Pedersen, N. T. et al. (1984) Acute nonlymphocytic leukemia, preleukemia, and acute myeloproliferative syndrome secondary to treatment of other malignant diseases. II. Bone marrow cytology, cytogenetics, results of HLA typing, response to antileukemic chemotherapy, and survival in a total series of 55 patients. *Cancer*, **54**, 452-462.
32. Brusamolino, E., Papa, G., Valagussa, P. et al. (1987) Treatment-related leukemia in Hodgkin's disease: A multi-institution study on 75 cases. *Hematol. Oncol.*, **5**, 83-98.
33. Pedersen-Bjergaard, J., Philip, P., Mortensen, B. T. et al. (1981) Acute nonlymphocytic leukemia, preleukemia, and acute myeloproliferative syndrome secondary to treatment of other malignant diseases. Clinical and cytogenetic characteristics and results of in vitro culture of bone marrow and HLA typing. *Blood*, **57**, 712-723.
34. Vardiman, J. W., Golomb, H. M., Rowley, J. D. and Variakojis, D. (1978) Acute nonlymphocytic leukemia in malignant lymphoma. A morphologic study. *Cancer*, **42**, 229-242.
35. Aksoy, M., Dincol, K., Akgün, T. et al. (1971) Haematological effects of chronic benzene poisoning in 217 workers. *Br. J. Ind. Med.*, **28**, 296-305.
36. Le Beau, M. M., Albain, K. S., Larson, R. A. et al. (1986) Clinical and cytogenetic correlations in 63 patients with therapy-related myelodysplastic syndromes and acute nonlymphocytic leukemia: Further evidence for characteristic abnormalities of chromosomes no. 5 and 7. *J. Clin. Oncol.*, **4**, 325-345.
37. Whitlock, J. A., Greer, J. P. and Lukens, J. N. (1991) Epipodophyllotoxin-related leukemia. Identification of a new subset of secondary leukemia. *Cancer*, **68**, 600-604.
38. Witz, G., Latriano, L. and Goldstein, B. D. (1989) Metabolism and toxicity of trans, trans-muconaldehyde, and opening microsomal metabolite of benzene. *Environ. Health Perspect.*, **82**, 19-22.
39. Mitelman, F., Nilsson, P. G., Brandt, L. et al. (1981) Chromosome pattern, occupation, and clinical features in patients with acute nonlymphocytic leukemia. *Cancer Genet. Cytogenet.*, **4**, 197-214.
40. Golomb, H. M., Alimena, G., Rowley, J. D. et al. (1982) Correlation of occupation and karyotype in adults with acute nonlymphocytic leukemia. *Blood*, **60**, 404-411.
41. Fagioli, F., Cuneo, A., Piva, N. et al. (1992) Distinct cytogenetic and clinicopathologic features in acute myeloid leukemia after occupational exposure to pesticides and organic solvents. *Cancer*, **70**, 77-85.
42. Renz, J. F. and Kalf, G. F. (1991) Role for interleukin-1 (IL-1) in benzene-induced hematotoxicity: Inhibition of conversion of pre-IL-1 α to mature cytokine in murine macrophages by hydroquinone and prevention of benzene-induced hematotoxicity in mice by IL-1 α . *Blood*, **78**, 938-944.

43. Cox, L. A., Jr. (1991) Biological basis of chemical carcinogenesis: Insights from benzene. *Risk Analysis*, **11**, 453-464.
44. Paterni, L. and Russo, G. (1960) Il Primo caso di anomalia Pelgheriana nella emopatia benzenica; associazione con nanismo cellulare. *Haematologica*, **45**, 213-220.
45. Aksoy, M., Dincol, K., Erdem, S. *et al.* (1972) Details of blood changes in 32 patients with pancytopenia associated with long-term exposure to benzene. *Br. J. Ind. Med.*, **29**, 56-64.
46. Lai, J. L., Zandecki, M., Fenaux, P. *et al.* (1990) Translocations (5;17) and (7;17) in patients with de novo or therapy-related myelodysplastic syndromes or acute nonlymphocytic leukemia: a possible association with acquired pseudo-Pelger-Huet anomaly and small vacuolated granulocytes. *Cancer Genet. Cytogenet.*, **46**, 173-183.
47. Whang-Peng, J., Young, R. C., Lee, E. C. *et al.* (1988) Cytogenetic studies in patients with secondary leukemia/dysmyelopoietic syndrome after different treatment modalities. *Blood*, **71**, 403-414.
48. Committee on the Biologic Effects of Ionizing Radiation (BEIR). (1990) Radiogenic cancer at specific sites. In *Health Effects of Exposure to Low Levels of Ionizing Radiation*, BEIR V Report, pp. 242-351. Washington, DC: National Academy Press.
49. Spiers, A. S. D., Bain, B. J. and Turner, J. E. (1977) The peripheral blood in chronic granulocytic leukaemia: Study of 50 untreated Philadelphia-positive Cases. *Scand. J. Haematol.*, **18**, 25-38.
50. Shepherd, P. C. A., Ganesan, T. S. and Galton, D. A. G. (1987) Haematological classification of the chronic myeloid leukaemias. *Bail's Clin. Haematol.*, **1**, 887-906.
51. Hernberg, S., Savilahti, M., Ahlman, K. and Asp, S. (1966) Prognostic aspects of benzene poisoning. *Br. J. Ind. Med.*, **23**, 204-209.
52. Hammond, D., Sather, H., Nesbit, M. *et al.* (1986) Analysis of prognostic factors in acute lymphoblastic leukemia. *Med. Pediatr. Oncol.*, **14**, 124-134.
53. Yin, S.-N., Li, G. and Lian, Y. (1979) Experimental studies on the effect of Xuezaishan in treatment for benzene-intoxicated rats. *J. Inst. Health*, **8**, 54-58.
54. Smith, A. R. (1928) Chronic benzol poisoning among women industrial workers: A study of the women exposed to benzol fumes in six factories. In *The Journal of Industrial Hygiene*, edited by A. R. Smith, vol. 10, pp. 73-93. New York.
55. Pearson, M. and Rowley, J. D. (1985) The relation of oncogenesis and cytogenetics in lymphoma and leukemia. *Ann. Rev. Med.*, **36**, 471-483.
56. Le Beau, M. M., Lemons, R. S., Espinosa, (III) R. *et al.* (1989) Interleukin-4 and interleukin-5 Map to human chromosome 5 in a region encoding growth factors and receptors and are deleted in myeloid leukemias with a del (5q). *Blood*, **73**, 647-650.

Chemico-Biological Interactions. In press.

**Integrating WHO 2001-2008 criteria for the diagnosis of Myelodysplastic Syndrome (MDS):
a case-case analysis of benzene exposure**

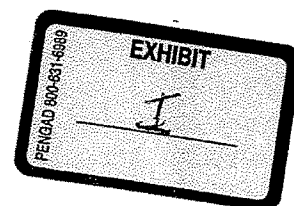
Richard D. Irons^{a,b,c,d}, Sherilyn A. Gross^{a,c}, Anh Le^c, Xiao Qin Wang^{a,f}, Yan Chen^a, John Ryder^{a,d}, A. Robert Schnatter^e,

^aFudan-Cinpathogen Clinical and Molecular Research Center, Institutes of Biomedical Sciences, Fudan University, Shanghai, China; ^bCinpathogen, Inc., Boulder, CO and Shanghai, China. ^cMolecular Toxicology and Environmental Health Sciences Program, School of Pharmacy, University of Colorado Denver, CO; ^dDepartment of Pathology, School of Medicine; University of Colorado Denver, CO; ^eExxonMobil Biomedical Sciences, Inc., 1545 Route 22 East, Annandale, NJ, 08801-0971 USA, ^fHuashan Hospital, Fudan University, Shanghai, China.

Running Title: Myelodysplastic Syndrome and Benzene

Type of Manuscript: Original

Corresponding Author: Richard Irons, Professor & Director
Fudan-Cinpathogen Clin. and Mol. Research Center
(86-21) 6163-3871 phone (China)
(86-21) 6163-3870 fax (China)
(303)724-3558 phone (USA)
(303)724-3673 fax (USA)
richard.iron@cinpathogen.com



Abstract

We characterized the prevalence of hematopoietic and lymphoid disease for 2,923 consecutive patients presenting at 29 hospitals from Aug 2003 to Jun 2007. Diagnoses were made in our laboratory using WHO criteria based on morphologic, immunophenotypic, cytogenetic, FISH and molecular data. A total of 611 subjects (322 males/289 females) were prospectively diagnosed with MDS using WHO (2001) criteria. Update and re-evaluation of cases using MDS (2008) criteria resulted in 649 MDS cases. Using WHO (2008) criteria, refractory cytopenia with multilineage dysplasia (RCMD) accounted for 68% of total cases, refractory anemia with excess blasts (RAEB), 16.3%, refractory anemia (RA), 6.5%, refractory cytopenia with unilineage dysplasia (RCUD), 4%, and MDS-unclassifiable (MDS-U), 4.5%. Subjects were administered questionnaires and information on previous disease, work histories and exposures to potential etiologic agents such as benzene (BZ) was obtained. A total of 80/649 (13.2%) were determined to have some BZ exposure. The frequency of clonal cytogenetic abnormalities in all MDS was 30%, the most common being $+8 > del(20)q > del(7q) > del(5q)$, while the analogous frequency in BZ-exposed cases was only 24%. To further investigate the characteristics of MDS associated with BZ, we identified a subset of cases with high BZ exposure. These BZ signal cases were each matched by age and gender to 2 cases with no known BZ exposure. When contrasting BZ signal cases vs matched cases with no BZ exposure, we found a high odds ratio (OR) for the WHO subtype MDS-U (OR = 11.1), followed by RAEB and RCUD (OR = 1), RA (OR = 0.7) and RCMD (OR = 0.6). Multilineage dysplasia with abnormal eosinophils (MDS-Eo) was strongly associated with BZ exposure, whereas the relative risk of clonal cytogenetic abnormalities was reduced for high BZ exposed cases (OR = 0.5). These findings are strongly indicative that MDS subtypes are influenced by BZ exposure, and taken together with previous studies, the features of MDS-Eo suggest that altered immune regulation plays a major role in the pathogenesis of MDS following chronic exposure to BZ.

1. Introduction

During the 1960's and 1970's there was increasing appreciation of a group of relatively obscure hematologic disorders that were associated with progressive bone marrow failure, were not characterized by increases in the number of circulating cells found in myeloproliferative or leukemic diseases and that shared certain common features of abnormal maturation and development of hematopoietic precursor cells in the bone marrow. Precision in diagnosis and prognosis has developed considerably for these debilitating, often fatal and sometimes "preleukemic" conditions now known as myelodysplastic syndromes (MDS). Understanding the nature and pathogenesis of MDS remains a work in progress. However, considerable advances have been made over the last decade in standardizing criteria for the diagnosis of the disease, with the widespread adoption of the WHO (2001)- and the recent introduction of WHO (2008)- classification criteria [1-3].

Today, MDS are recognized as a heterogeneous group of hematopoietic malignancies that are characterized by ineffective blood cell production, or hematopoiesis, that is accompanied by abnormal maturation and dysplasia in one or more blood cell lineages in the bone marrow (BM) [1]. Although MDS is usually progressive, the prognosis is highly variable. Some patients with MDS will undergo transformation to acute myeloid leukemia (AML) while others may become transfusion-dependent and eventually succumb to bleeding or infection. In still other cases the patient's clinical condition can remain relatively stable for long periods of time. The heterogeneity and clinical variability of MDS poses major challenges for prognosis as well as the rational development of effective therapeutic strategies. Principal differences between WHO (2001) and WHO (2008) criteria focus on the introduction of a new category in WHO (2008), refractory cytopenia with unilineage dysplasia (RCUD), which extends MDS to include BM failure syndromes with single lineage dysplasias in the granulocytic and megakaryocytic lineages, and some refinement in the definitions applied to MDS unclassifiable (MDS-U) [1].

Regional differences in the prevalence of individual MDS subtypes have been reported, primarily between Asian and Western patients [4-6]. We previously characterized a group of 176 MDS patients diagnosed in Shanghai according to WHO (2001) [7] and more recently reported on the prevalence, clinical and cytogenetic characteristics and survival of 435 patients diagnosed with *de novo* MDS [8]. Our results reveal major differences in the age at onset and prevalence of individual subtypes of MDS between Asian and Western patients with a median age of approximately 55 years and a predominance of refractory cytopenia with multilineage dysplasia (RCMD) that approaches 70% of all cases. Although previous studies have suggested MDS as an outcome in workers exposed to BZ [9;10], until recently identification of MDS or its subtypes associated with BZ exposure using modern criteria has been lacking [11]. Herein we extend our characterization of MDS in Shanghai in order to evaluate the impact of WHO (2008) criteria on the analysis of disease prevalence and to assess the influence of chronic benzene (BZ) exposure on the development of MDS.

2. Material and methods

2.1 Patients

All patients, ≥ 18 years of age, presenting at 29 Shanghai hospitals with initial clinical findings consistent with a hematopoietic abnormality between July, 2003 and July, 2007 were candidates for inclusion in this study. Informed consent was obtained according to the Declaration of Helsinki, 2004 and the NIH Common Rule (45CFR46), and together with the protocol, were approved by the Combined Institutional Review Board of the University of Colorado Health Sciences Center in Denver, Colorado and the Internal Review Board at Fudan University in Shanghai, China. Peripheral blood, bone marrow aspirates and core biopsies were obtained on all individuals using standardized procedures and evaluated in our laboratory using morphologic, immunophenotypic, molecular and cytogenetic techniques. Cases initially were diagnosed according to WHO 2001 criteria [2]. Patients presenting with concomitant nutritional deficiencies (Vitamin B12, folate or iron), congenital anemias, viral (including HCV or HIV), recent bacterial infections, or receiving concomitant cytotoxic therapy with alkylating or anti-metabolic agents were excluded in this analysis. Follow up evaluation was routinely provided. Diagnoses were

updated at 6-12 month intervals when possible, and all cases were re-evaluated in 2009 using WHO 2008 criteria [1].

2.2 *Sample collection and clinical laboratory analysis*

Peripheral blood, bone marrow aspirates, tissue and core biopsies were collected in conjunction with diagnostic procedures. Peripheral blood smears were obtained by finger stick. Blood samples were collected by venipuncture and processed for routine CBC (Cell Dyne 3700, Abbott, Abbott Park, IL) and viral serology (HCV and HIV) (Imx, Abbott). Serum vitamin B12 and folate were measured by chemical luminescence (Beckman Coulter Dxi800), and total iron binding capacity (TIBC) was determined using a Beckman Coulter LX20.

Bone marrow aspirates and core biopsies were obtained by needle extraction (Jamshidi) from the posterior iliac crest. Aspirate cell suspensions were stained with fluorochrome-conjugated antibodies for flow cytometric analysis of bone marrow cellular subsets. Multiparameter analysis was performed using a dual laser flow cytometer (FC-500, Beckman Coulter, Hialeah, FL; Immunotech, Miami FL) equipped with compensation software (Software CXP, Beckman Coulter). A broad panel of antibodies was used for immunophenotyping of BM cells. (Beckman Coulter, Immunotech).

2.3 *Morphology*

Morphology and immunophenotype analysis were conducted on both bone marrow aspirate (flow cytometry) and core biopsy (immunohistochemistry) material. Bone marrow aspirate and peripheral blood smears were prepared from fresh tissue and evaluated using Wright-Giemsa stained preparations and special stains, including an iron stain. Core biopsy sections were evaluated using Hematoxylin-Eosin (H&E), Gomori trichrome, iron and immunoperoxidase-immunohistochemistry stains for selected markers. Morphology was independently evaluated by two of us (R.D.I., J.R.). Microscopic analysis was performed using Olympus BX51 bright field microscopes (Olympus Optical Ltd, Tokyo). Standardized criteria for determining dysplastic changes and lineage involvement have been described in detail elsewhere [7].

2.4 *Cytogenetic and fluorescence in situ hybridization (FISH) analysis*

Cytogenetic studies were performed on either bone marrow or peripheral blood collected at diagnosis. Metaphases were prepared from unstimulated, short-term culture preparations (24- and 48-hour) and G-banded with trypsin-Giemsa staining. A minimum of 20 metaphases were analyzed in each case. FISH analysis was performed on short-term cultures of bone marrow or blood cells. Systematic screening for -5/5q-, -7/7q-, +8, del(20q) and 11q23/*MLL* rearrangements was performed on each patient. In some cases, additional FISH studies were used to either characterize chromosome abnormalities (CA) observed in banded chromosome studies or to confirm the presence of cytogenetic aberrations suggested by other diagnostic work-up. A minimum of 500 nuclei and 10 metaphases were analyzed in interphase and metaphase analysis, respectively.

2.5 *Questionnaire Description*

Questionnaire administration and data collection procedures are described elsewhere [12]. Briefly, all subjects were interviewed by trained personnel in the hospital setting. In a few cases, subjects were interviewed at home if they had left the hospital prior to interview. The questionnaires used in this study were designed in English, translated into Chinese and then administered in the native Chinese language. Information obtained in the questionnaire included patient demographics, family history of disease, patient medical history (diseases, medications), patient occupational history and patient non-occupational exposure history (*e.g.* hobbies, smoking, alcohol use). Clerical staff entered the data in duplicate from the questionnaires into a database that was verified via an external quality assurance audit. Any disagreements between questionnaire entries were resolved quickly by referring to the original paper record or the questionnaire administrator. A summary file was generated from the questionnaire data, which did not include any of the clinical information, such as clinical diagnoses, that could compromise blinding. This summary file was assessed and edited via a comprehensive series of logic and consistency checks to assure data integrity.

Information from different fields on the questionnaire were combined to define an enhanced and more inclusive variable for analysis. These instances included: (a) information on diabetes and diabetes treatments (*i.e.* tolbutamide) for a diabetes indicator, (b) information on tuberculosis (TB) and TB

treatments for a tuberculosis indicator (c) growing crops indicator which used information on fertilizers, insecticides, pesticides, and growing crops, and (d) an inflammation indicator that combined information on infections and inflammatory diseases such as arthritis, hepatitis and TB.

The questionnaire that solicited exposure information for subjects consisted of a detailed assessment of each patient's work history. This work history queried jobs held over each patient's entire career. Subsequent exposure assessment steps involved at least one, but often several, of the following steps: (a) location of exposure measurement records for the job and location where the subject worked through the Shanghai Institute of Public Health Supervision (IPHS) database, (b) location of records for surrogate factories, industries or jobs in the IPHS database, (c) assessment of exposures detailed in the Chinese literature for relevant industries (d) assessment of regulatory and technology changes for key industries, (e) monitoring data from nearby facilities, and/or (f) conducting task simulations. An expert panel assessed exposures using the above data. Additional independent checks with source data further refined the expert panel assessment.

2.6 Exposure Assessment

Five ordinal categories of exposure: 0, <1 mg/m³, 1-<10 mg/m³, 10-<100 mg/m³, and 100+ mg/m³ were formed. Each job/location scenario was placed into one of these five categories using the procedures summarized above. Category 1 was assigned a 'score' of 1, category 2 a score of 2, etc. We then further categorized the third category (10-100 mg/m³) into 3.1 (10-32 mg/m³), 3.2 (33-66 mg/m³) and 3.3 (67-100 mg/m³) and calculated the months exposed at each estimated concentration level. We believe the scores represent an accurate assessment of relative BZ exposure in diverse Chinese industries, and should be considered one of the strongest exposure assessments for BZ in the literature to date. While we are confident that the relative degree of BZ exposure is represented in the scoring scheme used, we are more cautious regarding precise exposure concentrations assigned to each score. Therefore, we have chosen to report exposure grades rather than assigning a midpoint concentration to each category in order to calculate a measure analogous to 'ppm' or 'ppm-months'.

2.7 Case case selection

An objective of this study was to compare both the demographic and clinical characteristics of MDS cases highly exposed to BZ with a similar population of MDS cases with no documented BZ exposure. Although it is impossible to determine the etiology of any individual case within a group, we hypothesized that BZ exposure is most likely to have a role in the development of MDS for the most highly exposed cases in our series. Therefore, our rationale was to establish a clear contrast between background cases (unexposed) and those that could reasonably be attributed to BZ. Consequently, for some of the analyses performed in this study we defined “signal cases” as individuals who were exposed to >67 mg/m^3 (*i.e.* categories 3.3 or 4) for at least 6 months with a mean exposure duration of 144 months ($N=29$). We matched these cases by gender and exact age to two cases from a randomized group of MDS cases with no documented BZ exposure (*i.e.* score category 0).

2.8 *Blinding*

All study personnel involved in the clinical laboratory diagnosis of disease, as well as members of the expert exposure assessment panel, were blinded to the exposure status of subjects throughout the data acquisition phase of the study.

2.9 *Statistical analyses*

t- Tests (pooled variance) or tests for independent proportions, where appropriate, were used to examine differences between clinical features for MDS subtypes. Kaplan–Meier survival analysis was used to estimate overall survival (OS), and conditional logistic regression analysis was used to calculate odds ratios (OR), along with 95% confidence intervals, for matched case-case analyses, both employing STATA 9.0 software (StataCorp, College Station, Texas). All *P*-values were two-sided and values less than 0.05 were considered statistically significant.

3. **Results**

3.1 *Prevalence and age distribution of MDS in Shanghai*

The total number of cases of MDS initially diagnosed according to WHO 2001 was 611, including 322 males (52.7%) and 289 females (47.3%). A comparison of the prevalence of MDS

subtypes diagnosed according to 2001 and 2008 WHO revisions is provided in Table 1. Diagnosis using 2008 criteria resulted in a 6% increase in the total number of MDS cases (N=649). This included 9 cases which were not initially diagnosed with MDS, but met criteria for a diagnosis of RCMD with subsequent follow-up evaluation. An additional 26 cases with single lineage dysplasia that initially were not diagnosed with MDS using 2001 criteria were reassessed according to 2008 criteria and diagnosed with RCUD. The age and gender distribution of MDS cases diagnosed according to WHO 2008 is presented in Figure 1a. The ratio of males to females (341:308) diagnosed using 2008 criteria remained unchanged from WHO 2001 as did the median age at diagnosis: WHO (2001) males/females: 56/52yr; WHO (2008) males/females: 57/52yr. Based on a median age of 70 years typically reported for MDS in the West, these results confirm and extend major differences in the age distribution and prevalence of individual subtypes of MDS between Asian and Western patients [6-8]. Asian patients tend to present with MDS at a much earlier age and develop predominantly RCMD.

3.2 *Frequency of cytogenetic abnormalities in MDS in Shanghai*

The overall frequency of clonal cytogenetic abnormalities in MDS diagnosed according to WHO (2008) was 30.2% (196/649). Although both banded chromosome analysis and FISH were routinely employed in diagnosis, only 10 cases presenting with a normal karyotype were found to have a clonal abnormality using FISH alone. The majority of these involved del(20q). The overall frequency of clonal abnormalities was somewhat less than reported in Western studies and is consistent with the predominance of RCMD (Table 2). Trisomy 8 was the most frequent abnormality encountered in our MDS cases, followed by del(20q) > del(7q) > del(5q) abnormalities (Table 3). Chromosome abnormalities involving both del(7q) and del(5q) in combination were invariably associated with complex karyotypes involving 3 or more abnormalities.

3.3 *Benzene exposure and MDS*

A total of 80 out of 649 subjects (13.2%) diagnosed with MDS were determined to have some BZ exposure (i.e. BZ exposure grade ≥ 1). Our exposure assessment for BZ was derived from questionnaire responses, along with a detailed assessment of the presence and degree of BZ exposure in the jobs and

industries observed from our work history data. This led to the development of the ordinal exposure categories that were further assessed by independent scientists using various ranking schemes. The frequency of CA in the BZ “ever-exposed” group was lower than that observed in the total population of MDS cases (*i.e.* 24% vs 30%). The median age of the subset of 29 BZ highly exposed cases, which were defined as “signal cases,” was compared to 569 cases which were determined to have no BZ exposure (*i.e.* exposure grade = 0). BZ-exposed signal cases (Median age = 49) were significantly younger at diagnosis than this comparison group (Median = 55, $p < .001$) (Figure 1b). Gender differences between BZ signal cases and the total population of MDS cases were observed as well, with the proportion of females in the BZ signal group (20/29) significantly higher than for female MDS cases not in the BZ signal group (288/620) ($p < .05$).

3.4 *Case-case comparisons: clinical and cytogenetic features*

Comparison of the prevalence of individual MDS subtypes between BZ signal cases and matched unexposed cases indicated a marked increase in MDS-U, no differences in refractory anemia with excess blasts (RAEB) or RCUD, and relative deficits of RCMD and refractory anemia (RA) in BZ signal cases compared to cases with no BZ exposure (Table 4). The increased number of MDS-U in BZ signal cases reflects a frequently observed imbalance between cytopenias found in peripheral blood and lineage-specific dysplasia in the bone marrow of these patients (primarily normal or near-normal hemoglobin (Hb) values in the presence of marked bone marrow dyserythropoiesis).

A comparison of the clinical features between BZ signal cases and matching cases for which there is no documented exposure to BZ is presented in Table 5. Features that frequently characterized BZ signal cases included marked erythroid dysplasia in the bone marrow (Figures 2 and 3), no evidence of increased ring sideroblasts, near-normal hemoglobin values (Hb) in the face of marked BM dyserythropoiesis, a tendency toward low-to-normal BM cellularity, and a striking increase in multilineage dysplasia with abnormal eosinophils (MDS-Eo) (Figure 4), hematophagocytosis (Figure 5) and stromal degeneration. (Figure 3). Quantitative case-case comparison of clinical features in BZ signal cases are presented in Table 6. Hb levels $> 10\text{g/dL}$ were increased and the prevalence of MDS-Eo

between BZ signal cases and matched unexposed cases revealed an infinite OR. No cases of peripheral eosinophilia were observed in any of these subjects. The prevalence of clonal cytogenetic abnormalities was lower in BZ signal cases than matched unexposed cases with relative deficits observed for trisomy 8 as well as del(7q) abnormalities. Clonal CA involving del(5q) alone were not found in BZ signal cases. Other CA observed in the BZ signal cases were del(9q22) and +X, which each occurred once. These findings indicate that CA in MDS cases developing secondary to high BZ exposure are not consistent with the paradigm involving unbalanced loss of chromosomes 5 and/or 7 that is characteristic of tMDS/tAML secondary to treatment with alkylating chemotherapeutic agents.

3.5 *Survival*

Analysis of overall survival (OS) between the BZ signal group and matched unexposed cases revealed differences in the pattern of OS between these two groups (Figure 6). Initial survival (<10 months) after diagnosis was lower in BZ signal cases than in matched unexposed cases. The reasons for this are not known. However, long term OS was markedly increased in BZ signal cases. One possible explanation for the latter observation is that we have found Hb, which is higher in BZ signal cases relative to unexposed cases, is a significant favorable independent variable in predicting OS in MDS [8]. These disparate outcomes suggest biologically significant differences in the pathogenesis of MDS between BZ highly exposed and unexposed (*i.e. de novo*) cases. Comparison of OS between matched unexposed cases and a larger subset of *de novo* MDS cases for which follow up data was available (435) revealed no significant differences between matched unexposed cases and other *de novo* MDS cases (data not shown) [8].

4. Discussion

MDS is a heterogeneous set of disorders for which the pathogenesis remains obscure. Genetic, infectious and environmental influences all have been suggested to play important roles in the development and evolution of MDS, with clonal cytogenetic abnormalities, altered gene regulation, abnormal cytokine production and immune activation variously hypothesized to be responsible for clonal

selection and progression in MDS.

MDS developing secondary to therapy with alkylating chemotherapeutic agents is well described, the clinical features of which frequently include multilineage dysplasia, increased ring siderblasts, loss of chromosomes 5 and/or 7, and a rapid progression to AML [1;13]. Recently, distinctive gene expression profiles have been described for several different cytogenetic abnormalities associated with therapy-related MDS, including abnormalities involving chromosome 5 and/or 7. Monosomy 7 is associated with overexpression of several known oncogenes including HOX9A, BRCA2 and PLAB [14]. In addition, Qian and colleagues have demonstrated a distinct profile for t-MDS/t-AML involving both chromosomes 5 and 7 that is characterized by a higher expression profile of genes involved in cell cycle control and growth [15]. These patterns support a role for clonal cytogenetic or molecular injury early in the clonal evolution of these tumors. In contrast, MDS involving trisomy 8 is associated with higher expression of immune and inflammatory genes, such as TGF- β , IL-10 and VCAM-1 [14], and is consistent with either inflammatory or cytogenetic etiologies playing a dominant role early in the clonal evolution of the disease.

Previous studies, including some from our laboratory, have assumed that clonal cytogenetic injury is a predisposing event in the initiation of BZ-induced BM injury [16-21]. Nevertheless, direct demonstration of clonal CA in the pathogenesis of chronic BZ hematotoxicity has not been established, and several features of MDS associated with BZ exposure reported herein suggest that its pathogenesis is distinct from either therapy-related MDS or *de novo* MDS. These include a decrease in both the frequency and pattern of clonal CA observed in BZ associated MDS, altered prevalence of MDS subtypes, differences in clinical features and a significant variation in the pattern of survival in BZ associated MDS. The predominant morphologic pattern encountered in BM of BZ signal cases, involving MDS-Eo, is essentially identical to that reported by Ruiz et al in the BM of Brazilian workers heavily exposed to BZ [22].

Whether all forms of MDS have truly clonal origins beginning with a single cytogenetic misadventure has never been established, and it has been suggested that the emergence of cytogenetic

clones may be a secondary phenomenon [23]. The evidence implicating immunological targeting of antigens in the hematopoietic environment early in the pathogenesis of MDS is also considerable [24-27]. Frequent findings in MDS include lymphocytopenia, inverted CD4/CD8 T cell ratios, increases in cytotoxic CD8+ T cells (CTL), and evidence of T cell receptor (TCR) gene rearrangements [28-31]. Clonal expansion of T cell subsets is also a prominent finding in the development of aplastic anemia [32-34]. Positive clinical responses to immunosuppressive therapy with anti-thymocyte globulin (ATG) or cyclosporin A is also effective in some patients with MDS [26;30;35]. Independently, there is evidence to suggest that altered patterns of gene regulation observed in tissue-specific autoimmune disease are mediated by collaboration between epigenetic events, such as immune cell activation and leukotriene production [36-39].

We believe that the integration of clinical and histopathologic observations in patients together with molecular findings remains the most promising avenue for hypothesis-based studies on the pathogenesis of BM-induced disease. The predominant pattern of BM pathology in BZ-exposed MDS cases, namely multilineage dysplasia, abnormal eosinophils, hematophagocytosis, together with stromal degeneration, is consistent with an ongoing inflammatory response persisting for many years after cessation of BZ exposure. Immunologic abnormalities are also observed in MDS developing in workers previously exposed to high concentrations of BZ, including increases in circulating large granular lymphocytes (LGLs), altered distribution of CD4 and CD8 T cells and clonal expansion of T cell subpopulations in BM, including prominent clonal proliferations of $\gamma\delta$ T cells [11]. Independently, susceptibility to the development of MDS following BZ exposure is associated with an increase in the prevalence of a rare (-238) tumor necrosis factor (TNF- α) polymorphism [40].

Although the mechanisms of persistent BM injury following chronic exposure to BZ remain unknown, a subpopulation of CD34+ BM cells have been implicated as targets, both *in vivo* and *in vitro*, with a variety of studies indicating that BZ metabolites directly alter proliferation and differentiation in BM hematopoietic progenitor cells (HPC). Given the unique ability of BZ among solvents to produce

chronic BM damage, it is likely that BZ metabolites play a direct role in establishing the unique pattern of injury that leads to persistent BM pathology long after exposure has ended. Hydroquinone (HQ), a major polyphenolic metabolite of BZ, enhances granulocyte/macrophage-colony stimulating factor (GM-CSF)-dependent clonal proliferation of human CD34+ HPC via activation of extracellular signal-related kinase (ERK) and activation protein-1 (AP-1) [17;41-46]. Hydroquinone also synergizes with TNF- α to produce apoptosis in human CD34+ HPC via a mechanism that involves the inhibition of Nuclear Factor Kappa-B (NF κ B) [44]. Eosinophilic dysplasia is a prominent feature in MDS associated with BZ exposure and is also observed in AML with abnormalities involving chromosome 16 (p13;q22) in which production of the CBF β /MYH11 fusion protein is suggested to result in the expression of antigens which initiate oligoclonal T-cell expansion and leukemic blast lysis [37]. It is also possible that epigenetic events may result in comparable alterations in regulation of gene expression. For example, HQ synergizes with LTD4 via the ligand binding domain of the CysLT1 receptor to activate granulocytic/eosinophilic differentiation [47] and $\gamma\delta$ T cell subsets that are activated by TNF- α also have been shown to promote hematophagocytosis and modulate eosinophilic inflammation in other tissues. Taken together with the observed human experience in China and Brazil, the evidence strongly suggests that tissue specific BZ metabolism and altered immune regulation plays a predisposing role in the pathogenesis of persistent BM injury and the development of MDS following chronic exposure to BZ.

Acknowledgements

The authors gratefully acknowledge all the hospitals and physicians who participated, including Huashan Hospital, Xinhua Hospital, Long March Hospital, Huang Pu Central District Hospital, Renji Hospital, Ruijin Hospital, Huadong Hospital, Jin An Central Hospital, No. 1 People's Hospital, No. 5 People's Hospital, No. 6 People's Hospital, No. 9 People's Hospital, Yang Pu Central Hospital, Zha Bei Central Hospital, Shu Guang Hospital, Chang Ning Central Hospital, Tong Ji Hospital, Shong Jin Central Hospital, Zhong Shan Hospital, Railway Hospital, Rong Hua Hospital, Changhai Hospital, Occupational Disease Hospital, Jiading Central Hospital, 455 Hospital, Shidong Hospital, No. 1 Baoshan Hospital, and

Putuo Central Hospital. We would also like to extend our appreciation to Ann Loudon for manuscript and clerical assistance.

The CMRC received funds from the Benzene Health Research Consortium consisting of ExxonMobil, BP Amoco, Chevron-Exxon, Conoco-Philips and Shell Chemical Companies. This work was supported in part by Cinpathogen, Inc. R.D.I. has received consulting fees from law firms in cases involving benzene. All other authors declare no competing financial interests.

References

- [1] S.H. Swerdlow, E. Campo, N.L. Harris *et al.* WHO Classification of Tumours of Haematopoietic and Lymphoid Tissue in: Swerdlow SH, Campo E, Harris NL *et al.* WHO Classification of Tumours of Haematopoietic and Lymphoid Tissue. IARC, Lyon, France: 2008.
- [2] E. Jaffe, N. Harris, H. Stein, J. Vardiman, World Health Organization Classification of Tumours. Pathology and genetics of tumours of haematopoietic and lymphoid tissues in: Jaffe E, Harris N, Stein H, Vardiman J. World Health Organization Classification of Tumours. Pathology and genetics of tumours of haematopoietic and lymphoid tissues. IARC Press, Lyon, France: 2001.
- [3] U. Germing, N. Gattermann, C. Strupp, M. Aivado, C. Aul, Validation of the WHO proposals for a new classification of primary myelodysplastic syndromes: a retrospective analysis of 1600 patients, *Leukemia Research* 24 (2000) 983-92.
- [4] A. Matsuda, U. Germing, I. Jinnai, M. Misumi, A. Kuendgen, S. Knipp, M. Aivado, M. Iwanaga, Y. Miyazaki, H. Tsushima, M. Sakai, M. Bessho, M. Tomonaga, Difference in clinical features between Japanese and German patients with refractory anemia in myelodysplastic syndromes, *Blood* 106 (2005) 2633-40.
- [5] A. Kuendgen, A. Matsuda, U. Germing, Differences in Epidemiology of MDS Between Western and Eastern Countries: Ethnic Differences or Environmental Influence?, *Leukemia Research* 31 (2007) 103-4.
- [6] B. Chen, W.L. Zhao, J. Jin, Y.Q. Xue, X. Cheng, X.T. Chen, J. Cui, Z.M. Chen, Q. Cao, G. Yang, Y. Yao, H.L. Xia, J.H. Tong, J.M. Li, J. Chen, S.M. Xiong, Z.X. Shen, S. Waxman, Z. Chen, S.J. Chen, Clinical and cytogenetic features of 508 Chinese patients with myelodysplastic syndrome and comparison with those in Western countries, *Leukemia* 19 (2005) 767-75.
- [7] R.D. Irons, X. Wang, S.A. Gross, L. Bao, J. Ryder, Y. Chen, H. Chen, H. Sun, J. Zhou, M. Ji, X. Du, H. Fu, G. Lin, Prevalence of MDS subtypes in Shanghai, China: A comparison of the World Health Organization and French American British classifications, *Leukemia Research* 30 (2006) 769-775.
- [8] X.Q. Wang, J. Ryder, S.A. Gross, G. Lin, R.D. Irons, Prospective analysis of clinical and cytogenetic features of 435 cases of MDS diagnosed using the WHO (2001) classification: a

prognostic scoring system for predicting survival in RCMD, *International Journal of Hematology* (In Press).

- [9] A. Cuneo, F Fagioli, I Pazzi, A Tallarico, R Previati, N Piva, GM Carli, M Balboni, G Castoldi, Morphologic, immunologic and cytogenetic studies in acute myeloid leukemia following occupational exposure to pesticides and organic solvents, *Leukemia Research* 16 (1992) 789-796.
- [10] R.B. Hayes, S.N. Yin, M. Dosemeci, G.L. Li, S. Wacholder, L.B. Travis, C.Y. Li, N. Rothman, R.N. Hoover, M.S. Linet, Benzene and the dose-related incidence of hematologic neoplasms in China, *J.Natl.Cancer Inst.* 89 (1997) 1065-1071.
- [11] R.D. Irons, L. Lv, S.A. Gross, X. Ye, L. Bao, X.Q. Wang, J. Ryder, T.W. Armstrong, Y. Zhou, L. Miao, A.T. Le, P.J. Kerzic, W. Ni, H. Fu, Chronic exposure to benzene results in a unique form of dysplasia, *Leukemia Research* 29 (2005) 1371-80.
- [12] T. Armstrong, Y. Zhou, C. Zhang, S. Bowes, Y. Liang, O. Wong, F. Hua, Exposure assessment for a case-control epidemiology study based in Shanghai, China: Summary of methods and results.
- [13] S.M. Smith, M.M. Le Beau, D. Huo, T. Karrison, R.M. Sobecks, J. Anastasi, J.W. Vardiman, J.D. Rowley, R.A. Larson, Clinical-cytogenetic associations in 306 patients with therapy-related myelodysplasia and myeloid leukemia: the University of Chicago series, *Blood* 102 (2003) 43-52.
- [14] G. Chen, W. Zeng, A. Miyazato, E. Billings, J.P. Maciejewski, S. Kajigaya, E.M. Sloand, N.S. Young, Distinctive Gene Expression Profiles of Cd34 Cells From Patients With Myelodysplastic Syndrome Characterized by Specific Chromosomal Abnormalities, *Blood* 104 (2004) 4210-8.
- [15] Z. Qian, A.A. Fernald, L.A. Godley, R.A. Larson, M.M. Le Beau, Expression Profiling of Cd34+ Hematopoietic Stem/ Progenitor Cells Reveals Distinct Subtypes of Therapy-Related Acute Myeloid Leukemia, *Proceedings of the National Academy of Sciences of the United States of America* 99 (2002) 14925-30.
- [16] R.D. Irons, W.S. Stillman, The process of leukemogenesis, *Environ.Health Perspect.* 104 (1996) 1239-1246.
- [17] W.S. Stillman, M Varella-Garcia, RD Irons, The benzene metabolite, hydroquinone, selectively induces 5q31-and-7 in human CD34⁺CD19⁻ bone marrow cells, *Exp.Hematol.* 28 (2000) 169-176.
- [18] W.S. Stillman, M. Varella-Garcia, J.J. Gruntmeir, R.D. Irons, The benzene metabolite, hydroquinone, induces dose-dependent hypoploidy in a human cell line, *Leukemia* 11 (1997) 1540-1545.
- [19] W.S. Stillman, M. Varella-Garcia, R.D. Irons, The benzene metabolites hydroquinone and catechol act in synergy to induce dose-dependent hypoploidy and-5q31 in a human cell line, *Leuk.Lymphoma* 35 (1999) 269-281.
- [20] M.T. Smith, LP Zhang, M Jeng, YX Wang, WH Guo, P Duramad, AE Hubbard, G Hofstadler, NT Holland, Hydroquinone, a benzene metabolite, increases the level of aneusomy of chromosomes 7 and 8 in human CD34-positive blood progenitor cells, *Carcinogenesis* 21 (2000) 1485-1490.
- [21] M.T. Smith, L.P. Zhang, Y.X. Wang, R.B. Hayes, G.L. Li, J. Wiemels, M. Dosemeci, N. Titenko-

- Holland, L.Q. Xi, P. Kolachana, S.N. Yin, N. Rothman, Increased translocations and aneusomy in chromosomes 8 and 21 among workers exposed to benzene, *Cancer Res.* 58 (1998) 2176-2181.
- [22] M.A. Ruiz, L.G. Augusto, J. Vassallo, A.C. Vigorito, I. Lorand-Metze, C.A. Souza, Bone Marrow Morphology in Patients With Neutropenia Due to Chronic Exposure to Organic Solvents (Benzene): Early Lesions, *Pathology, Research & Practice* 190 (1994) 151-4.
- [23] M. Cazzola, L. Malcovati, Myelodysplastic syndromes--coping with ineffective hematopoiesis, *N Engl J Med* 352 (2005) 536-8.
- [24] A.J. Barrett, Myelodysplastic syndrome--an example of misguided immune surveillance?, *Leukemia Research* 28 (2004) 1123-4.
- [25] C. Rosenfeld, A. List, A hypothesis for the pathogenesis of myelodysplastic syndromes: implications for new therapies, *Leukemia* 14 (2000) 2-8.
- [26] D.H. Biesma, J.G. van den Tweel, L.F. Verdonck, Immunosuppressive therapy for hypoplastic myelodysplastic syndrome, *Cancer*. 79 (1997) 1548-51.
- [27] T. Matsutani, T. Yoshioka, Y. Tsuruta, T. Shimamoto, J.H. Ohyashiki, R. Suzuki, K. Ohyashiki, Determination of T-cell receptors of clonal CD8-positive T-cells in myelodysplastic syndrome with erythroid hypoplasia, *Leukemia Research*. 27 (2003) 305-12.
- [28] T.J. Hamblin, Immunological abnormalities in myelodysplastic syndromes, *Seminars in Hematology* 33 (1996) 150-62.
- [29] Y. Sauntharajah, J.L. Molldrem, M. Rivera, A. Williams, M. Stetler-Stevenson, L. Sorbara, N.S. Young, J.A. Barrett, Coincident Myelodysplastic Syndrome and T-Cell Large Granular Lymphocytic Disease: Clinical and Pathophysiological Features, *British Journal of Haematology* 112 (2001) 195-200.
- [30] T. Shimamoto, T. Iguchi, K. Ando, T. Katagiri, T. Tauchi, Y. Ito, M. Yaguchi, K. Miyazawa, Y. Kimura, M. Masuda, H. Mizoguchi, K. Ohyashiki, Successful Treatment With Cyclosporin A for Myelodysplastic Syndrome With Erythroid Hypoplasia Associated With T-Cell Receptor Gene Rearrangements, *British Journal of Haematology* 114 (2001) 358-61.
- [31] H. Kook, W. Zeng, C. Guibin, M. Kirby, N.S. Young, J.P. Maciejewski, Increased cytotoxic T cells with effector phenotype in aplastic anemia and myelodysplasia, *Experimental Hematology* 29 (2001) 1270-7.
- [32] A.M. Risitano, J.P. Maciejewski, S. Green, M. Plasilova, W. Zeng, N.S. Young, In-vivo dominant immune responses in aplastic anaemia: molecular tracking of putatively pathogenetic T-cell clones by TCR beta-CDR3 sequencing, *Lancet* 364 (2004) 355-64.
- [33] W. Zeng, J.P. Maciejewski, G. Chen, N.S. Young, Limited heterogeneity of T cell receptor BV usage in aplastic anemia, *Journal of Clinical Investigation* 108 (2001) 765-73.
- [34] A.W. Langerak, T. Szczepanski, M. van der Burg, I.L. Wolvers-Tettero, J.J. van Dongen, Heteroduplex PCR analysis of rearranged T cell receptor genes for clonality assessment in suspect T cell proliferations, *Leukemia* 11 (1997) 2192-9.

- [35] A. Jonasova, R. Neuwirtova, J. Cermak, V. Vozobulova, K. Mocikova, M. Siskova, I. Hochova, Cyclosporin A therapy in hypoplastic MDS patients and certain refractory anaemias without hypoplastic bone marrow, *British Journal of Haematology* 100 (1998) 304-9.
- [36] G. Par, D. Rukavina, E.R. Podack, M. Horanyi, J. Szekeres-Bartho, G. Hegedus, M. Paal, L. Szereday, G. Mozsik, A. Par, Decrease in CD3-negative-CD8dim(+) and Vdelta2/Vgamma9 TcR+ peripheral blood lymphocyte counts, low perforin expression and the impairment of natural killer cell activity is associated with chronic hepatitis C virus infection, *Journal of Hepatology* 37 (2002) 514-22.
- [37] G.A. Banat, K. Ihlow, N. Usluoglu, S. Hoppmann, M. Hoeck, H. Pralle, Core-binding factor-beta positive acute myeloid leukaemia cells induce T-cell responses, *British Journal of Haematology* 123 (2003) 819-29.
- [38] Y.S. Hahn, C. Taube, N. Jin, L. Sharp, J.M. Wands, M.K. Aydinoglu, M. Lahn, S.A. Huber, R.L. O'Brien, E.W. Gelfand, W.K. Born, Different potentials of gamma delta T cell subsets in regulating airway responsiveness: V gamma 1+ cells, but not V gamma 4+ cells, promote airway hyperreactivity, Th2 cytokines, and airway inflammation, *Journal of Immunology* 172 (2004) 2894-902.
- [39] A. Kanehiro, M. Lahn, M.J. Makela, A. Dakham, M. Fujita, A. Joetham, R.J. Mason, W. Born, E.W. Gelfand, Tumor necrosis factor-alpha negatively regulates airway hyperresponsiveness through gamma-delta T cells, *American Journal of Respiratory and Critical Care Medicine* 164 (2001) 2229-38.
- [40] L. Lv, P. Kerzic, G. Lin, A.R. Schnatter, L. Bao, Y. Yang, H. Zou, H. Fu, X. Ye, S.A. Gross, T.W. Armstrong, R.D. Irons, The TNF-Alpha 238a Polymorphism Is Associated With Susceptibility to Persistent Bone Marrow Dysplasia Following Chronic Exposure to Benzene, *Leukemia Research* 31 (2007) 1479-85.
- [41] R.D. Irons, WS Stillman, DB Colagiovanni, VA Henry, Synergistic action of the benzene metabolite hydroquinone on myelopoietic stimulating activity of granulocyte/macrophage colony-stimulating factor *in vitro*, *Proc.Natl.Acad.Sci.USA* 89 (1992) 3691-3695.
- [42] P. Baines, H. Mayani, M. Bains, J. Fisher, T. Hoy, A. Jacobs, Enrichment of CD34 (My10)-positive myeloid and erythroid progenitors from human marrow and their growth in cultures supplemented with recombinant human granulocyte-macrophage colony-stimulating factor, *Exp.Hematol.* 16 (1988) 785-789.
- [43] H. Quentmeier, WG Dirks, D Fleckenstein, M Zaborski, HG Drexler, Tumor necrosis factor-alpha-induced proliferation requires synthesis of granulocyte-macrophage colony-stimulating factor, *Experimental Hematology* 28 (2000) 1008-15.
- [44] R.D. Irons, WS Stillman, Cell proliferation and differentiation in chemical leukemogenesis, *Stem Cells* 11 (1993) 235-242.
- [45] R.D. Irons, WS Stillman, Impact of benzene metabolites on differentiation of bone marrow progenitor cells, *Environ.Health Perspect.* 104 Suppl. 6 (1996) 1247-1250.
- [46] J.H. Zheng, DW Pyatt, SA Gross, AT Le, PJ Kerzic, RD Irons, Hydroquinone modulates the GM-CSF signaling pathway in TF-1 cells, *Leukemia* 18 (2004) 1296-1304.

- [47] M.B. Jordan, D. Hildeman, J. Kappler, P. Marrack, An animal model of hemophagocytic lymphohistiocytosis (HLH): CD8⁺ T cells and interferon gamma are essential for the disorder, *Blood* 104 (2004) 735-43.

Table 1. Comparison of WHO 2001/2008 Criteria MDS Subtypes in Shanghai, China			
WHO 2001	Total Cases	WHO 2008	Total Cases
RA	38 (6.2%)	RA	38 (5.9%)
RARS	7 (1.1%)	RARS	7 (1.1%)
RAEB	106 (17.3%)	RAEB	106 (16.3%)
RCMD	432 (70.7%)	RCMD	441 (68%)
MDS-U	26 (4.3%)	MDS-U	29 (4.5%)
MDS 5q-	2 (0.3%)	MDS 5q-	2 (0.3%)
		RCUD	26 (4.0%)
Total	611	Total	649

Table 2. Clonal Cytogenetic Abnormalities by MDS Subtype		
MDS Subtypes	Total Cases	Clonal Abn
RA+RARS	45	4 (8.9%)
RAEB	106	64 (60.4%)
RCMD	441	112 (25.4%)
RCUD	26	2 (7.7%)
MDS-U	29	12 (41.4%)

Table 3. Clonal Cytogenetic Abnormalities MDS (2008) N = 649		
Clonal Abnormality	N	%
Total	196	30.2%
+ 8	53	8.2%
del(20q)	26	4.0%
7q-/-7	22	3.4%
5q-/-5	20	3.1%
-5/-7 ^a	19	2.9%
-Y	7	1.1%
del(9q)	4	0.6%
11q23	5	0.8%
Ch 3	5	0.8%
del(13q)	3	0.5%
-X	3	0.5%
Other	29	4.5%
Complex Karyotype ≥ 3 Abnl	46	7.1%

^aExclusively in complex karyotypes

Table 4. Odds Ratios for MDS subtypes in Benzene Signal Cases			
Subtype	N	OR	CI
RCMD	16	0.58	0.24 - 1.4
RAEB	2	1.4	0.19 - 11.1
MDS-U	7	11.12 ^a	1.34 - 92.4
RCUD	2	1.0	0.18 - 5.46
RA	2	0.67	0.13 - 3.3

^ap<0.05

Table 5. Comparison of Hematologic Parameters BZ Signal Cases vs Matched Unexposed Cases										
MDS Cases	Bone Marrow						Peripheral Blood			
	Cellularity			Blasts		MDS-Eo	Neutrophils x10⁹/L	Lymphocytes x10⁹/L	Hg g/dL	Platelets x10⁹/L
	Hypo	Normo	Hyper	0-1.8%	>1.8%					
BZ Signal Cases	14 (61%)	7 (30.4%)	2 (8.6%)	27 (93%)	2 (7%)	21/29** (72.4%)	1.61 (N=29) [0.85]	0.94 (N=29) [0.46]	11.35* (N=29) [2.6]	104.9 (N=29) [63]
Matched Unexposed Cases	26 (59%)	10 (23%)	8 (18%)	46 (84%)	9 (16%)	1/58** (1.7%)	1.29 (N=53) [1.02]	1.24 (N=53) [0.91]	8.23* (N=55) [2.7]	85.1 (N=55) [111]

*p<.001 (t-test, pooled variance)

[Std Dev.]

**p<.0001 (hypothesis testing for 2 independent proportions)

Table 6. Odds Ratios for Clinical Features in Benzene Signal Cases			
Feature	N	OR	CI
MDS-Eo	21	∞	
Hg	23	6.4 ^a	2.11 - 19.21
BM Hyper.	2	0.39	0.07 - 2.05
Clonal Ab. (total) ^b	5	0.46	0.16 - 1.3
+8	2	0.43	0.081 - 2.3
-7	1	1.0	0.091 - 11.02

^ap<0.001

^b For other see text

Figure 1a

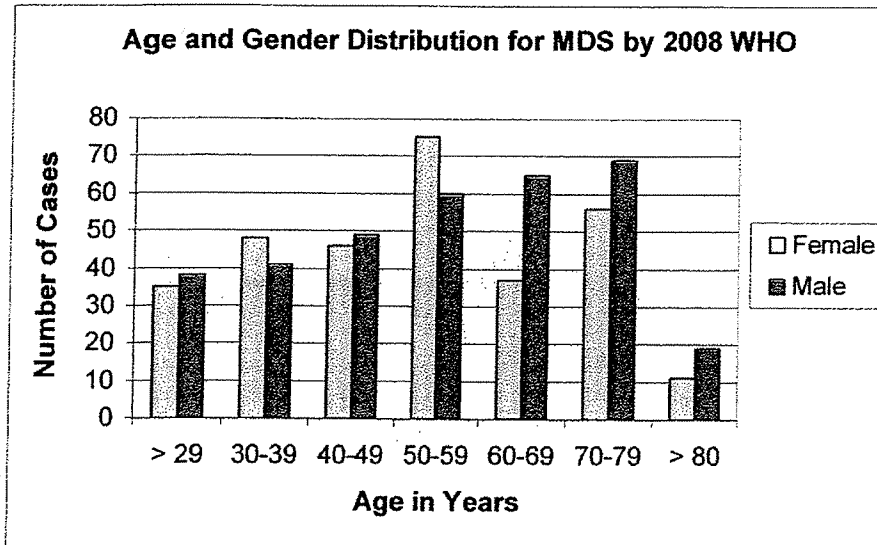


Figure 1b

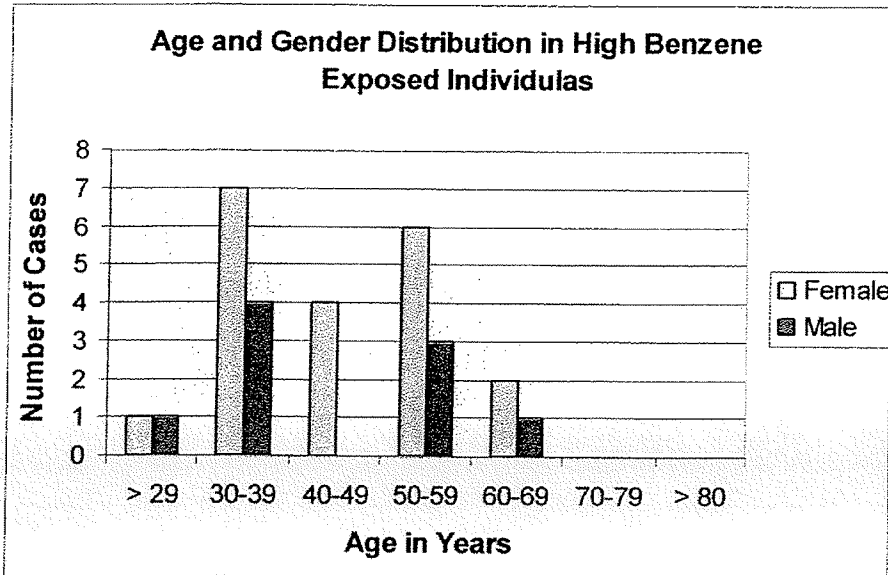


Figure 2

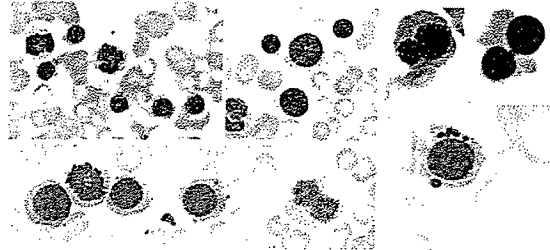


Figure 3

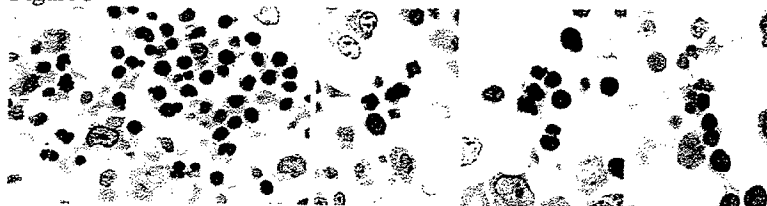


Figure 4

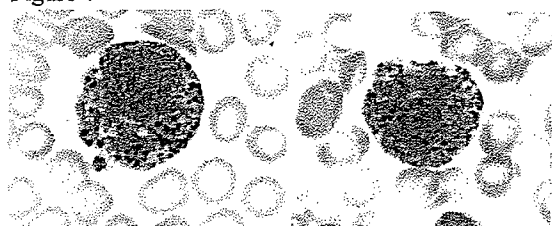


Figure 5

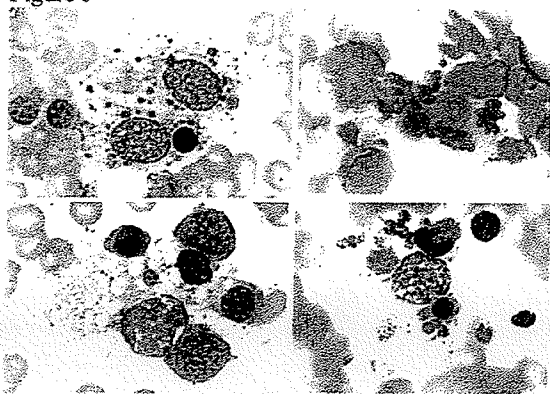


Figure 6

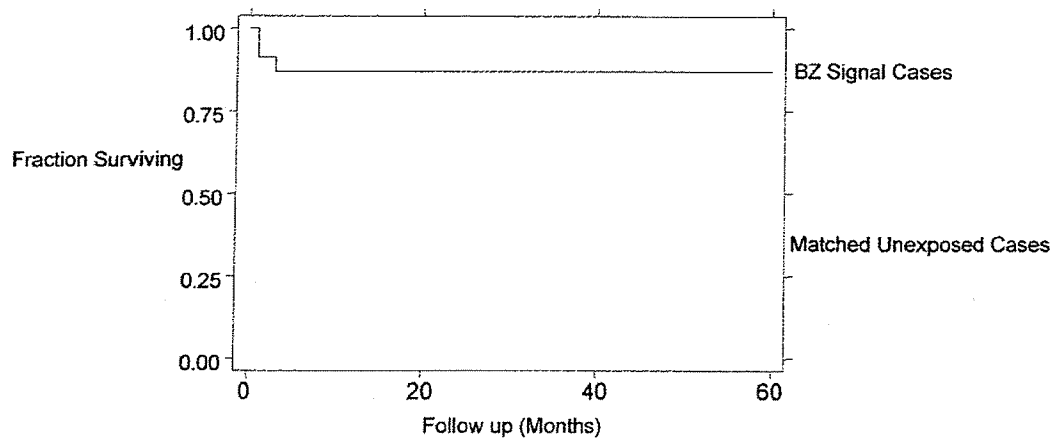


Figure Legends

- Figure 1a. Age and gender distribution of WHO (2008) cases grouped by decade.
- Figure 1b. Age and gender distribution of benzene signal cases grouped by decade.
- Figure 2. Dyserythropoiesis with megaloblastic changes and nuclear bridging in MDS associated with previous high BZ exposure. Bone marrow aspirate with Wright-Giemsa stain (original magnification X1000). Reproduced with permission [11].
- Figure 3. Dyserythropoiesis and stromal degeneration accompanying MDS-Eo associated with previous high BZ exposure. Core biopsy section. Hematoxylin-Eosin stain (original magnification X1000). Reproduced with permission [11].
- Figure 4. Abnormal eosinophilic precursor cells in MDS-Eo associated with previous high BZ exposure. Cells exhibit megaloblastic nuclear abnormalities, nuclear hypersegmentation and atypical giant cytoplasmic granulation. Bone marrow aspirate with Wright-Giemsa stain (original magnification X1000). Reproduced with permission [11].
- Figure 5. Hematophagocytosis accompanying MDS-Eo associated with previous high BZ exposure. Activated histiocytic cells exhibit prominent phagocytosis of degenerating erythroid granulocytic cells typical of an immune-mediated inflammatory process. Bone marrow aspirate with Wright-Giemsa stain (original magnification X1000). Reproduced with permission [11].

Figure 6. Kaplan-Meier overall survival analysis for benzene signal cases versus matched unexposed MDS cases.

Myelodysplastic/myeloproliferative neoplasm, unclassifiable

J.W. Vardiman
J.M. Bennett
B.J. Bain
I. Baumann
J. Thiele
A. Orazi

Definition

Myelodysplastic/myeloproliferative neoplasm, unclassifiable, (MDS/MPN, U) meets the criteria for the MDS/MPN category in that, at the time of initial presentation, there are clinical, laboratory and morphological features that overlap both MDS and MPN. Cases classified as MDS/MPN, U do not meet the criteria for chronic myelomonocytic leukaemia, juvenile myelomonocytic leukaemia or atypical chronic myeloid leukaemia. The finding of a *BCR-ABL1* fusion gene or of rearrangement of *PDGFRA*, *PDGFRB* or *FGFR1* excludes the diagnosis of MDS/MPN, U.

It is important that the designation MDS/MPN, U not be used for patients with a previous, well-defined MPN who develop dysplastic features in association with transformation to a more aggressive phase. However, MDS/MPN, U may include some patients in whom the chronic phase of an MPN was not previously detected, and who initially present in transformation with myelodysplastic features. If the underlying MPN cannot be identified, the designation of MDS/MPN, U is appropriate. If there has been any recent cytotoxic or growth factor therapy, follow-up clinical and laboratory observations are essential to demonstrate that the peripheral blood (PB) and bone marrow (BM) changes are not due to the treatment.

ICD-O code 9975/3

Synonyms

Mixed myeloproliferative/myelodysplastic syndrome, unclassifiable; "overlap" syndrome, unclassifiable.

Sites of involvement

The BM and PB are always involved; spleen, liver and other extramedullary tissues may be involved.

Clinical features

The clinical features of MDS/MPN, U overlap those found in diseases of the MDS and MPN categories [129, 1588, 2311].

Table 4.04 Diagnostic criteria for myelodysplastic/myeloproliferative neoplasm, unclassifiable (MDS/MPN, U).

- The case has clinical, laboratory and morphological features of one of the categories of MDS (refractory cytopenia with unilineage dysplasia, refractory anaemia with ring sideroblasts, refractory cytopenia with multilineage dysplasia, refractory anaemia with excess of blasts) and <20% blasts in the blood and bone marrow and
 - Has prominent myeloproliferative features, e.g. platelet count $\geq 450 \times 10^9/L$ associated with megakaryocytic proliferation, or WBC count $\geq 13 \times 10^9/L$, with or without prominent splenomegaly and
- Has no preceding history of an underlying MPN or of MDS, no history of recent cytotoxic or growth factor therapy that could explain the myelodysplastic or myeloproliferative features, and no Philadelphia chromosome or *BCR-ABL1* fusion gene, no rearrangement of *PDGFRA*, *PDGFRB* or *FGFR1*, and no isolated *del(5q)*, *t(3;3)(q21;q26)* or *inv(3)(q21q26)* or
- The patient has *de novo* disease with mixed myeloproliferative and myelodysplastic features and cannot be assigned to any other category of MDS, MPN or of MDS/MPN.

Morphology and cytochemistry

These disorders are characterized by proliferation of one or more myeloid lineages that is ineffective, dysplastic or both and simultaneously, by effective proliferation, with or without dysplasia, in one or more of the other myeloid lineages. Laboratory features usually include anaemia of variable severity, with or without macrocytosis and often dimorphic red blood cells on the peripheral smear. In addition, there is evidence of effective proliferation in one or more lineages, either as thrombocytosis (platelet count $\geq 450 \times 10^9/L$) or leukocytosis (white blood cell count $\geq 13 \times 10^9/L$). Neutrophils may show dysplastic features and there may be giant or hypogranular platelets. Blasts account for <20% of the leukocytes in the PB and of the nucleated cells of the BM, and a finding of >10% blasts in the PB or BM likely indicates transformation to a more aggressive stage. The BM biopsy specimen is hypercellular and may show proliferation in any or all of the myeloid lineages. However, dysplastic features are simultaneously present in at least one cell line.

Cytochemical findings may be similar to those seen in MDS or in MPN.

Immunophenotype

May be similar to findings in MDS and/or MPN.

Genetics

There is no cytogenetic or molecular genetic finding specific for this group. A Philadelphia chromosome and *BCR-ABL1* fusion gene should always be excluded prior to making the diagnosis of MDS/MPN, U. Cases with rearrangements of *PDGFRA*, *PDGFRB* or *FGFR1* or with isolated *del(5q)* or *t(3;3)(q21;q26)* or *inv(3)(q21q26)* are excluded from this category as well. In difficult cases, the presence of a *JAK2 V617F* mutation may help to confirm a haematopoietic neoplasm, though the significance of such mutations in this entity is uncertain. Occasional cases with isolated *del(5q)* and *JAK2 V617F* mutation have been reported to have features that overlap MDS and MPN [1005].

Postulated cell of origin

Haematopoietic stem cell.

Refractory anaemia with ring sideroblasts (RARS) associated with marked thrombocytosis

Definition

In the third edition of the WHO Classification, RARS-T, previously also referred to as essential thrombocythaemia (ET) with ring sideroblasts, was proposed as a provisional entity to encompass patients who have the clinical and morphological features of the myelodysplastic syndrome.



RARS, but who also have marked thrombocytosis associated with abnormal megakaryocytes similar to those observed in the *BCR-ABL1* negative MPN, such as ET or early-stage primary myelofibrosis (PMF) [865, 1077, 2109]. However, some investigators have suggested that RARS-T is not a unique entity but instead represents cases of other subtypes of MDS or well-defined MPN that have acquired ring sideroblasts as a secondary form of dysplasia [1966]. It is not clear whether RARS-T is a distinct entity, one end of the spectrum of RARS, a progression of RARS due to an additional acquired genetic abnormality, or less likely, the occurrence of two rare diseases in the same patient. Therefore, until these questions are more clearly answered, RARS-T remains a provisional entity.

In support of a myeloproliferative component to this neoplasm, the majority of cases reported as RARS-T have shown the *JAK2* V617F mutation, or much less commonly, the *MPL* W515K/L mutation [234, 354, 762, 1835, 1839, 1969, 2081, 2139, 2358]. On the other hand, the few reported cases with this mutation that have been studied for endogenous colony formation *in vitro* have demonstrated a pattern more akin to that of MDS [234, 1835]. Thus it may be that the provisional designation of an MDS/MPN accurately reflects the underlying biology in a substantial proportion of the patients [762]; more study is needed to further clarify this disorder.

Cases with isolated *del*(5q), *t*(3;3)(q21;q26) or *inv*(3)(q21q26) are excluded from this category, as are cases with a *BCR-ABL1* fusion gene. In addition, if there has been a prior diagnosis of an MPN without ring sideroblasts, or there is evidence that the ring sideroblasts might be a consequence of therapy or represent disease progression in a patient with features that meet the criteria of another well-defined MPN, this designation should not be used.

ICD-O code 9982/3

Morphology

These cases have features of RARS (anaemia with no blasts in the PB and dysplastic, ineffective erythroid proliferation often with megakaryoblastoid features, ring sideroblasts $\geq 15\%$ of the erythroid precursors, and $< 5\%$ blasts in the BM) and thrombocytosis with a platelet count $\geq 450 \times 10^9/L$ associated with proliferation

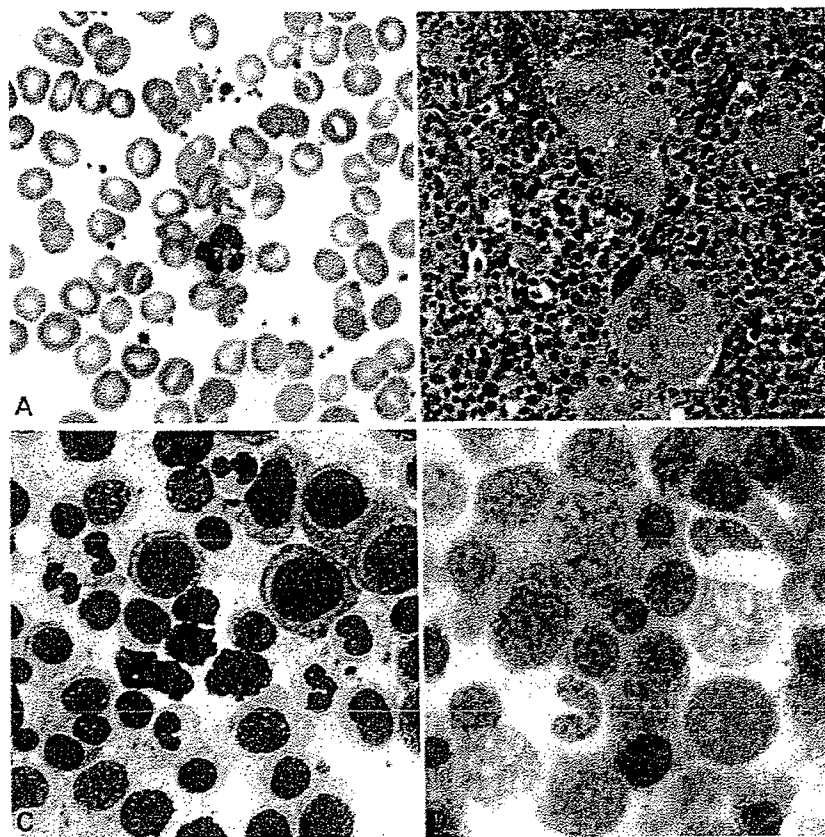


Fig. 4.13 Refractory anaemia with ring sideroblasts and thrombocytosis. This sequence of microphotographs illustrate blood and bone marrow of a 62-year-old man who presented with severe anaemia and a platelet count of $850 \times 10^9/L$. A Abnormal red cells and thrombocytosis. B Erythroid proliferation and abnormal megakaryocytes resembling megakaryocytes seen in ET. C Mild dyserythropoiesis. D The majority of erythroid precursors were ring sideroblasts.

of large atypical megakaryocytes similar to those observed in *BCR-ABL1* negative MPN (See Chapter 2).

The minimum platelet count required for inclusion has been lowered to $450 \times 10^9/L$ from $600 \times 10^9/L$ for consistency with the defining criterion for ET, and because several studies have demonstrated that patients with platelet counts lower than $600 \times 10^9/L$ may have biological features, including *JAK2* V617F mutations, similar to those with counts $\geq 600 \times 10^9/L$ [354]. It is important to note that the criteria for RARS-T includes morphologically abnormal megakaryocytes similar to those observed in ET and in PMF. This criterion should aid in distinguishing RARS-T from those cases of RARS commonly reported to have a modest increase in their platelet count. Nevertheless, we recommend testing for *JAK2* V617F when the platelet count is elevated in patients with RARS until the borderline between RARS and RARS-T is more clearly defined.

Genetics

The recent discovery that up to 60% of patients with RARS-T harbour the *JAK2* V617F mutation (an incidence similar to that found in ET and PMF) or less commonly, the *MPL* W515K/L mutation, not only elucidates the reason for the proliferative aspect of RARS-T but also would seem to move it closer to the MPN category [234, 354, 762, 1835, 1839, 1969, 2081, 2139, 2358]. Thus, studies for *JAK2* V617F and, if indicated, for the *MPL* W515K/L mutation should always be performed in such cases.



Wolters Kluwer
Health

Lippincott
Williams & Wilkins

INVOICE NO.
51260831

DATE
11/19/07

ACCOUNT NO. P.O. NUMBER

INVOICE NO. 51260831
147009688

PUBLICATION

AMER JRNL MEDICAL SCI

ISSUE

11/01/07

S
O
L
D
T
O
METHODIST ACADEMIC MEDICINE
ETHAN NATELSON
THE METHODIST HOSPITAL
SMITH TOWER 1001
6550 FANNIN ST
HOUSTON, TX 77030-2717

Quantity	Article code	Description	Miscellaneous order	Pages	Amount
0	MAJ20035	BENZENE EXPOSURE AND REFRACTORY.... Page Charges Ship to account	147009688	5	200.00 0.00

(FEIN) 132932696

GST # 895524239

PAYMENT MADE VIA WIRE TRANSFERS SHOULD BE MADE
M&T BANK, 25 SOUTH CHARLES STREET
BALTIMORE, MD 21202, USA, BANK ABA: 022-000-046,
ACCT.#: 060-9576-0, NAME ON ACCT: LIPPINCOTT
WILLIAMS & WILKINS. INCLUDE AMOUNT OF TRANSFER,
CUSTOMER & INVOICE NUMBER.

SUBTOTAL \$ 200.00
SHIPPING / HANDLING 0.00
SALES TAX
LESS PAYMENT

AMOUNT DUE \$ 200.00

LATE PAYMENT SUBJECT TO COLLECTION CHARGE

← IMPORTANT: Detach here and return the lower portion to ensure proper credit to your account. →

INVOICE NUMBER

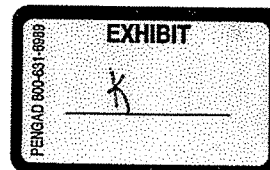
51260831

For Address
Change
Check Here
And See
Reverse Side

5126083100014700968800014700968800000200000931*****MAJ1

AMOUNT ENCLOSED

METHODIST ACADEMIC MEDICINE
ETHAN NATELSON
THE METHODIST HOSPITAL
SMITH TOWER 1001
6550 FANNIN ST
HOUSTON, TX 77030-2717



Payable to

Lippincott Williams & Wilkins
P.O. Box 64931
Baltimore, Md 21264-4931
USA

Credit Card (✓) ☐ AMEX ☐ DISC ☐ MC ☐ VISA

Card No.

Expire Date

Remit in U.S. Dollars Drawn on U.S. Bank

On the Field, Stamp or Bank Code

Telephone No. ()

Authorized Signature